FDA Briefing Document
Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

September 10-11, 2020

Oxycontin Abuse Deterrent Formulation (ADF)

Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought our reviews of the results of required postmarketing studies (Postmarketing Requirements 3051-1, 3051-2, 3051-3, and 3051-4) that evaluated the effect of the reformulation of OXYCONTIN (oxycodone hydrochloride extended-release tablets, manufactured by Purdue Pharma L.P., NDA 022272) on abuse, misuse, and fatal and non-fatal overdose associated with OXYCONTIN, and our reviews of other information from the published literature related to whether this product has resulted in a meaningful reduction in these outcomes, and related to the broader public health impact of OXYCONTIN's reformulation to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FDA Briefing Document Contents

Office of Surveillance and Epidemiology Summary Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 10-11, 2020

To: Members of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee

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Subject: Postmarket Evaluation of the Effectiveness and Public Health Impact of OxyContin's Reformulation as an Abuse-deterrent Formulation

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1 INTRODUCTION AND BACKGROUND

1.1 PURPOSE OF THIS ADVISORY COMMITTEE MEETING

We are convening a joint meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) Advisory Committees to discuss and solicit committee members' opinions on the results of the OxyContin abuse-deterrent formulation (ADF) postmarketing requirement (PMR) study findings, as well as related findings from the published literature, that evaluate whether the postmarketing data indicate that OxyContin's reformulation did deter its abuse by snorting and injecting, as expected based on experimental data. While FDA recognizes that an ADF of a single product cannot solve the opioid crisis, we are asking the committees to discuss and provide their viewpoints on broader public health impacts, both positive and negative, of OxyContin's reformulation within the complex and evolving landscape of opioid use, abuse, addiction, and overdose.

__A note on terminology and stigma__: In this briefing document, FDA frequently uses the term __abuse__ when discussing data related to reformulated OxyContin. With regard to ADFs, FDA considers abuse to refer to the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect.[1] We recognize that some language can perpetuate stigma and negative bias toward individuals with substance use disorders and create barriers to effective treatment. For example, the term __abuse__ has been identified as having a high association with negative judgments and punishment.[2] The term __abuse__ is used here to describe a specific behavior that confers a risk of adverse health outcomes; it is not intended to imply moral judgment. FDA is committed to reducing stigma, expanding therapeutic options, and ensuring access to evidence-based treatment for individuals with substance use disorders.

1.2 BRIEF HISTORY OF ABUSE-DETERRENT FORMULATION (ADF) OPIOID ANALGESIC DEVELOPMENT AND MARKETING IN THE U.S.

Some general history of ADF development provides context for considering the reformulation of OxyContin (oxycodone hydrochloride extended-release tablets, Purdue Pharma L.P.) and the impact this formulation had on abuse and related outcomes. For roughly a decade, FDA has encouraged the development of ADF opioid analgesics. While recognizing that ADF technology cannot make an opioid analgesic abuse-proof or non-addictive, FDA has supported ADF

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[1] *Abuse-deterrent Opioids—Evaluation and Labeling: Guidance for Industry*. April 2015.

[2] National Institute on Drug Abuse: *Words Matter - Terms to Use and Avoid When Talking About Addiction*. https://www.drugabuse.gov/nidamed-medical-health-professionals/health-professions-education/words-matter-terms-to-use-avoid-when-talking-about-addiction

development as one of many strategies intended to mitigate the harms associated with prescription opioid abuse while maintaining access to opioid analgesics for patients who need them. ADF development has primarily focused on deterring abuse by snorting and injection of extended-release (ER) opioid analgesic products. Non-oral routes of abuse, particularly injection, are associated with risks such as soft-tissue infections, endocarditis, and transmission of HIV and hepatitis C; additionally, ER products typically contain larger amounts of opioid than immediate-release (IR) products and therefore pose increased risks to those abusing these drugs if the medications are manipulated (e.g., crushed or dissolved) to cause the active ingredient to "dose dump," i.e., to be released all at once. To date, however, extended-release/long-acting (ER/LA) opioid analgesics represent less than 10 percent of the outpatient opioid analgesic prescriptions dispensed in the United States;[3] the remainder consists of IR opioid analgesics, predominantly IR opioid-acetaminophen combination products. ADFs comprise approximately 25% of ER/LA opioid analgesic prescriptions dispensed. Recognizing that most opioid analgesic misuse and abuse occurs through the oral route, FDA has encouraged development of products with properties that could meaningfully deter all relevant forms of abuse, including the common method of abuse, swallowing intact tablets or capsules.

In April 2015, FDA issued final guidance, *Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry*,[4] outlining the agency's current thinking on the studies that should be conducted to demonstrate that a given opioid formulation has abuse-deterrent properties. The guidance outlines several principles for evaluating the abuse-deterrent characteristics of an opioid formulation. First, studies should be scientifically rigorous, incorporating use of appropriate comparators and endpoints, and should take into consideration the known routes of abuse and whether the deterrent effects can be expected to have a meaningful impact on specific routes as well as the overall abuse of the product. The guidance describes four categories of studies to evaluate the abuse-deterrent characteristics of an opioid formulation:

> Category 1: Laboratory-based in vitro manipulation and extraction studies
> Category 2: Pharmacokinetic studies
> Category 3: Clinical abuse potential studies (i.e., "drug liking" studies)
> Category 4: Postmarket studies (i.e., epidemiologic studies)

The guidance states that the goal of postmarketing (Category 4) studies is to determine whether the marketing of a product with abuse-deterrent properties results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting. It also notes that because the science of abuse deterrence is relatively new and methods for evaluating those technologies are evolving, FDA intends to take a flexible, adaptive

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[3] Source: IQVIA, National Prescription Audit (NPA) and static data 2006-2011. January 2006-December 2019. Static data extracted March 2017, 2012-2017 data extracted February 2018, 2018 data extracted March 2019, 2019 data extracted Jan 24, 2020

[4] https://www.fda.gov/media/84819/download

approach to evaluation and labeling of potentially abuse-deterrent products. The agency also stated that because of the evolving nature of this field, no absolute magnitude of effect could be set for establishing abuse-deterrence, and that it intended to consider the totality of evidence when reviewing the results of studies evaluating abuse-deterrence.

As of 2019, ADF opioid analgesics represented approximately two percent of the opioid analgesic market,[3] and multiple ADF opioid analgesic products approved by FDA have been voluntarily withdrawn by their application holders or are not currently being marketed. In November 2017, FDA issued final guidance on evaluation of generic ADF opioid analgesics, *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products: Guidance for Industry.*[5] To date, no generic versions of ADF opioid analgesics have been approved.

1.3   REGULATORY HISTORY OF REFORMULATED OXYCONTIN

FDA approved the original formulation of OxyContin in December 1995. In the first decade following approval, the product became widely abused, often following manipulation to defeat its extended-release properties and to administer it via unintended routes. In April 2010, the FDA approved a reformulated version of OxyContin, which contained a matrix of high molecular weight (HMW) polyethylene oxide (PEO) to make the tablet more difficult to manipulate (i.e., crush, dissolve in solution) for purposes of abuse, particularly via snorting and injection. In August 2010, Purdue stopped shipping original OxyContin to pharmacies and began shipment of the reformulated product. At the time of approval of reformulated OxyContin, FDA required that the application holder conduct postmarketing studies to determine whether the reformulation actually resulted in a decrease in the risks of misuse and abuse, and their consequences, addiction, overdose, and death. Following an October 2010 Advisory Committee meeting discussing Purdue's proposed postmarketing studies, the agency provided Purdue with additional questions and design considerations relating to these studies, acknowledging that this was a new area of scientific inquiry without established methods or data sources.

At the time of reformulated OxyContin's approval in April 2010, FDA required a risk evaluation and mitigation strategy (REMS) for this product. (See Division of Risk Management memo) The REMS consisted of elements to assure safe use (ETASU), which included healthcare provider training and Dear Healthcare Professional letters. In addition, the REMS included a Medication Guide, since it was determined that OxyContin had serious risks that may affect a patient's decision to use, or continue to use, OxyContin. In July 2012, OxyContin became a member of the shared system Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics (ER/LA) REMS. Under the ER/LA REMS, application holders were required to make continuing education (CE) programs available to prescribers. The CE courses were required to include the content and messages of a "blueprint" developed by FDA for this purpose. The ER/LA REMS was expanded

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[5] https://www.fda.gov/media/96643/download

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and modified in September 2018 to include all application holders of immediate-release (IR) opioid analgesics that are expected to be used in the outpatient setting and that are not already covered by another REMS program. The Opioid Analgesic REMS requires that training be made available to healthcare providers, including prescribers, nurses, and pharmacists, involved in the treatment and monitoring of patients with pain. The currently approved FDA Blueprint focuses on the fundamentals of acute and chronic pain management and provides a contextual framework for the safe prescribing of opioid analgesics. The Opioid Analgesic REMS also includes a Patient Counseling Guide for healthcare providers to assist in properly counseling patients on their responsibilities for using these medicines safely and to provide patients with additional written safety information.

In April 2013, FDA approved a supplemental application for reformulated OxyContin, approving changes to Section 9.2 of the product labeling that describe certain abuse-deterrent properties of the reformulated product. [See April 2013 Federal Register Notice] The new labeling language described the findings of the *in vitro* manipulation studies, pharmacokinetic studies, and clinical abuse potential studies (i.e., Category 1-3 studies) submitted by the application holder, and included the following summary statement about reformulated OxyContin's abuse-deterrent properties based on these findings [See OxyContin Prescribing Information]:

> *The* in vitro *data demonstrate that OXYCONTIN has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the in vitro data, also indicate that OXYCONTIN has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OXYCONTIN by these routes, as well as by the oral route, is still possible.*

> *Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of OXYCONTIN on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.*

Also in April 2013, the FDA determined that the benefits of original OxyContin no longer outweighed its risks and that original OxyContin had been withdrawn from sale for reasons of safety or effectiveness. This determination was made because original OxyContin provided the same therapeutic benefits as reformulated OxyContin but posed an increased potential for abuse by certain routes of administration, when compared to reformulated OxyContin. In addition, FDA determined that the reformulated product may be safer than the original by deterring certain types of misuse in a therapeutic context, for example misusing the product by crushing it and then sprinkling it onto food or to administer it through a gastric tube. Accordingly, the agency did not accept or approve any abbreviated new drug applications (generics) that relied upon the approval of original OxyContin. The agency reached this decision following careful review and analysis of data from *in vitro* manipulation studies, pharmacokinetic studies, and clinical abuse potential

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("drug liking") studies, as well as early findings of postmarketing studies that suggested, but did not confirm, a reduction in non-oral abuse of reformulated OxyContin in the community, compared to the original formulation. In reaching its decision, FDA also considered several relevant citizen petitions and comments submitted to the public dockets associated with these petitions. [See April 2013 Federal Register Notice]

In October 2014, Purdue submitted a labeling supplement requesting placement of a claim in the labeling describing a real-world effect of the abuse-deterrent formulation (ADF) of OxyContin. An Advisory Committee meeting was scheduled to be held on July 7 and 8, 2015, to discuss the results of postmarketing studies submitted to support this claim. CDER prepared briefing materials for Committee members that included CDER's review of the study findings (in accordance with its usual practice). On June 22, 2015, the materials were also provided to Purdue, consistent with the process described in the Agency's *Guidance for Industry: Advisory Committee Meetings – Preparation and Public Availability of Information Given to Advisory Committee Members*. Purdue submitted a request to withdraw the supplement. The Advisory Committee meeting was subsequently cancelled; consequently, there was no public discussion of the results of the supplement or supporting studies that were submitted. {See Regulatory History Memorandum]

In March 2016, FDA issued a new postmarketing requirement (PMR) letter, formalizing the required studies and milestone dates. CDER's review of the studies included in Purdue's October 2014 submission helped refine the agency's thinking about which studies and analyses would best inform our ability to assess whether the reformulated OxyContin actually deterred abuse and its adverse consequences. In addition to three studies assessing the impact of the ADF on OxyContin abuse rates (PMRs 3051-1, 3051-2, and 3051-3), the agency required a claims-based study linked to mortality data to assess the impact of the reformulation on fatal and non-fatal opioid overdose (3051-4). However, the FDA review team determined that given the limitations of the available data (particularly, poor performance of code-based algorithms to measure abuse and addiction in electronic healthcare data), retrospective data would not be capable of rigorously evaluating whether the OxyContin's reformulation resulted in a decreased risk of addiction. The PMRs required that the application holder submit protocols and statistical analysis plans for FDA review and approval. [See Regulatory History Memorandum]

In September 2019, the application holder submitted the last of the final study reports for the four PMR studies evaluating the effectiveness of the ADF in reducing OxyContin abuse and related outcomes, including fatal and non-fatal overdose, in the post-approval setting.

1.4 PUBLIC HEALTH GOALS AND CONSIDERATION OF A BENEFIT-RISK FRAMEWORK FOR OPIOID ANALGESICS WITHIN A COMPLEX SYSTEM

Since the approval of reformulated OxyContin in 2010, the environment in which prescription opioid analgesics are prescribed, used, and abused has changed considerably. Prescribing of both ER and IR opioid analgesics has declined[3]—likely due to growing awareness of the serious risks associated with opioids and the combined effect of efforts to mitigate this crisis, such as opioid analgesic prescribing guidelines, REMS, other prescriber education programs, state legislation, prescription drug monitoring programs, law enforcement activity, changes to opioid analgesic labeling, and payer and health system restrictions on opioid analgesic prescribing. Meanwhile, potent, inexpensive heroin and illicitly manufactured fentanyl and fentanyl analogues have become readily available in many areas, contributing to shifting opioid abuse patterns and resulting in a precipitous rise in overdose deaths involving these substances.[6,7] The proliferation of online drug trafficking has further removed barriers to accessing the illicit drug market,[8] making illicit opioids easier to obtain than prescription drugs in some communities.[9]

FDA's regulatory decisions relating to opioids are guided by its goal to protect and advance public health. Achieving this goal involves ensuring that safe and effective therapies are available to meet the medical needs of people living with pain, maximizing the safety of those products, and conveying accurate information that can enable the public (patients, healthcare providers, insurers, and others) to make informed evidence-based decisions about the use of these products. At the same time, FDA has an imperative to make positive contributions to addressing the evolving public health crisis of addiction and overdose involving opioids.

Benefit-risk assessment is a foundation for FDA's regulatory review of all human drugs and biologics. Considerations guiding FDA's decision-making specific to opioid analgesics are outlined in the *Draft Guidance to Industry: Opioids Analgesic Drugs – Considerations for Benefit-Risk Assessment Framework*.[10] In general, FDA considers the benefits and risks to the patient when the drug is used as labeled. Additionally, for regulatory decisions regarding opioids, FDA considers the public health risks of the drug related to misuse, abuse, opioid use disorder, accidental exposure, and overdose in both patients and others, as well as any properties of the drug that may mitigate such risks.

Using this broader public health lens, FDA's benefit-risk assessment considers different populations who may be affected by the regulated product and/or by FDA's decision-making regarding that product. FDA recognizes that people's need for, experiences with, and risks related to opioid analgesics are all individual. Thus, in the case of opioid analgesics, "population" is used

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[6] Richard G. Frank, Ph.D., and Harold A. Pollack, Ph.D. Addressing the Fentanyl Threat to Public Health *N Engl J Med* 2017; 376:605-607.
[7] Hedegaard H, Minino AM, Warner M; NCHS Data Brief No. 329, November 2018. **https://www.cdc.gov/nchs/data/databriefs/db329-h.pdf**
[8] https://www.rand.org/pubs/research_reports/RR1607.html
[9] https://www.drugabuse.gov/publications/opioid-facts-teens/opioids-heroin
[10] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/opioid-analgesic-drugs-considerations-benefit-risk-assessment-framework-guidance-industry

to characterize a set of individuals in general terms by their pain therapeutic needs and opioid use behaviors. ***It is important to note that individuals may simultaneously fit into multiple populations and may move in and out of populations depending on their current situation.*** This characterization of populations, however, can be useful in considering the different benefits and risks of ADF opioid analgesics and the potential for different, including unintended, impacts in different groups. Broadly speaking, three important populations may be particularly relevant to evaluating the impact of OxyContin's reformulation as an ADF:

- *Individuals who require opioid analgesics for the treatment of pain, under the care of a healthcare provider (i.e., the intended population).* Importantly, these individuals may simultaneously fit into another category described below. A central goal for this population is availability of safe and effective therapies to manage their medical needs while minimizing the risks of opioid analgesic misuse and abuse, addiction, and overdose. A potential safety benefit of ADF opioid analgesics related specifically to this population is a reduction in medication errors related to crushing extended-release opioid analgesics, for example in patients with feeding tubes [See 2013 Federal Register Notice]. However, unintended adverse effects from added excipients may include choking, dysphagia, and rare intestinal obstruction, as described in the current OxyContin labeling based on postmarketing reports received by FDA following the product's reformulation [See section 2.4.1 of this memo].

- *Individuals who misuse or abuse opioid analgesics but do not regularly manipulate these products for use by routes (e.g., snorting, injecting) other than the intended route.* These individuals may obtain opioids from their own prescription or from other sources, and are considered to be at risk of harms from oral nonmedical use as well as transitioning to snorting or injection and the harms associated with these behaviors. These individuals may also engage in risky use of alcohol, other pharmaceuticals, or illicit substances. Important goals for this population are to reduce harms associated with nonmedical use of opioid analgesics, including harms associated with the transition to manipulation and non-oral use (e.g., infectious complications of injection), and risk of progression to more severe stages of a substance use disorder, overdose, and death.

- *Individuals who regularly manipulate opioid analgesics for use by routes (e.g., snorting, injecting) other than the intended route.* These behaviors may be associated with a more severe substance use disorder, and these individuals may be more likely to engage regularly in polysubstance use, including risky alcohol use, nonmedical use of other pharmaceuticals, and use of heroin or other illicit substances. A key goal related to this population is to reduce the likelihood and frequency of risky behaviors and adverse outcomes (e.g., injection-related harms, overdose) associated with these behaviors.

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It is clear that the opioid crisis remains one of the most complex public health issues facing the United States today, increasingly comprised of addiction and overdose that involve multiple drugs and drug classes. Effectively addressing the crisis is requiring multiple interventions—products, technologies, policies, and regulatory actions— working together. Evaluating the net public health impact of any one intervention is extremely challenging against a backdrop of many concurrent interventions and the ever-changing landscape. Aligned with recommendations made by the National Academies of Science, Engineering and Medicine,[11] FDA has begun to adopt a systems-based approach to assessing the benefits and risks of potential regulatory actions that may make meaningful gains in addressing the opioids crisis.[12] A systems approach focuses on an understanding of the underlying mechanisms of the crisis and assessing the potential short- and long-term effects of interventions to address the crisis, including intended and potential unintended consequences. Assessing ADF opioid analgesics through a systems approach means considering the broader ecosystem of interrelated clinical, sociocultural, economic, and policy factors that can affect opioid analgesic use, misuse, and subsequent health outcomes. It also means considering the decisions and behaviors of multiple stakeholders: healthcare providers, patients, communities, insurers and others. And finally, it means considering remaining uncertainties in our understanding of the system and the impact of various interventions.

2 FDA REVIEWS AND ANALYSES: SUMMARY OF FINDINGS

2.1 FDA ANALYSES OF PRESCRIPTION DISPENSING TRENDS FOR OXYCONTIN AND OTHER OPIOID ANALGESICS (SEE DRUG UTILIZATION REVIEW)

To support and contextualize our review of the OxyContin postmarketing data, FDA drug use analysts used the IQVIA, National Prescription Audit (NPA)™ database to provide the estimated number of prescriptions and tablets dispensed for original OxyContin, reformulated OxyContin, oxycodone ER original (brand and generic), reformulated oxycodone ER ("authorized generic"), and other opioid analgesics from U.S. outpatient retail pharmacies from 2006 through 2019.
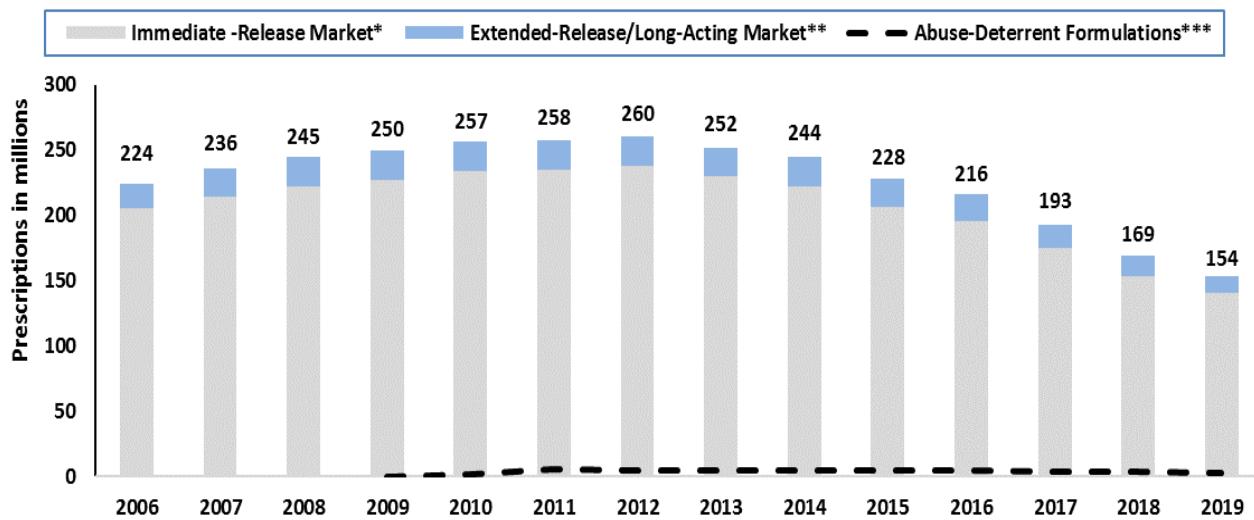
As shown in the figure below, total utilization of opioid analgesics peaked in 2012, with 260 million prescriptions dispensed, then declining 41% by 2019. Immediate-release (IR) formulations accounted for 91%, extended-release/long-acting (ER/LA) formulations accounted

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[11] https://www.nap.edu/catalog/24781/pain-management-and-the-opioid-epidemic-balancing-societal-and-individual

[12] FDA is leveraging a suite of systems approaches. For example, a qualitative framework was used in 2019 to support advisory committee discussions on issues specific to higher dose opioids analgesics (https://www.fda.gov/advisory-committees/advisory-committee-calendar/june-11-12-2019-joint-meeting-drug-safety-and-risk-management-advisory-committee-and-anesthetic-and). FDA is also currently developing a system dynamics simulation model, calibrated to US national-level data , which encompasses the range of behavioral aspects of opioid use, misuse, and use disorder, treatment, and overdose (https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-19-026.html). When complete, the model will be able to support a wide range of policy analyses related to the opioids system.

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for 9%, and ADFs accounted for approximately 2% of the total opioid analgesic prescriptions dispensed in 2019. IR opioid analgesic prescriptions peaked in 2012, with 238 million prescriptions, and the utilization of ER/LA products peaked in 2010, with 23 million prescriptions. As of 2019, 25% of ER/LA opioid analgesic prescriptions were for ADF products. The utilization of ADF formulations peaked in 2011, with 5.6 million prescriptions.. Reformulated oxycodone ER accounted for 73% of dispensed ADF opioid analgesic prescriptions in 2019.

Estimated number of prescriptions dispensed for all opioid analgesics from U.S outpatient retail pharmacies, 2006-2019

Source: IQVIA, National Prescription Audit (NPA) and static data 2006-2011. January 2006-December 2019.
Static data extracted March 2017, 2012-2017 data extracted February 2018, 2018 data extracted March 2019, 2019 data extracted Jan 24, 2020
*Immediate-Release formulations include oral solids, oral liquids, rectal, nasal, and transmucosal formulations
**Extended-Release/Long-Acting formulations include oral solids and transdermal patches
***Abuse-deterrent formulation opioid products include Arymo ER, Embeda ER, Hysingla ER, Morphabond ER, Xtampza ER, OxyContin ER Reformulated (Approval in April 2010), RoxyBond IR
Note: These data include non-injectable opioid analgesics only. Opioid-containing cough-cold products and opioid-containing medication-assisted treatment (MAT) products are not included.

In 2010, distribution of the original formulation of OxyContin ceased and was replaced by reformulated OxyContin. As shown in the figure below, dispensed prescriptions for OxyContin original formulation dropped abruptly from 2010 to 2011 as prescriptions for reformulated OxyContin rose. Of note, original generic oxycodone ER declined from 2007 to 2009, and then dropped further from 2010 to 2011, effectively exiting the market in 2011. Overall ER oxycodone prescription dispensing (original and reformulated, brand and generic) dropped by more than one million prescriptions from 2010 to 2011 and then continued to decline steadily through 2019.

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Estimated number of dispensed prescriptions for original and reformulated oxycodone ER products from U.S. outpatient retail pharmacies from 2006 through 2019, annually

Source: IQVIA National Prescription Audit™ (NPA) 2019. Data extracted Feb 2020. File: NPA Oxycodone ER and comparators by prescriptions 2006-2019. 02.15.2020.xlsx

2.2 FDA REVIEW OF POSTMARKETING REQUIREMENT (PMR) STUDIES EVALUATING THE EFFECT OXYCONTIN'S REFORMULATION ON ITS ABUSE AND RELATED ADVERSE OUTCOMES

The four PMR studies that will be discussed at this meeting all examine changes in rates of abuse-related outcomes in post-reformulation compared to pre-reformulation time periods for OxyContin, relative to changes observed in comparator opioid analgesics. The studies use four different sources of data, as described in the table below. The results of these four PMR studies were reviewed by the Division of Epidemiology (DEPI) II and the Division of Biometrics VII (DBVII). [See Division of Epidemiology Reviews of PMR 3051-2, 3051-2, 3051-3, 3051-4 and Division of Biometrics VII Memorandum].

Study	Data Source, Setting	Time Periods	Outcomes
3051-1	**NAVIPPRO ASI-MV[1]:** Individuals entering or being assessed for substance use disorder treatment	Pre-period: 3Q2008-2Q2010 Post-period: 1Q2011-4Q2014	Change in self-reported past 30-day abuse (non-oral and overall) for OxyContin, versus comparators

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Study	Data Source, Setting	Time Periods	Outcomes
3051-2	**RADARS[2] Poison Control:** Exposure calls to US Poison Centers	Pre-period: 3Q2008-2Q2010 Post-period: 1Q2011-4Q2015	Change in OxyContin <u>abuse</u> exposure call rates (overall and route-specific), versus comparators
3051-3	**RADARS Treatment Center:** Individuals entering opioid use disorder treatment (methadone clinics, other)	Pre-period: 3Q2008-2Q2010 Post-period: 1Q2011-4Q2015	Change in self-reported past-month <u>abuse</u> (overall only) for OxyContin, versus comparators
3051-4	**Commercial and Medicaid claims:** Individuals dispensed OxyContin or comparator opioids	Pre-period: 3Q2008-2Q2010 Post-period: 1Q2011-4Q2015 (- 4Q2012 for Medicaid)	Change in fatal/non-fatal opioid <u>overdose</u> incidence in those dispensed OxyContin, versus comparators

1. National Addictions Vigilance Intervention and Prevention Program Addiction Severity Index-Multimedia Version
2. Researched Abuse, Diversion and Addiction-Related Surveillance

Overarching considerations in interpreting findings of the PMR studies

As acknowledged in the 2015 Guidance for Industry, the science of ADF assessment is relatively new and continues to evolve. Evaluating the impact of OxyContin's abuse-deterrent formulation in real-world settings has proven challenging for a number of reasons. Many of these were outlined in the FDA Issues Paper accompanying a public scientific workshop FDA convened in July 2017 to discuss methods and data sources for evaluating ADFs in the postmarket setting.[13]

There are a number of overarching methodologic considerations that informed both the design and interpretation of the PMR studies. These issues are also discussed in the DBVII memo and in the individual DEPI reviews of the four PMR studies. Although observational study designs are often used to examine associations, we are interested in the ability to make causal inferences—we want to know if the ADF <u>caused</u> a reduction in abuse and related outcomes. This requires isolation of the effect of the ADF from the changing landscape of opioid use and abuse, as well as from other efforts to combat inappropriate prescribing and abuse of prescription opioids. Causal inference also requires distinguishing the effect of the reformulation from the influence of other sources of confounding and bias in the studies (i.e., other factors, unrelated to the reformulation, that can precipitate changes in observed abuse rates or patterns). For example, the use of non-representative convenience samples can create bias, in that the composition of the study populations change over time in a non-random fashion, complicating comparisons of abuse rates

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[13] https://www.fda.gov/media/105446/download

before and after reformulation. Product misclassification, missing data, and changes in survey instruments over time are potential sources of bias in self-reported data. Therefore, the studies include multiple definitions and sensitivity analyses to understand the impact of these factors, resulting in a range of plausible estimates. Additionally, all of the PMR studies employ comparator opioids to better understand background trends and to serve as negative controls, which are intended to approximate the "counterfactual," or what we expect to have seen in OxyContin abuse trends had it not been reformulated, and then compare that to what we do observe. As there was no single ideal comparator, each study used three primary comparators that were formally compared to OxyContin using statistical models. The studies also included secondary comparators, including heroin, to help further contextualize the results and understand changes in the broader opioid landscape.

Related to causal inference is the question of how best to account for the relationship between drug utilization (i.e., number of prescriptions or tablets dispensed) and abuse rates. Studies have shown that prescription volume correlates with abuse levels—this makes sense, as the drug has to be available to abuse. Although the exact nature of the relationship may not always be straightforward, the number of abuse-related events for a given number of tablets prescribed can be a useful metric for making comparisons across drugs and time periods. However, some of the observed decrease in OxyContin prescribing after the reformulation may have been the result of reduced desirability for abuse and diversion. Although this was likely one factor, it probably does not explain all the decline in OxyContin prescribing between pre- and post-reformulation time periods, as many factors can influence prescribing (e.g., formularies and insurance coverage, cost to patient, REMS, drug company marketing practices). Furthermore, even if all the observed reduction in OxyContin dispensing were due to the abuse-deterrent effect of the reformulation, one would still expect a reduction in levels of abuse for a given amount of drug dispensed (i.e., a reduced likelihood of abuse of tablets dispensed in the community) and that the reduction would be larger than that seen for comparator opioids. Thus, changes in prescribing may be considered both as a <u>mediator</u> (or intermediate step) in the causal pathway from reformulation to reductions in abuse—in which the reformulation reduced abuse through decreased prescribing and community availability of the product—but also as a <u>confounder</u>, where changes in prescribing were due to other factors, confounding the association between introduction of the ADF and changes in abuse rates. Which of these pathways predominates is unclear; failing to adjust for changes in utilization may overestimate the effect of the reformulation, whereas fully adjusting for utilization may underestimate the effect. To address this issue, PMR studies 3051-1 through 3051-3 each analyzed the data using several models, both unadjusted and adjusted for utilization, with the true effect of the reformulation on abuse rates likely lying somewhere within this range of estimates.

The impact of OxyContin's reformulation on the risk of overdose is an important question, as the sharp rise in prescription opioid overdose was one of the most pressing safety concerns leading FDA to encourage development of ADF opioid analgesics and to determine that original

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OxyContin was withdrawn for reasons of safety or effectiveness. However, the reformulation's impact on overdose risk has been one of the most difficult questions to study. Overdose data from death certificates and insurance claims do not generally identify specific drug products or formulations; poison center data vastly under-ascertain fatal drug poisonings (particularly unattended, out-of-hospital overdose deaths) and have limited ability to accurately identify specific products involved in these cases; and due to their inherent limitations, spontaneous adverse event reports cannot be used to estimate incidence or formally compare rates over time. Linkage of insurance claims data to a national mortality database allows estimation of the risk of fatal or non-fatal overdose (using a recently validated algorithm) in patients receiving a particular opioid product. PMR study 3051-4 analyzed three different claims databases, each linked to the National Death Index, to evaluate whether reformulated OxyContin conferred a reduced risk of fatal or non-fatal opioid overdose in patients. However, it is important to note this study was not able to measure any effect on overdose risk in individuals who paid for their opioid medication with cash or obtained their prescription opioids from sources other than their own prescription (e.g., a friend, family member, or dealer), or in individuals who stopped using OxyContin and/or switched to another opioid because of the reformulation. Therefore, PMR study 3051-4 provides only one piece of the story on ADF OxyContin and overdose, but it is an important piece that had not previously been available.

Given the many limitations and complexity of these data, the review team's approach was to qualitatively synthesize data from multiple quantitative analyses, including sensitivity analyses, to draw reasoned conclusions from the totality of the evidence. As described in the DEPI reviews and the DBVII memo, the team drew on fundamental epidemiologic principles around study design, data quality, and causal inference. In addition, DEPI reviewed the published literature to supplement the findings from the PMR studies. The key findings from the literature are described further in Section 2.3, below, and in the full review of the epidemiologic literature (See Division of Epidemiology Literature Review). The Division of Epidemiology reviews all contain rather detailed executive summaries describing the methodologic considerations, key results, overall interpretation and conclusions for each study.

2.2.1 PMR 3051-1: NAVIPPRO ASI-MV Study (See Division of Epidemiology Review of PMR Study 3051-1)

Study Overview:

PMR study 3051-1 assessed the change in self-reported past 30-day abuse of selected opioids via specific routes (swallowing intact, chewing and swallowing, dissolving and swallowing, snorting, smoking, and injecting) comparing the 2 years before to the 4 years after OxyContin reformulation, in a population of adults evaluated for substance use problems and treatment planning using the ASI-MV® assessment. Comparator opioids are included in this evaluation to

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aid in causal inference and provide contextual information on abuse trends unrelated to the reformulation. Due to the inherent uncertainties associated with these data and their interpretation, (e.g., the potential for bias due to misclassification, the dynamic study sample, and confounding secular trends), a number of different analyses were conducted, including varying the time period, definition of OxyContin (any OxyContin, reformulated OxyContin only in the post-period, or any ER oxycodone including brand and generic), site inclusion criteria, and models used to estimate abuse rates and account for changes in drug utilization over time. These varied approaches were used to provide a range of possible effect sizes and to assess robustness of the overall study findings.

FDA Review Team Findings:

- This study provided reasonably compelling evidence that the reformulation decreased non-oral abuse of OxyContin in people entering or being assessed for treatment, although it is not possible to quantify the size of this effect.

  o Although results varied quantitatively, analyses were largely consistent in demonstrating a reduction in non-oral abuse rates for OxyContin that differed from changes seen in comparator opioids.

  o Rates of snorting and injecting abuse of OxyContin both declined, while oral abuse rates slightly increased. Similarly, among those abusing OxyContin, the proportion who snorted it and injected it declined from the pre- to post-period, while the proportion who swallowed it increased. Similar shifts were not observed for comparator opioids.

- The reductions in non-oral OxyContin abuse appear to have occurred predominantly among people assessed to have moderate to severe addiction.

- The evidence for a reduction in overall OxyContin abuse (via any route) in this study was not compelling. Some analyses indicated declines in overall OxyContin abuse that were greater than declines for comparators, but findings were inconsistent.

  o This apparent lack of effect on overall OxyContin abuse rates likely reflects the persistently high levels of oral OxyContin abuse as well as some shift to oral OxyContin abuse in this population.

- After reformulation, utilization-adjusted abuse rates for OxyContin remained high relative to most other opioid analgesics examined, even via non-oral routes.

  o Such cross-sectional comparisons between drugs must be made cautiously, however, as this was not a nationally representative sample, and abuse rates may be substantially affected by product misclassification.

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- The findings of PMR 3051-1 were qualitatively consistent with multiple industry-funded published studies analyzing NAVIPPRO ASI-MV data, although decreases reported in these publications were generally larger than the decrease reported in PMR 3051-1, likely due to differences in sample selection, variable definitions, and other analysis parameters.

2.2.2 PMR 3051-2: RADARS Poison Control Center Study (**See Division of Epidemiology Review of PMR Study 3051-2**)

Study Overview:

PMR study 3051-2 assessed the change in rates of calls to United States poison control centers (PCCs) involving the abuse of OxyContin overall (any route), and by specific routes (oral, snorting, injecting), comparing the 2 years before to the 5 years after OxyContin reformulation. Comparator opioids were used as negative controls to aid in causal inference, and also provided contextual information on background trends in abuse call rates. Due to the inherent uncertainties associated with these data, (e.g., increasing missing formulation information over time, broader changes in PCC call patterns over time or other secular trends, and inability to reliably distinguish between brand and generic products), a number of different analyses were conducted, including imputing missing data, and varying the time period, definition of OxyContin (brand OxyContin only, or any ER oxycodone including brand and generic), geographical area covered, and models used to estimate abuse call rates and account for changes in drug utilization over time. These varied approaches provided a range of estimates and were used to assess the robustness of the overall study findings.

FDA Review Team Findings:

- The totality of findings from PMR study 3051-2 do not provide robust evidence that the observed decline in <u>overall</u> (i.e., via any route) abuse call rates for OxyContin is attributable to its reformulation rather than to broader secular trends.

    o The majority of abuse calls for OxyContin involved the oral route

    o While the observed declines in the overall abuse call rates for OxyContin were temporally associated with the market introduction of the reformulated product and of a reasonably large magnitude, there were declines in comparator opioids of similar magnitude—particularly when adjusting for changes in the amount of drug dispensed—as well as declines in calls for non-abuse-related exposure calls for both OxyContin and comparators. Taken together, these findings make the prospect of other factors driving down call rates as plausible as the reformulation, although some unknown combination of causes is certainly possible.

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- The study findings support the hypothesis that some decline in <u>non-oral</u> abuse call rates for OxyContin can be reasonably attributed to its reformulation, but the magnitude of the reformulation's impact on non-oral abuse call rates is uncertain.

  o Calls involving non-oral abuse made up a small proportion of OxyContin abuse calls overall, but unlike for overall abuse call rates (i.e., any route), declines in mean non-oral abuse call rates seen for OxyContin were not seen consistently for primary comparators. There was also a clear divergence in trend directions for OxyContin and "other schedule II opioids" non-oral abuse calls immediately following the reformulation.

- Data from the post-reformulation time period do not provide evidence for reformulated OxyContin being less likely to be abused than other opioid analgesics.

- Heroin abuse calls increased markedly after reformulated OxyContin was introduced; however, this study was not designed to evaluate substitution effects or causal associations between the reformulation and increases in calls involving other opioids.

- Results of this PMR were qualitatively similar to those seen in published studies using PCC data, although authors' conclusions with respect to the reformulation's impact on overall OxyContin abuse were generally favorable. These studies also used different comparators, time periods, and utilization denominators.

2.2.3 PMR 3051-3: RADARS Treatment Center Study ([See Division of Epidemiology Review of PMR Study 3051-3)](#)

Study overview:

PMR study 3051-3 assessed the change in self-reported past month abuse of selected opioids (overall—via any route), comparing the 2 years before to the 5 years after OxyContin's reformulation in a population of adults enrolling in methadone maintenance treatment programs (Opioid Treatment Program, or OTP) and a population of adults entering general substance abuse treatment programs who endorsed an opioid as their primary drug of abuse (Survey of Key Informants' Patients, or SKIP, program). This study was not able to assess changes in route-specific abuse, as this information was not collected in these programs at the time of the reformulation. Comparator opioids were used as negative controls to aid in causal inference, and also provided contextual information on background trends in abuse rates in this population. Due to the inherent uncertainties associated with these data and this study design (e.g., product misclassification and changes made to the survey instrument during the study period, use of a dynamic convenience sample, and potential for confounding by secular trends) a number of

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different analyses were conducted, including varying the time period, the definition of OxyContin (i.e., brand OxyContin only, any ER oxycodone), the site inclusion criteria, and the models used to estimate abuse rates and account for changes in drug utilization over time. These varied approaches were used to generate a range of possible estimates and to assess the robustness of the overall study findings.

FDA Review Team Findings:

- Findings were mixed and did not provide compelling evidence that the reformulation meaningfully reduced OxyContin abuse among adults enrolling in OUD treatment.

  o However, the lack of route-specific data limited the ability of this study to detect potential changes in non-oral abuse.

- Polysubstance abuse was common among those abusing OxyContin.

- The reformulation was followed by an increase in heroin abuse, primarily in the privately-funded treatment group (SKIP), although this study was not designed to assess whether the reformulation contributed causally to this increase.

- Adjusted for prescription volume, OxyContin abuse rates remained higher than primary comparator opioids after reformulation; however, such comparisons must be made cautiously due to the inherent limitations of these data.

- The findings from PMR 3051-3 were qualitatively consistent with published studies using this data source in finding decreases in OxyContin abuse rates after reformulation; however, the decreases in OxyContin abuse rates reported in these publications were generally of greater magnitude than what was found in the PMR study and were significantly larger than the change observed for comparators. These differences appear to be related to use of different time periods, regression models, and comparators.

2.2.4   PMR 3051-4: Claims-based Overdose Study ([See Division of Epidemiology Review of PMR Study 3051-4](#))

Study Overview:

PMR study 3051-4 analyzed three administrative claims databases (Medicaid and two commercial claims databases) linked to national mortality data to assess the impact of OxyContin's reformulation on the incidence of fatal or non-fatal opioid overdose (combined) among patients dispensed OxyContin. Analyses compared overdose rates in these patients in the 2 years before to the 5 years after OxyContin reformulation (2 years after in the Medicaid database), with comparisons to changes observed in patients dispensed selected other opioid analgesics. Comparator opioids were used as negative controls to aid in causal inference, and

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also provided contextual information on background trends in opioid overdose rates. Due to the complexity of these data, (e.g., many patients dispensed OxyContin concomitantly with intermittent dispensing of other opioid analgesics, and potential for confounding by patient characteristics) a number of different analyses were conducted to better understand the generalizability of study findings and role of potential biases. For example, analyses included the use of several exposure categories that included patients dispensed OxyContin with or without other opioid analgesics, and multiple methods were used to adjust for patient-level characteristics.

FDA Review Team Findings:

- The results of PMR 3051-4 do not demonstrate that the reformulation reduced the risk of opioid overdose in patients dispensed OxyContin, overall.

  o In the commercial claims populations, changes in estimated opioid overdose rates among patients dispensed OxyContin compared to the changes among patients dispensed comparators modestly favored OxyContin, but they were not statistically significantly different from each other. In Medicaid data analyses, results were actually somewhat *unfavorable* to OxyContin.

- When restricted to time that patients had a prescription for OxyContin or comparator *alone* (i.e., without any other opioids), results were somewhat more favorable with respect to the reformulation reducing opioid overdose risk, although the implications and generalizability of this specific finding are not entirely clear, for the following reasons:

  o These results were statistically significant in the commercial insurance claims populations and not in the Medicaid cohort.

  o OxyContin use without concomitant dispensing of any other opioid analgesics was relatively uncommon.

  - It is possible that OxyContin's abuse-deterrent properties did confer a reduced risk of overdose among patients using OxyContin without any other opioid analgesics. However, it is also plausible that patients receiving reformulated OxyContin were at inherently at lower risk of overdose than those who received OxyContin prior to its reformulation, either through changes in prescribing practices (i.e., prescribing lower dosage strengths), or through patient self-selection away from reformulated OxyContin among those seeking to abuse it via non-oral routes. While the latter explanations may be consistent with reformulated OxyContin having an abuse-deterrent effect, it does not necessarily follow that the abuse-deterrent properties conferred a reduced risk of overdose either among those exposed to the product or in those who migrated away

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from OxyContin because of its reformulation (e.g., if they shifted to abuse of illicit opioids).

2.3 **REVIEW OF OTHER PUBLISHED EPIDEMIOLOGIC LITERATURE (SEE DIVISION OF EPIDEMIOLOGY LITERATURE REVIEW)**

Overview of Literature Review:

To supplement and contextualize the formal PMR studies submitted by the application holder and to better understand the broader public health impact of OxyContin's reformulation, the Division of Epidemiology (DEPI) II conducted a comprehensive critical review of peer-reviewed and selected grey literature examining the impact of reformulated OxyContin on opioid use, abuse, morbidity, and mortality. Following a systematic search of the published literature, we identified 78 articles for detailed review and further categorized into three main categories: PMR-related studies (which used the same or similar data sources and methods as the four PMR studies), non-PMR-related original studies, and editorials. **PMR-related published studies were summarized and evaluated as part of the Division of Epidemiology reviews of the related PMR studies 3051-1 through 3051-4**. Six of the PMR-related studies and 13 of the non-PMR related studies were funded by Purdue or a Purdue-affiliated pharmaceutical company.

FDA Review Team Findings:

Our ability to draw firm conclusions from the published literature was limited, although it did provide some valuable information to supplement and contextualize the PMR study findings.

- Published studies indicate that sales of OxyContin declined after its reformulation, in both the U.S. and other countries, although this decline may have occurred due to a variety of reasons.

- Rates of self-reported nonmedical use (i.e., use other than as directed) of OxyContin also declined in the general U.S. population, returning to rates observed several years before the reformulation. It remains unclear to what extent declines in OxyContin prescribing drove declines in the prevalence of its nonmedical use, versus decreases in OxyContin's abuse potential driving reduced demand and prescribing.

- Despite some serious limitations, the totality of evidence from published studies suggests that OxyContin's reformulation reduced its attractiveness for diversion and abuse, particularly non-oral abuse in populations already abusing prescription opioids through tampering and non-oral routes.

- The literature does not provide definitive answers regarding the net public health impact of OxyContin's reformulation in the U.S.

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o We identified no reliable, longitudinal evidence regarding the effect of OxyContin's reformulation on the trajectory of opioid use disorder, the likelihood of transitioning from oral to non-oral abuse, the risk of addiction, or the risk of opioid overdose.

o Overall, the literature suggests that while some individuals shifted their use of OxyContin from non-oral to oral routes, others simply substituted different prescription and/or illicit opioids after OxyContin's reformulation. These apparent substitution effects varied across populations, likely reflecting heterogeneity in baseline substance abuse patterns and the availability and cost of other drugs. Polysubstance abuse is common, and drug use patterns are dynamic and likely influenced by many factors, including drug availability, price, and other sociocultural factors.

o Several analyses suggest that OxyContin's reformulation contributed to reductions in rates of fatal overdoses involving prescription opioids in the U.S., but that these declines were offset, or more than offset, by consequent increases in fatal overdoses from illicit opioids; however, the complex mixture of concurrent interventions, secular trends, and geographical heterogeneity in opioid availability and use patterns makes it difficult to determine the precise role of ADF OxyContin in these trends.

2.4   OTHER INFORMATION RELEVANT TO CONSIDERATION OF PUBLIC HEALTH IMPACTS

2.4.1   Polyethylene Oxide (PEO) and excipient harms (**See Division of Pharmacovigilance Memorandum**)

There are several safety issues that have arisen that relate specifically to the excipient PEO, which is used in reformulated OxyContin and some other ADF opioid analgesic products to make them more difficult to crush and dissolve.

Thrombotic microangiopathy (TMA) with intravenous abuse:

On March 13-14, 2017, FDA convened an Advisory Committee meeting to discuss the postmarketing data relating to another opioid analgesic product, Opana ER (oxymorphone hydrochloride extended-release tablets, Endo Pharmaceuticals), that, like OxyContin, was reformulated with PEO to deter abuse by non-oral routes. As described in the FDA briefing package for the 2017 meeting,[14] one postmarketing safety concern for reformulated Opana ER was the identification of 59 cases of thrombotic microangiopathy (TMA) associated with

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[14] https://www.fda.gov/files/advisory%20committees/published/FDA-Briefing-Information-for-the-March-13-14--2017-Joint-Meeting-of-the-Drug-Safety-and-Risk-Management-Advisory-Committee-and-the-Anesthetic-and-Analgesic-Drug-Products-Advisory-Committee.pdf

intravenous abuse of this product. Data from animal models have linked PEO of varying molecular weights to acute manifestations of TMA.

Language was subsequently added to the reformulated OxyContin prescribing information in Section 9.2 (Abuse) about this risk:

> *With parenteral abuse, the inactive ingredients in OXYCONTIN can be expected to result in local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, valvular heart injury, embolism, and death. Cases of thrombotic microangiopathy (a condition characterized clinically by thrombocytopenia and microangiopathic hemolytic anemia) associated with parenteral abuse have been reported.*

A recent search of the FDA Adverse Event Reporting System (FAERS) and published medical literature identified only six cases of TMA (all non-fatal) associated with intravenous abuse of reformulated OxyContin. The reports were received over six years (2014-2019), indicating an ongoing, but minimally reported event. All six cases in the series reported intravenous abuse of reformulated OxyContin, and half provided a brief description of the tampering method, all involving thermal manipulation. All patients presented with anemia, thrombocytopenia, evidence of hemolysis, and additional laboratory markers consistent with drug-induced TMA after intravenous use of OxyContin. Our analysis found that these cases appear to be consistent with the risk of TMA currently described in OxyContin labeling. FDA-supported work is ongoing to better understand the various factors that may contribute to the risk of TMA, for example, size of the PEO polymer, manufacturing process, and tampering methods.

Choking, dysphagia, nasal and intestinal obstruction:

In 2011, FDA initiated a safety review evaluating spontaneous adverse event reports it had received of choking, dysphagia, nasal and intestinal obstruction, exacerbation of diverticulitis, and medication residue in the stool associated with the newly reformulated OxyContin ([see Division of Pharmacovigilance 2011 Review](#)). The cases suggested that in some instances, the PEO-containing tablet turns into a "glue-like" substance upon contact with oral/nasal mucosa, causing choking or obstruction. The pills were also noted to not dissolve adequately and in some cases, pass through the GI tract intact without absorption. No serious outcomes were reported except in four patients who had underlying gastrointestinal disorders. This adverse event was subsequently added to the Warnings and Precautions section of the OxyContin label, as follows:

> *5.11 Difficulty in Swallowing and Risk for Obstruction in Patients at Risk for a Small Gastrointestinal Lumen: There have been post-marketing reports of difficulty in swallowing OXYCONTIN tablets. These reports included choking, gagging, regurgitation and tablets stuck in the throat…. There have been rare post-marketing reports of cases of intestinal obstruction, and exacerbation of diverticulitis, some of which have required medical intervention to remove the tablet. Patients with underlying GI disorders such as*

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*esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater
risk of developing these complications. Consider use of an alternative analgesic in
patients who have difficulty swallowing and patients at risk for underlying GI disorders
resulting in a small gastrointestinal lumen.*

2.4.2   CDER's Office of Communications (OCOMM) social science research on prescriber understanding of ADF opioid terminology (See Office of Communications Memorandum)

Findings from previous research conducted by CDER's OCOMM uncovered considerable
variability in health care professionals' (HCPs) awareness of, knowledge about, attitudes toward,
and experience with ADFs. This lack of awareness and knowledge – as well as potential
misunderstandings – about ADFs and the terminology used to describe them have been of
significant concern to FDA and are potentially relevant to discussions about the broader public
health impact of reformulated OxyContin. OCOMM and other FDA collaborators designed a
three-phase research project, which is currently underway, to build on the findings from an
earlier project by exploring and assessing ADF-related knowledge, attitudes, and behaviors
among opioid analgesic prescribers and dispensers/pharmacists and to explore possible
alternative language for describing these products. The mixed-methods approach being
undertaken for this project consists of three separate but iterative phases engaging healthcare
providers.

To date, the Phase 1 qualitative focus group data collection and analysis have been completed.
The following are key findings from this work:
- Prior knowledge of the term 'abuse-deterrent formulation' opioid was uncommon among prescribers and pharmacists.
- OxyContin was the most commonly prescribed ADF
- Most who were unfamiliar with the ADF term guessed incorrectly about what it means. Common misperceptions included:
    - ADFs are formulated to make someone sick when they are using an opioid or when someone takes too high a dose of opioids; similarity to Antabuse was mentioned
    - ADFs do not provide any type of high or euphoric feeling
    - ADF refers to a "policy" or "plan of care"
    - ADFs offer non-narcotic pain relief
    - Single participants also said ADFs had higher addiction potential, had higher abuse potential, were intended to end opioid use, and are a form of physical therapy.
- Some were confused about whether ADFs could be modified at all and about how they work/mechanism of action.

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- Some worried prescribing an ADF could lead to feelings of patient dissatisfaction with care or stigmatization
- A few noted they hadn't prescribed ADFs due to perceived ineffectiveness in their ability to prevent misuse, abuse, or addiction.
- Other barriers to use included the need for more information about them before prescribing them, including for data/studies specifically proving their efficacy in reducing abuse and addiction and the extent of those decreases, and about their side effects and mechanisms of action/how they work.
- Across all groups, participants reported limited training and education on ADFs and many suggested additional training would be beneficial.

3   FDA'S OVERALL INTERPRETATION OF THE EVIDENCE

Within the framing of the systems approach described in Section 1, FDA's interpretation of the evidence considers the direct effects of OxyContin's reformulation on its abuse patterns and the risk of overdose associated with its use. We also consider other important public health outcomes to which OxyContin's reformation may have contributed, such as drug substitution behaviors, development or progression of OUD, and harms associated with opioid abuse and OUD, particularly overdose deaths. FDA's interpretation of the evidence also considers the uncertainties that arise from the limitations of the available data and methods, as well as from the complex and evolving landscape of the opioid crisis, including trends in prescribing of opioid analgesics (both conventional and ADF), the availability and potency of illicit opioids, polysubstance use, and the potential for varying effects of the reformulation in different population subgroups. These uncertainties complicate our understanding of the net impact of OxyContin's reformulation as an intervention intended both to improve the safety of a specific opioid analgesic product and to mitigate the harms associated with prescription opioid abuse and the opioid crisis more broadly.

The following conclusions represent the FDA review teams' synthesis of the postmarketing data, guided by a systems approach and based on a critical review of the totality of evidence, including the four required PMR study reports as well as the published literature, the FAERS analysis and ongoing FDA research on prescriber understanding of ADFs and excipient harms.

1. **The totality of evidence from the PMR studies and published literature is fairly compelling that the reformulation of OxyContin has reduced abuse of this product via <u>non-oral</u> routes, including both snorting and injection, although the magnitude of effect cannot easily be quantified and likely varies across populations.**

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- This effect has primarily been observed in populations with more advanced substance use disorders, including individuals with moderate to severe addiction who are entering or being assessed for treatment and others who are already tampering with prescription opioids and abusing them through non-oral routes.

- The strongest evidence supporting this conclusion came from PMR 3051-1 (NAVIPPRO ASI-MV study). The conclusion was also supported by weaker, but largely consistent findings from PMR 3051-2 (RADARS Poison Center study) and several published studies conducted in different populations of individuals tampering with prescription opioids or entering treatment with opioids use disorders.

2. **Evidence was not robust that the reformulation caused a meaningful reduction in <u>overall</u> OxyContin abuse (i.e., via any route).**

   - Findings from PMRs 3051-1, 3051-2, and 3051-3, as well as our critical review of published studies contributed to this conclusion.

   - This conclusion was based primarily on our inability to disentangle the effect of the ADF from the effect of changes in the opioid analgesic and illicit opioid markets, and from other interventions and secular trends. The lack of a decisive effect of the reformulation on overall OxyContin abuse also likely reflects the predominance of oral abuse and a modest shift from non-oral to oral OxyContin abuse in some populations. Although the FDA guidance for industry notes the importance of considering the impact of the ADF on overall abuse, OxyContin was reformulated primarily to deter abuse by snorting and injecting, and the label states that it is expected to deter abuse by these routes, based on experimental study results.

3. **After adjusting for prescription volume, both overall and non-oral abuse rates for OxyContin remained relatively high among the schedule II opioids examined in the post-reformulation period, indicating that, while the reformulation may have improved the safety of OxyContin with respect to non-oral abuse, ADF OxyContin is not necessarily safer than other marketed opioid analgesics with respect to abuse and associated risks.**

   - It is important to note, however, that such direct cross-sectional comparisons must be interpreted cautiously due to non-representative samples, product misclassification, and missing data.

4. **It is unclear whether Oxycontin's reformulation reduced opioid overdoses or had a net public health benefit.**

- The evidence from PMR 3051-4 does not compellingly demonstrate that the reformulation of OxyContin reduced the risk of fatal or non-fatal opioid overdose in patients dispensed OxyContin, overall.

  - Of note, the target population for this study was not an enriched, higher-risk population (e.g., with OUD or abusing prescription opioid via non-oral routes) where effects of the reformulation might be more easily detected if they occurred

- When analyses were restricted to time in which patients received OxyContin *alone*, the findings were somewhat more favorable, although the implications of this are somewhat unclear for several reasons. First, the effect was only seen in the commercial claims cohorts and not in the Medicaid population. Second, OxyContin use without any other opioid analgesics was uncommon. Finally, it is possible that patients receiving OxyContin in the post-reformulation period were at inherently lower risk of overdose, if higher risk patients seeking to abuse it non-orally migrated away from OxyContin, perhaps to other prescription or illicit opioids. Prescribing of the highest dosage strengths of OxyContin also declined, which may confer a lower risk of overdose. Although both of these changes would be consistent with an abuse-deterrent effect, it remains unclear whether the abuse-deterrent properties actually conferred a reduced risk of overdose, either in patients receiving OxyContin or in those who may have avoided OxyContin due to the ADF.

- Multiple studies found that some individuals substituted other prescription or illicit opioids (i.e., heroin) after OxyContin's reformulation; however, these substitution effects appear to vary across populations, likely reflecting heterogeneity in pre-existing drug abuse patterns and available substitutes.

  - These shifts were seen in published studies using a variety of methods, as well as in the PMR studies.

  - Polysubstance abuse is common, especially in individuals with more advanced substance use disorders. There was not clear evidence that OxyContin's reformulation caused heroin-naïve individuals to initiate use, and the shifts from OxyContin to heroin and other opioids may have often occurred in the setting of pre-existing polysubstance abuse including these drugs.

- Several published analyses have suggested that any contribution of OxyContin's reformulation to reductions in fatal prescription opioid overdoses were offset, or more than offset, by consequent increases in fatal illicit opioid overdoses.

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- While this would be consistent with the substitution effects described in other studies, the direct effect of OxyContin's reformulation on national opioid overdose mortality remains difficult to isolate from the impacts of other interventions (e.g., Florida "pill mill" actions) and secular trends (e.g., availability, price, and purity of heroin).

- We found no credible information on whether the OxyContin ADF reduces the *initiation* of non-oral abuse (e.g., in patients receiving opioid analgesics for pain or in others abusing prescription opioids but via the oral route), prevents the progression of opioid use disorder, or reduces the incidence of new addiction.

  - Given the limitations of the available data (e.g., poor performance of code-based algorithms to measure abuse and addiction in electronic healthcare data), retrospective studies are likely not capable of rigorously evaluating whether OxyContin's reformulation resulted in a decreased risk of addiction. Answering these questions would likely have required launch of a prospective study in an at-risk population <u>prior to</u> introduction of reformulated OxyContin, and even then, it may have been infeasible to study rigorously.

4 ISSUES FOR COMMITTEE DISCUSSION

After hearing presentations by the application holder and FDA, as well as statements made during the open public hearing, committee members will be asked to discuss, and in some cases cast votes on questions related to the following topics:

1. **Discuss whether you believe OxyContin ADF has meaningfully reduced the risk of abuse (by one or more routes, or overall) and related adverse outcomes, particularly overdose. Please share the scientific rationale for your opinion.**

2. **Discuss whether the available evidence indicates that the reformulation of OxyContin had any unintended adverse consequences.**

3. **Considering the totality of evidence, discuss the overall public health impact of OxyContin's reformulation.**

4. **Discuss what information, if any, you believe is important to convey to clinicians, patients, and the public about the postmarketing evidence of ADF OxyContin's effectiveness in reducing abuse and related adverse outcomes, and/or its overall public health impact.**

Deputy Director for Safety Memorandum to File

Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research
Food and Drug Administration

NDA	*022272*
Drug names	*OxyContin*
Safety Issue	*Abuse-deterrent formulation postmarket requirements-Regulatory History*
Author name	*Judith A. Racoosin, MD, MPH*
Date	*See signature block*

This memo serves to summarize the regulatory history of the postmarket requirements (PMRs) that were required of Purdue at the time reformulated OxyContin was approved for marketing to determine whether the product deterred abuse in the "real world".

NDA 022272, OxyContin (oxycodone) extended-release tablets, was approved on April 5, 2010.[1] This "reformulated" version of the original OxyContin application (NDA 020553) was developed with excipients intended to deter abuse of the product. At the time of approval, FDA required that postmarketing studies be conducted to determine if the changes to the formulation actually result in a decrease in the risks of misuse and abuse, and their consequences. The following language was included in the April 5, 2010, approval letter:

POSTMARKETING REQUIREMENTS UNDER 505(o)

As you were informed in our December 30, 2009, Complete Response Letter, FDA has determined that you are required to conduct postmarketing studies of OxyContin (Oxycodone Hydrochloride Controlled-Release) Tablets to assess the known serious risks of OxyContin (Oxycodone Hydrochloride Controlled-Release) Tablets, in particular, whether the changes made to the OxyContin (Oxycodone Hydrochloride Controlled-Release) Tablets formulation that are the subject of this application and which are intended to deter misuse and abuse actually result in a decrease in the risks of misuse and abuse, and their consequences.

Specifically, we have determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct epidemiological studies to address whether the changes made to the OxyContin (Oxycodone Hydrochloride Controlled-Release) Tablets formulation that are the subject of this application result in a decrease in misuse and abuse, and their consequences: addiction, overdose, and death.

We acknowledge receipt of your proposal, included in your February 5, 2010, resubmission to this application, that contains brief descriptions of possible postmarketing studies to fulfill this requirement. Because of design and methodology challenges, we continue to be concerned that the proposed studies will not successfully capture the necessary information that will allow us to assess the impact, if any, attributable to the change in the OxyContin (Oxycodone Hydrochloride

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1 http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/022272s000ltr.pdf

Controlled-Release) Tablets formulation. Therefore, we will continue discussion of your postmarketing study proposals at an advisory committee meeting in the fall of 2010 on the design and methodology of the proposed studies.

For the study to be conducted first, you must submit the final protocol and the timetable for completion of the study by January 31, 2011. Likewise, for the study to be conducted last, you must submit the final protocol and timetable for completion of the study by March 1, 2011.

Submit future correspondences regarding your proposal(s) to address this requirement to your IND, with a cross-reference letter to this NDA. Prominently identify the submission(s) with the following wording in bold capital letters at the top of the first page of the submission:

- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

History

As indicated in the April 5, 2010, approval letter, FDA informed the applicant that we would continue discussion of the design and methodology of the proposed postmarketing studies at an Advisory Committee meeting, which was held in October 2010. Following the Advisory Committee discussion, and in response to FDA's comments on a draft proposal (dated December 21, 2010), Purdue proposed a program of epidemiologic studies intended "to meet FDA's post-marketing study requirement that Purdue study whether the changes made to the OxyContin tablet formulation that are intended to deter misuse and abuse actually result in a decrease in the risks of misuse and abuse, and their consequences." That submission to the Agency, dated January 24, 2011, included the following table with timelines to which the applicant committed.

Table 5. Timetable for Study Milestones and Reports

Study #	Title	Start Date	Study Period	Data Available for Analysis	Final Report Date
1	Routes of OxyContin Abuse among Entrants to Substance Abuse Treatment Programs in the ASI-MV and CHAT NAVIPPRO System	Already started	Aug 2010 to Dec 2012	Apr 2013	5 Jun 2013
2	Changes in Rates of Opioid Overdose and Poisoning Events in the Kaiser Permanente Health System with the Introduction of Reformulated OxyContin	Already started	Aug 2010 to Dec 2012	Apr 2013	5 Jun 2013
3	Exposures Reported to Poison Centers in the RADARS System	Already started	Aug 2010 to Dec 2012	Apr 2013	5 Jun 2013
4	Using Surveys to assess the Impact of a new Formulation of OxyContin	Already started	Aug 2010 to Dec 2012	Dec 2013	5 Jun 2014
5	Law Enforcement Events in the Drug Diversion Program of the RADARS System	Already started	Aug 2010 to Dec 2012	Apr 2013	5 Jun 2013
6	Doctor shopping for OxyContin as Measured by Prescription Monitoring Programs	June 2011	Aug 2010 to Dec 2012	Apr 2013	5 Jun 2013
7	Monitoring Internet Chat Room Discussions about OxyContin Abuse	Already started	Aug 2010 to Dec 2012	Apr 2013	5 Jun 2013
8	Changes in Abuse Patterns in a Cohort of People Abusing OxyContin in Rural Kentucky	Already started	Nov 2010 to Nov 2011	Feb 2012	5 Jun 2012

In response to the January 26, 2011, submission, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) sent General Advice letters on April 5, 2011, May 19, 2011, May 24, 2011, and May 23, 2013, providing design considerations and requesting additional information. In each annual report submitted after the initiation of the PMR studies in January 2011, Purdue provided documentation of the status of each of the studies listed in the table above.

Subsequently, Purdue submitted a supplement. An Advisory Committee meeting was scheduled to be held on July 7 and 8, 2015, to discuss the results of postmarketing studies evaluating the misuse and/or abuse of reformulated OxyContin. CDER prepared briefing materials for Committee members that included CDER's review of the study findings (in accordance with its usual practice). On June 22, 2015, the materials were also provided to Purdue, consistent with the process described in the Agency's *Guidance for Industry: Advisory Committee Meetings – Preparation and Public Availability of Information Given to Advisory Committee Members.*[2] Purdue submitted a request to withdraw the supplement.

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2 http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125650.pdf

The Advisory Committee meeting was subsequently cancelled;[3] consequently, there was no public discussion of the results of the supplement or supporting studies that were submitted.

Discussion

CDER's review of the studies included in Purdue's submission helped clarify what analyses would best inform our ability to assess whether the reformulated OxyContin actually deterred misuse and abuse and resulted in a decrease in the risks of addiction, overdose, and death. We concluded that those studies, as currently constituted, were not able to provide the information needed to fulfill the postmarketing requirement. In particular, these studies did not adequately evaluate the impact of the abuse-deterrent formulation on the risk of overdose and death. As FDA stated in the advisory committee background package, poison control center call data are not capable of adequately assessing changes in the risk of overdose and death. Given the public health importance of these outcomes, the scientific advances in this area, and the accumulation of sufficient person-time since product launch for a rigorous assessment of these outcomes, FDA determined that an additional investigation was necessary to fulfill the postmarketing requirement described in our April 2010 approval letter.

In addition to requiring this new study, the other three PMRs that were required were studies that Purdue had been conducting in the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO) and Researched Abuse, Diversion, and Addiction-Related Surveillance System (RADARS) Treatment Center Program (TCP) and Poison Center Program (PCP).

In March 2016, DAAAP chose to formalize the OxyContin PMRs with PMR descriptions and milestone dates to ensure that the PMR study analyses would incorporate the lessons learned from reviewing the data in the supplement, including enhanced efforts to assess the impact of the abuse-deterrent formulation on the outcomes of overdose and death.

The four formalized PMRs were linked to a PMR set number (3051) and milestone dates. Information regarding these studies were posted to the public-facing FDA Postmarket Requirements website in accordance with usual practices. The four PMRs in set 3051 were added to FDA's tracking database in April 2016, and because of the quarterly posting schedule, first appeared in the July 2016 quarterly update of the public-facing website. FDA did not specifically discourage Purdue from submitting data from other studies that may have been conducted, but only these four protocol-based studies were required as PMRs.

The text of the four PMRs follows below.

3051-1   Determine the change in overall past 30-day abuse and abuse via specific routes of administration (ROA), including swallowing intact, chewing and swallowing, dissolving and swallowing, snorting, smoking, and injecting, among individuals being assessed for substance abuse using the NAVIPPRO System Addiction

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3 http://www.fda.gov/advisorycommittees/calendar/ucm448718.htm

Severity Indicator – Multimedia Version (ASI-MV Connect) tool. Change in past 30-day abuse prevalence, both overall and via specific ROA, should be assessed for OxyContin, as well as previously agreed-upon comparator drugs (refer to May 2013 Advice Letter), through both means and trend analyses, comparing the pre-reformulation to post-reformulation period. A final analysis will be provided on data collected through 12/2015. This study should incorporate the following:

- Sensitivity analyses that restrict the study population to a subset of assessment sites that have contributed data consistently throughout the study period (e.g. at least five assessments during each study year);
- Assessment and appropriate adjustment (via stratification or other methods) for any observed shifts in the study population across the study period, including shifts in the distribution of geographic regions and treatment modality;
- Adjustment for quarterly utilization of each product or product group (in addition to unadjusted analyses), defined as the number of dosage units dispensed within the study catchment area. Additional analyses should be considered to explore the effect of such factors as lag time or non-linear relationship between utilization and abuse rates;
- Analysis of ROA for OxyContin and agreed upon comparators, comparing the pre- and post-reformulation periods, among individuals reporting past 30-day abuse of that drug;
- Post-reformulation OxyContin abuse rate analyses using 1) Any OxyContin and 2) Reformulated OxyContin only.
- Sensitivity analyses that extend the duration of the pre-reformulation period to a minimum of 2.5 years.

You will conduct this study according to the following timetable:

Final Protocol Submission:	08/2016
Study Completion:	10/2016
Final Report Submission:	03/2017

3051-2   Determine the change in the rate of poison center exposure calls, using the Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program. Exposure calls should be grouped as follows: (1) Intentional abuse and misuse, (2) Intentional—all, (3) Suicide, (4) Unintentional—all, and (5) Adverse reaction. Changes in rates, both overall and via specific routes of administration (ROA), should be assessed for OxyContin, as well as previously agreed-upon comparator drugs, through both means and trend analyses, comparing the pre-reformulation to post-reformulation period. A final analysis will be provided on data collected through 12/2015. This study should incorporate the following:

- Route-specific means and trend analyses for intentional abuse calls;

- The addition of heroin as a comparator, including in route-specific analyses;
- Population-adjusted means and trend analyses;
- Analyses that account for trends in calls to U.S. poison control centers (e.g. product-related calls as a proportion of exposure calls);
- Means and trend analyses that adjust for quarterly utilization of each product or product group, defined as the number of dosage units dispensed within the study catchment area. Additional analyses should be considered to explore the effect of such factors as lag time or non-linear relationship between utilization and abuse rates;
- Sensitivity analyses that extend the duration of the pre-reformulation period to a minimum of 2.5 years.

You will conduct this study according to the following timetable:

Final Protocol Submission:	08/2016
Study Completion:	10/2016
Final Report Submission:	03/2017

3051-3   Determine the change in the prevalence of self-reported past 30-day abuse of OxyContin and agreed-upon comparators using the The Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System Treatment Center Program (Opioid Treatment Program and Survey of Key Informants' Program). Changes in prevalence should be assessed for OxyContin, as well as previously agreed-upon comparator drugs, through both means and trend analyses, comparing the pre-reformulation to post-reformulation period. A final analysis will be provided on data collected through 12/2015. This study should incorporate the following:
- Sensitivity analyses that restrict the study population to a subset of sites that have contributed data consistently throughout the study period (e.g. at least 5 assessments during each study year or some other criterion for consistent participation in the surveillance program);
- Adjustment for quarterly utilization of each product or product group, defined as the number of dosage units dispensed within the study catchment area. Additional analyses should be considered to explore the effect of such factors as lag time or non-linear relationship between utilization and abuse rates;
- Population-adjusted analyses should also be included;
- Sensitivity analyses that extend the duration of the pre-reformulation period to a minimum of 2.5 years.

You will conduct this study according to the following timetable:

Final Protocol Submission:	08/2016

Study Completion: 10/2016
Final Report Submission: 03/2017

3051-4   Determine the change in the incidence of non-fatal and fatal overdose associated
                with OxyContin exposure relative to the change associated with exposure to
                appropriate comparators using electronic healthcare data with linkage to an
                appropriate death registry such as the National Death Index. This study should
                adhere to the principles as laid out in FDA's "Guidance for Industry and FDA
                Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic
                Safety Studies Using Electronic Healthcare Data," including but not limited to
                guidelines regarding validation of outcomes, exposure definition and
                ascertainment, and measurement of and control for potential confounders.

        You will conduct this study according to the following timetable:
                Final Protocol Submission: 09/2016
                Study Completion: 07/2017
                Final Report Submission: 10/2017

Due to the complex study methodology needed to be agreed upon by the Agency and the
Applicant, and the novel scientific issues involved, it took longer than anticipated for these
protocols to be finalized and for all the studies to be completed.

PMRs 3051-1, -2, and -3 received an "Acknowledge Final Protocol for Postmarketing
Requirement" letter on June 28, 2017, and the Final Report Submission milestone was revised to
March 31, 2018. The final study reports were submitted for PMRs 3051-1 and -2 on July 31,
2018. Due to newly identified issues with the source data, the final study report for PMR 3051-3
was delayed, and ultimately submitted on April 18, 2019.

With PMR 3051-4, there were additional complexities in finalizing the protocol, including time
needed for FDA to obtain advice and information from the Centers for Medicare and Medicaid
Services on some aspects of the study relating to use of Medicaid data. PMR 3051-4 received an
"Acknowledge Final Protocol for Postmarketing Requirement" letter on September 14, 2018, and
the Final Report Submission milestone was revised to August 31, 2019. The final study report for
PMR 3051-4 was submitted on August 26, 2019.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OXYCONTIN® safely and effectively. See full prescribing information for OXYCONTIN.

OXYCONTIN® (oxycodone hydrochloride) extended-release tablets, for oral use, CII
Initial U.S. Approval: 1950

WARNING: ADDICTION, ABUSE AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS
See full prescribing information for complete boxed warning.

- **OXYCONTIN exposes users to risks of addiction, abuse and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)**
- **To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.2)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow OXYCONTIN tablets whole to avoid exposure to a potentially fatal dose of oxycodone. (5.3)**
- **Accidental ingestion of OXYCONTIN, especially by children, can result in a fatal overdose of oxycodone. (5.3)**
- **Prolonged use of OXYCONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of oxycodone. (5.5, 7, 12.3)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.6, 7)**

Dosage and Administration (2.9)   10/2019
Warnings and Precautions (5.3, 5.14)   10/2019

---------------------------INDICATIONS AND USAGE--------------------------
OXYCONTIN is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in:

- Adults; and
- Opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.

Limitations of Use
- Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve OXYCONTIN for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)
- OXYCONTIN is not indicated as an as-needed (prn) analgesic. (1)

---------------------DOSAGE AND ADMINISTRATION-----------------------
- To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain. (2.1)

- OXYCONTIN 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. (2.1)
- Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid. (2.1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1).
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Instruct patients to swallow tablets intact and not to cut, break, chew, crush, or dissolve tablets (risk of potentially fatal dose). (2.1, 5.1)
- Instruct patients to take tablets one at a time, with enough water to ensure complete swallowing immediately after placing in mouth. (2.1, 5.10)
- Do not abruptly discontinue OXYCONTIN in a physically dependent patient because rapid discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.9)

Adults: For opioid-naïve and opioid non-tolerant patients, initiate with 10 mg tablets orally every 12 hours. See full prescribing information for instructions on conversion from opioids to OXYCONTIN, titration and maintenance of therapy. (2.2, 2.3, 2.5)
Pediatric Patients 11 Years of Age and Older
- For use only in pediatric patients 11 years and older already receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent for at least two days immediately preceding dosing with OXYCONTIN. (2.4)
- See full prescribing information for instructions on conversion from opioids to OXYCONTIN, titration and maintenance of therapy. (2.4, 2.5)
Geriatric Patients: In debilitated, opioid non-tolerant geriatric patients, initiate dosing at one third to one half the recommended starting dosage and titrate carefully. (2.7, 8.5)
Patients with Hepatic Impairment: Initiate dosing at one third to one half the recommended starting dosage and titrate carefully. (2.8, 8.6)

---------------------DOSAGE FORMS AND STRENGTHS---------------------
Extended-release tablets: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg. (3)

------------------------------CONTRAINDICATIONS------------------------------
- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Hypersensitivity to oxycodone (4)

-----------------------WARNINGS AND PRECAUTIONS-----------------------
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.7)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.8)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of OXYCONTIN in patients with circulatory shock. (5.9)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of OXYCONTIN in patients with impaired consciousness or coma. (5.10)
- Risk of Obstruction in Patients who have Difficulty Swallowing or have Underlying GI Disorders that may Predispose them to Obstruction: Consider use of an alternative analgesic. (5.11)

------------------------------ADVERSE REACTIONS------------------------------
Most common adverse reactions (incidence >5%) were constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, asthenia, and sweating. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Purdue Pharma L.P. at 1-888-726-7535 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

------------------------------DRUG INTERACTIONS------------------------------

- CNS Depressants: Concomitant use may cause hypotension, profound sedation, respiratory depression, coma, and death. If co-administration is required and the decision to begin OXYCONTIN is made, start with 1/3 to 1/2 the recommended starting dosage, consider using a lower dosage of the concomitant CNS depressant, and monitor closely. (2.6, 5.6, 7)
- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue OXYCONTIN if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with OXYCONTIN because they may reduce analgesic effect of OXYCONTIN or precipitate withdrawal symptoms. (5.14, 7)
- Monoamine Oxidase Inhibitors (MAOIs): Can potentiate the effects of morphine. Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping treatment with an MAOI. (7)

----------------------USE IN SPECIFIC POPULATIONS----------------------
Pregnancy: May cause fetal harm. (8.1)
Lactation: Not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ADDICTION, ABUSE AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

*Sections or subsections omitted from the full prescribing information are not listed

Reference ID: 4501029

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse
OXYCONTIN® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing OXYCONTIN and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)].*

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products *[see Warnings and Precautions (5.2)].* **Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to**
*   **complete a REMS-compliant education program,**
*   **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
*   **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
*   **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of OXYCONTIN. Monitor for respiratory depression, especially during initiation of OXYCONTIN or following a dose increase. Instruct patients to swallow OXYCONTIN tablets whole; crushing, chewing, or dissolving OXYCONTIN tablets can cause rapid release and absorption of a potentially fatal dose of oxycodone *[see Warnings and Precautions (5.3)].*

Accidental Ingestion
Accidental ingestion of even one dose of OXYCONTIN, especially by children, can result in a fatal overdose of oxycodone *[see Warnings and Precautions (5.3)].*

Neonatal Opioid Withdrawal Syndrome
Prolonged use of OXYCONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of

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neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.4)].*

Cytochrome P450 3A4 Interaction
The concomitant use of OXYCONTIN with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving OXYCONTIN and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.5), Drug Interactions (7), Clinical Pharmacology (12.3)].*

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.6), Drug Interactions (7)].*

- **Reserve concomitant prescribing of OXYCONTIN and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

1 INDICATIONS AND USAGE

OXYCONTIN is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in:

- Adults; and
- Opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations *[see Warnings and Precautions (5.1)]*, reserve OXYCONTIN for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

- OXYCONTIN is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

OXYCONTIN should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

OXYCONTIN 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. Adult patients who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)].*

- Initiate the dosing regimen for each patient individually; taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)].*

- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with OXYCONTIN and adjust the dosage accordingly *[see Warnings and Precautions (5.3)].*

Instruct patients to swallow OXYCONTIN tablets whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth *[see Patient Counseling Information (17)].* Instruct patients not to pre-soak, lick, or otherwise wet the tablet prior to placing in the mouth *[see Warnings and Precautions (5.11)].* Cutting, breaking, crushing, chewing, or dissolving OXYCONTIN tablets will result in uncontrolled delivery of oxycodone and can lead to overdose or death *[see Warnings and Precautions (5.1)].*

OXYCONTIN is administered orally every 12 hours.

2.2 Initial Dosage in Adults who are not Opioid-Tolerant

The starting dosage for patients who are not opioid tolerant is OXYCONTIN 10 mg orally every 12 hours.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression *[see Warnings and Precautions (5.3)].*

2.3 Conversion from Opioids to OXYCONTIN in Adults

Conversion from Other Oral Oxycodone Formulations to OXYCONTIN
If switching from other oral oxycodone formulations to OXYCONTIN, administer one half of the patient's total daily oral oxycodone dose as OXYCONTIN every 12 hours.

Conversion from Other Opioids to OXYCONTIN
Discontinue all other around-the-clock opioid drugs when OXYCONTIN therapy is initiated.

There are no established conversion ratios for conversion from other opioids to OXYCONTIN defined by clinical trials. Initiate dosing using OXYCONTIN 10 mg orally every 12 hours.

It is safer to underestimate a patient's 24-hour oral oxycodone requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral oxycodone dosage and manage an adverse reaction due to an overdose. While useful tables of opioid equivalents are readily available, there is substantial inter-patient variability in the relative potency of different opioids.

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal and for signs of oversedation/toxicity after converting patients to OXYCONTIN.

Conversion from Methadone to OXYCONTIN
Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

Conversion from Transdermal Fentanyl to OXYCONTIN
Treatment with OXYCONTIN can be initiated after the transdermal fentanyl patch has been removed for at least 18 hours. Although there has been no systematic assessment of such conversion, start with a conservative conversion: substitute 10 mg of OXYCONTIN every 12 hours for each 25 mcg per hour fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to OXYCONTIN, as there is limited documented experience with this conversion.

2.4 Initial Dosage in Pediatric Patients 11 Years and Older

The following dosing information is for use only in pediatric patients 11 years and older already receiving and tolerating opioids for at least five consecutive days. For the two days immediately preceding dosing with OXYCONTIN, patients must be taking a minimum of 20 mg per day of oxycodone or its equivalent. OXYCONTIN is not appropriate for use in pediatric patients requiring less than a 20 mg total daily dose. Table 1, based on clinical trial experience, displays the conversion factor when switching pediatric patients 11 years and older (under the conditions described above) from opioids to OXYCONTIN.

Discontinue all other around-the-clock opioid drugs when OXYCONTIN therapy is initiated.

There is substantial inter-patient variability in the relative potency of different opioid drugs and formulations. Therefore, a conservative approach is advised when determining the total daily dosage of OXYCONTIN. It is safer to underestimate a patient's 24-hour oral oxycodone requirements and provide rescue medication (e.g., immediate-release opioid) than to

overestimate the 24-hour oral oxycodone requirements and manage an adverse reaction due to an overdose.

Consider the following when using the information in Table 1.

- This is not a table of equianalgesic doses.

- The conversion factors in this table are only for the conversion from one of the listed oral opioid analgesics to OXYCONTIN.

- The table cannot be used to convert from OXYCONTIN to another opioid. Doing so will result in an over-estimation of the dose of the new opioid and may result in fatal overdose.

- The formula for conversion from prior opioids, including oral oxycodone, to the daily dose of OXYCONTIN is mg per day of prior opioid x factor = mg per day of OXYCONTIN. Divide the calculated total daily dose by 2 to get the every-12-hour OXYCONTIN dose. If rounding is necessary, always round the dose down to the nearest OXYCONTIN tablet strength available.

Table 1: Conversion Factors When Switching Pediatric Patients 11 Years and Older to OXYCONTIN

Prior Opioid	Conversion Factor	
	Oral	Parenteral*
Oxycodone	1	--
Hydrocodone	0.9	--
Hydromorphone	4	20
Morphine	0.5	3
Tramadol	0.17	0.2

*For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

Step #1: To calculate the estimated total OXYCONTIN daily dosage using Table 1:

- For pediatric patients taking a single opioid, sum the current total daily dosage of the opioid and then multiply the total daily dosage by the approximate conversion factor to calculate the approximate OXYCONTIN daily dosage.

- For pediatric patients on a regimen of more than one opioid, calculate the approximate oxycodone dose for each opioid and sum the totals to obtain the approximate OXYCONTIN daily dosage.

- For pediatric patients on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component of these products in the conversion.

Step #2: If rounding is necessary, always round the dosage down to the nearest OXYCONTIN tablet strength available and initiate OXYCONTIN therapy with that dose. If the calculated OXYCONTIN total daily dosage is less than 20 mg, there is no safe strength for conversion and do not initiate OXYCONTIN.

Example conversion from a single opioid (e.g., hydrocodone) to OXYCONTIN: Using the conversion factor of 0.9 for oral hydrocodone in Table 1, a total daily hydrocodone dosage of 50 mg is converted to 45 mg of oxycodone per day or 22.5 mg of OXYCONTIN every 12 hours. After rounding down to the nearest strength available, the recommended OXYCONTIN starting dosage is 20 mg every 12 hours.

Step #3: Close observation and titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal or for signs of over-sedation/toxicity after converting patients to OXYCONTIN. [*see Dosage and Administration (2.5)]* for important instructions on titration and maintenance of therapy.

There is limited experience with conversion from transdermal fentanyl to OXYCONTIN in pediatric patients 11 years and older. If switching from transdermal fentanyl patch to OXYCONTIN, ensure that the patch has been removed for at least 18 hours prior to starting OXYCONTIN. Although there has been no systematic assessment of such conversion, start with a conservative conversion: substitute 10 mg of OXYCONTIN every 12 hours for each 25 mcg per hour fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to OXYCONTIN.

If using asymmetric dosing, instruct patients to take the higher dose in the morning and the lower dose in the evening.

2.5 Titration and Maintenance of Therapy in Adults and Pediatric Patients 11 Years and Older

Individually titrate OXYCONTIN to a dosage that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving OXYCONTIN to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and adverse reactions, as well as monitoring for the development of addiction, abuse and misuse *[see Warnings and Precautions (5.1)]*. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for the use of opioid analgesics.

Patients who experience breakthrough pain may require a dosage adjustment of OXYCONTIN or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain

before increasing the OXYCONTIN dosage. Because steady-state plasma concentrations are approximated in 1 day, OXYCONTIN dosage may be adjusted every 1 to 2 days.

If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours. As a guideline for pediatric patients 11 years and older, the total daily oxycodone dosage usually can be increased by 25% of the current total daily dosage. As a guideline for adults, the total daily oxycodone dosage usually can be increased by 25% to 50% of the current total daily dosage, each time an increase is clinically indicated.

2.6 Dosage Modifications with Concomitant Use of Central Nervous System Depressants

If the patient is currently taking a central nervous system (CNS) depressant and the decision is made to begin OXYCONTIN, start with one-third to one-half the recommended starting dosage of OXYCONTIN, consider using a lower dosage of the concomitant CNS depressant, and monitor patients for signs of respiratory depression, sedation, and hypotension *[see Warnings and Precautions (5.6), Drug Interactions (7)]*.

2.7 Dosage Modifications in Geriatric Patients who are Debilitated and not Opioid-Tolerant

For geriatric patients who are debilitated and not opioid tolerant, start dosing patients at one-third to one-half the recommended starting dosage and titrate the dosage cautiously *[see Use in Specific Populations (8.5]*.

2.8 Dosage Modifications in Patients with Hepatic Impairment

For patients with hepatic impairment, start dosing patients at one-third to one-half the recommended starting dosage and titrate the dosage carefully. Monitor for signs of respiratory depression, sedation, and hypotension *[see Use in Specific Populations, (8.6), Clinical Pharmacology (12.3)]*.

2.9 Safe Reduction or Discontinuation of OXYCONTIN

Do not abruptly discontinue OXYCONTIN in patients who may be physically dependent on opioids. Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse. Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking OXYCONTIN, there are a variety of factors that should be considered,

including the dose of OXYCONTIN the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and follow-up plan so that patient and provider goals and expectations are clear and realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches, such as medication assisted treatment of opioid use disorder. Complex patients with comorbid pain and substance use disorders may benefit from referral to a specialist.

There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on OXYCONTIN who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition, monitor patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for a long duration and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic *[see Warnings and Precautions (5.14), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg.

- 10 mg film-coated extended-release tablets (round, white-colored, bi-convex tablets debossed with OP on one side and 10 on the other)
- 15 mg film-coated extended-release tablets (round, gray-colored, bi-convex tablets debossed with OP on one side and 15 on the other)
- 20 mg film-coated extended-release tablets (round, pink-colored, bi-convex tablets debossed with OP on one side and 20 on the other)

- 30 mg film-coated extended-release tablets (round, brown-colored, bi-convex tablets debossed with OP on one side and 30 on the other)
- 40 mg film-coated extended-release tablets (round, yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other)
- 60 mg film-coated extended-release tablets (round, red-colored, bi-convex tablets debossed with OP on one side and 60 on the other)
- 80 mg film-coated extended-release tablets (round, green-colored, bi-convex tablets debossed with OP on one side and 80 on the other)

4 CONTRAINDICATIONS

OXYCONTIN is contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.3)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.7)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.12)]*
- Hypersensitivity (e.g., anaphylaxis) to oxycodone *[see Adverse Reactions (6.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

OXYCONTIN contains oxycodone, a Schedule II controlled substance. As an opioid, OXYCONTIN exposes users to the risks of addiction, abuse, and misuse. Because extended-release products such as OXYCONTIN deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OXYCONTIN. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing OXYCONTIN, and monitor all patients receiving OXYCONTIN for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as OXYCONTIN, but use in such patients necessitates intensive counseling about the risks and proper use of OXYCONTIN along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of OXYCONTIN by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of oxycodone and can result in overdose and death *[see Overdosage (10)]*.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OXYCONTIN. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG .
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint .

5.3 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of OXYCONTIN, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of OXYCONTIN.

To reduce the risk of respiratory depression, proper dosing and titration of OXYCONTIN are essential *[see Dosage and Administration (2)]*. Overestimating the OXYCONTIN dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of OXYCONTIN, especially by children, can result in respiratory depression and death due to an overdose of oxycodone.

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper *[see Dosage and Administration (2.5)]*.

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of OXYCONTIN during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.5 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of OXYCONTIN with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression *[see Warnings and Precautions (5.3)]*, particularly when an inhibitor is added after a stable dose of OXYCONTIN is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in OXYCONTIN-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using OXYCONTIN with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in OXYCONTIN-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of OXYCONTIN until stable drug effects are achieved *[see Drug Interactions (7)]*.

Concomitant use of OXYCONTIN with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using OXYCONTIN with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid

dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur *[see Drug Interactions (7)]*.

5.6 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result if OXYCONTIN is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., non-benzodiazepines sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when OXYCONTIN is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7), Patient Counseling Information (17)]*.

5.7 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of OXYCONTIN in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: OXYCONTIN-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of OXYCONTIN *[see Warnings and Precautions (5.3)]*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.3)]*.

Monitor such patients closely, particularly when initiating and titrating OXYCONTIN and when OXYCONTIN is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.3, 5.6)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.8 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.9 Severe Hypotension

OXYCONTIN may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of OXYCONTIN. In patients with circulatory shock, OXYCONTIN may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of OXYCONTIN in patients with circulatory shock.

5.10 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), OXYCONTIN may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with OXYCONTIN.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of OXYCONTIN in patients with impaired consciousness or coma.

5.11 Difficulty in Swallowing and Risk for Obstruction in Patients at Risk for a Small Gastrointestinal Lumen

There have been post-marketing reports of difficulty in swallowing OXYCONTIN tablets. These reports included choking, gagging, regurgitation and tablets stuck in the throat. Instruct patients not to pre-soak, lick, or otherwise wet OXYCONTIN tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth.

There have been rare post-marketing reports of cases of intestinal obstruction, and exacerbation of diverticulitis, some of which have required medical intervention to remove the tablet. Patients with underlying GI disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small gastrointestinal lumen.

5.12 Risks of Use in Patients with Gastrointestinal Conditions

OXYCONTIN is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The oxycodone in OXYCONTIN may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.13 Increased Risk of Seizures in Patients with Seizure Disorders

The oxycodone in OXYCONTIN may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during OXYCONTIN therapy.

5.14 Withdrawal

Do not abruptly discontinue OXYCONTIN in a patient physically dependent on opioids. When discontinuing OXYCONTIN in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain *[see Dosage and Administration (2.9), Drug Abuse and Dependence (9.3)]*.

Additionally, avoid the use of mixed agonist/antagonist (e.g.., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including OXYCONTIN. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

5.15 Risks of Driving and Operating Machinery

OXYCONTIN may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of OXYCONTIN and know how they will react to the medication *[see Patient Counseling Information (17)]*.

5.16 Laboratory Monitoring

Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative". Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*
- Interactions With Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions (5.6)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.8)]*
- Severe Hypotension *[see Warnings and Precautions (5.9)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.11, 5.12)]*
- Seizures *[see Warnings and Precautions (5.13)]*
- Withdrawal *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trial Experience

Adult Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of OXYCONTIN was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OXYCONTIN in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

OXYCONTIN may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock *[see Overdosage (10)]*.

The most common adverse reactions (>5%) reported by patients in clinical trials comparing OXYCONTIN with placebo are shown in Table 2 below:

TABLE 2: Common Adverse Reactions (>5%)

Adverse Reaction	OXYCONTIN (n=227)	Placebo (n=45)
	(%)	(%)
Constipation	(23)	(7)
Nausea	(23)	(11)
Somnolence	(23)	(4)
Dizziness	(13)	(9)
Pruritus	(13)	(2)
Vomiting	(12)	(7)
Headache	(7)	(7)
Dry Mouth	(6)	(2)
Asthenia	(6)	-
Sweating	(5)	(2)

In clinical trials, the following adverse reactions were reported in patients treated with OXYCONTIN with an incidence between 1% and 5%:

Gastrointestinal disorders: abdominal pain, diarrhea, dyspepsia, gastritis

General disorders and administration site conditions: chills, fever

Metabolism and nutrition disorders: anorexia

Musculoskeletal and connective tissue disorders: twitching

Psychiatric disorders: abnormal dreams, anxiety, confusion, dysphoria, euphoria, insomnia, nervousness, thought abnormalities

Respiratory, thoracic and mediastinal disorders: dyspnea, hiccups

Skin and subcutaneous tissue disorders: rash

Vascular disorders: postural hypotension

The following adverse reactions occurred in less than 1% of patients involved in clinical trials:

Blood and lymphatic system disorders: lymphadenopathy

Ear and labyrinth disorders: tinnitus

Eye disorders: abnormal vision

Gastrointestinal disorders: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, stomatitis

General disorders and administration site conditions: withdrawal syndrome (with and without seizures), edema, peripheral edema, thirst, malaise, chest pain, facial edema

Injury, poisoning and procedural complications: accidental injury

Investigations: ST depression

Metabolism and nutrition disorders: dehydration

Nervous system disorders: syncope, migraine, abnormal gait, amnesia, hyperkinesia, hypoesthesia, hypotonia, paresthesia, speech disorder, stupor, tremor, vertigo, taste perversion

Psychiatric disorders: depression, agitation, depersonalization, emotional lability, hallucination

Renal and urinary disorders: dysuria, hematuria, polyuria, urinary retention

Reproductive system and breast disorders: impotence

Respiratory, thoracic and mediastinal disorders: cough increased, voice alteration

Skin and subcutaneous tissue disorders: dry skin, exfoliative dermatitis

Clinical Trial Experience in Pediatric Patients 11 Years and Older

The safety of OXYCONTIN has been evaluated in one clinical trial with 140 patients 11 to 16 years of age. The median duration of treatment was approximately three weeks. The most frequently reported adverse events were vomiting, nausea, headache, pyrexia, and constipation.

Table 3 includes a summary of the incidence of treatment emergent adverse events reported in ≥5% of patients.

Table 3: Incidence of Adverse Reactions Reported in ≥ 5.0% Patients 11 to 16 Years

System Organ Class Preferred Term	11 to 16 Years (N=140) n (%)
Any Adverse Event >= 5%	71 (51)
GASTROINTESTINAL DISORDERS	56 (40)
Vomiting	30 (21)
Nausea	21 (15)

Constipation	13 (9)
Diarrhea	8 (6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	32 (23)
Pyrexia	15 (11)
METABOLISM AND NUTRITION DISORDERS	9 (6)
Decreased appetite	7 (5)
NERVOUS SYSTEM DISORDERS	37 (26)
Headache	20 (14)
Dizziness	12 (9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	23 (16)
Pruritus	8 (6)

The following adverse reactions occurred in a clinical trial of OXYCONTIN in patients 11 to 16 years of age with an incidence between ≥1.0% and < 5.0%. Events are listed within each System/Organ Class.

Blood and lymphatic system disorders: febrile neutropenia, neutropenia

Cardiac disorders: tachycardia

Gastrointestinal disorders: abdominal pain, gastroesophageal reflux disease

General disorders and administration site conditions: fatigue, pain, chills, asthenia

Injury, poisoning, and procedural complications: procedural pain, seroma

Investigations: oxygen saturation decreased, alanine aminotransferase increased, hemoglobin decreased, platelet count decreased, neutrophil count decreased, red blood cell count decreased, weight decreased

Metabolic and nutrition disorders: hypochloremia, hyponatremia

Musculoskeletal and connective tissue disorders: pain in extremity, musculoskeletal pain

Nervous system disorders: somnolence, hypoesthesia, lethargy, paresthesia

Psychiatric disorders: insomnia, anxiety, depression, agitation

Renal and urinary disorders: dysuria, urinary retention

Respiratory, thoracic, and mediastinal disorders: oropharyngeal pain

Skin and subcutaneous tissue disorders: hyperhidrosis, rash

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of extended-release oxycodone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Abuse, addiction, aggression, amenorrhea, cholestasis, completed suicide, death, dental caries, increased hepatic enzymes, hyperalgesia, hypogonadism, hyponatremia, ileus, intentional overdose, mood altered, muscular hypertonia, overdose, palpitations (in the context of withdrawal), seizures, suicidal attempt, suicidal ideation, syndrome of inappropriate antidiuretic hormone secretion, and urticaria.

In addition to the events listed above, the following have also been reported, potentially due to the swelling and hydrogelling property of the tablet: choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in OXYCONTIN.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

7 DRUG INTERACTIONS

Table 4 includes clinically significant drug interactions with OXYCONTIN.

Table 4: Clinically Significant Drug Interactions with OXYCONTIN

Inhibitors of CYP3A4 and CYP2D6	
Clinical Impact:	The concomitant use of OXYCONTIN and CYP3A4 inhibitors can increase the plasma concentration of oxycodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of OXYCONTIN and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of OXYCONTIN is achieved *[see Warnings and Precautions (5.5)]*.
	After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone plasma concentration will decrease *[see Clinical Pharmacology*

	(12.3)], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to oxycodone.
Intervention:	If concomitant use is necessary, consider dosage reduction of OXYCONTIN until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the OXYCONTIN dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of OXYCONTIN and CYP3A4 inducers can decrease the plasma concentration of oxycodone *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to oxycodone *[see Warnings and Precautions (5.5)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the OXYCONTIN dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider OXYCONTIN dosage reduction and monitor for signs of respiratory depression.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Dosage and Administration (2.6), Warnings and Precautions (5.6)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue OXYCONTIN if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e.,

	cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.3)]*.
Intervention:	The use of OXYCONTIN is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of OXYCONTIN and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Oxycodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of OXYCONTIN and/or the muscle relaxant as necessary.
Examples:	cyclobenzaprine, metaxalone
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when OXYCONTIN is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.4)]*. There are no available data with OXYCONTIN in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, there was no embryo-fetal toxicity when oxycodone hydrochloride was orally administered to rats and rabbits, during the period of

organogenesis, at doses 1.3 to 40 times the adult human dose of 60 mg/day, respectively. In a pre- and postnatal toxicity study, when oxycodone was orally administered to rats, there was transiently decreased pup body weight during lactation and the early post-weaning period at the dose equivalent to an adult dose of 60 mg/day. In several published studies, treatment of pregnant rats with oxycodone hydrochloride at clinically relevant doses and below resulted in neurobehavioral effects in offspring *[see Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.4)]*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. OXYCONTIN is not recommended for use in women immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including OXYCONTIN, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Animal Data

Pregnant rats were treated with 0.5, 2, 4, and 8 mg/kg oxycodone hydrochloride (0.08, 0.3, 0.7, and 1.3 times the human daily dose of 60 mg/day, respectively based on a mg/m^2 basis) during the period of organogenesis. Oxycodone did not cause adverse effects to the fetus at exposures up to 1.3 times the human dose of 60 mg/day. The high dose produced maternal toxicity characterized by excessive gnawing on forelimbs and decreased body weight gain.

Pregnant rabbits were treated with 1, 5, 25, and 125 mg/kg oxycodone hydrochloride (0.3, 2, 8, and 40 times the human daily dose of 60 mg/day, respectively, based on a mg/m^2 basis) during the period of organogenesis. Oxycodone did not cause adverse effects to the fetus at exposures up to 40 times the human dose of 60 mg/day. The 25 mg/kg and 125 mg/kg doses high doses produced maternal toxicity characterized by decreased food consumption and body weight gain.

Pregnant rats were treated with 0.5, 2, and 6 mg/kg oxycodone hydrochloride (0.08, 0.32, and 1 times the human daily dose of 60 mg/kg, respective, based on a mg/m^2 basis, during the period of organogenesis through lactation. Decreased body weight was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to an adult human dose of 60 mg/day, on a mg/m^2 basis). However, body weight of these pups recovered.

In published studies, offspring of pregnant rats administered oxycodone hydrochloride during gestation have been reported to exhibit neurobehavioral effects including altered stress responses and increased anxiety-like behavior (2 mg/kg/day IV from Gestation Day 8 to 21 and Postnatal Day 1, 3, and 5; 0.3 times an adult human oral dose of 60 mg/day on a mg/m^2 basis), and altered learning and memory (15 mg/kg/day orally from breeding through parturition; 2.4 times an adult human oral dose of 60 mg/day on a mg/m^2 basis).

8.2 Lactation

Oxycodone is present in breast milk. Published lactation studies report variable concentrations of oxycodone in breast milk with administration of immediate-release oxycodone to nursing mothers in the early postpartum period. The lactation studies did not assess breastfed infants for potential adverse reactions. Lactation studies have not been conducted with extended–release oxycodone, including OXYCONTIN, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with OXYCONTIN.

Clinical Considerations

Infants exposed to OXYCONTIN through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility
Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Clinical Pharmacology (12.2)]*.

8.4 Pediatric Use

The safety and efficacy of OXYCONTIN have been established in pediatric patients ages 11 to 16 years. Use of OXYCONTIN is supported by evidence from adequate and well-controlled trials with OXYCONTIN in adults as well as an open-label study in pediatric patients ages 6 to 16 years. However, there were insufficient numbers of patients less than 11 years of age enrolled in this study to establish the safety of the product in this age group.

The safety of OXYCONTIN in pediatric patients was evaluated in 155 patients previously receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent on the two days immediately preceding dosing with OXYCONTIN. Patients were started on a total daily dose ranging between 20 mg and 100 mg depending on prior opioid dose.

The most frequent adverse events observed in pediatric patients were vomiting, nausea, headache, pyrexia, and constipation *[see Dosage and Administration (2.4), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Trials (14)]*.

8.5 Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone was slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% *[see Clinical Pharmacology (12.3)]*. Of the total number of subjects (445) in clinical studies of oxycodone hydrochloride controlled-release tablets, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected adverse reactions were seen in the elderly patients who received oxycodone hydrochloride controlled-release tablets. Thus, the usual doses and dosing intervals may be appropriate for elderly patients. However, a dosage reduction in debilitated, non-opioid-tolerant patients is recommended *[see Dosage and Administration (2.7)]*.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who are not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of OXYCONTIN slowly in these patients and monitor closely for signs of central nervous system and respiratory depression. *[see Warnings and Precautions (5.7)]*.

Oxycodone is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

A study of OXYCONTIN in patients with hepatic impairment demonstrated greater plasma concentrations than those seen at equivalent doses in persons with normal hepatic function *[see Clinical Pharmacology (12.3)]*. Therefore, a dosage reduction is recommended for these patients *[see Dosage and Administration (2.8)]*. Monitor closely for signs of respiratory depression, sedation, and hypotension.

8.7 Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function *[see Clinical Pharmacology (12.3)]*. Follow a conservative approach to dose initiation and adjust according to the clinical situation.

8.8 Sex Differences

In pharmacokinetic studies with OXYCONTIN, opioid-naïve females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

OXYCONTIN contains oxycodone, a Schedule II controlled substance.

9.2 Abuse

OXYCONTIN contains oxycodone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxymorphone, and tapentadol. OXYCONTIN can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

OXYCONTIN, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of OXYCONTIN

OXYCONTIN is for oral use only. Abuse of OXYCONTIN poses a risk of overdose and death. The risk is increased with concurrent use of OXYCONTIN with alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved OXYCONTIN enhances drug release and increases the risk of overdose and death.

With parenteral abuse, the inactive ingredients in OXYCONTIN can be expected to result in local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, valvular

heart injury, embolism, and death. Cases of thrombotic microangiopathy (a condition characterized clinically by thrombocytopenia and microangiopathic hemolytic anemia) associated with parenteral abuse have been reported.

Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

<u>Abuse Deterrence Studies</u>

OXYCONTIN is formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse. For the purposes of describing the results of studies of the abuse-deterrent characteristics of OXYCONTIN resulting from a change in formulation, in this section, the original formulation of OXYCONTIN, which is no longer marketed, will be referred to as "original OxyContin" and the reformulated, currently marketed product will be referred to as "OXYCONTIN".

In Vitro Testing
In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that, relative to original OxyContin, there is an increase in the ability of OXYCONTIN to resist crushing, breaking, and dissolution using a variety of tools and solvents. The results of these studies also support this finding for OXYCONTIN relative to an immediate-release oxycodone. When subjected to an aqueous environment, OXYCONTIN gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.

Clinical Studies
In a randomized, double-blind, placebo-controlled 5-period crossover pharmacodynamic study, 30 recreational opioid users with a history of intranasal drug abuse received intranasally administered active and placebo drug treatments. The five treatment arms were finely crushed OXYCONTIN 30 mg tablets, coarsely crushed OXYCONTIN 30 mg tablets, finely crushed original OxyContin 30 mg tablets, powdered oxycodone HCl 30 mg, and placebo. Data for finely crushed OXYCONTIN, finely crushed original OxyContin, and powdered oxycodone HCl are described below.

Drug liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale of 0 to 100 where 50 represents a neutral response, 0 represents the strongest negative response ("definitely would not take drug again") and 100 represents the strongest positive response ("definitely would take drug again").

Twenty-seven of the subjects completed the study. Incomplete dosing due to granules falling from the subjects' nostrils occurred in 34% (n = 10) of subjects with finely crushed OXYCONTIN, compared with 7% (n = 2) of subjects with finely crushed original OxyContin and no subjects with powdered oxycodone HCl.

The intranasal administration of finely crushed OXYCONTIN was associated with a numerically lower mean and median drug liking score and a lower mean and median score for take drug again, compared to finely crushed original OxyContin or powdered oxycodone HCl as summarized in Table 5.
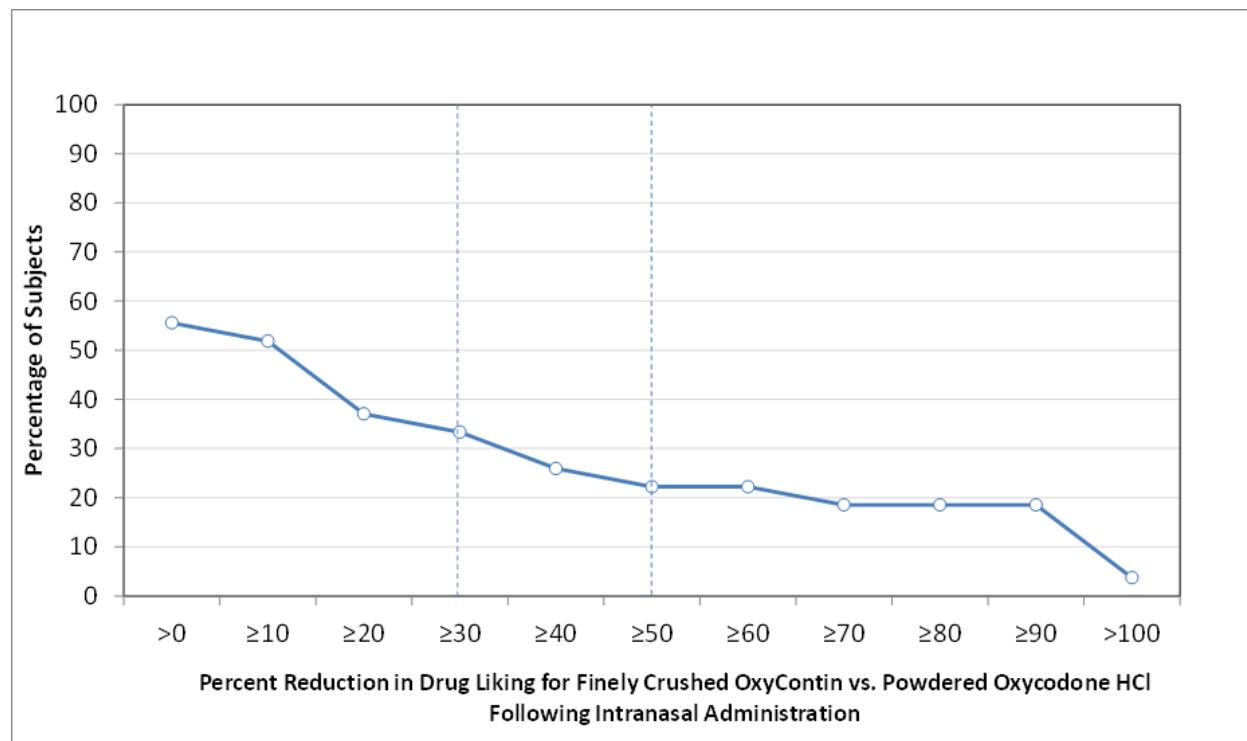
Table 5: Summary of Maximum Drug Liking (E$_{max}$) Data Following Intranasal Administration

VAS Scale (100 mm)*		OXYCONTIN (finely crushed)	Original OxyContin (finely crushed)	Oxycodone HCl (powdered)
Drug Liking	Mean (SE)	80.4 (3.9)	94.0 (2.7)	89.3 (3.1)
	Median (Range)	88 (36-100)	100 (51-100)	100 (50-100)
Take Drug Again	Mean (SE)	64.0 (7.1)	89.6 (3.9)	86.6 (4.4)
	Median (Range)	78 (0-100)	100 (20-100)	100 (0-100)

* Bipolar scales (0 = maximum negative response, 50 = neutral response, 100 = maximum positive response)

Figure 1 demonstrates a comparison of drug liking for finely crushed OXYCONTIN compared to powdered oxycodone HCl in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in drug liking for OXYCONTIN vs. oxycodone HCl powder greater than or equal to the value on the X-axis. Approximately 44% (n = 12) had no reduction in liking with OXYCONTIN relative to oxycodone HCl. Approximately 56% (n = 15) of subjects had some reduction in drug liking with OXYCONTIN relative to oxycodone HCl. Thirty-three percent (n = 9) of subjects had a reduction of at least 30% in drug liking with OXYCONTIN compared to oxycodone HCl, and approximately 22% (n = 6) of subjects had a reduction of at least 50% in drug liking with OXYCONTIN compared to oxycodone HCl.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for OXYCONTIN vs. oxycodone HCl, N=27 Following Intranasal Administration

The results of a similar analysis of drug liking for finely crushed OXYCONTIN relative to finely crushed original OxyContin were comparable to the results of finely crushed OXYCONTIN relative to powdered oxycodone HCl. Approximately 43% (n = 12) of subjects had no reduction in liking with OXYCONTIN relative to original OxyContin. Approximately 57% (n = 16) of subjects had some reduction in drug liking, 36% (n = 10) of subjects had a reduction of at least 30% in drug liking, and approximately 29% (n = 8) of subjects had a reduction of at least 50% in drug liking with OXYCONTIN compared to original OxyContin.

Summary
The *in vitro* data demonstrate that OXYCONTIN has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the *in vitro* data, also indicate that OXYCONTIN has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OXYCONTIN by these routes, as well as by the oral route, is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of OXYCONTIN on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

OXYCONTIN contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. OXYCONTIN can be abused and is

subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1)]*.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence is a physiological state in which the body adapts to the drug after a period of regular exposure, resulting in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Do not abruptly discontinue OXYCONTIN in a patient physically dependent on opioids. Rapid tapering of OXYCONTIN in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing OXYCONTIN, gradually taper the dosage using a patient specific plan that considers the following: the dose of OXYCONTIN the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for a long duration at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper *[see Dosage and Administration (2.5), Warnings and Precautions (5.14)]*.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdose with OXYCONTIN can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.
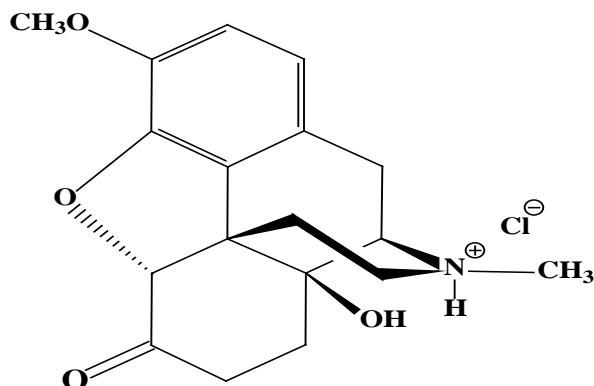
The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to oxycodone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose.

Because the duration of reversal is expected to be less than the duration of action of oxycodone in OXYCONTIN, carefully monitor the patient until spontaneous respiration is reliably reestablished. OXYCONTIN will continue to release oxycodone and add to the oxycodone load for 24 to 48 hours or longer following ingestion, necessitating prolonged monitoring. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

OXYCONTIN® (oxycodone hydrochloride) extended-release tablets is an opioid agonist supplied in 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablets for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:

$C_{18}H_{21}NO_4 \bullet HCl$ MW 351.83

The chemical name is 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7).

The 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg tablets contain the following inactive ingredients: butylated hydroxytoluene (BHT), hypromellose, polyethylene glycol 400, polyethylene oxide, magnesium stearate, titanium dioxide.

The 10 mg tablets also contain hydroxypropyl cellulose.

The 15 mg tablets also contain black iron oxide, yellow iron oxide, and red iron oxide.

The 20 mg tablets also contain polysorbate 80 and red iron oxide.

The 30 mg tablets also contain polysorbate 80, red iron oxide, yellow iron oxide, and black iron oxide.

The 40 mg tablets also contain polysorbate 80 and yellow iron oxide.

The 60 mg tablets also contain polysorbate 80, red iron oxide and black iron oxide.

The 80 mg tablets also contain hydroxypropyl cellulose, yellow iron oxide and FD&C Blue #2/Indigo Carmine Aluminum Lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxycodone is a full opioid agonist and is relatively selective for the mu receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesia. Like all full opioid agonists, there is no ceiling effect to analgesia for oxycodone. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

12.2 Pharmacodynamics

<u>Effects on the Central Nervous System</u>

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in CO_2 tension and electrical stimulation.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Overdosage (10)]*.

<u>Effects on the Gastrointestinal Tract and Other Smooth Muscle</u>

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

<u>Effects on the Cardiovascular System</u>

Oxycodone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

<u>Effects on the Endocrine System</u>

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6.2)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

<u>Effects on the Immune System</u>

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration –Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall subjective "drug effect", analgesia and feelings of relaxation.

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.5)]*.

Concentration –Adverse Reaction Relationships

There is a relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.5)]*.

12.3 Pharmacokinetics

The activity of OXYCONTIN is primarily due to the parent drug oxycodone. OXYCONTIN is designed to provide delivery of oxycodone over 12 hours.

Cutting, breaking, chewing, crushing or dissolving OXYCONTIN impairs the controlled-release delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from OXYCONTIN is pH independent. The oral bioavailability of oxycodone is 60% to 87%. The relative oral bioavailability of oxycodone from OXYCONTIN to that from immediate-release oral dosage forms is 100%. Upon repeated dosing with OXYCONTIN in healthy subjects in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life ($t_{1/2}$) of oxycodone following the administration of OXYCONTIN was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism.

Plasma Oxycodone Concentration over Time

Dose proportionality has been established for OXYCONTIN 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) *(see Table 6)*. Given the short elimination $t_½$ of oxycodone, steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OXYCONTIN. In a study comparing 10 mg of OXYCONTIN every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations.

TABLE 6

Mean [% coefficient of variation]

Regimen	Dosage Form	AUC (ng•hr/mL)*	C_{max} (ng/mL)	T_{max} (hr)
Single Dose†	10 mg	136 [27]	11.5 [27]	5.11 [21]
	15 mg	196 [28]	16.8 [29]	4.59 [19]
	20 mg	248 [25]	22.7 [25]	4.63 [22]
	30 mg	377 [24]	34.6 [21]	4.61 [19]
	40 mg	497 [27]	47.4 [30]	4.40 [22]
	60 mg	705 [22]	64.6 [24]	4.15 [26]
	80 mg	908 [21]	87.1 [29]	4.27 [26]

* for single-dose AUC = AUC_{0-inf}

†data obtained while subjects received naltrexone, which can enhance absorption

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from OXYCONTIN.

Distribution

Following intravenous administration, the steady-state volume of distribution (V_{ss}) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk *[see Use in Specific Populations (8.4)]*.

Elimination

Metabolism

Oxycodone is extensively metabolized by multiple metabolic pathways to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. CYP3A mediated *N*-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6 mediated *O*-demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs *[see Drug Interactions (7)]*.

Noroxycodone exhibits very weak anti-nociceptive potency compared to oxycodone, however, it undergoes further oxidation to produce noroxymorphone, which is active at opioid receptors. Although noroxymorphone is an active metabolite and present at relatively high concentrations in circulation, it does not appear to cross the blood-brain barrier to a significant extent. Oxymorphone is present in the plasma only at low concentrations and undergoes further metabolism to form its glucuronide and noroxymorphone. Oxymorphone has been shown to be active and possessing analgesic activity but its contribution to analgesia following oxycodone administration is thought to be clinically insignificant. Other metabolites (α- and ß-oxycodol, noroxycodol and oxymorphol) may be present at very low concentrations and demonstrate limited penetration into the brain as compared to oxycodone. The enzymes responsible for keto-reduction and glucuronidation pathways in oxycodone metabolism have not been established.

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free and conjugated oxycodone 8.9%, free noroxycodone 23%, free oxymorphone less than 1%, conjugated oxymorphone 10%, free and conjugated noroxymorphone 14%, reduced free and conjugated metabolites up to 18%. The total plasma clearance was approximately 1.4 L/min in adults.

Specific Populations

Age: Geriatric Population

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects (age 21-45).

Age: Pediatric Population

In the pediatric age group of 11 years of age and older, systemic exposure of oxycodone is expected to be similar to adults at any given dose of OXYCONTIN.

Sex

Across individual pharmacokinetic studies, average plasma oxycodone concentrations for female subjects were up to 25% higher than for male subjects on a body weight-adjusted basis. The reason for this difference is unknown *[see Use in Specific Populations (8.9)]*.

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than healthy subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The mean elimination $t_{1/2}$ for oxycodone increased by 2.3 hours.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) showed peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This was accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in mean elimination $t_{1/2}$ for oxycodone of 1 hour.

Drug Interaction Studies

CYP3A4 Inhibitors

CYP3A4 is the major isoenzyme involved in noroxycodone formation. Co-administration of OXYCONTIN (10 mg single dose) and the CYP3A4 inhibitor ketoconazole (200 mg BID) increased oxycodone AUC and C_{max} by 170% and 100%, respectively *[see Drug Interactions (7)]*.

CYP3A4 Inducers

A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone AUC and C_{max} values by 86% and 63%, respectively *[see Drug Interactions (7)]*.

CYP2D6 Inhibitors

Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs such as certain cardiovascular drugs (e.g., quinidine) and antidepressants (e.g., fluoxetine), such blockade has not been shown to be of clinical significance with OXYCONTIN *[see Drug Interactions (7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of oxycodone have not been conducted.

Mutagenesis

Oxycodone was genotoxic in the in vitro mouse lymphoma assay. Oxycodone was negative when tested at appropriate concentrations in the in vitro chromosomal aberration assay, the in vitro bacterial reverse mutation assay (Ames test), and the in vivo bone marrow micronucleus assay in mice.

Impairment of Fertility

In a study of reproductive performance, rats were administered a once daily gavage dose of the vehicle or oxycodone hydrochloride (0.5, 2, and 8 mg/kg/day). Male rats were dosed for 28 days before cohabitation with females, during the cohabitation and until necropsy (2-3 weeks post-cohabitation). Females were dosed for 14 days before cohabitation with males, during cohabitation and up to Gestation Day 6. Oxycodone hydrochloride did not affect reproductive function in male or female rats at any dose tested (up to 8 mg/kg/day), up to 1.3 times a human dose of 60 mg/day.

14 CLINICAL STUDIES

Adult Clinical Study

A double-blind, placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with persistent, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, OXYCONTIN 20 mg, but not 10 mg, was statistically significant in pain reduction compared with placebo.

Pediatric Clinical Study

OXYCONTIN has been evaluated in an open-label clinical trial of 155 opioid-tolerant pediatric patients with moderate to severe chronic pain. The mean duration of therapy was 20.7 days (range 1 to 43 days). The starting total daily doses ranged from 20 mg to 100 mg based on the patient's prior opioid dose. The mean daily dose was 33.30 mg (range 20 to 140 mg/day). In an extension study, 23 of the 155 patients were treated beyond four weeks, including 13 for 28 weeks. Too few patients less than 11 years were enrolled in the clinical trial to provide meaningful safety data in this age group.

16 HOW SUPPLIED/STORAGE AND HANDLING

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 10 mg are film-coated, round, white-colored, bi-convex tablets debossed with OP on one side and 10 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-410-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-410-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 15 mg are film-coated, round, gray-colored, bi-convex tablets debossed with OP on one side and 15 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-415-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-415-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 20 mg are film-coated, round, pink-colored, bi-convex tablets debossed with OP on one side and 20 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-420-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-420-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 30 mg are film-coated, round, brown-colored, bi-convex tablets debossed with OP on one side and 30 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-430-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-430-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 40 mg are film-coated, round, yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-440-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-440-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 60 mg are film-coated, round, red-colored, bi-convex tablets debossed with OP on one side and 60 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-460-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-460-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 80 mg are film-coated, round, green-colored, bi-convex tablets debossed with OP on one side and 80 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-480-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-480-20**).

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Store OXYCONTIN securely and dispose of properly *[see Patient Counseling Information (17)]*.

Dispense in tight, light-resistant container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

<u>Storage and Disposal</u>:

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store OXYCONTIN securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home *[see Warnings and Precautions (5.1, 5.3), Drug Abuse and Dependence (9.2)]*. Inform patients that leaving OXYCONTIN unsecured can pose a deadly risk to others in the home.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Expired, unwanted, or unused OXYCONTIN should be disposed of by flushing the unused medication down the toilet if a drug take-back option is not readily available. Inform patients that they can visit www.fda.gov/drugdisposal for a complete list of medicines recommended for disposal by flushing, as well as additional information on disposal of unused medicines.

<u>Addiction, Abuse and Misuse</u>

Inform patients that the use of OXYCONTIN, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share OXYCONTIN with others and to take steps to protect OXYCONTIN from theft or misuse.

<u>Life-Threatening Respiratory Depression</u>

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting OXYCONTIN or when the dosage is increased, and that it can occur even at recommended dosages *[see Warnings and Precautions (5.3)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

To guard against excessive exposure to OXYCONTIN by young children, advise caregivers to strictly adhere to recommended OXYCONTIN dosing.

<u>Accidental Ingestion</u>

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.3)]*.

Interactions with Benzodiazepines or Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if OXYCONTIN is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.6), Drug Interactions (7)]*.

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare provider if they are taking, or plan to take serotonergic medications *[see Drug Interactions (7)]*.

MAOI Interaction

Inform patients to avoid taking OXYCONTIN while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking OXYCONTIN *[see Drug Interactions (7)]*.

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.8)]*.

Important Administration Instructions

Instruct patients how to properly take OXYCONTIN, including the following:

- OXYCONTIN is designed to work properly only if swallowed intact. Taking cut, broken, chewed, crushed, or dissolved OXYCONTIN tablets can result in a fatal overdose *[see Dosage and Administration (2.1)]*.
- OXYCONTIN tablets should be taken one tablet at a time *[see Dosage and Administration (2.1)]*.
- Do not pre-soak, lick, or otherwise wet the tablet prior to placing in the mouth *[see Dosage and Administration (2.1)]*.
- Take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth *[see Dosage and Administration (2.1)]*.

Important Discontinuation Instructions

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue OXYCONTIN without first discussing a tapering plan with the prescriber *[see Dosage and Administration (2.5)]*.

<u>Hypotension</u>

Inform patients that OXYCONTIN may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.9)]*.

<u>Anaphylaxis</u>

Inform patients that anaphylaxis has been reported with ingredients contained in OXYCONTIN. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

<u>Pregnancy</u>

Neonatal Opioid Withdrawal Syndrome
Inform female patients of reproductive potential that prolonged use of OXYCONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity
Inform female patients of reproductive potential that OXYCONTIN can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

<u>Lactation:</u>

Advise patients that breastfeeding is not recommended during treatment with OXYCONTIN *[see Use in Specific Populations (8.2)]*

<u>Infertility</u>

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

<u>Driving or Operating Heavy Machinery</u>

Inform patients that OXYCONTIN may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.15)]*.

<u>Constipation</u>

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6)]*.

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

Purdue Pharma L.P.
Stamford, CT 06901-3431

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U.S. Patent Numbers 7,129,248; 8,309,060; 8,808,741; 8,821,929; 8,894,987; 8,894,988; 9,060,976; 9,073,933; 9,492,389, 9,492,391, 9,492,392, 9,492,393 ; 9,522,919 ; 9,675,610 ; 9,763,886; 9,763,933; 9,770,416; 9,775,808; 9,775,810; 9,775,811; 9,777,011, and 10,130,591.

Medication Guide
OXYCONTIN® (ox-e-KON-tin) (oxycodone hydrochloride) extended-release tablets, CII

OXYCONTIN is:
- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.
- Not for use in children less than 11 years of age and who are not already using opioid pain medicines regularly to manage pain severe enough to require daily around-the-clock long-term treatment of pain with an opioid.

Important information about OXYCONTIN:
- **Get emergency help right away if you take too much OXYCONTIN (overdose).** When you first start taking OXYCONTIN, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Taking **OXYCONTIN** with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your OXYCONTIN. They could die from taking it. Selling or giving away OXYCONTIN is against the law.
- Store OXYCONTIN securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

Do not take OXYCONTIN if you have:
- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking OXYCONTIN, tell your healthcare provider if you have a history of:
- head injury, seizures
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:
- **pregnant or planning to become pregnant.** Prolonged use of OXYCONTIN during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Not recommended during treatment with OXYCONTIN. It may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking OXYCONTIN with certain other medicines can cause serious side effects that could lead to death.

When taking OXYCONTIN:
- Do not change your dose. Take OXYCONTIN exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 12 hours at the same time every day. Do not take more than your prescribed dose in 12 hours. If you miss a dose, take your next dose at your usual time.
- Swallow OXYCONTIN whole. Do not cut, break, chew, crush, dissolve, snort, or inject OXYCONTIN because this may cause you to overdose and die.
- OXYCONTIN should be taken 1 tablet at a time. Do not pre-soak, lick, or wet the tablet before placing in your mouth to avoid choking on the tablet.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking OXYCONTIN without talking to your healthcare provider.**

Dispose of expired, unwanted, or unused OXYCONTIN by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

While taking OXYCONTIN DO NOT:
- Drive or operate heavy machinery until you know how OXYCONTIN affects you. OXYCONTIN can make you sleepy, dizzy, or lightheaded.
- Drink alcohol, or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with OXYCONTIN may cause you to overdose and die.

The possible side effects of OXYCONTIN are:
- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of OXYCONTIN. Call your doctor for medical advice about side effects.

You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

Manufactured by: Purdue Pharma L.P., Stamford, CT 06901-3431, **www.purduepharma.com or call 1-888-726-7535**

This Medication Guide has been approved by the U.S. Food and Drug Administration.   Revised: 10/2019

OxyContin® C II
(OXYCODONE HCl) EXTENDED-RELEASE TABLETS

states that ''The public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public is not included * * *'' within the definition of ''collection of information.''

FDA requests public comments on the information collection provisions described in this document and set forth in the following table:

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN [1]

Activity	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
Submission to Docket Number FDA–2008–D–0150	1	1	1	10	10
Cardiovascular Outcome Claim Supplement Submission ...	8	2.5	20	20	400
Total	....	....	....	....	410

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Dated: April 12, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013–09093 Filed 4–17–13; 8:45 am]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket Nos. FDA–2001–P–0238, FDA–2010–P–0526, FDA–2010–P–0540, FDA–2011–P–0473]

Determination That the OXYCONTIN (Oxycodone Hydrochloride) Drug Products Covered by New Drug Application 20–553 Were Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined that OXYCONTIN (oxycodone hydrochloride) extended-release tablets (10 milligrams (mg), 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 160 mg) approved under new drug application (NDA) 20–553 were withdrawn from sale for reasons of safety or effectiveness. The Agency will not accept or approve abbreviated new drug applications (ANDAs) for products that reference NDA 20–553.

FOR FURTHER INFORMATION CONTACT: Patrick Raulerson, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6368, Silver Spring, MD 20993–0002, 301–796–3522.

SUPPLEMENTARY INFORMATION:

I. Background

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417)

(the 1984 amendments), which authorized the approval of duplicate versions of drug products under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the ''listed drug,'' which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA).

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the ''Approved Drug Products With Therapeutic Equivalence Evaluations,'' which is known generally as the ''Orange Book.'' Under FDA regulations, drugs are removed from the list if the Agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 U.S.C. 355(j)(7)(C); 21 CFR 314.162).

A person may petition the Agency to determine, or the Agency may determine on its own initiative, whether a listed drug was withdrawn from sale for reasons of safety or effectiveness. This determination may be made at any time after the drug has been withdrawn from sale, but must be made before approving an ANDA that refers to the listed drug (§ 314.161 (21 CFR 314.161)). FDA may not approve an ANDA that does not refer to a listed drug.

OXYCONTIN (oxycodone hydrochloride) extended-release tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 160 mg (original OxyContin), are the subject of NDA 20–553, held by Purdue Pharma LP (Purdue) and initially approved on

December 12, 1995. A reformulated version of these products, OXYCONTIN (oxycodone hydrochloride) extended-release tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg (reformulated OxyContin), are the subject of NDA 22–272, also held by Purdue and initially approved on April 5, 2010. Reformulated OxyContin was developed with physicochemical properties that are intended to make the tablet more difficult to manipulate for purposes of abuse or misuse. Both original and reformulated OxyContin are opioid agonist products indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

In correspondence dated August 10, 2010, Purdue notified FDA that it had ceased shipment of original OxyContin, and FDA subsequently moved original OxyContin to the ''Discontinued Drug Product List'' section of the Orange Book. On April 16, 2013, FDA approved a supplemental application for reformulated OxyContin, approving changes to the product labeling that describe certain abuse-deterrent properties of the reformulated product.

Several parties have submitted citizen petitions under 21 CFR 10.30, requesting that the Agency determine whether original OXYCONTIN (oxycodone hydrochloride) extended-release tablets were voluntarily withdrawn from sale for reasons other than safety or effectiveness.[1]

Based on the information available at this time, FDA has determined under § 314.161 that original OxyContin was

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[1] Varam, Inc., Docket No. 2011–P–0473 (June 9, 2011) (10, 15, 20, 30, 40, 50, 80, and 160 mg); Sheppard, Mullin, Richter & Hampton LLP, Docket No. 2010–P–0540 (Oct. 8, 2010) (10, 15, 20, 30, 40, 60, and 80 mg); Lachman Consultant Services, Inc., Docket No. FDA–2010–P–0526) (Sept. 30, 2010) (10, 15, 20, 30, 40, 60, 80, and 160 mg). Lachman also submitted a petition in 2001 concerning just Purdue's 2001 withdrawal of the 160 mg strength. Docket No. FDA–2001–P–0473 (formerly Docket No. 2001P–0426) (Sept. 18, 2001).

withdrawn from sale for reasons of safety or effectiveness. FDA has reached this determination following a careful review and analysis of the following information: (1) The citizen petitions described previously; (2) the comments submitted to the dockets associated with these petitions; (3) the Agency records and other information concerning original and reformulated OxyContin and the withdrawal of original OxyContin; and (d) data, literature, and other information concerning postmarketing adverse events associated with original OxyContin, reformulated OxyContin, and other extended-release oxycodone products.

II. Initiatives To Address Abuse of Opioid Analgesics

Opioid analgesics are an important component of modern pain management. Abuse and misuse of these products, however, has grown into a public health epidemic. According to the Centers for Disease Control and Prevention, sales of prescription opioids in the United States increased over 300 percent from 1999 to 2008 (Ref. 1). Overdose deaths involving these products increased commensurately over the same period, from 4,000 to 14,800 (Refs. 1 and 2). In 2008 prescription opioids were involved in more overdose deaths than heroin and cocaine combined (Ref. 3). In 2010 the number of overdose deaths in which prescription opioids were involved rose to 16,651, which represented more than 75 percent of all overdose deaths involving prescription drugs (Ref. 4).

FDA, together with other Federal agencies, is working to address this large and growing problem while ensuring that patients in pain have appropriate access to opioid analgesics. FDA has worked to improve the labeling of OxyContin and other opioid analgesics to better warn prescribers and patients of the serious risks associated with abuse and misuse. FDA also has worked extensively with the sponsors of OxyContin and other extended-release or long-acting prescription (ER/LA) opioid analgesics to address these risks through a classwide risk evaluation and mitigation strategy (REMS) *http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf.*

This REMS, approved on July 9, 2012, requires sponsors of ER/LA opioids to make available training for health care professionals on proper prescribing practices and also to distribute educational materials to prescribers and patients on the safe use of these medications.

FDA considers the development of opioid analgesics that can deter abuse and misuse to be a public health priority. Opioid analgesics can be abused orally or by injection, snorting, or smoking and also may be misused in therapeutic contexts. Products may be designed to deter one or more of these methods of abuse or misuse. Following mandates in the 2011 White House prescription drug abuse prevention plan (Ref. 5) and section 1122(c) of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112–144) (126 Stat. 1075), FDA recently issued a draft guidance to industry on the evaluation and labeling of potentially abuse-deterrent opioid analgesics (Ref. 6).

III. Assessment of Abuse-Deterrent Properties of Reformulated OxyContin

All forms of opioid analgesic abuse are dangerous, and non-oral routes of abuse are particularly dangerous. Intranasal and intravenous opioid abuse is associated with serious adverse events including addiction, overdose, and death (Refs. 7, 8, and 9). Intravenous opioid abuse is associated with HIV and hepatitis B and C infection risk (Ref. 10). Further, as stated in the OxyContin labeling (see section 9.2), injection of OxyContin excipients "can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury." The label is available at *http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272s016lbl.pdf.* Intranasal opioid abuse is associated with nasal, palatal, and pharyngeal necrosis (Refs. 7 and 11).

Original OxyContin was often abused by manipulating the product to defeat its extended-release mechanism, causing the oxycodone to be released more rapidly. Original OxyContin also was manipulated for therapeutic purposes, for example, by crushing the product to sprinkle it onto food or to administer it through a gastric tube. As noted in the boxed warning of the labeling, disruption of the tablet and controlled-release mechanism for abuse or misuse "can lead to rapid release and absorption of a potentially fatal dose of oxycodone."

FDA has conducted an extensive review of data available to the Agency regarding reformulated OxyContin, including in vitro, pharmacokinetic, clinical abuse potential, and postmarketing study data. The data show that, when compared to original OxyContin, reformulated OxyContin has an increased ability to resist crushing, breaking, and dissolution using a variety of tools and solvents. The data also

demonstrate that, when subjected to an aqueous environment, reformulated OxyContin gradually forms a viscous hydrogel. The data also indicate that insufflation of finely crushed reformulated OxyContin was associated with lower "liking" compared to finely crushed original OxyContin in recreational opioid users with a history of intranasal drug abuse. FDA concludes, based on these data and our review of all data and information available to the Agency at this time, that the physicochemical properties of reformulated OxyContin are expected to make abuse via injection difficult and are expected to reduce abuse via the intranasal route. In addition, reformulated OxyContin also may deter certain types of misuse in therapeutic contexts.

Additional postmarketing studies intended to assess the impact of reformulated OxyContin on abuse and misuse in the community also have been conducted; some of these are still ongoing. FDA has reviewed the available data from these studies and has concluded that they suggest, but do not confirm, a reduction in non-oral abuse. The Agency will continue to review data from these studies as they become available, as well as any other relevant data that may be developed in the future.

FDA has long considered the abuse potential of a drug in numerous regulatory contexts. Where appropriate, FDA may take into account abuse potential as part of the safety profile of a drug when weighing its benefits and risks. In this case, FDA has considered the abuse potential as part of the Agency's determination of whether the original formulation of OxyContin was withdrawn from sale for reasons of safety or effectiveness. This approach is particularly appropriate here in light of the extensive and well-documented history of OxyContin abuse.

Original OxyContin has the same therapeutic benefits as reformulated OxyContin. Original OxyContin, however, poses an increased potential for abuse by certain routes of administration, when compared to reformulated OxyContin. Based on the totality of the data and information available to the Agency at this time, FDA concludes that the benefits of original OxyContin no longer outweigh its risks. FDA has determined that OXYCONTIN (oxycodone hydrochloride) extended release tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 160 mg (approved under new drug application 20–553), were withdrawn from sale for reasons of safety or effectiveness. Accordingly, the

Agency will remove OXYCONTIN (oxycodone hydrochloride) extended-release tablets (10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, and 160 mg) approved under NDA 20–553 from the list of drug products published in the Orange Book. FDA will not accept or approve ANDAs that refer to these drug products.

IV. References

The following references have been placed on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at *http:// www.regulations.gov*. (FDA has verified the Web site addresses in this reference section, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

1. National Center for Injury Prevention and Control, Centers for Disease Control and Prevention (CDC), ''Policy Impact: Prescription Painkiller Overdoses'' (*www.cdc.gov/ HomeandRecreationalSafety/pdf/ PolicyImpact-Prescription PainkillerOD.pdf*).
2. CDC, ''Vital Signs: Overdoses of Prescription Opioid Pain Relievers— United States, 1999–2008,'' *Morbidity and Mortality Weekly Report,* vol. 60, No. 43, pp. 1487–1492, 2011 (*www.cdc.gov/mmwr/pdf/wk/ mm6043.pdf*).
3. National Center for Injury Prevention and Control, CDC, ''Unintentional Drug Poisoning in the United States'' (*www.cdc.gov/HomeandRecreational Safety/pdf/poison-issue-brief.pdf*).
4. Jones, C.M., K.A. Mack, and L.J. Paulozzi, ''Pharmaceutical Overdose Deaths, United States, 2010,'' *Journal of the American Medical Association,* vol. 309, pp. 657–659, 2013.
5. FDA, ''FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics'' (*http:// www.fda.gov/downloads/drugs/ drugsafety/informationbydrugclass/ ucm277916.pdf*).
6. FDA, ''Draft Guidance for Industry: Abuse-Deterrent Opioids—Evaluation and Labeling,'' (*www.fda.gov/downloads/ Drugs/GuidanceCompliance RegulatoryInformation/Guidances/ UCM334743.pdf*).
7. Katz, N., R.C. Dart, E. Bailey, et al., ''Tampering With Prescription Opioids: Nature and Extent of the Problem, Health Consequences, and Solutions,'' *The American Journal of Drug and Alcohol Abuse,* vol. 37, pp. 205–217, 2011.
8. Silva, K., S.M. Schrager, A. Kecojevic, et al., ''Factors Associated With History of Non-Fatal Overdose Among Young Nonmedical Users of Prescription Drugs,'' *Drug and Alcohol Dependence,* vol. 128, pp. 104–110, 2013.
9. Degenhardt, L., C. Bucello, B. Mathers, et al., ''Mortality Among Regular or Dependent Users of Heroin and Other Opioids: A Systematic Review and Meta-Analysis of Cohort Studies,'' *Addiction,* vol. 106, pp. 32–51, 2011.
10. CDC, ''Integrated Prevention Services for HIV Infection, Viral Hepatitis, Sexually Transmitted Diseases, and Tuberculosis for Persons Who Use Drugs Illicitly: Summary Guidance From the CDC and the U.S. Department of Health and Human Services,'' *Morbidity and Mortality Weekly Report,* vol. 61, pp. 1–40, 2012.
11. Alexander, D., K. Alexander, and J. Valentino, ''Intranasal Hydrocodone-Acetaminophen Abuse-Induced Necrosis of the Nasal Cavity and Pharynx,'' *The Laryngoscope,* vol. 122, pp. 2378–2381, 2012.

Dated: April 12, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2013–09092 Filed 4–16–13; 4:15 pm]

BILLING CODE 4160–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Service Administration

Advisory Committee on Interdisciplinary, Community-Based Linkages; Notice of Meeting

In accordance with section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92–463), notice is hereby given of the following meeting:

Name: Advisory Committee on Interdisciplinary, Community-Based Linkages (ACICBL).

Dates and Times: April 22, 2013, 8:30 a.m.–5:00 p.m., April 23, 2013, 9:00 a.m.–5:00 p.m.

Place: Health Resources and Services Administration, U.S. Department of Health and Human Services, 5600 Fishers Lane, Rockville, Maryland 20852, Room 18–57.

Status: The meeting will be open to the public.

Purpose: The members of the ACICBL will begin discussions to develop the legislatively mandated 13th Annual Report to the Secretary of Health and Human Services and Congress. The Committee members will focus on the working topic: Optimizing the Interprofessional Team Member's Contributions to Population Health. The Committee has invited Dr. John Gilbert, former Principal and Professor Emeritus at the University of British Columbia, Canada; Ms. Rachel Watman, Senior Program Officer, The John A. Hartford Foundation; Dr. John Bulger, Chief Quality Officer, Geisinger Health System; Dr. Paul McGann, Deputy Chief Medical Officer for Innovation Grants, Centers for Medicare & Medicaid Services; Dr. Thomas Edes, Director of Home and Community-Based Care, U.S. Department of Veterans Affairs; and Dr. Alex Camacho, Deputy Director, Office of Performance Measurement, Health Resources and Services Administration. The meeting will afford committee members with the opportunity to identify and discuss population health; interprofessional education, care and competencies; and best practices and the like in an effort to formulate appropriate recommendations for the Secretary and the Congress.

Agenda: The ACICBL agenda includes an overview of the Committee's general business activities, presentations by and dialogue with experts, and discussion sessions specifically for the development of recommendations to be addressed in the 13th Annual ACICBL Report. The agenda will be available 2 days prior to the meeting on the HRSA Web site (*http://www.hrsa.gov/ advisorycommittees/bhpradvisory/ acicbl/acicbl.html*). Agenda items are subject to change as priorities dictate.

SUPPLEMENTARY INFORMATION: Members of the public and interested parties may request to provide comments or register to attend the meeting by emailing their first name, last name, and full email address to *BHPRAdvisoryCommittee@hrsa.gov* or by contacting Ms. Crystal Straughn at 301–443–3594. Registration is first come, first served as space is limited.

FOR FURTHER INFORMATION CONTACT: Anyone requesting information regarding the ACICBL should contact Dr. Joan Weiss, Designated Federal Official within the Bureau of Health Professions, Health Resources and Services Administration, in one of three ways: (1) Send a request to the following address: Dr. Joan Weiss, Designated Federal Official, Bureau of Health Professions, Health Resources and Services Administration, Parklawn Building, Room 9C–05, 5600 Fishers Lane, Rockville, Maryland 20857; (2) call (301) 443–6950; or (3) send an email to *jweiss@hrsa.gov*.

Dated: April 11, 2013.

Bahar Niakan,

Director, Division of Policy and Information Coordination.

[FR Doc. 2013–09135 Filed 4–17–13; 8:45 am]

BILLING CODE 4165–15–P

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	**September 10-11, 2020**
To:	**Members of the Joint Drug Safety and Risk Management (DSaRM) Advisory Committee and Anesthetic and Analgesic Drug Products Advisory Committee**
From:	**Division of Risk Management (DRM)** **Office of Medication Error Prevention and Risk Management (OMEPRM)** **Office of Surveillance and Epidemiology (OSE)**
Drug Name:	**OxyContin (oxycodone hydrochloride extended-release tablets)**
Subject:	**Risk Evaluation and Mitigation Strategy (REMS)**

In April 2010, a new formulation of OxyContin was approved, its design was to discourage misuse and abuse of the medication. At that time, OxyContin was approved with its own risk evaluation and mitigation strategy (REMS). The REMS consisted of elements to assure safe use (ETASU), and a timetable for submission of assessments. The ETASU included healthcare provider training and Dear Healthcare Professional letters. In addition, a Medication Guide was also required as part of the REMS since OxyContin had serious risks relative to the benefits that may affect a patient's decision to use, or continue to use, OxyContin.

In July 2012, OxyContin became a member of the shared system Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics (ER/LA) REMS. The ER/LA REMS was expanded and modified in September 2018 to include all application holders of immediate-release (IR) opioid analgesics that are expected to be used in the outpatient setting and that are not already covered by another REMS program. With the approval of this modification the ER/LA REMS was renamed the Opioid Analgesic REMS, of which OxyContin is a member. The Opioid Analgesic REMS is one strategy among multiple national and state efforts to reduce the risks of abuse, and misuse, addiction, overdose and deaths due to prescription opioid analgesics by making training available to healthcare providers.

The Opioid Analgesics REMS requires that training be made available to healthcare providers, including prescribers, nurses, and pharmacists, involved in the treatment and monitoring of patients with pain. The FDA believes that all healthcare providers (HCPs) involved in the

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management of patients with pain should be educated about the fundamentals of acute and chronic pain management and the risks and safe use of opioids so that when they write or dispense a prescription for an opioid analgesic, or monitor patients receiving these medications, they can help ensure the proper product is selected for the patient and used with appropriate clinical oversight.

Under the Opioid Analgesic REMS, application holders[1] are required to make education programs available to healthcare providers. The application holders are meeting this requirement by providing educational grants to accredited continuing education (CE) providers who offer training to healthcare providers at no or nominal cost. The training must include successful completion of a knowledge assessment and proof of successful program completion.

To be considered compliant with the Opioid Analgesic REMS, the CE courses are required to include the content and messages of a "blueprint" developed by FDA for this purpose. The currently approved FDA Blueprint, *FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain,*[2] focuses on the fundamentals of acute and chronic pain management and provides a contextual framework for the safe prescribing of opioid analgesics. This includes principles related to the acute and chronic pain management; non-pharmacologic treatments for pain; and pharmacologic treatments for pain (both non-opioid analgesic and opioid analgesic). The FDA Blueprint covers basic information about addiction medicine and opioid use disorder. The core messages are directed to prescribers, pharmacists, and nurses, but are also relevant for other healthcare providers who participate in the management of pain.

The Opioid Analgesics REMS also includes a patient counseling guide[3] for healthcare providers to assist in properly counseling patients on their responsibilities for using these medicines safely and to provide patients with additional written safety information. The approved labeling for opioid analgesics includes a product-specific one-page Medication Guide to be given to patients each time they receive a prescription of their opioid analgesic medicine. The Medication Guide contains consumer-friendly information on the safe use and disposal of opioid analgesics and instructions for patients to consult their healthcare providers before changing doses, signs of potential overdose and emergency contact instructions, and advice on safe storage to prevent accidental exposure to family members.

Attachments: Appendix X – FDA Blueprint (https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_analgesic_2018_09_18_FDA_Blueprint.pdf)

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1 Application holders refers to all the manufacturers of the new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for opioid analgesics that are subject to the REMS requirements. ANDAs refer to generic drugs. The applicant holders have come together as a consortium and formed the REMS Program Companies (RPC). Throughout this background document, the manufacturers may be referred to as application holders or RPC.

2 Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain. The FDA Blueprint contains core messages intended for use by CE providers to develop educational materials to train HCPs under the REMS.

3 https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_Analgesic_2019_11_14_Patient_Counseling_Guide.pdf

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Drug Utilization Review

Date: September 10-2020

Reviewer: Nabila Sadiq, PharmD
                                    Drug Utilization Analyst
                                    Division of Epidemiology II

Team Leader: Patty Greene, PharmD
                                    Drug Utilization Team Leader (Acting)
                                    Division of Epidemiology II

Deputy Director: Rajdeep Gill, PharmD
                                    Deputy Director for Drug Utilization (Acting)
                                    Division of Epidemiology II

Associate Director for   LCDR Grace Chai, PharmD
Special Initiatives (Acting):   Office of Surveillance and Epidemiology

Associate Director for   Judy Staffa, Ph.D., R.Ph.
Public Health Initiatives: Office of Surveillance and Epidemiology

Subject: Utilization of OxyContin Abuse-Deterrent Formulation (ADF)

Drug Name(s):   OxyContin (oxycodone extended-release (ER) tablets)

Application Type/Number: Multiple

Applicant/Sponsor: Multiple

OSE RCM #:   2019-1681

Table of Contents

EXECUTIVE SUMMARY

A joint Advisory Committee meeting will be held to discuss the results of post-marketing requirement (PMR) studies submitted by Purdue Pharma L.P. The PMR studies aimed to assess the impact of the reformulation on OxyContin abuse and risk of opioid overdose. To supplement and contextualize the PMR study results and to inform on the broader public health impact of the reformulation, the Division of Epidemiology II conducted a drug utilization review to examine the outpatient retail utilization of abuse-deterrent opioid analgesics, with a focus on single-ingredient oxycodone extended-release (ER) products.

In 2019, an estimated 154 million prescriptions were dispensed for all opioid analgesics from U.S. outpatient retail pharmacies, a decrease of 41% from a peak of 260 million prescriptions dispensed in 2012. Utilization of extended-release/long-acting (ER/LA) opioid analgesics peaked in 2010 at 18.4 million prescriptions and declined by 47% to 9.8 million prescriptions in 2019, with oxycodone ER accounting for 25% of ER/LA prescriptions.

Overall, prescriptions dispensed for oxycodone ER peaked at 7.4 million prescriptions dispensed in 2008 then decreased to 2.4 million prescriptions in 2019. In 2010, distribution of the original formulation of OxyContin and generic oxycodone ER ceased, and reformulated OxyContin became available in the market. As a result, prescriptions for original OxyContin and generic oxycodone ER formulations dropped from 6 million and 1.3 million prescriptions in 2010 to 136,000 and 138,000 prescriptions respectively in 2011. The vast majority of prescriptions dispensed for oxycodone ER was for the reformulated OxyContin at 5.5 million prescriptions dispensed in 2011. The authorized generics for the reformulated oxycodone ER were introduced in 2014, utilization peaked in 2016 with 560,000 prescriptions then steadily declined to 172,000 prescriptions dispensed in 2019. Reformulated OxyContin and its authorized generics accounted for the majority of utilization of abuse-deterrent opioid analgesics, accounting for 73% of prescriptions in 2019.

In terms of average milligrams per prescription (mg/Rx) for oxycodone ER based on the estimated aggregate volume of prescriptions dispensed, the average yearly aggregate of milligrams of oxycodone ER per prescription dispensed decreased from of 3,100 mg/Rx in 2009 to 1,700 mg/Rx in 2019. This decline may be due to the overall decrease in the utilization of higher strengths of oxycodone ER formulations. The most common strengths of oxycodone ER tablets were dispensed for 40 mg and 80 mg during the fourth quarter of 2009. However, this trend changed by the fourth quarter of 2019, where oxycodone ER 20 mg accounted for the highest proportions of all strengths.

Mid-level practitioners were the top prescribing specialties of the single-ingredient oxycodone ER TRx in 2019; family practice, internal medicine, general practitioner accounted for the highest proportion of TRx followed by mid-level practitioners in 2009 and 2012. Among specialists, although the total number of TRx dispensed for oxycodone ER decreased during the examined time-periods, the proportion of TRx written by pain medicine/anesthesiologists increased from 14% in 2009 to 22% in 2019.

Our findings show total utilization of oxycodone ER was highest in 2008 followed by a decline of 67% by 2019. The decrease of utilization of oxycodone ER formulation may due to several reasons including the strengthening of warnings on the drug label, expanding patient and prescriber educational campaigns, interventions implemented by federal, state, local governments, recommended limitations on opioid dosages, payer-based dispensing restrictions, prescription drug monitoring programs (PDMP), risk evaluation mitigation strategies (REMS) and issuing guidance for the pharmaceutical industry regarding the development of abuse-deterrent formulations of opioid products in addition to many other interventions.

1   INTRODUCTION

A joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) will be held on September 10-11, 2020 to discuss the results of post-marketing requirement (PMR) studies submitted by Purdue Pharma L.P (sponsor). The PMR studies aimed to assess the specific impact of the OxyContin reformulation on OxyContin abuse and risk of opioid overdose. To supplement and contextualize the PMR study results submitted by the sponsor and to better understand the broader public health impact of OxyContin's reformulation, the Division of Epidemiology (DEPI) II conducted a drug utilization review to examine the outpatient retail utilization of abuse-deterrent opioid analgesics, with a focus on oxycodone ER formulations to provide background for the Advisory Committee discussion.

2   BACKGROUND AND REGULATORY HISTORY[1]

Reformulated OxyContin (oxycodone hydrochloride) is a single-ingredient extended-release (ER) opioid product developed by Purdue Pharma L.P. (sponsor); it was approved for marketing in the U.S. on April 5, 2010. It replaced the original OxyContin formulation approved on December 12, 1995. On August 5, 2010, the sponsor stopped shipping original OxyContin tablets to pharmacies and exclusively started shipping reformulated OxyContin tablets on August 9, 2010. However, pharmacies were still able to dispense their remaining stock of original OxyContin tablets after August 5, 2010. In correspondence dated August 10, 2010, the sponsor notified the U.S Food and Drug Administration (FDA) that it had ceased shipment of original OxyContin.

In October 2014, the sponsor submitted a labeling supplement requesting placement of claims in the label describing a real-world beneficial effect of the ADF of OxyContin. An Advisory Committee meeting was scheduled to be held in July 2015 to discuss the results of post-marketing studies that were submitted in support of the requested label claim. Subsequently, the sponsor submitted a request to withdraw the supplement, citing the need to complete additional analyses.

In April 2015, FDA issued the final *Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry*, outlining the Agency's current thinking on studies that should be conducted to demonstrate that a given opioid formulation has abuse-deterrent properties. The guidance makes recommendations about how those studies should be performed and evaluated and discusses how to describe those studies and their implications in product labeling.

In March 2016, a new PMR letter was issued, formalizing the required studies and timelines. In addition to three studies assessing the impact of the ADF on OxyContin abuse rates, the Agency required a claims-based study linked to mortality data to assess the impact of the reformulation on fatal and non-fatal opioid overdose.

In 2018 and 2019, the sponsor submitted the final study reports for four PMR studies evaluating the effectiveness of the ADF in reducing OxyContin abuse and related outcomes, including fatal and non-fatal overdose, in the post-approval setting. On [September 10-11, 2020 a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk

Management Advisory Committee (DSaRM) will be held to discuss the results of these findings.

3   METHODS AND MATERIALS

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[1] Center for Drug Evaluation and Research. (2019, December 21). Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse. Retrieved May 1, 2020, from https://www.fda.gov/drugs/information-drug-class/timeline-selected-fda-activities-and-significant-events-addressing-opioid-misuse-and-abuse

3.1 PRODUCTS INCLUDED

Table 1 below shows the oxycodone-containing opioid analgesics, including formulations designed to deter abuse, that are included in this review. Other opioid analgesics defined as schedule-II under the Controlled Substance Act (CSA) (single-ingredient, combination, extended-release/long-acting and immediate-release opioid analgesics, as well as transdermal and suppository formulations) are also included in this review. This review focused on non-injectable opioid analgesics mainly dispensed in the outpatient retail pharmacy setting. We did not include injectable formulations of opioid analgesics, opioid-containing medication-based therapy products and opioid-containing cough/cold products in these analyses.

Table 1[2]

Single-Ingredient Oxycodone ER formulations	All other schedule-II opioid analgesics
OxyContin	Arymo ER
Oxycodone ER	Codeine
Xtampza ER	Embeda ER
	Fentanyl
	Hydrocodone
	Hydromorphone
	Hysingla ER
	Levorphanol
	Meperidine
	Methadone
	Morphabond ER
	Morphine
	Opium
	Oxycodone
	Oxymorphone
	Roxybond IR
	Tapentadol

3.2 DATA SOURCES USED

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[2] Drug Enforcement Administration. (n.d.). List of Controlled Substances. Retrieved June 15, 2020, from https://www.deadiversion.usdoj.gov/schedules/

Proprietary databases available to the Agency were used to conduct the drug utilization analyses in this review (see Appendix A) for full database descriptions).

3.2.1 Determining Settings of Care

The IQVIA National Sales Perspectives™ (NSP) database was used to determine the primary setting of care for the utilization of oxycodone ER products based on the estimated number of bottles or packages of these products sold from manufacturers to various settings of care in 2019. Of note, our analysis includes all single-ingredient oxycodone ER products, however, main focus of this review is original and reformulated formulations of OxyContin and its generics.

3.2.2 Prescription Data

The IQVIA, National Prescription Audit (NPA)™ database was used to provide the estimated number of prescriptions and tablets dispensed for OxyContin original, OxyContin reformulated, oxycodone ER original, oxycodone ER reformulated and other opioid analgesics comparators from U.S. outpatient retail pharmacies from 2006 through 2019, annually and quarterly. This database was also used to provide the prescriber specialties for oxycodone ER prescriptions dispensed from U.S. outpatient retail pharmacies for different time-periods (original OxyContin in 2009, after reformulation in 2012, and in 2019).

There was a change in the underlying data and methodology of the proprietary database, IQVIA NPA, to manage prescription claims that are voided or reversed. Prescription volumes dispensed from the retail pharmacies have been historically adjusted back to January 2017, data prior to January 2017 have not been adjusted to the new methodology; therefore, there is a trend break between 2016 and 2017 and any changes over time should be interpreted in the context of the changes in methodology. Of note, in 2018, an estimated 2% of total prescription claims for opioid analgesics dispensed from U.S. retail pharmacies appears to have been voided or reversed

Symphony Health PHAST Prescription Monthly (SHS) database was used to create the "choropleth map". These maps represent the variability of oxycodone ER utilization across all regions in the U.S. Information on total population in each state was derived from U.S. Census Bureau for 2009, 2012 and 2018.[3,4,5] The rates were mapped to a color gradient scale based on range and intensity of the oxycodone ER utilization among individual states. The utilization of dispensed prescriptions for oxycodone ER per 10,000 residents was determined by dividing the number of prescriptions dispensed for oxycodone ER in 2009, 2012 and 2018 individually by the census population estimate per state multiplied by 10,000.

4 RESULTS

In 2019, approximately 77% of bottles or packages of oxycodone ER products were sold to the outpatient retail setting; therefore, this review examined the utilization of opioid analgesics from U.S. retail pharmacies. [6]

4.1 PRESCRIPTION DATA

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[3] U.S. Census Bureau; American Community Survey, 2009 American Community Survey 1-Year Estimates. Accessed January 2020.

[4] Annual Estimates of the Resident Population by Single Year of Age and Sex for the United States, States, and Puerto Rico Commonwealth: April 1, 2010 to July 1, 2012. Source: U.S. Census Bureau, Population Division. Release Date: June 2013

[5] Annual Estimates of the Resident Population by Single Year of Age and Sex for the United States, States, and Puerto Rico Commonwealth: April 1, 2010 to July 1, 2018. Source: U.S. Census Bureau, Population Division. Release Date: June 2019
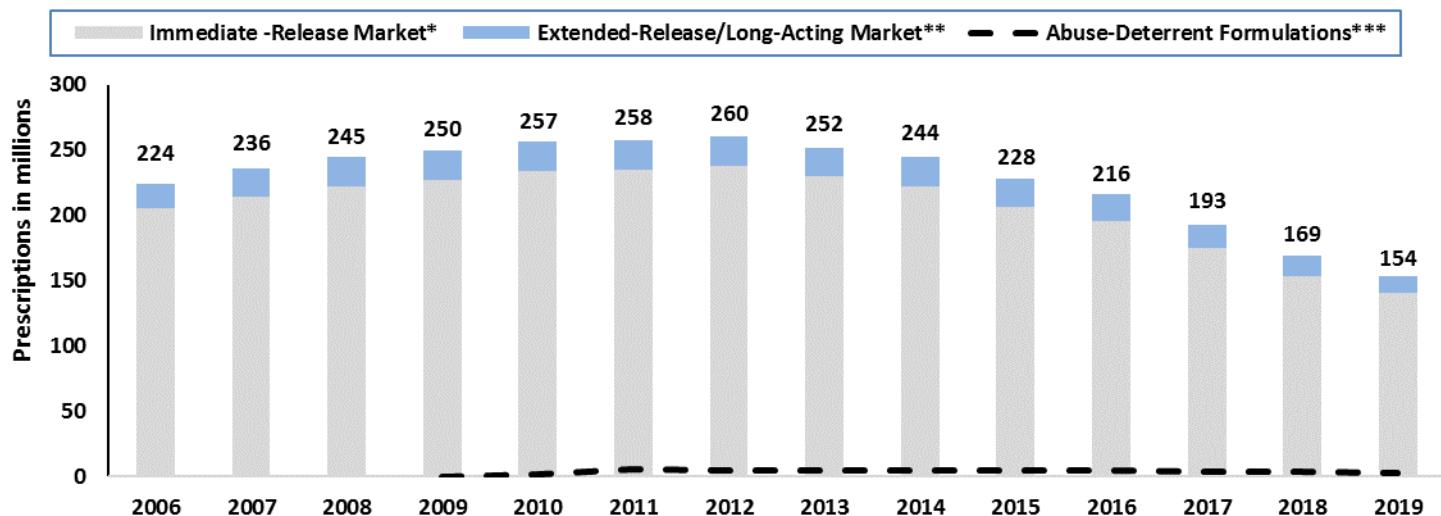
[6] Source: IQVIA National Sales Perspectives™ 2019. Data extracted February 2020. File: NSP Oxycodone ER distribution 2019. 02.24.2020.xlsx

4.1.1 Opioid Analgesics

Figure 1 shows the estimated number of prescriptions dispensed for all opioid analgesics (single and combination products), stratified by formulation (immediate-release, extended-release, and abuse-deterrent) from U.S. outpatient retail pharmacies from January 2006 through December 2019. The total utilization of opioid analgesics peaked in 2012 with 260 million prescriptions then declined by 41% to 154 million prescriptions in 2019. Immediate-release (IR) formulations accounted for 91% and extended-release/long-acting (ER/LA) formulations accounted for 9% of the total opioid analgesic prescriptions dispensed in 2019.

The utilization of IR opioid analgesic prescriptions peaked in 2012 (238 million prescriptions) followed by a 41% steady decline in 2019 (141 million prescriptions). The utilization of ER/LA products was highest (23 million prescriptions) in 2010 with a decline of 43% by 2019 (13 million prescriptions). Abuse-deterrent formulations were introduced to the market in 2009. The utilization of ADF formulations peaked in 2011 (5.6 million prescriptions), followed by a decline of 51% (to 2.7 million prescriptions) in 2019.

Figure 1: Estimated number of prescriptions dispensed for all opioid analgesics from U.S outpatient retail pharmacies, 2006-2019

Source: IQVIA, National Prescription Audit (NPA) and static data 2006-2011. January 2006-December 2019.
Static data extracted March 2017, 2012-2017 data extracted February 2018, 2018 data extracted March 2019, 2019 data extracted Jan 24, 2020
*Immediate-Release formulations include oral solids, oral liquids, rectal, nasal, and transmucosal formulations
**Extended-Release/Long-Acting formulations include oral solids and transdermal patches
***Abuse-deterrent formulation opioid products include Arymo ER, Embeda ER, Hysingla ER, Morphabond ER, Xtampza ER, OxyContin ER Reformulated (Approval in April 2010), RoxyBond IR
Note: These data include non-injectable opioid analgesics only. Opioid-containing cough-cold products and opioid-containing medication-assisted treatment (MAT) products are not included.

4.1.2 Schedule-II Opioid Analgesics

Figure 2 and Table 2 in Appendix B show the estimated number of dispensed prescriptions for schedule-II opioid analgesics, stratified by molecule from U.S. outpatient retail pharmacies from 2006 through 2019. The utilization of schedule-II opioid analgesics peaked in 2011 with 208 million prescriptions followed by a 47% decline by 2019 (111 million prescriptions). Hydrocodone IR combination products accounted for the highest proportion of use (53%, 57 million prescriptions) followed by the oxycodone IR combination products (21%, 23 million prescriptions) and single-ingredient oxycodone IR (14%, 16 million prescriptions) in 2019.

Hydrocodone IR combination prescriptions declined by 56% from a peak of 131 million prescriptions in 2011 to 57 million prescriptions in 2019. Similar patterns were observed for the oxycodone IR combination products with a 38% decline. In contrast, single-ingredient oxycodone IR increased throughout the study period, from 4 million prescriptions in 2006 to 16 million prescriptions in 2019.

Figure 2: Estimated number of dispensed prescriptions for schedule-II opioid analgesics, stratified by molecule from U.S. outpatient retail pharmacies from 2006 through 2019, annually

Source: IQVIA, National Prescription Audit (NPA) and static data 2006-2014. recent data January 2015-December 2019.
Note: These data include non-injectable opioids only. Opioid-containing cough-cold products and opioid-containing medication-assisted treatment (MAT) products are not included.
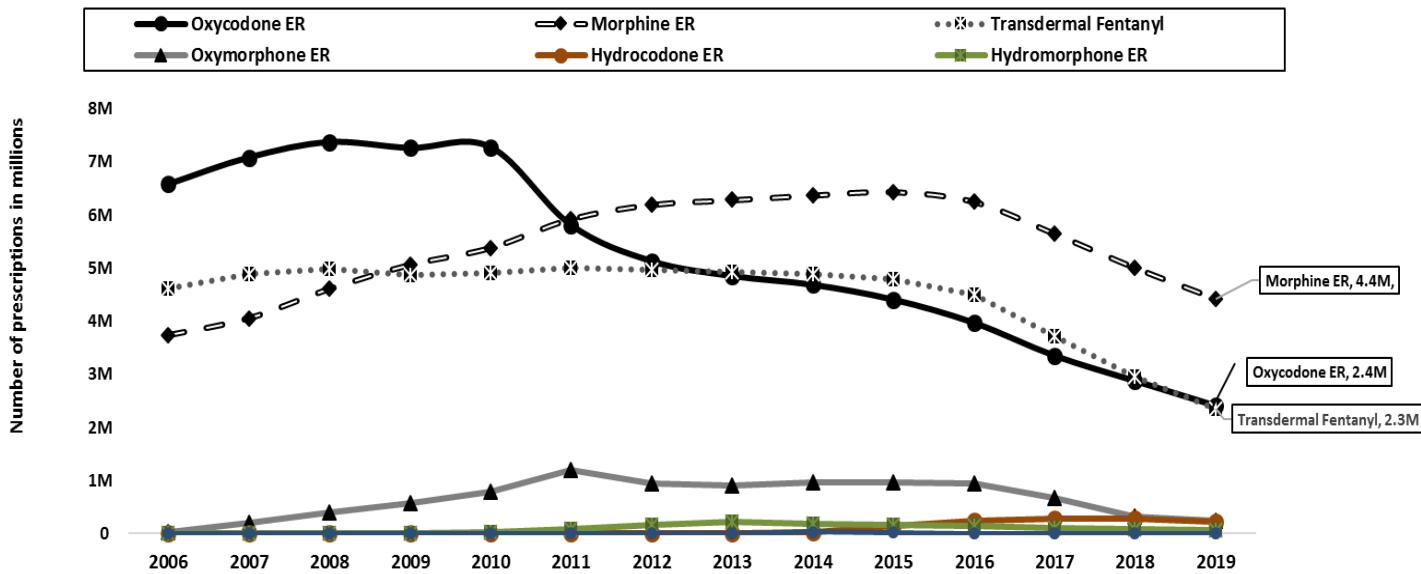
4.1.3 Schedule-II Extended-Release/Long-Acting Opioid Analgesics

Figure 3 and Table 3 in Appendix B show the estimated number of prescriptions dispensed for schedule-II ER/LA opioid analgesics, stratified by molecule from U.S. outpatient retail pharmacies from 2006 through 2019. The utilization of ER/LA opioid analgesics peaked in 2010 with 18.4 million prescriptions dispensed then declined by 47% to 9.8 million prescriptions dispensed in 2019.

Morphine ER accounted for 46% (4 million prescriptions), followed by oxycodone ER (25%, 2.4 million prescriptions) and transdermal fentanyl (24%, 2.3 million prescriptions) of the estimated total number of prescriptions dispensed for schedule II opioid analgesics in 2019. Oxycodone ER prescriptions decreased by 67% from a peak of 7.4 million prescriptions in 2008. Morphine ER prescriptions peaked to 6.4 million in 2015 and declined by 31% in 2019. The utilization of transdermal fentanyl patches remained consistent from 2006-2016 (4.6-4.9 million prescriptions), but thereafter declined by 53% in 2019.

Figure 3: Estimated number of dispensed prescriptions for schedule-II ER/LA opioid analgesics, stratified by molecule from U.S. outpatient retail pharmacies from 2006 through 2019, annually

**Oxycodone ER** ⬥ ◇ **Morphine ER** ⊡ **Transdermal Fentanyl**
Oxymorphone ER **Hydrocodone ER** **Hydromorphone ER**

Number of prescriptions in millions

8M
7M
6M
5M
4M
3M
2M
1M
0

2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019

Morphine ER, 4.4M,
Oxycodone ER, 2.4M
Transdermal Fentanyl, 2.3M
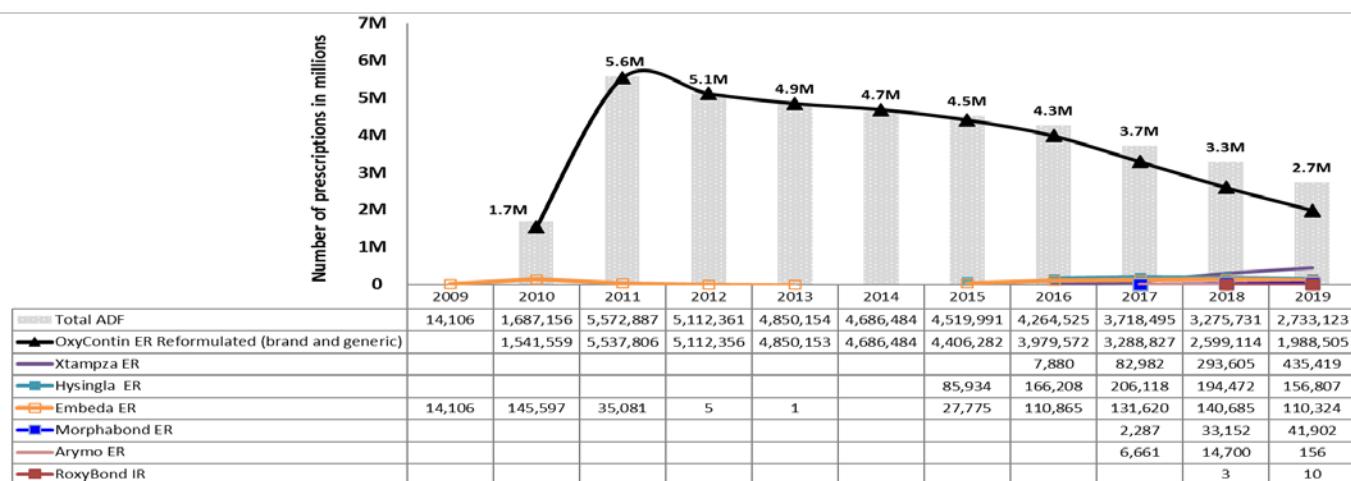
Source: IQVIA, National Prescription Audit (NPA) and static data 2006-2014. recent data January 2014-December 2019.

4.1.4 Abuse-Deterrent Formulations of Opioid Analgesics

Figure 4 shows the estimated number of prescriptions dispensed for abuse-deterrent formulations (ADFs) of opioid analgesics, stratified by product from U.S. outpatient retail pharmacies from 2009 through 2019. An estimated 5.6 million prescriptions were dispensed for abuse-deterrent opioid analgesics which peaked in 2011 then decreased by 51% to approximately 2.7 million prescriptions in 2019. Of these prescriptions, reformulated oxycodone ER accounted for the largest proportion of ADF opioid analgesics with 5.5 million prescriptions in 2011 then decreased by 64% to approximately 2 million prescriptions in 2019. Reformulated oxycodone ER accounted for 73% of dispensed prescriptions in 2019, followed by Xtampza ER (16%), Hysingla ER (6%), Embeda ER (4%) and other ADF products (2% or less).

Figure 4: Estimated number of prescriptions dispensed for abuse-deterrent formulations (ADFs) of opioid analgesics* from U.S. outpatient retail pharmacies from 2009-2019, yearly

Number of prescriptions in millions

7M
6M
5M
4M
3M
2M
1M
0

2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019

1.7M 5.6M 5.1M 4.9M 4.7M 4.5M 4.3M 3.7M 3.3M 2.7M

|	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Total ADF	14,106	1,687,156	5,572,887	5,112,361	4,850,154	4,686,484	4,519,991	4,264,525	3,718,495	3,275,731	2,733,123
OxyContin ER Reformulated (brand and generic)		1,541,559	5,537,806	5,112,356	4,850,153	4,686,484	4,406,282	3,979,572	3,288,827	2,599,114	1,988,505
Xtampza ER								7,880	82,982	293,605	435,419
Hysingla ER							85,934	166,208	206,118	194,472	156,807
Embeda ER	14,106	145,597	35,081	5	1		27,775	110,865	131,620	140,685	110,324
Morphabond ER									2,287	33,152	41,902
Arymo ER									6,661	14,700	156
RoxyBond IR										3	10

Source: IQVIA, National Prescription Audit (NPA) and static January 2009-December 2019.
Static data extracted March 2017 2012-2017 data extracted February 2018, 2018 data extracted March 2019, 2019 data extracted Jan 24, 2019
.

4.1.5 All Oxycodone (IR, ER and combination) Products

Figure 5 and Table 4 in Appendix B show the estimated number of prescriptions dispensed for all oxycodone (IR, ER and combination), stratified by product from U.S. outpatient retail pharmacies from 2006 through 2019. During the examined time period, oxycodone IR (single-ingredient and combination) accounted for 94% of the total prescriptions and oxycodone ER accounted for 6% of the total prescriptions. The total utilization of oxycodone IR increased 13% during the examined time-period with the highest proportions of prescriptions dispensed (59% of the total oxycodone prescriptions) in 2019. Single-ingredient oxycodone IR accounted for 41% of the total utilization. The utilization of oxycodone ER decreased 67% from 7.4 million prescriptions in 2008 to 2.4 million prescriptions dispensed in 2019.

Figure 5: Estimated number of prescriptions dispensed for all oxycodone (IR, ER, and combination) products from U.S. outpatient retail pharmacies from 2006-2019, yearly
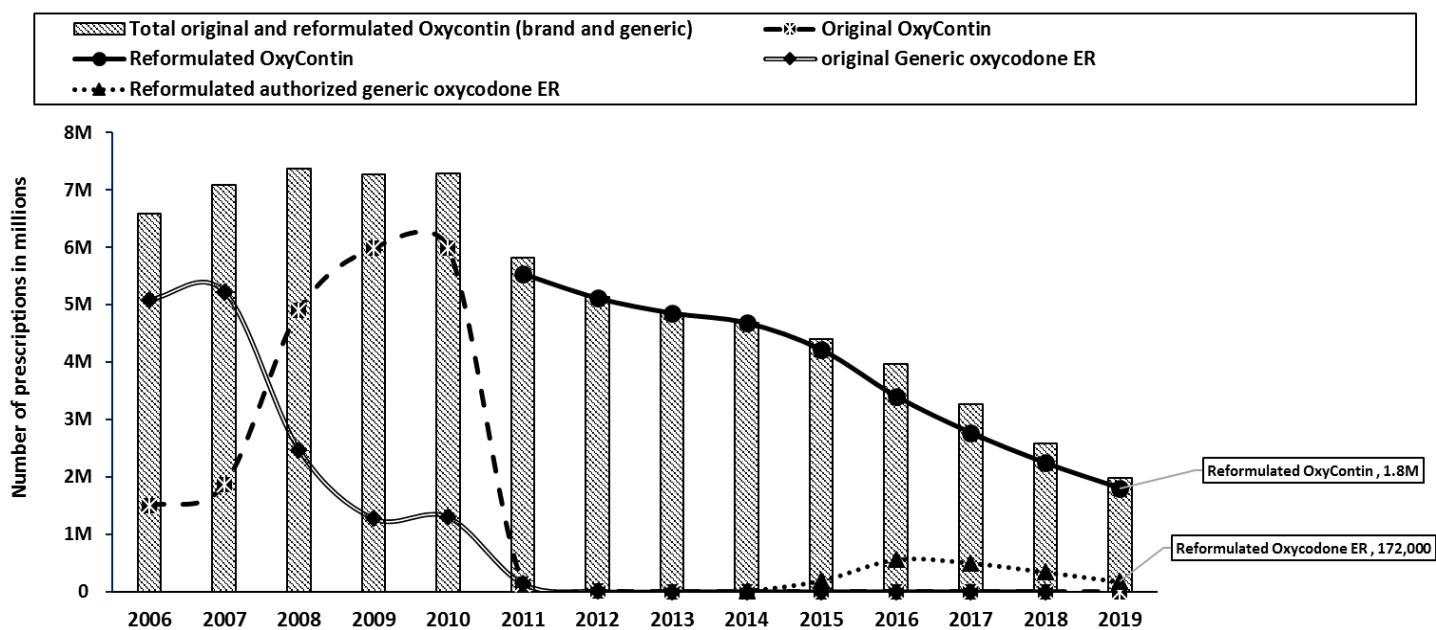
Source: IQVIA National Prescription Audit™ (NPA) 2019. Data extracted Feb 2020. File: NPA Oxycodone ER and comparators by prescriptions 2006-2019. 02.15.2020.xlsx

4.1.6 Oxycodone ER- brand and generics

Figure 6 below and Table 5 in Appendix B show the estimated number of prescriptions dispensed for original OxyContin, reformulated OxyContin, original generic oxycodone ER and reformulated authorized generic oxycodone ER, from U.S. outpatient retail pharmacies from 2006 through 2019.

In August 2010, distribution of the original formulation of OxyContin ceased and reformulated OxyContin became available in the market. As a result, prescriptions for OxyContin original formulation dropped abruptly from 6 million prescriptions in 2010 to 136,000 prescriptions in 2011. The reformulated OxyContin accounted for approximately 5.5 million prescriptions in 2011, however, by 2019, decreased to 1.8 million prescriptions. The reformulated authorized generic oxycodone ER was introduced in 2014, utilization peaked in 2016 with 560,000 prescriptions then steadily declined to 172,000 prescriptions dispensed in 2019.

Figure 6: Estimated number of dispensed prescriptions for original and reformulated oxycodone ER products from U.S. outpatient retail pharmacies from 2006 through 2019, annually
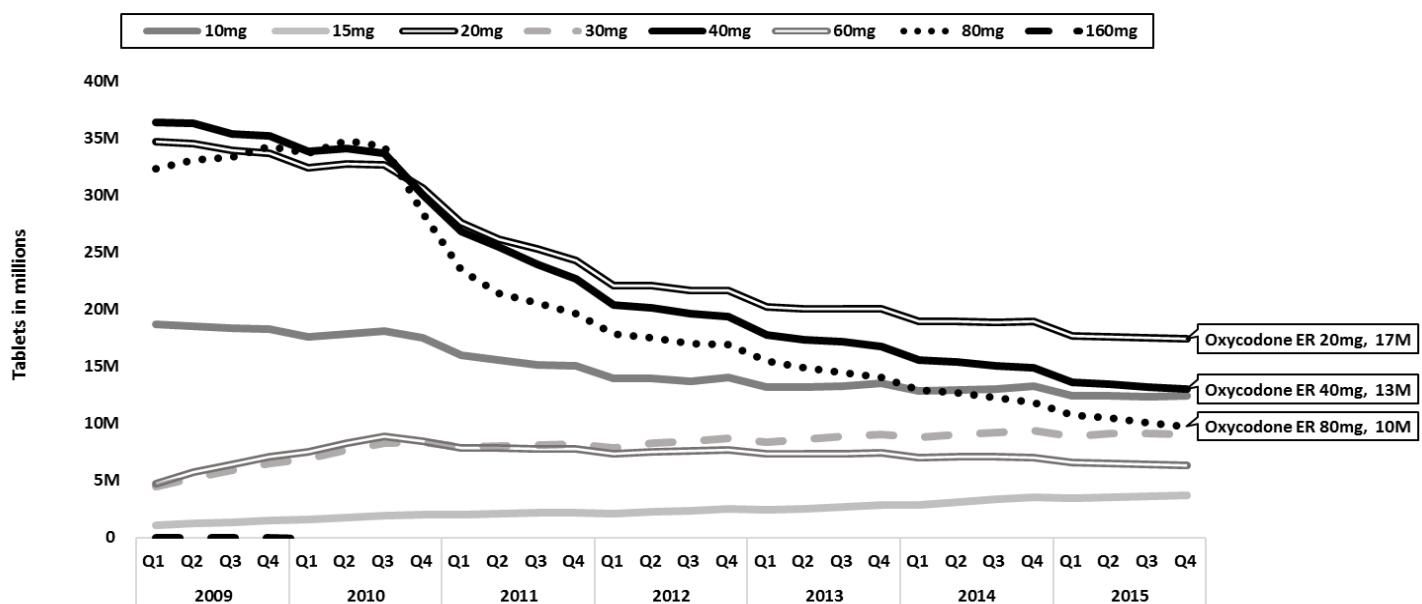

Source: IQVIA National Prescription Audit™ (NPA) 2019. Data extracted Feb 2020. File: NPA Oxycodone ER and comparators by prescriptions 2006-2019. 02.15.2020.xlsx

Figure 7 and Table 6 in Appendix B show the estimated number of tablets dispensed for original and reformulated oxycodone ER formulations from U.S. outpatient retail pharmacies stratified by strength from 2009 through 2015, quarterly. Approximately 72 to 138 million oxycodone ER tablets were dispensed quarterly from 2009 through 2015 with a peak of 138 million tablets in the third quarter of 2010. The highest number of tablets dispensed for the 20mg and 40mg strength was during the first quarter of 2009 with 35 million tablets and 36 million tablets, respectively. The highest number of tablets dispensed for the 80 mg strength was during the second quarter of 2010 with 35 million tablets.

During the fourth quarter of 2015, original and reformulated oxycodone ER 20 mg accounted for the most common strength dispensed (17 million tablets), which is a 50% decrease from its peak (35 million tablets) in the first quarter of 2009. Although, the total utilization of oxycodone ER decreased during the examined time period, the 10mg and 20mg strength remained the most commonly dispensed with 23% (6.4 million) and 26% (7.4 million) of the total tablets dispensed, respectively during the fourth quarter of 2019 (data not shown)[7]; 80mg oxycodone ER tablets accounted for 8% (2.3 million tablets) of the total tablets dispensed during the fourth quarter of 2019.

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[7] IQVIA National Prescription Audit™ (NPA) 2019. Data extracted Feb 2020. File: ADHOC data-Oxycodone ER - units by strengths 2009-2019. 02.18.2020.xlsx

Figure 7: Estimated number of tablets dispensed for original and reformulated oxycodone ER stratified by strength from U.S. outpatient retail pharmacies from 2009 through 2015, quarterly


Source: IQVIA National Prescription Audit™ (NPA) 2019. Data extracted Feb 2020. File: ADHOC data-Oxycodone ER - units by strengths 2009-2019. 02.18.2020.xlsx
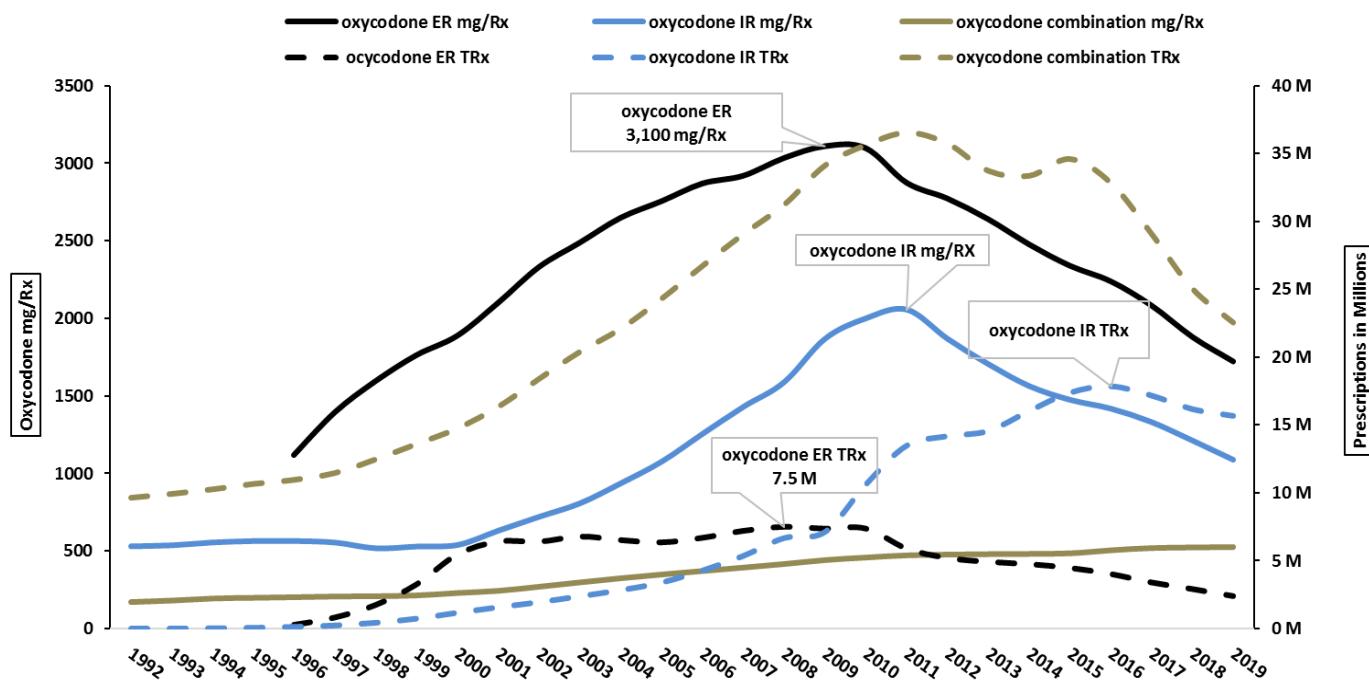
Figure 8 shows the estimated number of dispensed prescriptions and average milligrams per prescription (mg/Rx) for oxycodone (IR, ER, and combination) from U.S. outpatient retail pharmacies from 1992 through 2019, yearly. The aggregate average mg/Rx was calculated based on the estimated total number of mg of oxycodone dispensed per year divided by the aggregate estimated number of prescriptions dispensed per calendar year.

The aggregate average mg/Rx of oxycodone ER prescriptions decreased 45% from its peak of 3,100 mg/Rx in 2009 to 1700 mg/Rx in 2019 and the total number of prescriptions dispensed for oxycodone ER decreased 67% from its peak in 2008 (7.4 million prescription) to 2.4 million prescriptions in 2019.

For single-ingredient oxycodone IR products, the average mg/Rx decreased 47% from its peak of 2,000 mg/Rx in 2011 to 1,100 mg/Rx in 2019 and the total number of prescriptions dispensed decreased 12% from its peak in 2016 (17.9 million prescriptions) to 15.7 million prescriptions in 2019.

The average mg/Rx for combination oxycodone IR products has increased during the examined time to 524 mg/Rx by 2019; however, the total number of prescriptions dispensed for combination oxycodone IR products decreased 38% from its peak in 2011 (36.5 million prescriptions) to 22.6 million prescriptions in 2019.

Figure 8: Estimated number of prescriptions and yearly aggregate average milligram/prescriptions dispensed for oxycodone (IR, ER, and combination) from U.S. outpatient retail pharmacies from 1992 through 2019, yearly

Source: IQVIA National Prescription Audit™. 2019. Data extracted Feb 2020. File: MG Rx and MME graph with 2019 data oxycodone in kilograms 03.25.2020 (002).xlsx

4.2 PRESCRIBER SPECIALTIES

Table 7 shows the top prescriber specialties for oxycodone ER prescriptions dispensed from U.S. outpatient retail pharmacies in 2009 (original), 2012 (after reformulation), and 2019 (recent).

In 2019, mid-level practitioners (physician assistants/nurse practitioners) prescribed approximately 30% of the total oxycodone ER prescriptions dispensed, followed by FP/GP/IM (family practice/general practice/internal Medicine) at 26% and pain-medicine/anesthesiology at 22%. In contrast, FP/GP/IM accounted for the highest proportion of prescriptions followed by mid-level practitioners in 2009 and 2012. Although the number of prescriptions dispensed for oxycodone ER decreased during the examined time-period, the proportion of prescriptions written by pain medicine/ anesthesiologists increased from 14% to 22% of the total prescriptions dispensed in 2019.

Table 7: Top prescriber specialties of Oxycodone ER in 2009 (original), 2012 (after reformulation), and 2019 (recent), based on the estimated number of dispensed prescriptions from U.S. outpatient retail pharmacies
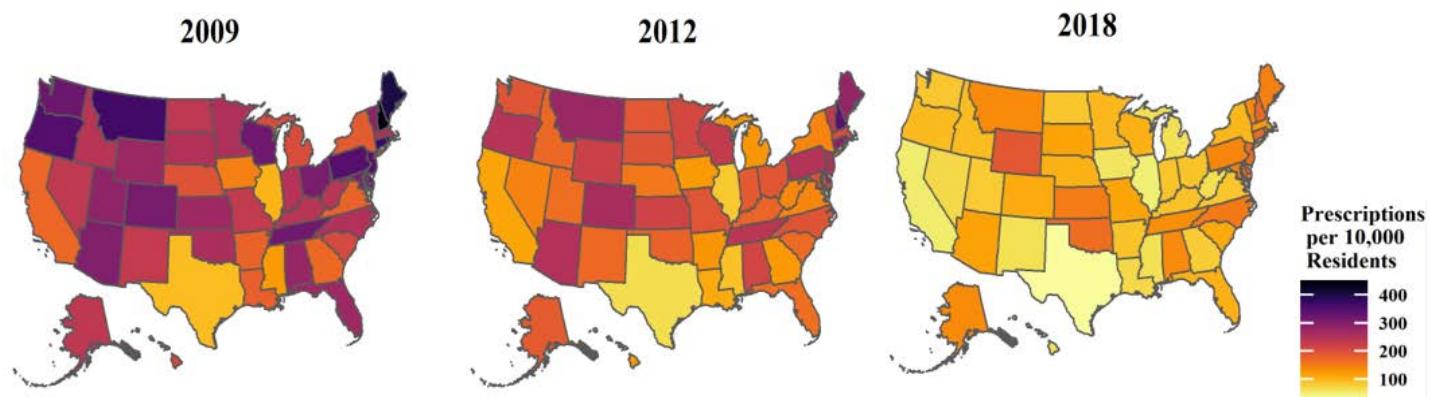
	2009		2012		2019	
	Rx (N)	*Share (%)*	**Rx (N)**	*Share (%)*	**Rx (N)**	*Share (%)*
Total oxycodone ER	**7,263,121**	*100%*	**5,148,478**	*100%*	**2,423,605**	*100.0%*
Physician Assistants/Nurse Practitioners	**662,957**	*9.1%*	749,257	*14.6%*	**716,834**	*29.6%*
Family Practice/General Practice/Internal Medicine	**3,132,887**	*43.1%*	1,939,505	*37.7%*	**627,461**	*25.9%*
Pain Medicine/Anesthesiology	1,039,697	*14.3%*	844,602	*16.4%*	530,063	*21.9%*
Physical Medicine & Rehab	630,075	*8.7%*	489,882	*9.5%*	249,731	*10.3%*
Oncology	279,665	*3.9%*	212,015	*4.1%*	77,983	*3.2%*
Neurology	206,661	*2.8%*	127,385	*2.5%*	44,578	*1.8%*
Orthopedic Surgery	305,232	*4.2%*	210,027	*4.1%*	31,763	*1.3%*
Specialty Unspecified	150,094	*2.1%*	94,305	*1.8%*	11,790	*0.5%*
All Others	855,851	*11.8%*	481,499	*9.4%*	133,403	*5.5%*

Source: IQVIA National Prescript ion Audit™. 2019. Data extracted Feb 2020. File: Updated-NPA top 10-Speciality and ADHOC-Oxycodone ER 2015-2019 Retail only Feb-11-2020

4.3 OXYCODONE ER PRESCRIPTIONS PER 10,000 RESIDENTS

Figure 9 below and Table 8 in Appendix B show the number of dispensed prescriptions of oxycodone ER per 10,000 residents from U.S outpatient retail pharmacies stratified by U.S states in 2009, 2012 and 2018. In 2009, oxycodone ER prescriptions ranged from 93-439 prescriptions per 10,000 residents per state. The number of prescriptions dispensed for oxycodone ER were highest in Rhode Island, New Hampshire and Maine in 2009 with over 400 prescriptions per 10,000 residents. In 2012, the oxycodone ER Prescriptions ranged from 83-340 prescriptions per 10,000 residents. The highest prescription to resident ratio remained in Rhode Island, New Hampshire and Maine. By 2018, the utilization of oxycodone ER decreased, ranging from 33-188 prescription per 10,000 residents with the highest prescription to resident ratio in Wyoming, Delaware and New Hampshire.

Figure 9: **Estimated number of Prescriptions dispensed for oxycodone ER per 10,000 residents from U.S. outpatient retail pharmacies in 2009[8], 2012[9] and 2018[10]**

Source: Symphony Health PHAST Prescription Monthly. Data extracted April 2020 File: SHS Oxycodone ER Geo Map by Prescriptions and residents 2009-2012 and 2018. 04.15.2020.xlsx

5   DISCUSSION

This review examined the outpatient retail utilization of oxycodone ER, IR and combination products, schedule-II opioid analgesic and abuse-deterrent opioid analgesics, with a focus on single-ingredient original and reformulated oxycodone ER to provide background for the Advisory Committee discussion.

Findings from our analysis showed the utilization of oxycodone ER decreased by 67% from a peak of 7.4 million prescriptions in 2008 to 2.4 million prescriptions dispensed in 2019. Oxycodone ER accounted for 6% of oxycodone prescriptions and oxycodone IR (single-ingredient and combination) accounted for 94% of oxycodone prescriptions in 2019. Reformulated OxyContin was approved in April 2010 along with a withdrawal of the distribution of original formulation of OxyContin resulting in abrupt drop of prescriptions dispensed for OxyContin original formulation.

In addition to a decline in the number of prescriptions dispensed, the strength and dosage of oxycodone ER prescriptions also decreased in recent years. Similar to the peak in the number of prescriptions dispensed for oxycodone ER in 2008, the aggregate average mg/Rx for oxycodone ER was highest in 2009 at 3,100 mg/Rx before decreasing to 1700 mg/Rx in 2019. This finding is in line with patterns in the most common strengths of oxycodone ER dispensed over time. The most common strengths of oxycodone ER tablets were dispensed for 40 mg and 80 mg during the fourth quarter of 2009. However,

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[8] 2009: U.S. Census Bureau; American Community Survey, 2009 American Community Survey 1-Year Estimates. Accessed January 2020.

[9] 2012: Annual Estimates of the Resident Population by Single Year of Age and Sex for the United States, States, and Puerto Rico Commonwealth: April 1, 2010 to July 1, 2012: Source: U.S. Census Bureau, Population Division Release Date: June 2013

[10] 2018: Annual Estimates of the Resident Population by Single Year of Age and Sex for the United States, States, and Puerto Rico Commonwealth: April 1, 2010 to July 1, 2018. Source: U.S. Census Bureau, Population Division Release Date: June 2019

this trend changed by the fourth quarter of 2019, where oxycodone ER 20 mg accounted for the highest proportions of all strengths.

Mid-level practitioners were the top-prescribing specialties of the total oxycodone ER prescriptions, followed by FP/GP/IM (Family Practice/General Practice/Internal Medicine) in 2019. Of note, FP/GP/IM accounted for the highest proportion of prescriptions followed by mid-level practitioners in 2009 and 2012. This change in the type of providers writing for oxycodone is likely due to the changes increasing prescriptive authority for mid-level practitioners as well as the increasing number of mid-level practitioners providing care. Changes include the American Medical Association (AMA) nurse practitioner prescriptive authority in 2017 that allows prescriptive authority to nurse practitioners for drugs falling into schedule II[11]. In addition, although the number of prescriptions dispensed for oxycodone ER decreased during the examined time-period (2009, 2012 and 2019), the proportion of prescriptions written by pain medicine/anesthesiologists increased for the total prescriptions dispensed in 2019.

Although the decline in utilization of oxycodone ER began after 2008 and continued after reformulation, there were changes in the patterns of oxycodone ER such as the decrease in mg/Rx and lower utilization of the higher strength formulations. The decrease of utilization of oxycodone ER formulation may due to several reasons including the strengthening of warnings on the drug label, expanding patient and prescriber educational campaigns, interventions implemented by federal, state, local governments, recommended limitations on opioid dosages, payer-based dispensing restrictions, prescription drug monitoring programs (PDMP), risk evaluation mitigation strategies (REMS) and issuing guidance for the pharmaceutical industry regarding the development of abuse-deterrent formulations of opioid products in addition to many other interventions.[12]

6 CONCLUSION

After the introduction of ADFs in 2009, utilization of oxycodone ER prescriptions decreased 67% by 2019. Similarly, in terms of dosing, the peak of average mg of oxycodone/prescription of oxycodone ER was observed in 2009 with 3100mg/Rx followed by a decline to 1700mg/Rx in 2019. The most common strengths of oxycodone ER tablets were dispensed for 40 mg and 80 mg during the fourth quarter of 2009. By the fourth quarter of 2019 oxycodone ER 20 mg accounted for the highest proportions of all strengths.

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[11] Nurse Practitioner Prescriptive Authority. (n.d.). Retrieved from https://nursinglicensemap.com/resources/nurse-practitioner-prescriptive-authority/

[12] Chai, Grace. "New Opioid Analgesic Approvals and Outpatient Utilization of Opioid Analgesics in the United States, 1997 through 2015." *Anesthesiology | ASA Publications*, 1 May 2018, anesthesiology.pubs.asahq.org/article.aspx?articleid=2675976.

7 APPENDIX A DRUG UTILIZATION DATABASE DESCRIPTIONS

IQVIA National Sales Perspectives™ (NSP)

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and nonretail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. The manufacturer sales distribution data do not provide an estimate of direct patient use but do provide a national estimate of units sold from the manufacturer to various retail and non-retail settings of care. The amount of product purchased by these settings of care may be a possible surrogate for use if we assume that facilities purchase drugs in quantities reflective of actual patient use.

IQVIA National Prescription Audit™ (NPA)

The IQVIA National Prescription Audit (NPA) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over 3.7 billion prescription claims per year, captured from a sample of the universe of approximately 58,900 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 92% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 60 – 86% (varies by class and geography) of mail service pharmacies and approximately 75 – 83% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month. Due to the changing pharmaceutical marketplace, IQVIA has implemented changes to its prescription database to manage prescription voids, reversals, and abandonments that span multiple weeks. Beginning in January 2019, IQVIA has projected published prescription volumes dispensed from the retail pharmacies based on sold date, instead of date of adjudication (i.e., fill date). Projected estimates have been adjusted and restated in the database to January 2017, data prior to 2017 remain unadjusted. As a result, a trend break occurs between 2016 and2017 prescription volumes dispensed from the retail pharmacies, any changes over time must be interpreted in the context of the changes in the underlying data and methodology.

Dispensed prescription estimates are nationally projected based on a sample of prescriptions claims from mail-order/ specialty and retail pharmacies. Summarization of these projected estimates across time periods and/or settings of care may lead to differences in prescription count due to rounding attributable to the projection methodology utilized. No statistical tests were performed on these estimates to determine statistically significant changes over time. Therefore, all changes over time should be considered approximate, and may be due to random error.

Findings from this review should be interpreted within the context of the known limitations of the databases used. Dispensed prescription estimates are nationally projected based on a sample of

prescriptions claims from U.S. retail pharmacies. Summarization of these projected estimates across time periods and/or products may lead to differences in prescription count due to rounding attributable to the projection methodology utilized. Moreover, the utilization patterns of opioid analgesics in the retail setting might not represent the utilization patterns in other settings of care such as inpatient and clinic settings, which were not examined in this review.

PHAST™ *Prescription Monthly*

PHAST Prescription Monthly is a syndicated view of U.S. retail and mail order pharmacy prescription activity, updated on a monthly basis. PHAST Prescription Monthly covers over 65,000 pharmacies in the sample including retail, mail order, specialty and other non-retail outlets. The dispensed prescriptions in the sample represent approximately 92% of all U.S. retail prescriptions (cash, Medicaid, commercial) as well as 69% of all U.S. mail order prescriptions. The retail and mail order prescriptions are projected to the national level.

8 APPENDIX B DRUG UTILIZATION TABLES

Table 2: Estimated number of dispensed prescriptions for schedule-II opioid analgesics, stratified by molecule from U.S. outpatient retail pharmacies from 2006 through 2019, annually

	2006		2007		2008		2009		2010		2011		2012	
	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)
Total Oxycodone ER	**6,580,531**	*100%*	**7,084,898**	*100%*	**7,373,310**	*100%*	**7,263,667**	*100%*	**7,281,009**	*100%*	**5,811,684**	*100%*	**5,131,465**	*100%*
Oxycontin Original	1,492,308	22.7%	1,870,454	26.4%	4,905,290	66.5%	5,990,029	82.5%	5,984,113	82.2%	135,709	2.3%	14,002	0.3%
Oxycontin Reformulated	--	--	--	--	--	--	--	--	--	--	5,537,806	95.3%	5,112,356	99.6%
Oxycodone ER Original	5,088,223	77.3%	5,214,444	73.6%	2,468,020	33.5%	1,273,638	21.3%	1,296,896	17.8%	138,169	2.4%	5,107	0.1%
Oxycodone ER Reformulated	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Xtampza ER	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Other Opioid C II Analgesics	**155,553,040**	*100%*	**166,782,957**	*100%*	**175,600,653**	*100%*	**183,573,025**	*100%*	**192,401,829**	*100%*	**202,158,019**	*100%*	**201,792,766**	*100%*
Hydrocodone IR Combination	109,458,295	70.4%	116,028,774	69.6%	120,045,910	68.4%	123,560,313	67.3%	126,486,873	65.7%	130,931,707	64.8%	130,755,781	64.8%
Oxycodone IR Combination	26,880,965	17.3%	29,168,003	17.5%	31,294,342	17.8%	34,173,202	18.6%	35,660,363	18.5%	36,546,292	18.1%	35,737,524	17.7%
Oxycodone IR	4,277,980	2.8%	5,347,486	3.2%	6,650,239	3.8%	7,097,660	3.9%	10,576,205	5.5%	13,427,054	6.6%	14,108,130	7.0%
Morphine ER	3,738,260	2.4%	4,058,238	2.4%	4,612,829	2.6%	5,067,499	2.8%	5,386,291	2.8%	5,930,760	2.9%	6,198,303	3.1%
Transdermal Fentanyl	4,619,907	3.0%	4,886,973	2.9%	4,987,252	2.8%	4,866,117	2.7%	4,912,480	2.6%	4,997,384	2.5%	4,961,133	2.5%
Hydromorphone IR	1,541,318	1.0%	1,790,722	1.1%	2,052,870	1.2%	2,408,979	1.3%	2,595,238	1.3%	2,912,786	1.4%	3,086,274	1.5%
Morphine IR	1,204,302	0.8%	1,295,979	0.8%	1,431,924	0.8%	1,581,532	0.9%	1,687,895	0.9%	1,793,771	0.9%	1,845,083	0.9%
Methadone*	3,425,724	2.2%	3,637,978	2.2%	3,760,772	2.1%	3,863,991	2.1%	3,935,176	2.0%	3,938,607	1.9%	3,725,332	1.8%
Oxymorphone ER	21,375	<0.1%	196,975	0.1%	400,138	0.2%	582,710	0.3%	786,827	0.4%	1,196,953	0.6%	939,908	0.5%
Hydrocodone ER	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Oxymorphone IR	8,927	<0.1%	62,409	<0.1%	113,167	0.1%	165,094	0.1%	180,894	0.1%	239,560	0.1%	163,380	0.1%
Hydromorphone ER	1	<0.1%	1	<0.1%	--	--	2	<0.1%	27,011	<0.1%	95,823	<0.1%	170,654	0.1%
Transmucosal Fentanyl	375,986	0.2%	309,419	0.2%	251,210	0.1%	205,926	0.1%	166,576	0.1%	147,322	0.1%	101,264	0.1%
Acetaminophen/Oxycodone ER	--	--	--	--	--	--	--	--	--	--	--	--	--	--
All Others C II	--	--	--	--	--	--	--	--	--	--	--	--	--	--

	2013		2014		2015		2016		2017		2018		2019	
	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)
Total Oxycodone ER	**4,851,762**	*100%*	**4,686,915**	*100%*	**4,406,612**	*100%*	**3,970,627**	*100%*	**3,351,303**	*100%*	**2,875,446**	*100%*	**2,408,210**	*100%*
Oxycontin Original	1,327	<0.1%	293	<0.1%	227	<0.1%	83	<0.1%	33	<0.1%	39	<0.1%	14	<0.1%
Oxycontin Reformulated	4,850,153	100%	4,679,869	100%	4,214,781	95.6%	3,404,029	85.7%	2,769,866	82.7%	2,243,041	78.0%	1,803,717	74.9%
Oxycodone ER Original	282	<0.1%	138	<0.1%	103	<0.1%	76	<0.1%	24	<0.1%	1	<0.1	--	--
Oxycodone ER Reformulated	--	--	6,615	0.1%	191,604	4.3%	558,934	14.1%	499,580	14.9%	340,981	11.9%	172,160	7.1%
Xtampza ER	--	--	--	--	--	--	7,880	0.2%	82,982	2.5%	293,605	10.2%	435,419	18.1%
Other Opioid C II Analgesics	**192,907,539**	*100%*	**183,651,757**	*100%*	**165,937,370**	*100%*	**156,287,903**	*100%*	**139,190,290**	*100%*	**120,667,622**	*100%*	**108,866,618**	*100%*
Hydrocodone IR Combination	123,656,888	64.1%	113,397,454	61.7%	92,347,145	55.7%	84,899,055	54.3%	74,796,385	53.7%	64,041,349	53.1%	57,269,463	52.6%
Oxycodone IR Combination	33,718,084	17.5%	33,337,954	18.2%	34,573,991	20.8%	32,819,232	21.0%	29,065,659	20.9%	25,026,512	20.7%	22,561,496	20.7%
Oxycodone IR	14,513,238	7.5%	15,972,555	8.7%	17,317,048	10.4%	17,801,720	11.4%	17,135,194	12.3%	16,136,935	13.4%	15,691,229	14.4%
Morphine ER	6,288,088	3.3%	6,375,570	3.5%	6,441,121	3.9%	6,256,262	4.0%	5,651,221	4.1%	5,008,279	4.2%	4,426,406	4.1%
Transdermal Fentanyl	4,923,139	2.6%	4,881,447	2.7%	4,791,686	2.9%	4,502,576	2.9%	3,724,634	2.7%	2,963,377	2.5%	2,346,870	2.2%
Hydromorphone IR	3,044,891	1.6%	3,031,568	1.7%	3,011,224	1.8%	2,790,646	1.8%	2,452,803	1.8%	2,112,413	1.8%	1,915,093	1.8%
Morphine IR	1,869,195	1.0%	1,892,574	1.0%	1,888,174	1.1%	1,873,243	1.2%	1,798,190	1.3%	1,737,889	1.4%	1,646,865	1.5%
Methadone*	3,484,537	1.8%	3,242,281	1.8%	2,846,882	1.7%	2,591,013	1.7%	2,241,870	1.6%	1,918,665	1.6%	1,646,190	1.5%
Oxymorphone ER	901,307	0.5%	960,933	0.5%	968,029	0.6%	947,081	0.6%	667,401	0.5%	324,858	0.3%	238,006	0.2%
Hydrocodone ER	--	--	35,093	0.0%	149,957	0.1%	240,748	0.2%	274,804	0.2%	275,302	0.2%	227,124	0.2%
Oxymorphone IR	186,550	0.1%	212,113	0.1%	212,759	0.1%	209,437	0.1%	168,141	0.1%	117,095	0.1%	93,322	0.1%
Hydromorphone ER	226,452	0.1%	185,035	0.1%	160,632	0.1%	138,126	0.1%	115,219	0.1%	96,703	0.1%	72,200	0.1%
Transmucosal Fentanyl	95,170	<0.1	95,992	0.1%	90,556	0.1%	62,892	<0.1%	38,272	<0.1%	23,177	<0.1%	14,109	<0.1%
Acetaminophen/Oxycodone ER	--	--	31,188	<0.1	19,355	<0.1%	6,994	<0.1%	2,622	<0.1%	13	<0.1%	4	<0.1%
All Others C II	--	--	--	--	1,117,300	0.6%	1,218,764	0.8%	1,098,769	0.8%	908,245	0.8%	732,354	0.7%

Source: IQVIA National Prescript ion Audit™ 2019. Data extracted Feb 2020. File: NPA Oxycodone ER and comparators by prescriptions 2006-2019. 02.15.2020.xlsx
*Immediate molecules include will be oral solids, liquids, rectal, transmucosal and nasal products.

Table 3: Estimated number of dispensed prescriptions for schedule-II ER/LA opioid analgesics, stratified by molecule from U.S. outpatient retail pharmacies from 2006 through 2019, annually

	2006		2007		2008		2009		2010		2011		2012	
	Rx (N))	Share (%)	Rx (N))	Share (%)	Rx (N))	Share (%)	Rx (N))	Share (%)	Rx (N))	Share (%)	Rx (N))	Share (%)	Rx (N))	Share (%)
Total ER-LA	14,960,074	100%	16,227,085	100%	17,373,529	100%	17,779,995	100%	18,393,618	100%	18,032,604	100%	17,401,463	100%
Oxycodone ER	6,580,531	44.0%	7,084,898	43.7%	7,373,310	42.4%	7,263,667	40.9%	7,281,009	39.6%	5,811,684	32.2%	5,131,465	29.5%
Morphine ER	3,738,260	25.0%	4,058,238	25.0%	4,612,829	26.6%	5,067,499	28.5%	5,386,291	29.3%	5,930,760	32.9%	6,198,303	35.6%
Transdermal Fentanyl	4,619,907	30.9%	4,886,973	30.1%	4,987,252	28.7%	4,866,117	27.4%	4,912,480	26.7%	4,997,384	27.7%	4,961,133	28.5%
Oxymorphone ER	21,375	0.1%	196,975	1.2%	400,138	2.3%	582,710	3.3%	786,827	4.3%	1,196,953	6.6%	939,908	5.4%
Hydrocodone ER	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Hydromorphone ER	1	<0.1%	1	<0.1%	--	--	2	<0.1%	27,011	0.1%	95,823	0.5%	170,654	1.0%
Acetaminophen/Oxycodone ER	--	--	--	--	--	--	--	--	--	--	--	--	--	--

	2013		2014		2015		2016		2017		2018		2019	
	Rx (N))	Share (%)	Rx (N))	Share (%)	Rx (N))	Share (%)	Rx (N))	Share (%)	Rx (N))	Share (%)	Rx (N))	Share (%)	Rx (N))	Share (%)
Total ER-LA	17,190,748	100%	17,156,181	100%	16,937,392	100%	16,062,414	100%	13,787,204	100%	11,543,978	100%	9,718,820	100%
Oxycodone ER	4,851,762	28.2%	4,686,915	27.3%	4,406,612	26.0%	3,970,627	24.7%	3,351,303	24.3%	2,875,446	24.9%	2,408,210	24.8%
Morphine ER	6,288,088	36.6%	6,375,570	37.2%	6,441,121	38.0%	6,256,262	38.9%	5,651,221	41.0%	5,008,279	43.4%	4,426,406	45.5%
Transdermal Fentanyl	4,923,139	28.6%	4,881,447	28.5%	4,791,686	28.3%	4,502,576	28.0%	3,724,634	27.0%	2,963,377	25.7%	2,346,870	24.1%
Oxymorphone ER	901,307	5.2%	960,933	5.6%	968,029	5.7%	947,081	5.9%	667,401	4.8%	324,858	2.8%	238,006	2.4%
Hydrocodone ER	--	--	35,093	0.2%	149,957	0.9%	240,748	1.5%	274,804	2.0%	275,302	2.4%	227,124	2.3%
Hydromorphone ER	226,452	1.3%	185,035	1.1%	160,632	0.9%	138,126	0.9%	115,219	0.8%	96,703	0.8%	72,200	0.7%
Acetaminophen/Oxycodone ER	--	--	31,188	0.2%	19,355	0.1%	6,994	0.1%	2,622	<0.1%	13	<0.1%	4	<0.1%

Source: IQVIA National Prescription Audit™ 2019. Data extracted Feb 2020. File: NPA Oxycodone ER and comparators by prescriptions 2006-2019. 02.15.2020.xlsx

Table 4: Estimated number of prescriptions dispensed for all oxycodone (IR, ER, and combination) products* from U.S. outpatient retail pharmacies from 2006-2019, yearly

	2006		2007		2008		2009		2010		2011		2012	
	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)
Total Oxycodone (ER,IR)	37,739,476	100%	41,600,387	100%	45,317,891	100%	48,534,529	100%	53,517,577	100%	55,785,030	100%	54,977,119	100%
Total Oxycodone IR	31,158,945	82.6%	34,515,489	83.0%	37,944,581	83.7%	41,270,862	85.0%	46,236,568	86.4%	49,973,346	89.6%	49,845,654	90.7%
Combination oxycodone IR	26,880,965	86.3%	29,168,003	84.5%	31,294,342	82.5%	34,173,202	82.8%	35,660,363	77.1%	36,546,292	73.1%	35,737,524	71.7%
Single ingredient Oxycodone IR	4,277,980	13.7%	5,347,486	15.5%	6,650,239	17.5%	7,097,660	17.2%	10,576,205	22.9%	13,427,054	26.9%	14,108,130	28.3%
Single ingredient Oxycodone ER	6,580,531	17.4%	7,084,898	17.0%	7,373,310	16.3%	7,263,667	15.0%	7,281,009	13.6%	5,811,684	10.4%	5,131,465	9.3%

	2013		2014		2015		2016		2017		2018		2019	
	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)
Total Oxycodone (ER,IR)	53,083,084	100%	53,997,424	100%	56,297,651	100%	54,591,579	100%	49,552,156	100%	44,038,893	100%	40,660,935	100%
Total Oxycodone IR	48,231,322	90.9%	49,310,509	91.3%	51,891,039	92.2%	50,620,952	92.7%	46,200,853	93.2%	41,163,447	93.5%	38,252,725	94.1%
Combination oxycodone IR	33,718,084	69.9%	33,337,954	67.6%	34,573,991	66.6%	32,819,232	64.8%	29,065,659	62.9%	25,026,512	60.8%	22,561,496	59.0%
Single ingredient Oxycodone IR	14,513,238	30.1%	15,972,555	32.4%	17,317,048	33.4%	17,801,720	35.2%	17,135,194	37.1%	16,136,935	39.2%	15,691,229	41.0%
Single ingredient Oxycodone ER	4,851,762	9.1%	4,686,915	8.7%	4,406,612	7.8%	3,970,627	7.3%	3,351,303	6.8%	2,875,446	6.5%	2,408,210	5.9%

Source: IQVIA National Prescript ion Audit™ 2019. Data extracted Feb 2020. File: NPA Oxycodone ER and comparators by prescriptions 2006-2019. 02.15.2020.xlsx

Table 5: Estimated number of dispensed prescriptions for original and reformulated single-ingredient oxycodone ER products from U.S. outpatient retail pharmacies from 2006 through 2019, annually

	2006		2007		2008		2009		2010		2011		2012	
	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)
Total Oxycodone ER	6,580,531	100%	7,084,898	100%	7,373,310	100%	7,263,667	100%	7,281,009	100%	5,811,684	100%	5,131,465	100%
Original Oxycontin	1,492,308	22.7%	1,870,454	26.4%	4,905,290	66.5%	5,990,029	82.5%	5,984,113	82.2%	135,709	2.3%	14,002	0.3%
ReformulatedOxyContin	--	--	--	--	--	--	--	--	--	--	5,537,806	95.3%	5,112,356	99.6%
OriginalOxycodone ER	5,088,223	77.3%	5,214,444	73.6%	2,468,020	33.5%	1,273,638	21.3%	1,296,896	17.8%	138,169	2.4%	5,107	0.1%
Reformulated Oxycodone ER	--	--	--	--	--	--	--	--	--	--	--	--	--	--

	2013		2014		2015		2016		2017		2018		2019	
	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)	Rx (N)	Share (%)
Total Oxycodone ER	4,851,762	100%	4,686,915	100%	4,406,612	100%	3,963,122	100%	3,269,503	100%	2,584,062	100%	1,975,891	100%
Original Oxycontin	1,327	<0.1%	293	<0.1%	227	<0.1%	83	<0.1%	33	<0.1%	39	<0.1%	14	<0.1%
ReformulatedOxyContin	4,850,153	100%	4,679,869	100%	4,214,781	95.6%	3,404,029	85.9%	2,769,866	84.7%	2,243,041	86.8%	1,803,717	91.3%
OriginalOxycodone ER	282	<0.1%	138	<0.1%	103	<0.1%	76	<0.1%	24	<0.1%	1	<0.1%	--	--
Reformulated Oxycodone ER	--	--	6,615	0.1%	191,604	4.3%	558,934	14.1%	499,580	15.3%	340,981	13.2%	172,160	8.7%

Source: IQVIA National Prescript ion Audit™ 2019. Data extracted Feb 2020. File: NPA Oxycodone ER and comparators by prescriptions 2006-2019. 02.15.2020.xlsx

Table 6: Estimated number of tablets dispensed for original and reformulated oxycodone ER from U.S. outpatient retail pharmacies stratified by strength from 2009 through 2015, quarterly

	Q1 2009		Q2 2009		Q3 2009		Q4 2009		Q1 2010		Q2 2010		Q3 2010		Q4 2010		Q1 2011		Q2 2011		Q3 2011		Q4 2011		Q1 2012		Q2 2012	
	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)
Total oxycodone ER	132,505,805	100%	134,802,018	100%	134,801,788	100%	136,654,349	100%	133,738,166	100%	137,311,178	100%	137,955,735	100%	125,561,460	100%	111,678,695	100%	106,483,233	100%	103,023,327	100%	99,874,203	100%	91,575,635	100%	91,760,339	100%
10mg	18,680,818	14.1%	18,567,406	13.8%	18,362,041	13.6%	18,281,516	13.4%	17,614,967	13.2%	17,859,341	13.0%	18,105,341	13.1%	17,515,022	13.9%	16,005,448	14.3%	15,580,710	14.6%	15,183,847	14.7%	15,048,308	15.1%	13,934,445	15.2%	13,919,112	15.2%
15mg	1,030,869	0.8%	1,207,329	0.9%	1,334,892	1.0%	1,488,899	1.1%	1,581,449	1.2%	1,756,149	1.3%	1,915,036	1.4%	2,021,613	1.6%	2,014,404	1.8%	2,072,004	1.9%	2,134,926	2.1%	2,149,742	2.2%	2,129,150	2.3%	2,247,260	2.4%
20mg	34,743,428	26.2%	34,530,151	25.6%	33,984,048	25.2%	33,730,274	24.7%	32,454,747	24.3%	32,780,756	23.9%	32,738,859	23.7%	30,696,833	24.4%	27,595,212	24.7%	26,164,883	24.6%	25,301,353	24.6%	24,316,776	24.3%	22,133,419	24.2%	22,082,121	24.1%
30mg	4,479,393	3.4%	5,254,306	3.9%	5,887,840	4.4%	6,529,547	4.8%	6,933,644	5.2%	7,675,931	5.6%	8,316,961	6.0%	8,322,998	6.6%	7,968,290	7.1%	7,991,254	7.5%	8,087,844	7.9%	8,216,571	8.2%	7,843,201	8.6%	8,271,963	9.0%
40mg	36,472,543	27.5%	36,375,563	27.0%	35,446,589	26.3%	35,203,605	25.8%	33,872,582	25.3%	34,152,347	24.9%	33,695,316	24.4%	30,062,723	23.9%	26,834,010	24.0%	25,464,081	23.9%	23,961,620	23.3%	22,683,104	22.7%	20,383,309	22.3%	20,158,301	22.0%
60mg	4,745,604	3.6%	5,709,349	4.2%	7,073,594	5.2%	7,544,048	5.6%	8,300,162	6.0%	8,914,896	6.5%	8,439,668	6.7%	7,823,578	7.0%	7,823,414	7.3%	7,788,913	7.6%	7,787,079	7.8%	7,328,254	8.0%	7,539,184	8.2%		
80mg	32,352,607	24.4%	33,157,402	24.6%	33,403,768	24.8%	34,346,774	25.1%	33,736,660	25.2%	34,786,493	25.3%	34,269,326	24.8%	28,502,501	22.7%	23,437,753	21.0%	21,386,886	20.1%	20,564,823	20.0%	19,672,554	19.7%	17,823,856	19.5%	17,542,398	19.1%
160mg	543	<0.1%	513	<0.1%	137	<0.1%	140	<0.1%	70	<0.1%	--	--	--	--	101	<0.1%	--	--	--	--	--	--	71	<0.1%	--	--	--	--

	Q3 2012		Q4 2012		Q1 2013		Q2 2013		Q3 2013		Q4 2013		Q1 2014		Q2 2014		Q3 2014		Q4 2014		Q1 2015		Q2 2015		Q3 2015		Q4 2015	
	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)	Tablets (N)	Share(%)
Total oxycodone ER	90,607,744	100%	90,989,388	100%	84,888,401	100%	84,082,151	100%	83,845,318	100%	83,697,522	100%	79,041,597	100%	79,188,320	100%	78,799,210	100%	78,927,041	100%	73,363,622	100%	73,097,627	100%	72,257,047	100%	71,828,740	100%
10mg	13,735,607	15.2%	14,067,362	15.5%	13,181,444	15.5%	13,183,319	15.7%	13,254,236	15.8%	13,575,163	16.2%	12,841,608	16.2%	12,920,640	16.3%	12,999,081	16.5%	13,324,134	16.9%	12,451,803	17.0%	12,439,963	17.0%	12,361,825	17.1%	12,456,498	17.3%
15mg	2,381,386	2.6%	2,487,634	2.7%	2,421,756	2.9%	2,549,808	3.0%	2,695,751	3.2%	2,837,717	3.4%	2,875,486	3.6%	3,109,727	3.9%	3,350,941	4.3%	3,556,296	4.5%	3,424,515	4.7%	3,511,835	4.8%	3,624,689	5.0%	3,725,655	5.2%
20mg	21,713,100	24.0%	21,716,640	23.9%	20,228,323	23.8%	20,101,575	23.9%	20,043,373	23.9%	20,034,723	23.9%	18,950,538	24.0%	18,982,899	24.0%	18,896,500	24.0%	18,943,734	24.0%	17,663,322	24.1%	17,634,174	24.1%	17,512,028	24.2%	17,427,750	24.3%
30mg	8,457,747	9.3%	8,696,078	9.6%	8,391,456	9.9%	8,594,325	10.2%	8,838,064	10.5%	9,033,879	10.8%	8,779,202	11.1%	9,024,403	11.4%	9,176,915	11.6%	9,342,997	11.8%	8,913,544	12.1%	9,102,994	12.5%	9,095,899	12.6%	9,079,383	12.6%
40mg	19,663,729	21.7%	19,400,623	21.3%	17,790,129	21.0%	17,356,876	20.6%	17,148,991	20.5%	16,734,712	20.0%	15,588,291	19.7%	15,387,245	19.4%	15,093,465	19.2%	14,855,640	18.8%	13,618,155	18.6%	13,461,938	18.4%	13,199,342	18.3%	13,015,243	18.1%
60mg	7,624,365	8.4%	7,728,269	8.5%	7,372,462	8.7%	7,373,693	8.8%	7,387,168	8.8%	7,401,824	8.8%	7,040,758	8.9%	7,095,383	9.0%	7,055,678	9.0%	7,022,187	8.9%	6,543,459	8.9%	6,491,818	8.9%	6,424,822	8.9%	6,371,327	8.9%
80mg	17,031,810	18.8%	16,892,782	18.6%	15,502,831	18.3%	14,922,555	17.7%	14,477,735	17.3%	14,079,505	16.8%	12,965,713	16.4%	12,668,023	16.0%	12,226,630	15.5%	11,882,054	15.1%	10,748,824	14.7%	10,454,906	14.3%	10,038,442	13.9%	9,752,883	13.6%
160mg	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

Table 8: **Estimated number of prescriptions dispensed for oxycodone ER per 10,000 residents from U.S. outpatient retail pharmacies in 2009[9], 2012[10] and 2018[11] (50 contiguous)**

	2009			2012			2018		
	Precriptions ((N)	Population	Prescriptions per 10,000 residents	Precriptions(N)	Population	Prescriptions per 10,000 residents	Precriptions (N)	Population	Prescriptions per 10,000 residents
Alabama	130,857	4,708,708	277	102,958	4,822,023	213	67,151	4,887,871	137
Alaska	16,528	698,473	236	13,567	731,449	185	10,122	737,438	137
Arizona	197,971	6,595,778	300	163,212	6,553,255	249	83,765	7,171,646	116
Arkansas	51,061	2,889,450	176	37,836	2,949,131	128	26,299	3,013,825	87
California	636,985	36,961,664	172	433,086	38,041,430	113	206,229	39,557,045	52
Colorado	155,963	5,024,748	310	135,173	5,187,582	260	61,453	5,695,564	107
Connecticut	130,714	3,518,288	371	104,723	3,590,347	291	60,111	3,572,665	168
Delaware	30,539	885,122	345	26,987	917,092	294	16,555	967,171	171
District of Columbia	16,102	599,657	268	13,022	632,323	205	7,680	702,455	109
Florida	504,796	18,537,969	272	316,205	19,317,568	163	220,734	21,299,325	103
Georgia	167,597	9,829,211	170	121,903	9,919,945	122	84,434	10,519,475	80
Hawaii	27,097	1,295,178	209	17,047	1,392,313	122	8,602	1,420,491	60
Idaho	37,544	1,545,801	242	27,269	1,595,728	170	16,481	1,754,208	93
Illinois	130,426	12,910,409	101	106,928	12,875,255	83	63,461	12,741,080	49
Indiana	158,015	6,423,113	246	121,518	6,537,334	185	58,851	6,691,878	87
Iowa	44,308	3,007,857	147	37,637	3,074,186	122	18,267	3,156,145	57
Kansas	76,310	2,818,747	270	62,266	2,885,905	215	43,943	2,911,505	150
Kentucky	104,083	4,314,113	241	75,997	4,380,415	173	39,649	4,468,402	88
Louisiana	80,768	4,492,076	179	50,007	4,601,893	108	32,423	4,659,978	69
Maine	52,783	1,318,301	400	37,456	1,329,192	281	19,505	1,338,404	145
Maryland	174,055	5,699,478	305	114,701	5,884,563	194	89,037	6,042,718	147
Massachusetts	165,614	6,593,587	251	134,262	6,646,144	202	84,992	6,902,149	123
Michigan	202,721	9,969,727	203	125,075	9,883,360	126	63,766	9,995,915	63
Minnesota	133,167	5,266,215	252	112,720	5,379,139	209	54,576	5,611,179	97
Mississippi	35,748	2,951,996	121	26,756	2,984,926	89	18,779	2,986,530	62
Missouri	137,593	5,987,580	229	116,070	6,021,988	192	69,906	6,126,452	114
Montana	35,636	974,989	365	27,637	1,005,141	274	14,599	1,062,305	137
Nebraska	34,975	1,796,622	194	28,923	1,855,525	155	19,833	1,929,268	102
Nevada	62,080	2,643,085	234	39,937	2,758,931	144	21,145	3,034,392	69
New Hampshire	58,013	1,324,575	437	44,956	1,320,718	340	23,128	1,356,458	170
New Jersey	298,961	8,707,740	343	218,915	8,864,590	246	148,390	8,908,520	166
New Mexico	46,392	2,009,671	230	35,523	2,085,538	170	13,247	2,095,428	63
New York	360,887	19,541,453	184	279,487	19,570,261	142	191,689	19,542,209	98
North Carolina	234,186	9,380,884	249	189,070	9,752,073	193	159,120	10,383,620	153
North Dakota	15,323	646,844	236	13,327	699,628	190	6,558	760,077	86
Ohio	356,382	11,542,645	308	221,272	11,544,225	191	102,530	11,689,442	87
Oklahoma	94,681	3,687,050	256	67,503	3,814,820	176	65,299	3,943,079	165
Oregon	133,079	3,825,657	347	95,475	3,899,353	244	39,964	4,190,713	95
Pennsylvania	434,041	12,604,767	344	314,597	12,763,536	246	180,508	12,807,060	140
Rhode Island	46,315	1,053,209	439	32,118	1,050,292	305	13,292	1,057,315	125
South Carolina	94,661	4,561,242	207	79,280	4,723,723	167	55,756	5,084,127	109
South Dakota	20,240	812,383	249	16,177	833,354	194	10,220	882,235	115
Tennessee	199,698	6,296,254	317	154,678	6,456,243	239	90,261	6,770,010	133
Texas	232,244	24,782,302	93	170,436	26,059,203	65	96,703	28,701,845	33
Utah	79,598	2,784,572	285	46,978	2,855,287	164	25,514	3,161,105	80
Vermont	17,968	621,760	288	14,439	626,011	230	8,716	626,299	139
Virginia	138,900	7,882,590	176	116,509	8,185,867	142	73,078	8,517,685	85
Washington	215,214	6,664,195	322	133,381	6,897,012	193	63,357	7,535,591	84
West Virginia	43,898	1,819,777	241	26,051	1,855,413	140	11,674	1,805,832	64
Wisconsin	179,769	5,654,774	317	131,369	5,726,398	229	60,284	5,813,568	103
Wyoming	14,901	544,270	273	12,704	576,412	220	10,915	577,737	188

Source: Symphony Health PHAST Prescription Monthly. Data extracted April 2020 File: SHS Oxycodone ER Geo Map by prescriptions and residents 2009-2012 and 2018. 04.15.2020.xlsx

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of OxyContin PMR Final Study Report 3051-1

Date:	August 2020
Reviewer(s):	Celeste Mallama, Ph.D., M.P.H., Epidemiology Reviewer Division of Epidemiology II
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Associate Office Director:	Judy Staffa, Ph.D., R.Ph., Associate Director for Public Health Initiatives Office of Surveillance and Epidemiology
Subject:	OxyContin Postmarketing Final Study Report 3051-1
Drug Name(s):	OxyContin (oxycodone hydrochloride extended-release)
Application Type/Number:	NDA 022272/IND 029038
Applicant/sponsor:	Purdue Pharma L.P.
OSE RCM #:	2018-1650

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ABBREVIATIONS:

-1y/3y: 1-year Period Before Reformulation (3Q2009-2Q2010) and 3-year Period After Reformulation (1Q2011-4Q2013), Excluding Transition Period

-2y/4y: 2-year Period Before Reformulation (3Q2008-2Q2010) and 4-year Period After Reformulation (1Q2011-4Q2014), Excluding Transition Period

ADF: Abuse Deterrent Formulation

AIC: Akaike Information Criteria

APAP: Acetaminophen (or Paracetamol)

ASI-MV®: Addiction Severity Index-Multimedia Version

CDC: Centers for Disease Control

CI: Confidence Interval

DEA: Drug Enforcement Administration

DEPI: Division of Epidemiology II

DUI: Driving Under the Influence

DWI: Driving While Intoxicated

ER: Extended Release

FDA: Food and Drug Administration

HIPAA: Health Insurance Portability and Accountability Act

IR: Immediate Release

ITS: Interrupted Time Series

LAAM: Levomethadyl Acetate

mg: Milligram

NA: Not Applicable

NAVIPPRO®: National Addictions Vigilance Intervention and Prevention Program

NDA: New Drug Application

NOS: Not Otherwise Specified

NPA: National Prescription Audit

NPDS: National Poison Data System

ORF: Reformulated OxyContin

PHI: Personal Health Information

PMR: Post-marketing Requirements

Q: Yearly quarter (3-month period)

RADARS®: Researched Abuse, Diversion, and Addiction-Related Surveillance System

REMS: Risk Evaluation and Mitigation Strategy

RORR: Ratio of Rate Ratios

SAP: Statistical Analysis Plan

SE: Single-entity

TANF: Temporary Assistance for Needy Families

TIRF: Transmucosal IR Fentanyl

US: United States

EXECUTIVE SUMMARY

Background

The objective of this review is to determine whether findings from Postmarketing Requirement (PMR) study 3051-1 (hereafter, PMR 3051-1) provide evidence that OxyContin®'s (hereafter, OxyContin) reformulation reduced non-oral abuse of Oxycontin among individuals being assessed for substance abuse treatment. As a secondary objective, the PMR assesses whether OxyContin's reformulation reduced overall abuse of OxyContin in this population.

This study was one of four studies the United States (US) Food and Drug Administration (FDA) required of Purdue Pharma (hereafter, the sponsor) to evaluate the impact of OxyContin's 2010 reformulation - with properties expected to deter abuse via the intranasal and injection routes - on "real-world" abuse and overdose associated with this product. Specifically, PMR study 3051-1 aimed to assess the effect of OxyContin's reformulation on rates of non-oral OxyContin abuse in an enriched convenience sample of individuals being assessed for or entering substance abuse treatment programs.

Overview of Study Methods

This study analyzed data from Inflexxion®'s (hereafter, Inflexxion) National Addictions Vigilance Intervention and Prevention Program® (hereafter, NAVIPPRO) Addiction Severity Index-Multimedia Version® (hereafter, ASI-MV) database and IQVIA National Prescription Audit™ (hereafter, IQVIA NPA). The NAVIPPRO ASI-MV is a proprietary surveillance system that collects data on substances used and abused by individuals being assessed for treatment of substance abuse disorders. The ASI-MV is a computerized standard clinical intake assessment used by a dynamic network of treatment centers and other types of facilities such as correctional institutions that assess individuals for substance abuse. The number and type of centers submitting intake assessments in this network is not static, but changes over time. Although it covers a wide geographic area, it is not nationally representative. The IQVIA NPA measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, and long-term care facilities into the hands of consumers via formal prescriptions in the US. Data from IQVIA were used in this study to estimate the number of dosage units dispensed for a product or product grouping in the study coverage area.

The main analyses used a pre-reformulation baseline period of July 2008 - June 2010, a 6-month transition period, and a post-reformulation period of January 2011 - December 2014. The study used a pre- vs. post-period "difference-in-differences" design, comparing changes in mean abuse rates and an interrupted time series (ITS) approach, comparing slope and immediate shift (i.e., level change) for OxyContin to those for a pre-specified set of comparator products. The study used three primary comparator opioids to approximate background trends in abuse rates (i.e., unrelated to the reformulation) to aid

in causal inference. Additional, secondary comparators were also included to provide contextual information and contribute to the overall interpretation of study findings.

This study provided descriptive data and used Poisson regression models to estimate and compare changes in rates of abuse of OxyContin and comparators. There is no single, standard scientifically agreed-upon denominator or modeling approach to estimate abuse rates. Therefore, the study generated estimates using a population-based model (model 1: number of ASI-MV assessments used as the denominator [i.e., offset]), a utilization-based model (model 2: dosage units dispensed used as the denominator), and utilization-adjusted (model 3: dosage units dispensed included as a covariate). In addition, due to the inherent uncertainties associated with these data and this design (e.g., potential for bias due to product misclassification, use of a dynamic study sample, confounding secular trends), a number of sensitivity analyses were conducted, including varying the time period, definition of an OxyContin abuse case (e.g., any OxyContin, any ER oxycodone, original/reformulated OxyContin), and site inclusion criteria (with main analyses using a smaller, consistent sample of sites and sensitivity analyses using a larger sample that changed over time). Together, these different models and sensitivity analyses were used to estimate a range of possible effect sizes and assess robustness of the overall study findings with regard to the effect of reformulation on abuse rates in this population.

Selected Key Study Findings

<u>Utilization data:</u> The average number of OxyContin tablets dispensed per month decreased 21% from the 2-year pre-period to the 4-year post-period. In contrast, the primary comparators ER morphine, IR hydrocodone and "other schedule II opioids" (a composite category composed of IR oxycodone and ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine), all showed increased utilization during the study period, as did secondary comparators IR oxycodone and ER oxymorphone. Methadone (prescribed for analgesia) was the only secondary comparator for which dispensing decreased.

<u>Descriptive trends:</u> Visual inspection of trends in quarterly non-oral abuse rates per 100 assessments for OxyContin and primary comparators (Figure A) showed a pre-period increase followed by an apparent sustained decrease in rates of non-oral abuse of OxyContin beginning 4Q2010. This sustained post-period decrease was not seen for primary comparators. OxyContin had higher levels of non-oral abuse than IR hydrocodone or ER morphine in the pre-period, but after reformulation and the subsequent decrease in the non-oral abuse rate, OxyContin had a non-oral abuse rate that was similar to these comparator opioids.

Figure A: Estimated quarterly rates of <u>non-oral abuse cases per 100 assessments</u> for OxyContin and primary comparator opioids (Model 1)

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Figure 7-9. Model-estimated rate of abuse cases per assessments over time for OxyContin and primary comparator opioids (Model 1). P. 52.)

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Visual inspection of trends in quarterly rates of non-oral abuse per 10,000 dosage units dispensed (Figure B) also showed an apparent decrease for OxyContin after reformulation, although the magnitude of decline appears smaller than for the population abuse rates. There is also some suggestion of declining trends in ER morphine abuse rates. Here, the OxyContin non-oral abuse rate was elevated above those of comparators in the pre-period and remained elevated above those of comparators in the post-period.

Figure B: Estimated quarterly rate of <u>non-oral abuse cases per 10,000 dosage units dispensed</u> over time for OxyContin and primary comparator opioids (Model 2)

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study.

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Figure 7-10 Model-estimated rate of abuse cases per dosage units dispensed over time for OxyContin and primary comparator opioids. P. 53.)

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Visual inspection of trends in quarterly rates of abuse via any route per 100 assessments show an apparent drop in overall abuse of OxyContin immediately following the transition period, returning to rates fairly similar to those seen in the early pre-period, and then declining further following ASI-MV screen changes.

Figure C: Model 1 descriptive trend analysis figure: any route of abuse for OxyContin and primary comparator opioids per 100 assessments, 3Q2008-1Q2016

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 10-1. Model 1 descriptive trend analysis figure: Any route of abuse. P. 351.)

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 1 models abuse rate per ASI-MV assessments

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Visual inspection of trends in quarterly rates of abuse per 10,000 tablets dispensed shows a great deal of quarter-to-quarter variability, without a clear downward turn following the transition period. Notable, however, is that rates for OxyContin remained elevated above those for comparators throughout the study period.

Figure D: Model 2 descriptive trend analysis figure: any route of abuse for OxyContin and primary comparator opioids per 10,000 tablets, 3Q2008-1Q2016

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study. OxyContin was reformulated in August 2010.

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 10-2. Model 2 descriptive trend analysis figure: Any route of abuse. P.352.)

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2 models abuse rate per tablets dispensed

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Pre-post means analysis: As shown in Figure E, the estimated pre- to post-period change in OxyContin mean non-oral abuse rates ranged from -29.3% to -55.6%, depending on how the models adjusted for population and utilization. OxyContin was the only opioid studied for which all main analysis estimates were significantly below zero.

Figure E: Range of values for percent change in mean quarterly non-oral abuse rates for OxyContin and primary comparators, including main parameters* and all regression models

% Change

(Source: FDA generated figure from sponsor data)

Key: ER: Extended Release; IR: Immediate Release;*Main parameters: -2y/4y, original OxyContin + Reformulated OxyContin, sites contributing >1 assessment/quarter;†Most "Conservative": Smallest pre-post reduction (or largest increase) in non-oral abuse; ‡Least "Conservative": Largest pre-post reduction (or smallest increase) in non-oral abuse

Sensitivity analyses based on site inclusion criteria, definition of OxyContin, time period and regression model produced estimates ranging from a -8.4% to a -70.0% change in the mean OxyContin non-oral abuse rate. Although these estimates ranged considerably, results were qualitatively consistent in showing declines in non-oral abuse of OxyContin.
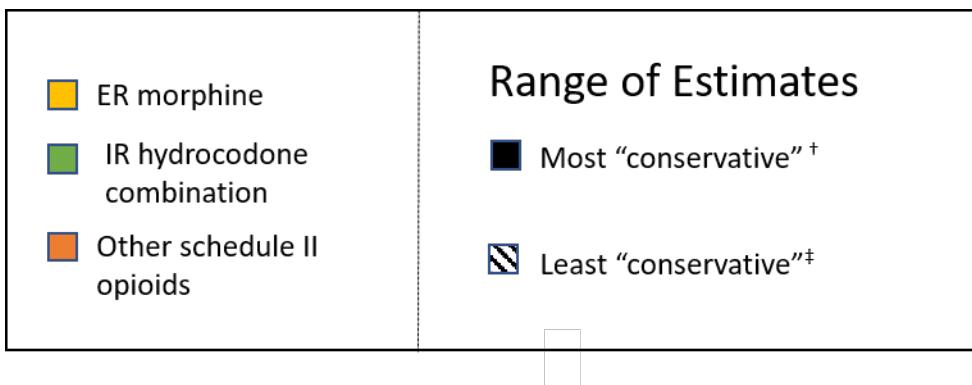
Comparative (difference-in-difference) means analysis: A ratio of rate ratios (RORR) was used to formally test the difference in pre-post changes in mean abuse rates, comparing OxyContin's change (or rate ratio [RR]) to the comparator's change (RORR = [comparator RR] / [OxyContin RR]). A RORR >1 reflects a more favorable change in abuse rates for OxyContin relative to that of a comparator; in this context, favorable could mean a greater reduction or a smaller increase in abuse rates for OxyContin comparing periods relative to comparators, or even no change for OxyContin but

increasing abuse rates for comparators. A RORR <1 indicates a more favorable change for the comparator.

As shown in Figure F, comparative analyses (RORRs) showed a significant decrease in OxyContin non-oral abuse in the post-period relative to the change for IR hydrocodone and "other schedule II opioids" using all models. Comparative analyses of change in OxyContin non-oral abuse relative to change in ER morphine showed mixed results. Utilization-based analysis (model 2, which uses tablets as a denominator) produced the most "conservative" RORR estimate (i.e., smallest change in OxyContin non-oral abuse relative to comparator's change) and did not show a significantly larger decrease in change in OxyContin abuse relative to ER morphine. Utilization- and population-adjusted analysis (model 3a, which uses utilization and assessments as covariates) produced the least "conservative" RORR estimate (i.e., largest change in OxyContin non-oral abuse relative to comparator's change) and was statistically significant.

Figure F: Range of RORRs for pre-post change in non-oral abuse, primary comparators vs. OxyContin, including main parameters* and all regression models
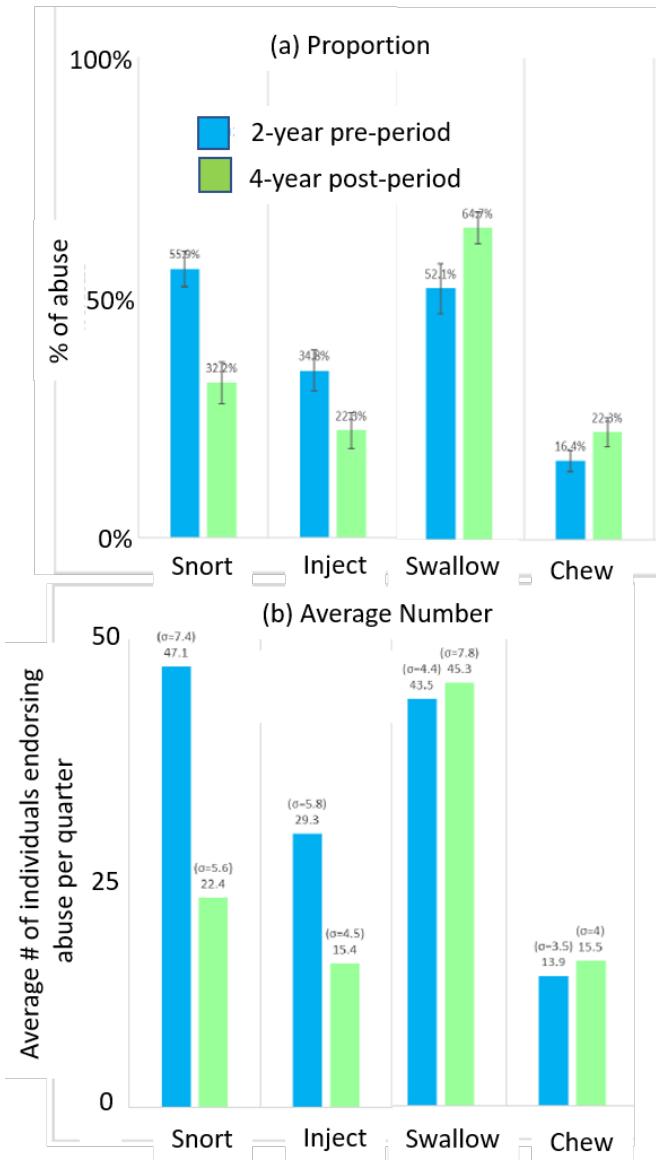
ER morphine	Range of Estimates
IR hydrocodone combination	Most "conservative" †
Other schedule II opioids	Least "conservative"‡

(Source: FDA generated figure from sponsor data)

Key: ER: Extended Release; IR: Immediate Release; *Main parameters: -2y/4y, original OxyContin + Reformulated OxyContin, sites contributing >1 assessment/quarter; †Most "Conservative": Smallest pre-post reduction (or largest increase) in OxyContin non-oral abuse relative to comparator's change; ‡Least "Conservative": Largest pre-post reduction (or smallest increase) in OxyContin non-oral abuse relative to comparator's change
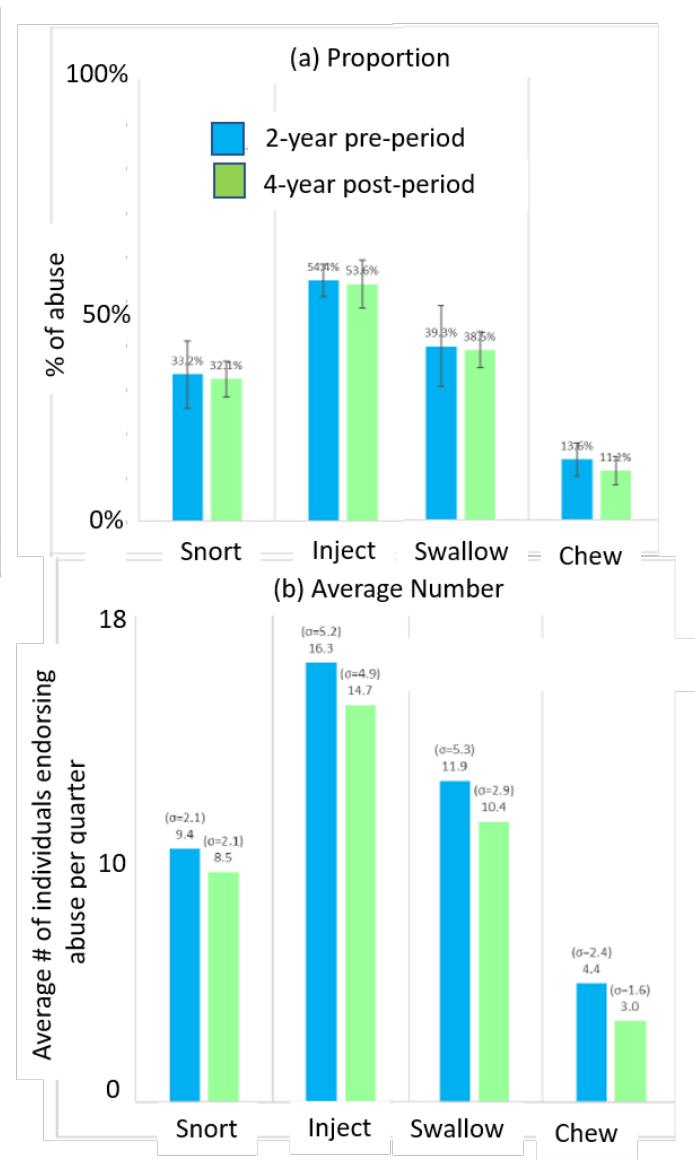
Unmodeled descriptive data for specific routes of abuse: As shown in Figure G, upper left panel, there was a pre- to post-period decrease in the percentage of individuals abusing OxyContin who reported abusing it via snorting and injecting, from 55.9% to 32.2% for snorting and from 34.8% to 22.3% for injecting. Similar decreases in snorting and injecting were not evident for ER morphine (upper right panel) or the other primary comparators (not shown). As shown in the lower left panel, the average quarterly number of individuals endorsing OxyContin abuse via snorting and injecting also decreased. Large decreases were not observed for ER morphine (lower right panel) or other comparators (not shown). Both the percentage and number of individuals abusing OxyContin via swallowing increased slightly, while the percent abusing it via chewing did not change.

Figure G: Proportion (a) and average number (b) of individuals reporting abuse of OxyContin* (left) or ER morphine (right) via specific routes per quarter, -2y/4y

OxyContin

ER morphine

(Source: FDA generated figure from PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised figure 7-1: Proportion (a) and average number (b) of OxyContin (original and reformulated) abusers via specific routes per quarter -2y/4y. P. 5. Title: Revised figure 7-1: Proportion (a) and average number (b) of OxyContin (original and reformulated) abusers via specific routes per quarter -2y/4y. P. 6)
Key: Sigma=standard deviation; *Oxycontin: Original OxyContin or Reformulated OxyContin; sites contributing ≥1 assessment/quarter

Pre-post and comparative (difference-in-difference) means analysis for specific route of abuse: The percent reduction in the OxyContin mean abuse rate via snorting ranged from -62.5% to -40.3%. The most and least "conservative" RORR estimates versus IR hydrocodone and "other schedule II opioids" showed a significantly larger decrease in snorting abuse for OxyContin than the comparator. For ER morphine, the least "conservative" RORR estimate was statistically significant; however, while the most

"conservative" estimate showed a greater decrease in snorting abuse for OxyContin than ER morphine, it was not statistically significant.

The estimated percent reduction in OxyContin mean abuse rate via injection ranged from -54.6% to -33.3%. Comparative analyses showed that the OxyContin abuse rate via injection decreased significantly compared to the change in "other schedule II opioids". For ER morphine, the least "conservative" RORR estimate was significant; however, while the most "conservative" estimate showed a greater decrease in injection abuse for OxyContin than for ER morphine, it was not statistically significant. Injection of IR hydrocodone was extremely infrequent and therefore this comparator had limited utility for this particular analysis.

Pre-post means analysis stratified by severity index: As shown in Table A, rates of OxyContin abuse varied considerably by Addiction Severity Index score; individuals with no real or slight problem had a mean abuse rate of <1 OxyContin endorsement per 100 assessments, while those with a considerable to extreme problem had a mean abuse rate of ~13 OxyContin endorsements per 100 assessments. Observed reductions in non-oral abuse rates appeared to be driven by rate decreases in those with more severe substance abuse problems. Patients assessed as having no real or slight problem had no significant change in mean non-oral abuse rate, while rates decreased more than 30% in those with moderate to extreme problems. Oral abuse showed small, non-significant increases across all severity indices.

Table A: Pre-period and post-period OxyContin mean abuse rates ("any OxyContin" cases per 100 assessments) and percent change, stratified by Addiction Severity Index score and route

	Overall (any route)			Oral			Non-oral		
	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)
0-3: No real problem-slight problem	0.529 (0.407, 0.689)	0.546 (0.415, 0.719)	3.2 (-19.4, 32.1)	0.422 (0.314, 0.568)	0.458 (0.344, 0.610)	8.5 (-17.1, 42.1)	0.124 (0.088, 0.174)	0.132 (0.098, 0.177)	6.5 (-27.6, 56.6)
4-5: Moderate problem	2.987 (2.456, 3.631)	2.595 (2.171, 3.102)	-13.1 (-26.9, 3.2)	1.794 (1.463, 2.201)	2.001 (1.675, 2.390)	11.5 (-8.2, 35.4)	1.804 (1.422, 2.289)	1.151 (0.906, 1.463)	-36.2 (-49.1, -20.0)
6-9: Considerable problem-extreme problem	13.367 (10.876, 16.427)	10.614 (9.122, 12.350)	-20.6 (-30.8, -8.9)	6.304 (5.433, 7.316)	7.065 (6.313, 7.907)	12.1 (-0.2, 25.8)	10.622 (8.232, 13.707)	7.137 (5.805, 8.775)	-32.8 (-42.0, -22.2)

(Source: FDA Postmarketing Requirement Study 3051-1, Purdue Response to FDA Information and Analyses Request on May 30, 2019 Phase 1 Part 2. Title: Table 7: Stratified by ASI-MV® score based on Original + Reformulated OxyContin: sites with >1 assessment/year during 2y/4y time period. P. 31.)

Interrupted time series analysis: As shown in Figure H, interrupted time series (ITS) analysis was conducted to understand changes in abuse while controlling for pre-existing

trends, estimating both the change in slope and the immediate shift change in quarterly non-oral abuse rates following OxyContin's reformulation. When adjusting for number of assessments, there were significant decreases in both the slope and immediate shift for OxyContin non-oral abuse rates. Although the change in slope was also significant for ER morphine, the immediate shift for this comparator was not significant, and neither change in slope nor immediate shift were significant for IR hydrocodone or "other schedule II opioids".

Comparative ITS (CITS) is an extension of the difference-in-differences approach described above for means analyses. CITS examines changes in level and slope of abuse rate for OxyContin relative to those of comparators. These analyses showed a significant decrease in immediate shift for OxyContin non-oral abuse that was larger than that for IR hydrocodone or "other schedule II opioids." The decrease in slope for OxyContin, while numerically larger than any of the comparators, was not significantly greater than IR hydrocodone or "other schedule II opioids." The slope for ER morphine's abuse rate also decreased significantly, and this comparator showed a small decrease in immediate shift. Neither of these values was significantly different from the changes in OxyContin slope and immediate shift.

Figure H: Interrupted Time Series—Modeled slope and immediate shift for non-oral abuse of OxyContin and primary comparator opioids per 100 assessments

Opioid	Slope in pre	Slope in post	Change in slope (95% CI)	Immediate shift (95% CI)	Comparison: P-value Slope change	Comparison: P-value Immediate shift
OxyContin	0.05	-0.03	-0.08 (-0.15, -0.01)	-0.52 (-0.87, -0.17)	Ref	Ref
ER morphine	0.08	-0.03	-0.12 (-0.23, -0.01)	-0.08 (-0.58, 0.42)	0.6	0.2
IR hydrocodone	0.004	-0.002	-0.006 (-0.095, 0.083)	0.14 (-0.29, 0.57)	0.2	0.02
Other schedule II opioids	0.05	-0.0003	-0.05 (-0.11, 0.01)	0.18 (-0.10, 0.46)	0.5	0.002

(Source: Purdue Response to FDA Information and Analyses Request on May 30, 2019 Postmarketing Requirement Study 3051-1 (received February 2020) Title: Figure 3-1A-1-1. Slopes from Interrupted Time Series Analysis in Non-Oral Abuse Rate Using Sites with at least 1 Assessment per Quarter: Any OxyContin (Original + Reformulated) with Primary Comparator Opioids – Model 1i: assessments as offset. P. 13.)

In utilization-based ITS analyses, below, there was a significant downward immediate shift in OxyContin non-oral abuse rates after reformulation; however, the slope did not change significantly. Neither immediate shift nor slope change were significant for any comparators. CITS results found that neither change in slope nor immediate shift were significantly different for any comparators vs. OxyContin.

**Figure I: Interrupted Time Series—Modeled slope and immediate shift for non-oral abuse of OxyContin and primary comparator opioids per 10,000 dosage units dispensed**

Opioid	Slope in pre	Slope in post	Change in slope (95% CI)	Immediate shift (95% CI)	Comparison: P-value slope change	Comparison: P-value immediate shift
OxyContin	0.04	0.007	-0.04 (-0.14, 0.07)	-0.57 (-1.11, -0.04)	Ref	Ref
ER morphine	0.04	-0.03	-0.07 (-0.24, 0.10)	-0.24 (-1.01, 0.52)	0.8	0.5
IR hydrocodone	-0.02	0.02	0.04 (-0.10, 0.17)	-0.16 (-0.82, 0.50)	0.4	0.3
Other schedule II opioids	0.01	0.02	0.007 (-0.09, 0.10)	-0.06 (-0.49, 0.38)	0.5	0.1

(Source: Purdue Response to FDA Information and Analyses Request on May 30, 2019 Postmarketing Requirement Study 3051-1 (received February 2020) Title: Figure 3-1A-1-2. Slopes from Interrupted Time Series Analysis in Non-Oral Abuse Rate Using Sites with at least 1 Assessment per Quarter: Any OxyContin (Original + Reformulated) with Primary Comparator Opioids – Model 2i: dosage units dispensed as offset. P. 14.)

Discussion

Overall, the data show that non-oral OxyContin abuse rates decreased substantially after reformulation among individuals being assessed for treatment at substance abuse centers participating in the NAVIPPRO ASI-MV surveillance system. Main analysis estimates for pre-post changes in non-oral abuse rates for OxyContin showed a consistent decrease, ranging from -29.3% to -55.6%. In comparison, the ranges for comparator opioids included both negative and positive estimates of change in non-oral abuse rates. Comparative analyses (RORRs) showed a significantly larger decreases in OxyContin non-oral abuse rates relative to IR hydrocodone and "other schedule II opioids," regardless of model. The most "conservative" estimates of the pre-post decrease in OxyContin relative to ER morphine (utilization-based analysis) were non-statistically significant, but the least "conservative" estimates were statistically significant. The utilization-based analyses help us understand how the decreasing rate of OxyContin tablets dispensed was a factor in the decreasing rate of abuse of OxyContin. However, utilization-based analyses probably underestimate the effect of the reformulation on abuse rates, because they do not account for the possibility that the decrease in dispensing might, at least in part, have been caused by a decrease in desirability of the drug for abuse purposes. It is also important to keep in mind that these estimates included any OxyContin abuse endorsements in the post-period, which included a non-trivial number of original OxyContin endorsements in addition to reformulated OxyContin endorsements. Although this definition was chosen as primary to avoid potential misclassification bias exaggerating the effect of the reformulation, it may have created bias in the other direction, attenuating the "true" change in OxyContin abuse post-reformulation.

Estimated rates of abuse via both snorting and injection showed consistent decreases for OxyContin, suggesting no evidence of a shift to more dangerous routes. Among those reporting abuse of OxyContin, unmodeled analyses showed reductions in the percent of OxyContin abuse via both snorting and injection. Similar reductions were not seen for comparators. Estimated oral OxyContin abuse rates via swallowing whole did not show a

consistent direction of change across models, although the percentage of people who endorsed OxyContin abuse who reported swallowing whole increased slightly. Of note, the largest decreases in non-oral OxyContin abuse were observed among those categorized as having moderate to severe addiction, based on addiction severity score.

ITS findings provided some additional support for the hypothesis that the reformulation reduced non-oral abuse of OxyContin in this population. Although the results were not uniformly favorable to OxyContin's having an abuse-deterrent effect, they were qualitatively consistent with findings of the means analyses. ITS findings demonstrated a significant decrease in slope and immediate shift of non-oral OxyContin abuse in population-based analyses, and a significant immediate shift in non-oral OxyContin abuse in utilization-based analyses. In comparative ITS (CITS) analyses, OxyContin showed a larger immediate downward shift than IR hydrocodone and "other schedule II opioids" in population-based analyses, but differences between OxyContin and comparators were attenuated and not statistically significant in other CITS analyses.

In terms of overall abuse of OxyContin, results were mixed. Estimates of percent change in overall OxyContin abuse (via any route) ranged from +5.8% to -38.6%, and were generally not statistically significantly different from those for comparators. Descriptive trend figures of quarterly prevalence of abuse via any route for OxyContin and comparator opioids showed little change in overall abuse rates for OxyContin from the pre- to post-reformulation time periods.

Individuals reporting abuse of OxyContin endorsed abusing a median of six different opioids during the past 30 days during both the pre- and post-reformulation period, illustrating the polysubstance nature of opioid abuse and addiction. Although this study was not designed to examine the impact of OxyContin's reformulation on the abuse of other opioids, it is useful to examine the change in rates of abuse for other opioids across the study period to better understand overall changes in the landscape of opioid abuse. There was a sharp increase in IR oxycodone endorsements starting in 2010, although this increase was likely due, at least in part, to the addition of IR SE oxycodone to the ASI-MV survey. This increase in IR oxycodone endorsements largely drives the increase seen in "other schedule II opioids" group, and it is difficult to determine how much of the increase was due to better ascertainment versus individuals shifting to these products after OxyContin's reformulation. A large increase in ER oxymorphone endorsements was also evident after OxyContin's reformulation. In the broader set of treatment sites that included sites in the Northeast, descriptive trends of non-oral abuse of heroin suggested steady increases in heroin endorsement in the post-period.

This was an ecological study that compared aggregate measures of abuse across time periods. This type of study has particular limitations compared to studies that link an

exposure/intervention and an outcome at the individual level.[1] Associations and patterns seen at the aggregate or group level may not reflect associations at the individual level— here, the likelihood, or risk, that an individual exposed to a product will abuse it. Therefore, caution is warranted in drawing inferences from an observed reduction in aggregate abuse prevalence or rates about the risk of people abusing a product, of transitioning from one route to another, or of progressing to more severe opioid use disorder.

In general, PMR 3051-1 findings were qualitatively consistent with a number of published papers describing the changes in abuse for OxyContin and comparators during the time of OxyContin reformulation using NAVIPPRO ASI-MV data. Generally, these studies (most co-authored or supported by the sponsor) found a decrease in snorting and injection of OxyContin, which agrees with the study results from PMR 3051-1, although the magnitude of the decreases reported in the literature were larger.

Overall Interpretation of the Study Findings

This study provided reasonably compelling evidence that the reformulation decreased non-oral abuse of OxyContin in people who are entering or being assessed for treatment for substance use disorder, although it's difficult to quantify the size of this effect. Results varied depending on the specific parameters, but analyses were largely consistent in demonstrating a reduction in non-oral abuse rates for OxyContin that differed from the changes in non-oral abuse rates observed in comparator opioids. These findings appear to have been driven primarily by a reduction in non-oral abuse among people assessed to have moderate to severe addiction. Among individuals abusing OxyContin, the proportions who reported snorting and injecting the product both declined, and the proportion who reported abusing it orally slightly increased. Similar changes were not observed for comparator opioids. Results of published studies analyzing ASI-MV data were qualitatively consistent with this main finding, although decreases reported in the literature were larger.

Given the many limitations and complexity of these data and methods, the approach for this review was to qualitatively synthesize data from multiple quantitative analyses to draw reasoned conclusions from the totality of the evidence using fundamental epidemiologic principles around study design, data quality, and causal inference. The study employed multiple models and comparators, conducting both means and trend analyses to address the complexity and limitations of this data source and the nature of the research question. We considered some of the most important limitations of this data

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[1] Morgenstern H. Ecologic Studies in Epidemiology: Concepts, Principles, and Methods. Annu Rev. Public Health. 1995. 16: 61-81.

source to be: 1) concerns about product misclassification, particularly the substantial original OxyContin endorsements during the post-period, when original OxyContin was no longer being dispensed, 2) the dynamic nature of the sample, in which treatment sites with differing drug abuse patterns contribute assessments sporadically, and with the main analyses restricted to a small number of sites that contributed assessments consistently but were not representative of all geographic regions, and 3) changes in screen order/questionnaires multiple times throughout the study period, which appeared to impact the number of endorsements of abuse of OxyContin as well as the change to the questionnaire to include collecting information on IR oxycodone SE endorsements the quarter before reformulation. Sensitivity analyses addressing the chosen time period, model, site selection, and OxyContin definition served as a qualitative assessment of the robustness of main analysis results. The results of these sensitivity analyses were largely consistent with main study findings, although the point estimates varied quite widely, making it difficult to make any quantitative determination about the magnitude of OxyContin's abuse-deterrent effect in this population.

The evidence for the reformulation leading to a reduction in overall OxyContin abuse (via any route) in this population was much weaker. Although some analyses indicated an overall decline in OxyContin abuse that was greater than that of comparators, findings were inconsistent across the various models and inspection of visual trends did not suggest meaningful changes in overall OxyContin abuse rates after reformulation. This lack of strong evidence for a reduction in overall abuse of OxyContin was likely due, at least in part, to persistent oral OxyContin abuse, which remained a common route reported throughout the study period in this population.

After reformulation, utilization-based abuse rates of non-oral and overall abuse of OxyContin remained relatively high among the opioids examined; however, such cross-sectional comparisons between drugs must be made cautiously as data from treatment centers are not a nationally representative sample of all persons abusing opioids, or even all persons with substance use disorders or entering treatment, and relative abuse rates may be substantially affected by design of the assessment tool, order in which products are presented, and other sources of product misclassification.

Conclusion

PMR study 3051-1 provides reasonably compelling evidence that reformulation decreased non-oral abuse of OxyContin in people who are entering or being assessed for treatment, although it is not possible to quantify the size of this effect. This reduction appears to have occurred predominantly among people assessed to have moderate to severe addiction. Oral abuse of OxyContin was common in this population both before and after reformulation, and this study did not provide compelling evidence that the reformulation reduced overall OxyContin abuse (via any route) in this population. After

reformulation, utilization-based overall and non-oral abuse rates (per 10,000 tablets dispensed) for OxyContin remained high relative to most other opioid analgesics examined.

1 INTRODUCTION

Postmarket required (PMR) study 3051-1 is one of four studies the United States (US) Food and Drug Administration (FDA) required to evaluate the impact of OxyContin® (hereafter, OxyContin) reformulation (August 2010) on its abuse. In brief, PMR study 3051-1 aimed to assess the effect of OxyContin's reformulation on non-oral abuse of OxyContin in a large dynamic convenience sample, consisting of individuals being assessed for substance abuse treatment at centers which can drop in and out of the network over time. OxyContin (oxycodone hydrochloride, controlled release; New Drug Application [NDA] 022272) was reformulated with physicochemical properties that are intended to deter tablet manipulation for the purposes of abuse primarily via insufflation (snorting) and injection. The reformulation incorporated a high molecular weight polymer (polyethylene oxide) matrix with the intention of making the tablet more difficult to manipulate for the purposes of misuse or abuse. In 2013, based on review of *in vitro* and clinical study data, FDA concluded that reformulated OxyContin had properties expected to reduce abuse, and the label[2] was updated with its current language:

"The in vitro data demonstrate that OXYCONTIN has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the in vitro data, also indicate that OXYCONTIN has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OXYCONTIN by these routes, as well as by the oral route, is still possible."

Observational studies, including PMR study 3051-1, were required to provide further information on the ability of reformulated OxyContin to deter abuse and reduce harms associated with abuse in the postmarket setting. Study 3051-1 used serial cross-sectional data to measure changes in the rates of route specific abuse of OxyContin, comparing the pre-reformulation period of OxyContin marketing to the post-reformulation period, relative to comparable opioid analgesic drugs marketed during that time. The three additional required studies evaluate changes from the pre- to post-reformulation in: 1) opioid abuse exposure calls to US poison control centers, using data from the RADARS® Poison Control Program (PMR 3051-2); 2) opioid abuse in a sentinel population of adults entering methadone and non-methadone treatment programs for opioid use disorder, using data from the RADARS® Treatment Center Program (PMR 3051-3), and 3) fatal and non-fatal opioid overdose among a population of patients prescribed OxyContin or comparator opioids (PMR 3051-4).

The objective of this review was to determine whether data from PMR study 3051-1 support OxyContin's reformulation causing a reduction in non-oral abuse of OxyContin among individuals being assessed for substance abuse treatment.

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[2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022272s027lbl.pdf

In conjunction with the other PMR studies (3051-2, 3, and 4) and other relevant information, the findings of this study can be used to help inform the overarching question of whether OxyContin's reformulation meaningfully reduced its abuse and associated harms. While each study can alone provide important information on the impact of the reformulation, it is ultimately necessary to evaluate the totality of evidence from all sources to answer this question. (See OSE Summary Memo)

2   REVIEW METHODS AND MATERIALS

FDA approved a final study protocol for PMR 3051-1 in May 2017, and the sponsor submitted a final report for the study in July 2018. PMR 3051-1 assesses the changes in rates and routes of abuse of OxyContin among people assessed for treatment at substance abuse treatment centers using the National Addictions Vigilance Intervention and Prevention Program® (hereafter, NAVIPPRO) Addiction Severity Index-Multimedia Version® (hereafter, ASI-MV) system.

To prepare this document, DEPI reviewed:
- PMR study 3051-1 final study report (EPI8011ORF) - "*Changes in Rates and Routes of Abuse of OxyContin after its Reformulation with Abuse Deterrent Properties among People Assessed for Treatment at Substance Abuse Treatment Centers using the NAVIPPRO® ASI-MV® System*" (received July 2018) Study protocol
  - o Study protocol
  - o Statistical Analysis Plan (SAP)
  - o Study results, including all appendices
  - Sponsor submitted responses to information requests and teleconferences (received May 2019, October 2019, January 2020, March 2020) related to study 3051-1.
    - o Received August 2019
    - o Received October 2019
    - o Received November 2019
    - o Received February 2020
    - o Received March 2020
    - o Received July 2020

In brief, this review document provides a critical review of study 3051-1 including a summary of the study methods and main findings, as well as a discussion of relevant methodological issues and how these issues impact inferences that can be made based on the study results. The findings of this review will be used to inform the broader question of whether OxyContin's reformulation was effective in reducing abuse and associated harms (See OSE Summary Memo).

DEPI also conducted a review of published studies that used NAVIPPRO Inflexxion® (hereafter, Inflexxion) data that may provide context or supplemental information to aid

the interpretation of PMR study 3051-1; search terms and strategy are described in (Ref Lit Review). Six studies were identified that used the same data sources or study participants as PMR study 3051-1, and these were reviewed for any additional information that could inform our interpretation of the findings of PMR study 3051-1.

3   REVIEW RESULTS

3.1   STUDY OVERVIEW

PMR study 3051-1 assesses the change in self-reported past 30-day abuse of selected opioids via specific routes (swallowing intact, chewing and swallowing, dissolving and swallowing, snorting, smoking, and injecting) before and after OxyContin reformulation, in a population of adults evaluated for substance use problems and treatment planning using the ASI-MV assessment. Comparator opioids are included in this evaluation to provide contextual information on abuse trends unrelated to the reformulation and to aid in causal inference. Due to the inherent uncertainties associated with these data, (e.g., the potential for bias due to misclassification, the dynamic study sample, and confounding secular trends), a number of different analyses were conducted, including varying the time period, definition of OxyContin, site inclusion criteria, and models and offsets/covariates used to estimate abuse rates and account for changes in drug utilization over time. These varied approaches were used to assess robustness of the overall study findings with regard to the effect of reformulation on abuse rates in this population.

3.2   STUDY OBJECTIVES/SPECIFIC AIMS/SCOPE

Primary objectives

1. Assess the impact of OxyContin reformulation on non-oral OxyContin abuse in the two years before reformulation versus (vs.) the four years after reformulation (-2y/4y)
2. Assess changes in non-oral abuse for primary comparator opioids vs. OxyContin (-2y/4y)
3. Assess the impact of OxyContin reformulation on non-oral abuse in the one year before reformulation vs. the three years after reformulation (-1y/3y)
4. Assess the changes in non-oral abuse for primary comparator opioids vs. OxyContin (-1y/3y)

Secondary Objectives

1. Asses the changes in abuse of OxyContin and comparator opioids by additional routes of abuse among all ASI-MV assessments
2. Assess quarterly trends in abuse for OxyContin using both descriptive and interrupted time series (ITS) analyses
3. Assess changes in OxyContin and comparator opioid abuse via specific routes using unmodeled data
4. Assess changes in non-oral abuse for secondary comparator opioids (-2y/4y)

5. Assess changes in non-oral abuse for secondary comparator opioids (-1y/3y)
6. Evaluate sources of potential misclassification due to continued reporting of original OxyContin and by specific opioid reported by respondents with assessments completed before and after survey screen changes
7. Assess the relationship between dosage units dispensed and number of abuse cases per respondents 3-digit ZIP

3.3 STUDY METHODS

3.3.1 Design & Setting

3.3.1.1 Study Type

Ecological times series using serial cross-sectional survey data.

3.3.1.2 Databases

NAVIPPRO Inflexxion database

The NAVIPPRO ASI-MV is a proprietary data stream of the NAVIPPRO System that collects data on substances used and abused by individuals being assessed for treatment of substance abuse disorders. The ASI-MV is a computerized standard clinical intake assessment used by a dynamic network of treatment centers and other types of facilities such as correctional institutions that assess individuals for substance abuse. Although it covers a wide geographic area including 39 states, it is not nationally representative, and centers drop in and out of the network over time.

The ASI-MV captures individual patient-level data across a series of domains and includes product-specific questions on use and abuse of prescription medications in the past 30 days, including questions on route of administration. The ASI-MV is a computerized version built upon the Addiction Severity Index (ASI) interview, a standard intake assessment designed for use on admission to drug and alcohol treatment.

IQVIA National Prescription Audit™

The IQVIA (formerly known as IMS Health or QuintilesIMS) National Prescription Audit™ (hereafter, NPA) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, and long-term care facilities into the hands of consumers via formal prescriptions in the US; data for the NPA audit is a national level estimate of the drug activity from these three channels. The pharmacies in the database account for most retail pharmacies and represent ~92% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data are also collected from approximately 60 – 86% (varies by class and

geography) of mail service pharmacies and approximately 75 – 83% of long-term care pharmacies.

3.3.2 Drug Utilization Methodology

Nationwide trends in monthly tablets dispensed were estimated for OxyContin, primary comparators, and secondary comparators using IQVIA NPA data. These trends were used to understand differences in dispensing patterns of OxyContin and prescription opioid comparators over the entire time period. Estimates generated from the IQVIA NPA data source were used additionally in the regression models that used dosage units dispensed as either an offset or a covariate. Dispensed tablets were estimated for ER oxycodone, OxyContin (original or reformulated), generic ER oxycodone, IR oxycodone single entity, IR oxycodone – acetaminophen combination products, ER morphine products, ER oxymorphone products, methadone products, IR hydrocodone combination products and "other schedule II opioids".

3.3.3 Overarching Methodological Considerations

The ASI-MV is a computerized standard clinical intake assessment used by a dynamic network of treatment centers and other types of institutions, such as correctional facilities, to assess individuals for substance use disorders. The ASI-MV assessment captures product-specific data related to past 30-day use and abuse of prescription opioid products using visual images to aid in identification of products. ASI-MV results estimate the prevalence of abuse of OxyContin and comparator opioids in a convenience sample of individuals being assessed for substance use disorder. There are a number of overarching methodologic considerations that informed the design and analytics approaches used in this study. Foremost among these were concurrent population-based opioid interventions during the selected time-period, product misclassification, the use of non-representative convenience samples that change over time, and changes in prescribing/dispensing of opioids. To address these possible sources of bias and understand how they might affect the estimates, model parameters were varied in analyses, including those defining time periods, comparators and specific products included, sites included, and different statistical methods to adjust for retail dispensing volume. There is not yet a standard scientific approach to defining all parameters of an analysis of abuse rates over time, and therefore a range of estimates were produced by varying these parameters in an attempt to understand the bounds of the estimates.

3.3.4 Site Inclusion Criteria, and Time Period

The population for PMR 3051-1 is a large dynamic, convenience sample of adults aged 18-90 years being assessed for substance abuse problem severity and treatment planning

with the NAVIPPRO ASI-MV. Participating sites upload new versions of the ASI-MV according to varying schedules. In the post-reformulation period, the analytic sample was limited to individuals who were given the ASI-MV version containing questions and images about abuse of reformulated OxyContin. Assessments from individuals who had already taken an ASI-MV assessment in the previous 30 days were excluded from the analytic sample.
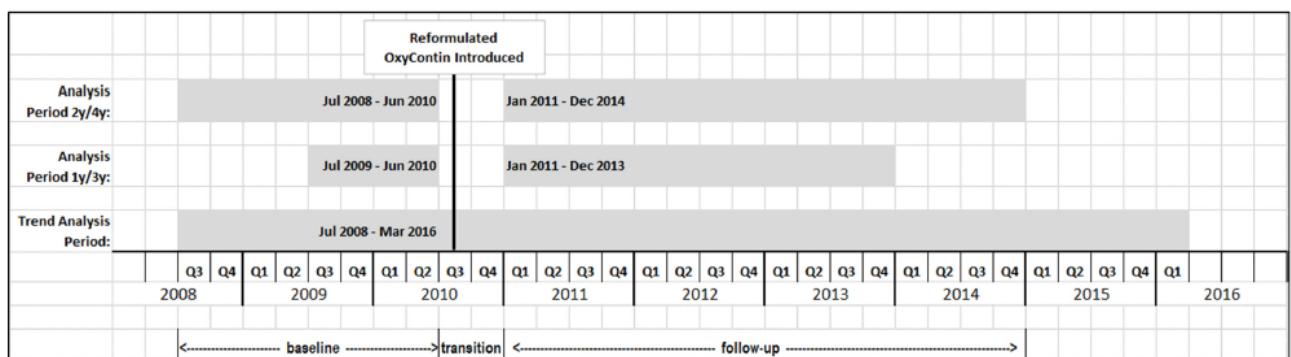
The sample of all eligible ASI-MV assessments meeting the study inclusion criteria varied by quarter. The main analyses included sites that contributed ≥1 assessment/quarter in order to maintain a consistent set of sites and number of assessments, and the less restrictive ≥1 assessment/year was used in secondary analyses to increase sample size and geographic representation.

- o ≥1 assessment/quarter (main)
- o ≥1 assessment/year
- o ≥1 assessment/year excluding New Mexico[3]

Site inclusion numbers also depended on the time period assessed, which included 2 years pre-reformulation (pre-period) compared to 4 years post-reformulation (post-period) and 1-year pre-period compared to 3 years post-period.

The study period for PMR 3051-1 is broken down into three components: 1) baseline period before OxyContin reformulation (pre-period), 2) transition period during the transition from original OxyContin to reformulated OxyContin, and 3) period after OxyContin reformulation (post-period). Two time periods were selected, a -2y/4y period (main), and a -1y/3y period (sensitivity) (Figure 1).

Figure 1: Study time periods

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Figure 6-1. Study time periods. P. 20.)

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[3] While New Mexico had complete coverage in the pre-period, due to a change in state law, there were few New Mexico sites that contributed surveys in the latter post-reformulation period after 2012.

Table 1: Summary of study periods
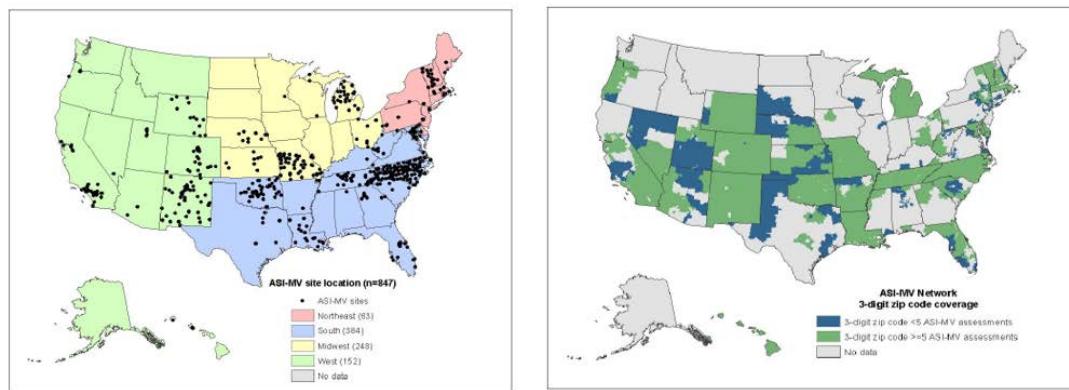
Label	Description	Number of sites and states (>1 assessment/quarter)	Number of sites and states (>1 assessment/year)
-2y/4y	2-year pre-reformulation (3Q2008-2Q2010)/ 4-year post-reformulation (1Q2011-4Q2014)	• 34 sites • 10 states	• 175 sites • 23 states
-1y/3y	1-year pre-reformulation (3Q2009-2Q2010)/ 3-year post-reformulation (1Q2011-4Q2013)	• 91 sites • 17 states	• 228 sites • 24 states
Transition	6-month transition (3Q2010-4Q2010)*		

(Source: FDA generated table from final study report 3051-1.)

∗ The transition period does not have any sites or states specified because these data were excluded in the majority of the analyses

Figure 2 shows a map of the entire ASI-MV network which includes all 847 site locations. Patient home 3-digit ZIP codes were then used to determine dosage units dispensed for those models that utilized dosage units dispensed as either an offset or covariate.

Figure 2: Map of ASI-MV network and patient home 3-digit ZIP code
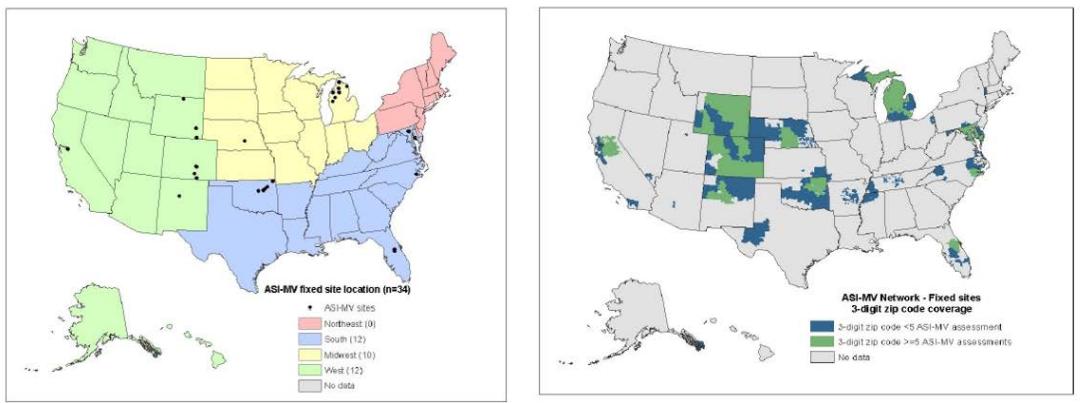
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Figure 1. Map of ASI-MV® network. P. 116. (right)
Title: Figure 2. ASI-MV Network: Patient Home 3-digit ZIP-code. P. 117.(left))

The ASI-MV network constitutes a convenience sample. This sample is dynamic in nature, and new sites are regularly added to, and dropped from, the network. Sites within the ASI-MV network contribute data on a varying schedule and with varying sample sizes. To maintain consistency within the analytic sample, main analyses for this study require that sites contribute >1 assessment/quarter to be included. Figure 3 (left panel)

shows a map of ASI-MV sites that contributed >1 assessment/quarter throughout the study period and were therefore included in the analytic sample for the main analyses. This sample consists of 34 sites. *Of note, this more restricted set of sites does not include any sites in the Northeast.* Figure 3 (right panel) shows the 3-digit ZIP codes of respondents from within this sample.

Figure 3: Map of ASI-MV network among fixed sites (n=34) and patient home 3-digit ZIP code among fixed sites

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Figure 3. Map of ASI-MV network among fixed sites (n=34). P. 117. (Right) Title: Figure 4. ASI-MV® Network: Patient Home 3-digit ZIP-code among Fixed Sites (n=34). P. 118. (Left))

3.3.5   OxyContin Definition

The primary outcome for this study is past 30-day non-oral abuse* of OxyContin and comparator opioids. Secondary outcomes include: 1) any past 30-day abuse* of OxyContin, 2) abuse of OxyContin via oral routes (swallowing intact, chewing and swallowing, dissolving and swallowing).

*The definition of abuse[4] in NAVIPPRO ASI-MV is any strictly non-medical use of a prescription opioid medication. Non-medical use is determined by responses to the following series of questions to determine whether use of each medication was legitimate for treatment of pain:

- have a current pain problem and have taken [DRUG] for pain the past 30 days;
- obtained [DRUG] only from their own prescription; and

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[4] In previous regulatory documents, FDA has defined *abuse* as the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. In this review, we use Inflexxion's definition of abuse as described here. FDA recognizes that the term *abuse* has been identified as potentially stigmatizing to individuals with substance use disorders. This is in no way our intent; rather, we are using the term abuse to describe a specific behavior as defined in the PMR study.

- have not used [DRUG] via an alternate route of administration.
- deny using [DRUG] in the past 30 days "not in a way prescribed by your doctor, that is, for the way it makes you feel and not for pain relief."

To estimate past 30-day abuse per quarter, and better understand the effect of misclassification on OxyContin abuse rates given the differing availability of brand and generic ER oxycodone during the time period, multiple definitions of OxyContin abuse endorsement were used. The three OxyContin definitions used in the study were:

- o Original OxyContin or Reformulated OxyContin (main)
- o Reformulated OxyContin only
- o Original OxyContin or Reformulated OxyContin or generic ER oxycodone

Different routes of abuse were also assessed in order to estimate changes in abuse via any non-oral route, any oral route, specific oral and non-oral routes, and any (oral or non-oral) routes. In the ASI-MV survey, respondents are asked "How have you usually used 'drug name'?" Routes of abuse assessed in the study included:

- o Non-oral: snort, inject (main)
- o Swallow whole
- o Other oral (chewed, dissolved, drank)
- o Any route

Finally, the investigators described and conducted several analyses to examine the impact of screen changes in the ASI-MV assessment tool. Screen changes in the ASI-MV tool are listed below:

- August 9, 2010: screen depicting ER oxycodone products was changed to include a) the addition of some strengths of original OxyContin, so that all strengths were shown and depicted with truer colors, b) images of the original OxyContin were re-labeled as "Old OxyContin" (marked with "OC") and c) all strengths of the reformulated OxyContin were depicted with true colors, labeled as "OxyContin Reformulated" marked with "OP".
- In 2013 the background and color scheme for the prescription opioid question was changed and all prescription opioids listed were displayed in one row instead of two (Figure 43 in appendix 6.1).
- In May 2014, images of reformulated OxyContin were moved to the first (left-most) position on the ER oxycodone screen, followed by OxyContin marked with "EX", followed by OxyContin marked with "CDN". The remainder of the screen contained boxes with text (without images) reading, "Xartemis XR", "Old OxyContin" (marked with "OC"), "Other extended release non-combination oxycodone not shown", "Other extended-release oxycodone with acetaminophen not shown" and "None" (Figure 44 in appendix 6.1).
- In March 2015, along with an order change on ER oxycodone products, the ER oxycodone screen was moved from the first opioid screen presented to

respondents to the fourth, preceded, in order, by hydrocodone products, IR oxycodone combination products, and IR, SE oxycodone products (Figure 45 in appendix 6.1).
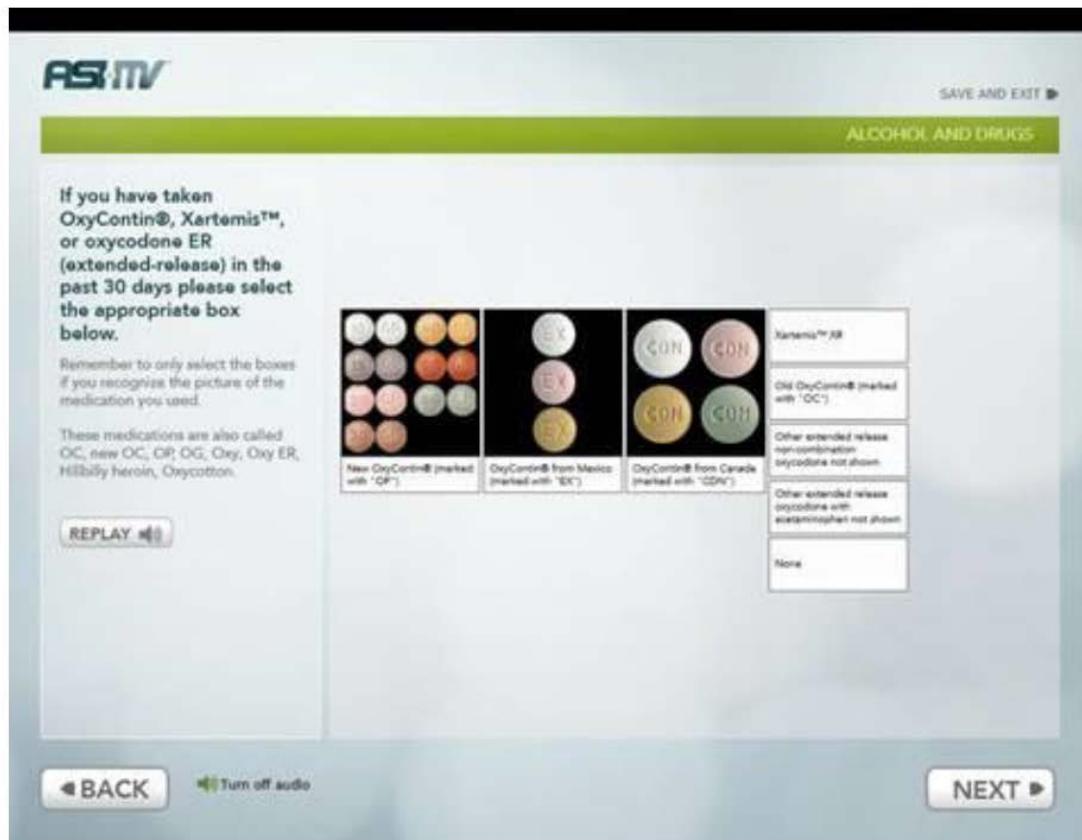
- In 2016, Xtampza ER was added as an option with images, and OxyContin from Latin America, Apo-oxycodone, and co-oxycodone CR images were removed and replaced with options for "Other extended-release non-combination oxycodone not shown" and "Other extended-release oxycodone with acetaminophen not shown".

Figure 4: Sample screen shot of a prescription opioid question on the ASI-MV in 2010, following market introduction of reformulated OxyContin

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 12-2. Sample screen shot of a prescription opioid question on the ASI-MV® in 2010. P. 372.)

Figure 5: Sample screen shot of a prescription opioid question on the ASI-MV in May 2014

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 12-4. Sample screen shot of a prescription opioid question on the ASI-MV® in May 2014. P. 374.)

3.3.6 Selection of Comparators

Primary and secondary opioid comparators were selected to assess background, or secular, changes in abuse of opioids during the study period. No comparator opioid is ideally suited to this purpose, and therefore several comparators were selected, each with different strengths and limitations. ER morphine, IR hydrocodone-combination products, and a composite "other schedule II opioids" category (see Table 2) were chosen as primary comparators for the study. ER morphine and IR hydrocodone combination products were chosen as primary comparators because of their large and stable market shares, potential for abuse by various routes, and because they were consistently measured by the ASI-MV assessment tool. The composite "other schedule II opioids" category was chosen by the sponsor as a primary comparator because it is less likely to be influenced by changes in formulation or utilization of specific products as it includes many products. Of note, the relative composition of this comparator group can change over time, as the market share of the component opioid products shifts. For example, oxycodone IR SE had an increase of +74.8% from the pre- to post-periods (see Figure 8). In addition, abuse of oxycodone IR SE was not asked about in the ASI-MV assessment

until early 2010, which is important to keep in mind when interpreting pre-post changes in the "other schedule II opioids" comparator.

Table 2 – Summary of comparators

Primary Comparators	Secondary Comparators
ER morphine	ER oxymorphone
IR hydrocodone-acetaminophen combination products	IR SE oxycodone
"Other schedule II opioid" analgesic tablets and capsules excluding OxyContin and methadone: includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone	IR oxycodone-acetaminophen IRSE oxycodone + IR oxycodone-acetaminophen
	Heroin
	Methadone

(Source: FDA generated table from final study report 3051-1)

3.3.7 Additional Analyses to Explore the Possible Effects of Other Opioid Interventions
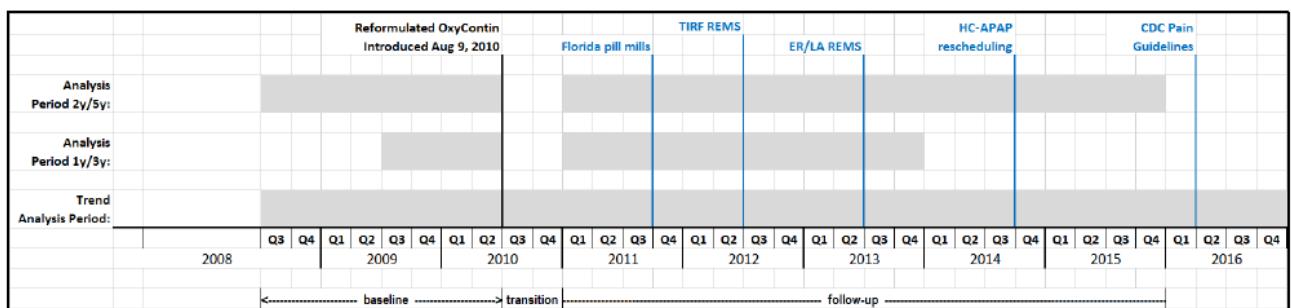
To understand the causal association between reformulation and change in abuse rate of OxyContin, we need to isolate the effect of the abuse deterrent formulation (ADF) from the changing landscape of opioid use and abuse. Below is a description of concurrent population-based opioid interventions that might have affected OxyContin abuse rates.

Acknowledging the potential for various other interventions to affect trends in opioid use and abuse, the sponsor included Figure 6, based on a 2017 publication, which depicts a timeline of *some* population-based opioid interventions occurring during and following the three study time periods. For example, multifaceted legislation in Florida, was enacted starting in 2010, intended to eliminate pill mills in one state where they had proliferated, supplying prescription drugs to other states through interstate trafficking (Surrat, 2014)[5]. The Drug Enforcement Agency (DEA) coordinated "Operation Oxy Alley" in February 2010 and "Operation Pill Nation" in February 2011-August 2012, taking major actions to arrest pill mill owners, physicians, and staff and seizing assets

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[5] Surratt HL, O'Grady C, Kurtz SP, Stivers Y, Cicero TJ, Dart RC, et al. Reductions in prescription opioid diversion following recent legislative interventions in Florida. *Pharmacoepidemiol Drug Saf*. 2014;23(3):314–20.

(Kennedy-Hendricks, 2016)[6]. Also noted are the transmucosal IR fentanyl (TIRF) risk evaluation and mitigation strategy (REMS) and the extended release/long acting (ER/LA) REMS, both of which had the goal of reducing serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of these classes of prescription opioids. In 3rd quarter 2014 hydrocodone combination products were rescheduled by the DEA from schedule III to schedule II of the controlled substances act, and in 1st quarter of 2016 the Centers for Disease Control (CDC) released their pain guideline that gave expert-consensus recommendations for opioid prescribing in primary care. Of note, a REMS for OxyContin was approved in 2010, and is not included in the figure.

Figure 6: Timeline of examples of population-based opioid interventions

Reference: (Dart et al., 2017); Florida Pill Mills = multifaceted legislation in Florida, enacted June 2011, was designed to eliminate "pill mills" (medical practices suspected of irresponsibly prescribing opioid analgesics for dubious health benefit) and are hypothesized to have had an effect beyond Florida due to interstate diversion. TIRF REMS = transmucosal IR fentanyl risk evaluation and mitigation strategy. ER/LA REMS = extended release/long-acting risk evaluation and mitigation strategy. HC-APAP rescheduling = rescheduling of hydrocodone-acetaminophen combination products from Schedule III to Schedule II (DEA, 2014); CDC Pain Guideline = Centers for Disease Control and Prevention (Dowell et al., 2016).

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Figure 6-2. Timeline of key population-based opioid interventions effecting utilization and abuse. P.20.)

3.3.8 Statistical Models and Covariates

There is yet no single, standard scientifically agreed-upon denominator or modeling approach to estimate abuse rates. Using assessments (i.e., treatment admissions) as a denominator allows us to understand prevalence, or proportion, of abuse of particular products within the population surveyed. Using utilization (i.e., prescriptions or tablets) as a denominator allows us to understand the rate of abuse of a specific drug, relative to the prescribed availability of that drug. Prescribed availability is important to account for when comparing abuse rates across different drugs and time periods, as a drug has to be available in the community to be abused; however, this does not take into consideration that desirability for abuse might also drive prescribing and dispensing of a drug. Therefore, this study used both utilization and population-based (as a denominator) and adjusted (as a covariate) abuse estimates to analyze change in rates over time,

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[6] Kennedy-Hendricks A, Richey M, McGinty EE, Stuart EA, Barry CL, Webster DW. "Opioid Overdose Deaths and Florida's Crackdown on Pill Mills", *American Journal of Public Health* 2016;106(2):291-297.

incorporating utilization metrics (here, number of tablets dispensed in the coverage area) as either an offset (i.e., modeling the change in utilization-based rate) or a covariate (i.e., adjusting for the independent contribution of utilization to abuse estimates). For additional detail on model specifications, see DBVII review.

Table 3: Statistical model parameterization and specification

Model number	Regression Structure	Offset	Covariate	Objective
Model 1	Poisson Regression Model	Total Assessments	NA	Pre-post means analysis, descriptive trend analysis
Model 2	Poisson Regression Model	Dosage Units Dispensed	NA	Pre-post means analysis, descriptive trend analysis
Model 2a	Poisson Regression Model	Dosage Units Dispensed	Total Assessments	Pre-post means analysis, descriptive trend analysis
Model 3	Poisson Regression Model	NA	Dosage Units dispensed (continuous)	Pre-post means analysis, descriptive trend analysis
Model 3a	Poisson Regression Model	NA	Dosage Units Dispensed (continuous), Total Assessments	Pre-post means analysis, descriptive trend analysis
Model 4	Poisson Regression Model	NA	Dosage Units Dispensed (categorical)	Pre-post means analysis, descriptive trend analysis
Model 4a	Poisson Regression Model	NA	Dosage Units Dispensed (categorical), Total assessments	Pre-post means analysis, descriptive trend analysis

Model 1i*	Interrupted Time Series Poisson	Total Assessments	NA	Interrupted Time Series (ITS), immediate shift and change in slope
Model 2i*	Interrupted Time Series Poisson	Dosage Units Dispensed	NA	ITS, immediate shift and change in slope
Model 2ai*	Interrupted Time Series Poisson	Dosage Units Dispensed	Total Assessments	
Model 3i	Interrupted Time Series Poisson	NA	Dosage units dispensed (continuous)	ITS, immediate shift and change in slope
Model 3ai	Interrupted Time Series Poisson	NA	Dosage Units Dispensed (continuous), Total Assessments	

*These models were originally model 5, 6, and 6a in the study protocol.

Descriptive analyses were performed, stratifying by demographic characteristics of the study population before and after reformulation, for individuals endorsing each drug. The percentage of the study population endorsing OxyContin and each comparator, stratified by age, gender, race, self-reported pain, treatment modality, history of injection, and number of opioids endorsed in past 30 days is presented in section 3.4.2.
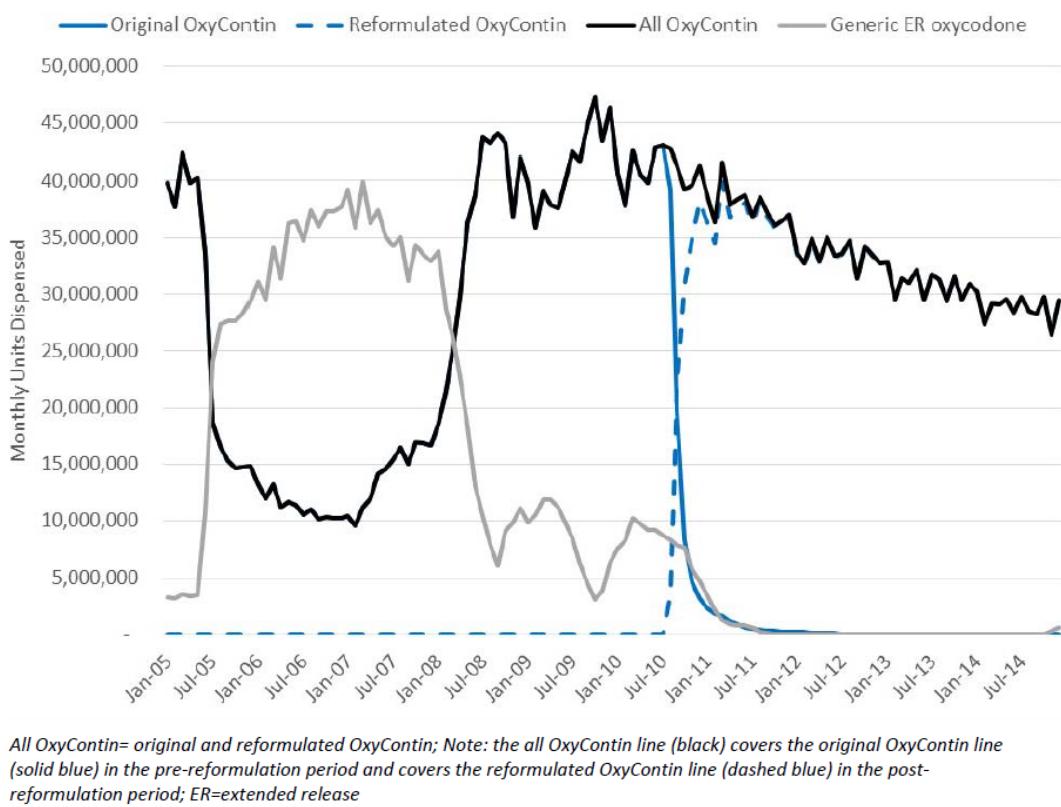
A note on terminology - in the final study report, the sponsor refers to a "ratio of risk ratios" to assess changes in abuse rate for OxyContin versus comparators. It is important to keep in mind that this is an ecologic study using serial cross-sectional data and does not assess risk in the traditional sense, i.e., the probability of an event occurring as a function of time, as in a cohort study where well-defined populations at risk for an outcome are followed through time to estimate the incidence of an event of interest over a particular time period. Instead, this study measures the number of reports of abuse of specific drugs over defined periods of time and can be conceptualized as either a proportion or prevalence (e.g., percent of total surveys endorsing a specific drug) or a rate or even a ratio (e.g., abuse reports per units of drug dispensed during a time period). **In this review, we use the term "rate" in a general manner to refer to the various estimates produced by regression models, and to RORR as "ratio of rate ratios".** In this study report, we limit our use of the term "significant" to indicate statistical significance, indicating a confidence interval that does not span zero, or a p value less than 0.05. Significance in this review does not necessarily indicate clinical or public health significance.

3.4 STUDY RESULTS

3.4.1 Drug Utilization Patterns During Study Period

Trends in OxyContin utilization varied widely throughout the study period (Figure 7). There was a sharp decline in OxyContin units dispensed in January 2005 due to a temporary loss of patent, during which time there was a subsequent increase in generic ER oxycodone units dispensed. The OxyContin patent was reinstated in 2007, after which OxyContin units dispensed increased to similar levels as those before the patent was lost. Generic ER oxycodone products decreased sharply at this point, and by 2011, generic dispensing had further declined to trivial levels. There was a rapid transition from original to reformulated OxyContin after introduction of the reformulated product in August 2010. Since then, there has been a steady decrease in OxyContin utilization.

Figure 7: Estimated number of OxyContin tablets dispensed per quarter between 1Q2005 and 4Q2014 in the IQVIA database
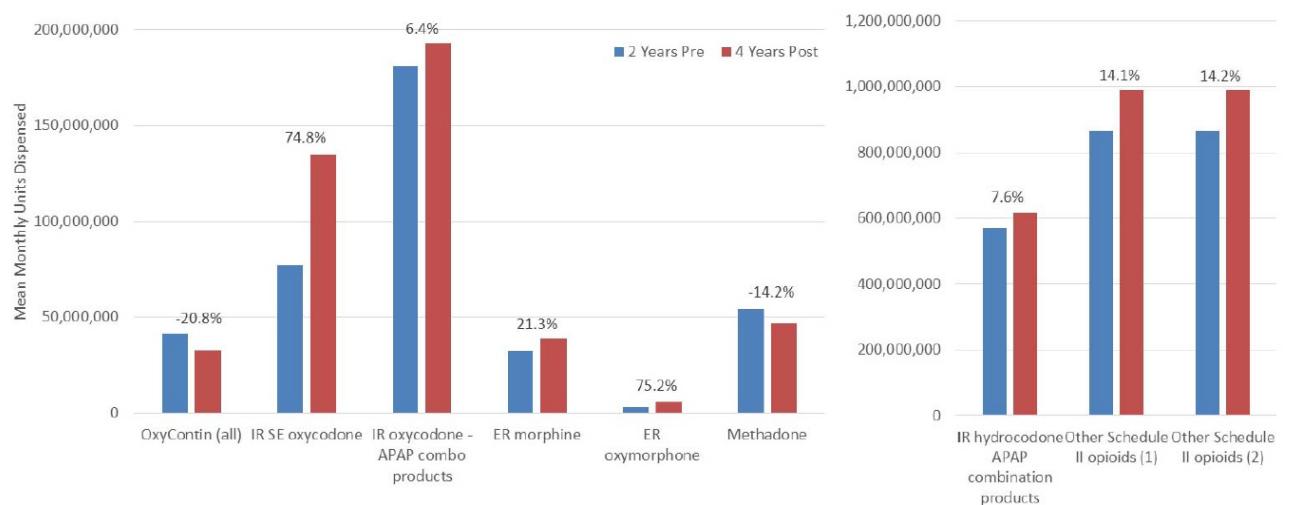
All OxyContin= original and reformulated OxyContin; Note: the all OxyContin line (black) covers the original OxyContin line (solid blue) in the pre-reformulation period and covers the reformulated OxyContin line (dashed blue) in the post-reformulation period; ER=extended release

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 4-1. OxyContin tablets per quarter between 1Q2005 and 4Q2014 as assessed by retail pharmacy dispensing in the IQVIA database. P. 269.)

As shown in Figure 8, there was a -20.8% decrease in tablets dispensed per month for all OxyContin in the 2-year pre-period compared to the 4-year post-period. In contrast, IR oxycodone, ER morphine, ER oxymorphone, IR hydrocodone, and "other schedule II opioids" all showed an increase in dispensing in the post-period. Drug utilization for the

composite "other schedule II opioids" was analyzed with and without ER hydromorphone because ER hydromorphone entered the market 3 months before OxyContin reformulation, and therefore was not consistently on the market throughout the entire study period. The second definition of "other schedule II opioids", which includes ER hydromorphone, was the definition used in the study. Methadone was the only comparator to show a decrease in utilization similar to OxyContin, falling -14.2% from the pre- to the post-period.

Figure 8: Percent change in tablets for OxyContin and comparator opioids from the 2 years before to 4 years after reformulation
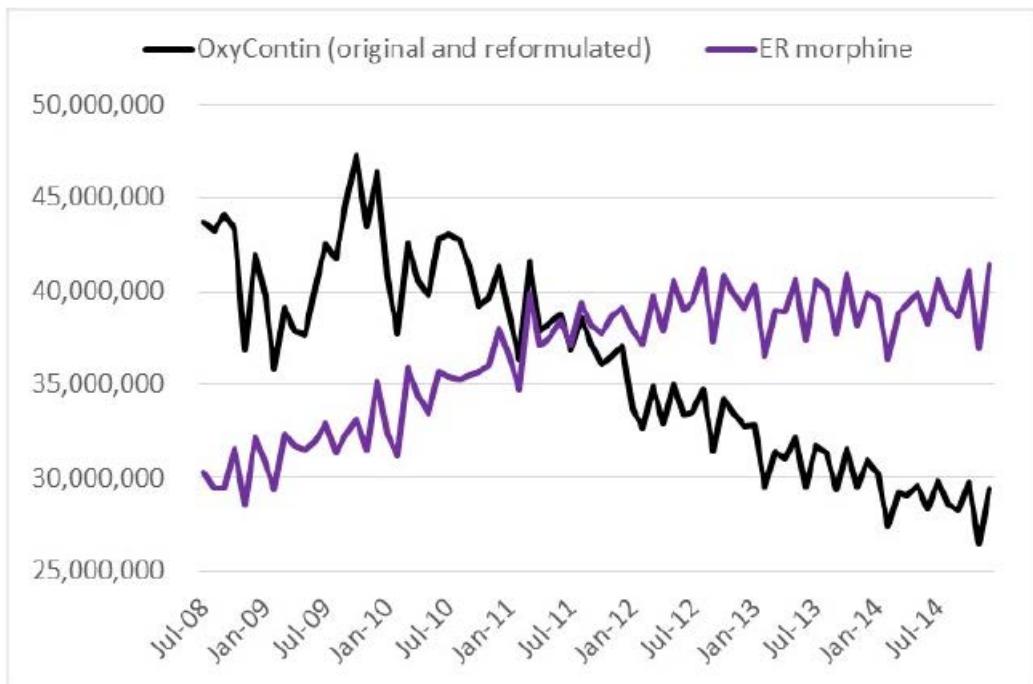
IR=immediate release; SE=single entity; ER=extended release; other Schedule II opioids (1) = IR SE oxycodone, IR oxycodone combination products, ER morphine, ER oxymorphone, IR hydrocodone combination products; other Schedule II opioids (2) = IR SE oxycodone, IR oxycodone combination products, ER morphine, ER oxymorphone, IR hydrocodone combination products, ER hydromorphone (This definition was used in the study.)

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 4-2. Percent change in tablets for OxyContin and comparator opioids from 2 years before to 4 years after reformulation. P. 270.)

Key: IR: Immediate Release; SE: Single Entity; ER: Extended Release; APAP: acetaminophen

Figure 9 shows monthly dosage units dispensed over the study period for OxyContin and ER morphine, which is a primary comparator in the study. While OxyContin shows some variability from 2008-2010, followed by a general decrease in monthly dosage units dispensed beginning around the time of the reformulation in 2010, ER morphine shows a steady increase from 2008-2012, followed by stable dispensing from 2013-2014.

Figure 9: Estimated number of monthly dosage units dispensed for all OxyContin and ER morphine from US Pharmacies from July 2008-December 2014
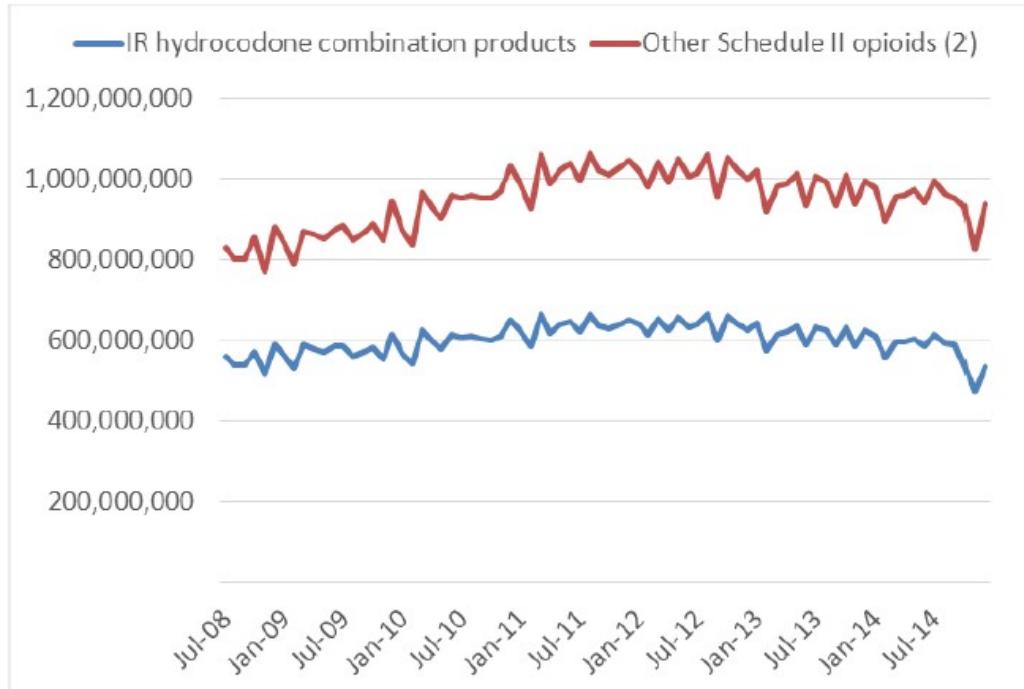
ER=extended release

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Figure 7-8. Monthly dosage units dispensed for all OxyContin and ER morphine from July 2008-December 2014. P. 49.)

Key: ER: Extended Release

"Other schedule II opioids" and IR hydrocodone each show an increase in dispensing from 2008 until about 2011, at which point dispensing declined modestly (Figure 10).

Figure 10: Estimated number of monthly tablets dispensed for IR hydrocodone acetaminophen combination products and "other schedule II opioids" from US pharmacies from July 2008-December 2014

IR=immediate release; other Schedule II opioids (2) = IR SE oxycodone, IR oxycodone combination products, ER morphine, ER oxymorphone, IR hydrocodone combination products, ER hydromorphone

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 4-3. Monthly tablets for IR hydrocodone acetaminophen combination products and other schedule II opioids from July 2008-December 2014. P. 271.)

Key: IR: Immediate Release

3.4.2 Descriptive Characteristics of Individuals and Treatment Modalities Captured in ASI-MV

Table 4 shows descriptive data for demographics and other characteristics of individuals assessed during the study period within the consistent set of sites that contributed assessments in every quarter of the study period. The majority of those endorsing abuse of OxyContin or comparator opioids were aged 21 to 34. The proportion abusing OxyContin who were younger than 21 years decreased in the post-period and the proportion who were 35-54 years increased slightly. A slight majority were male across all opioids and a large majority were white. Treatment modality was residential/inpatient for approximately half of the population across all opioids in the pre- and post-periods. This proportion increased slightly for those reporting abuse of OxyContin in the post-period. The next largest treatment modality was outpatient/non-methadone at ~30%, and this decreased slightly among those reporting abuse of OxyContin in the post-period. The percentage of patients reporting abuse of OxyContin who had a history of injection of at least one prescription opioid was similar in the pre- and post-periods (54.0% and 55.7%, respectively). This was higher than history of injection abuse among those reporting abuse of IR hydrocodone or "other schedule II opioids", but lower than the percentage of

those reporting abuse of ER morphine with previous history of injection. The median number of opioids endorsed for abuse in the past 30-days remained relatively constant among those reporting abuse of OxyContin, at 6 opioids in the pre- and post-period. The median number of opioids endorsed in past 30 days decreased in the post-period for ER morphine, IR hydrocodone, and "other schedule II opioids".

Table 4: Demographic characteristics of individuals indicating past 30-day abuse of OxyContin, ER morphine, IR hydrocodone combination products, and "other schedule II opioids" in the pre- and post-periods for sites contributing quarterly data.

Response		All OxyContin Pre (n=483)	All OxyContin Post (n=542)	ER Morphine Pre (n=183)	ER Morphine Post (n=334)	IR Hydrocodone Pre (n=266)	IR Hydrocodone Post (n=588)	Other Schedule II Pre (n=539)	Other Schedule II Post (n=1,463)
Age (%)	Younger than 21	19.25	14.58	16.94	15.57	22.56	19.73	19.11	15.65
	21 to 34	62.32	62.18	65.57	65.57	51.13	53.74	53.99	58.78
	35 to 54	17.81	21.22	16.94	18.86	26.32	23.30	26.16	23.31
	55 and older	0.62	2.03	0.55	0.00	0.00	3.23	0.74	2.26
Gender (%)	Male	56.94	55.72	52.46	52.99	53.01	51.36	56.59	53.45
	Female	43.06	44.28	47.54	47.01	46.99	48.64	43.41	46.55
Race (%)	White	82.82	75.09	91.26	88.32	79.32	77.89	79.41	75.73
	Black	6.42	10.70	2.19	2.99	7.14	9.35	9.28	10.94
	Hispanic	7.66	11.07	2.73	5.69	8.65	7.99	7.42	9.98
	Other	3.11	3.14	3.83	2.99	4.89	4.76	3.90	3.35
Self-reported pain (%)	Yes	44.72	49.82	49.18	55.09	52.26	54.93	51.02	52.90
	No	55.28	50.00	50.82	44.61	47.37	44.90	48.61	46.82
	Unknown/Missing	0.00	0.18	0.00	0.30	0.38	0.17	0.37	0.27
Modality (%)	Residential/Inpatient	55.28	57.20	56.28	55.09	45.86	42.69	49.17	49.35
	Outpatient/Non-methadone	29.61	24.54	34.97	36.83	34.96	36.90	32.65	30.08
	Methadone/LAAM	3.73	6.83	2.73	2.10	1.88	4.25	2.60	6.22
	Drug Court	0.83	1.66	1.09	0.90	1.13	2.21	1.11	1.44
	Probation/Parole	5.80	2.77	2.19	1.20	6.39	4.25	6.86	3.96
	DUI/DWI	1.45	0.92	1.64	0.60	2.26	2.55	2.23	2.19
	Other corrections	0.83	0.92	0.00	0.90	2.63	1.70	1.67	1.23
	TANF (Welfare)	0.41	0.18	0.00	0.00	0.00	0.00	0.00	0.07
	Other	2.07	3.51	1.09	0.90	4.89	4.08	3.71	3.90
	Unknown/Missing	0.00	1.48	0.00	1.50	0.00	1.36	0.00	1.57
History of injection (%)	At least one prescription opioid injected	54.04	55.72	78.69	75.15	31.95	31.46	43.60	42.24
Number of opioids past 30 days	Mean	6.84	6.55	8.97	6.78	6.38	5.23	6.32	4.81
	Median	6	6	8	6	5	4	5	4

All OxyContin=original and reformulated OxyContin; LAAM=Levacetylmethadol; DUI=driving under the influence; DWI=driving while intoxicated; TANF=temporary assistance for needy families; ER=extended release; IR Hydrocodone=immediate release hydrocodone combination products

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Table 7-1. Population characteristics of non-oral abusers among sites contributing quarterly assessment data -2y/4y. P. 34.)

Key: ER: Extended Release; IR: Immediate Release; LAAM: Levomethadyl Acetate; DUI: Driving Under the Influence; DWI: Driving While Intoxicated; TANF: Temporary Assistance for Needy Families

A descriptive graph of OxyContin wholesale acquisition price can be found in appendix 6.2.

3.4.3 Assessment of Trends in Non-oral Abuse for OxyContin, Primary, and Secondary Comparator Opioids Using Descriptive Graphs of Quarterly Estimates

Figures below show trends in model estimated quarterly rates of abuse by non-oral routes for OxyContin and comparator opioids.
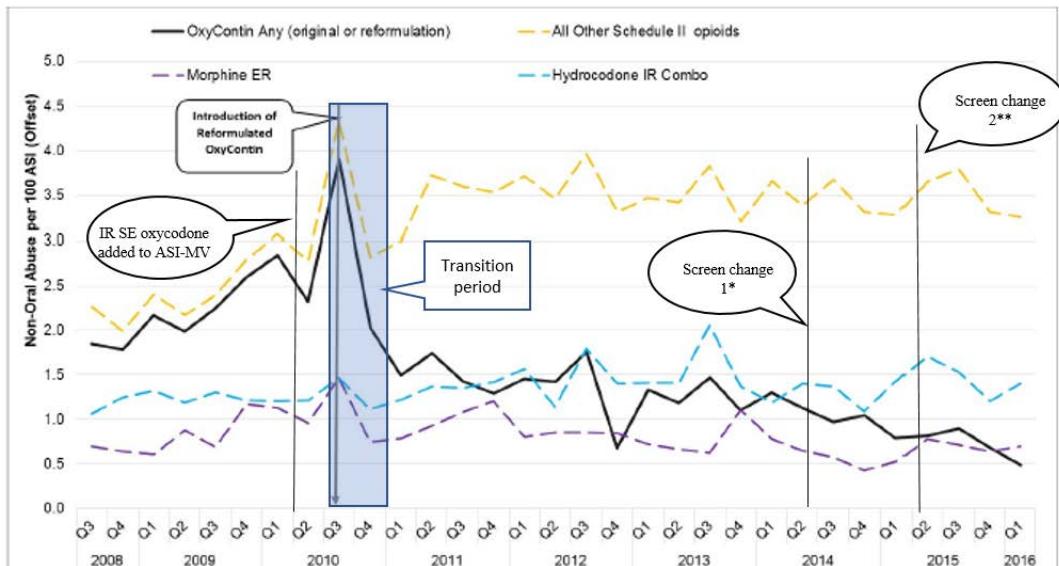
Analysis parameters:
- Sites: contributing $\geq$ 1 assessment/quarter *
- OxyContin definitions
    - Any OxyContin (original or reformulated)
    - Original pre-period, reformulated post-period
- Unit of analysis: 3-digit ZIP
- Model #1:
    - Offset: Total Assessments
    - Covariates: NA
- Model #2:
    - Offset: Dosage units dispensed
    - Covariate: NA
- Model #3:
    - Offset: NA
    - Covariate: Dosage units dispensed (continuous)

*With the exception of Figure 15, which is $\geq$1 assessment/year

Figure 11 depicts trends in quarterly non-oral abuse rates per 100 assessments for OxyContin and primary comparators. OxyContin and "all other schedule II opioids" have the highest abuse rates until OxyContin reformulation at 3Q2010, at which point OxyContin rates decrease to levels similar to ER morphine and IR hydrocodone combination products. Comparator opioids shown in the graph do not have a similar decrease at the time of transition. The decreased rate of OxyContin abuse first observed after reformulation continues into the rest of the post-period.

Figure 11: Model 1 estimated rate of <u>non-oral </u>abuse cases <u>per 100 assessments</u> over time for OxyContin and primary comparator opioids

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study.

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Figure 7-9. Model-estimated rate of abuse cases per assessments over time for OxyContin and primary comparator opioids (Model 1). P. 52.)

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 1 models abuse rate per ASI-MV assessments

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Figure 13 below stratifies the composite "other schedule II opioids", demonstrating that the rise in the composite category is largely driven by the increase in IR oxycodone in 2Q2010 when IR SE oxycodone was incorporated into the ASI-MV survey. The similarity in trends observed for OxyContin and "other schedule II opioids" until 3Q2010 is due to a high level of individuals that endorsed both OxyContin and another schedule II opioid (see table 21 in appendix 6.3).

Figure 12: Past 30-day <u>non-oral</u> abuse rates <u>per 100 assessments</u> for individual drug groups that make up the "other schedule II opioids" group and OxyContin from 3Q2008-1Q2016

(Source: FDA Postmarketing Requirement Study 3051-1, Purdue Response to FDA Information and Analyses Request on October 2019 Phase 1 Part 2. Title: Figure 1: Past 30-day abuse for individual drug groups that make up the other schedule II opioids group and OxyContin from 3Q2008-1Q2016 (Model 1). p. 39.)
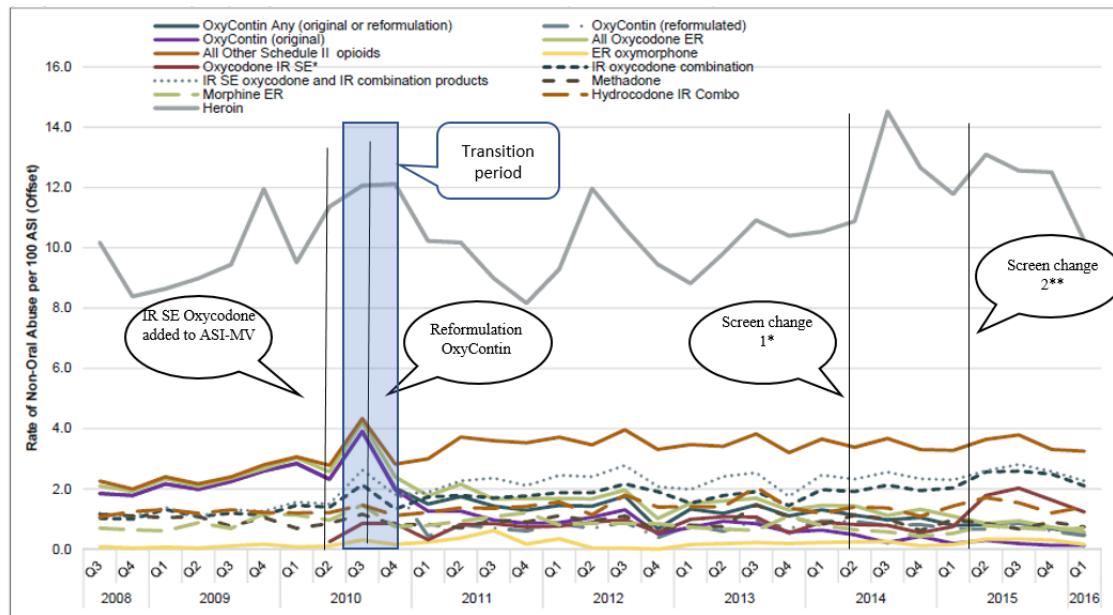
Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 1 models abuse rate per ASI-MV assessments

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Figure 14 depicts quarterly trends in non-oral abuse prevalence per 100 assessments for OxyContin and all comparators. High rates of heroin non-oral abuse make assessing individual trends for other opioids difficult here. It is notable that there was not an apparent increase in heroin abuse (non-oral) in this population following OxyContin's reformulation, although this differs for the ≥1 assessment/year population, Figure 15 below. Of note as well, is the decreased rate of abuse of reformulated OxyContin alone compared to any OxyContin, which includes the endorsements of original OxyContin that continued into the post-period. ER oxycodone overall has a higher rate of abuse post-period than OxyContin, alone, even though dispensing of generic ER oxycodone in the post-period was trivial.

Figure 13: Model 1 estimated rate of <u>non-oral</u> abuse cases <u>per 100 assessments</u> over time for OxyContin and all comparator opioids

IR=immediate release; ER=extended release; *Data for oxycodone IR single-entity (SE) is not presented prior to 2Q2010.

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 13-1. Model 1: Past 30-day non-oral abuse among sites contributing at least one assessment each quarter from the two-year pre-period to the four-year post-period, ASI-MV® assessments as offset (3Q2008-1Q2016). P. 525.)
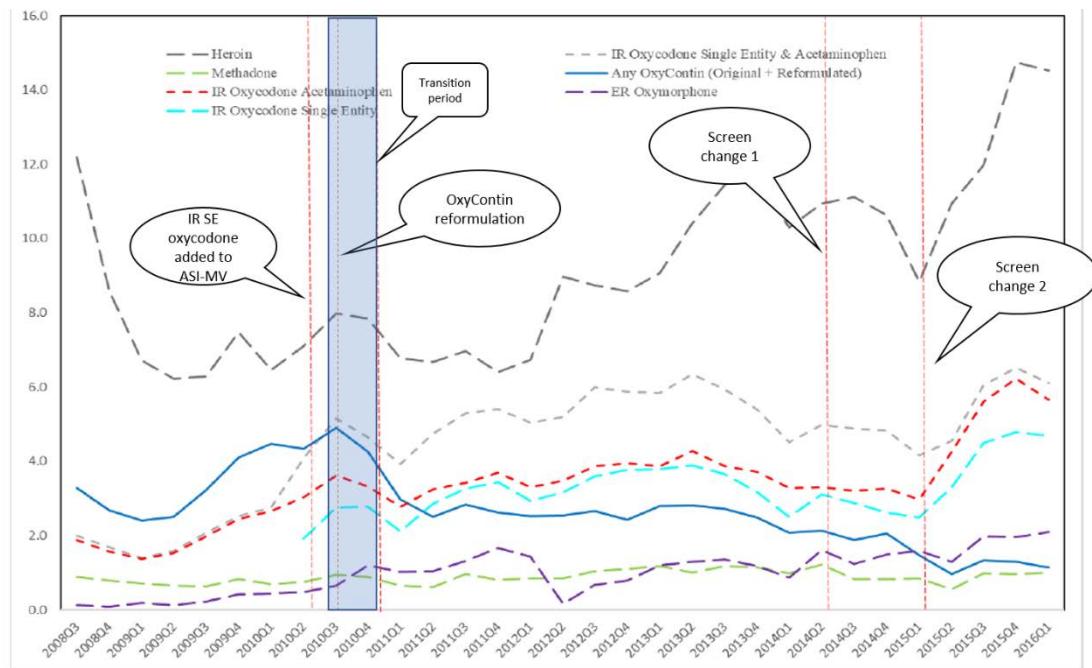
Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 1 models abuse rate per ASI-MV assessments

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Figure 15 below shows estimated non-oral abuse cases per 100 assessments for sites contributing >1 assessments/year. This sample includes a larger number of sites and includes sites in the Northeast region. With this expanded sample, heroin abuse decreased from 2008-2009, then remained relatively constant until early 2012 when abuse cases began to rise.

Figure 14: Model 1 estimated <u>non-oral</u> abuse cases <u>per 100 assessments</u> for OxyContin and all comparator opioids, <u>>1 assessments/year</u>

(Source: Sponsor response to FDA information request sent March 12, 2020, received April 24, 2020. Figure 7-1: Trend analysis in non-oral abuse rate using sites with at least 1 assessment per year: any OxyContin (original + reformulated) with secondary comparator opioids – Model 1: assessments as offset. P. 4.)
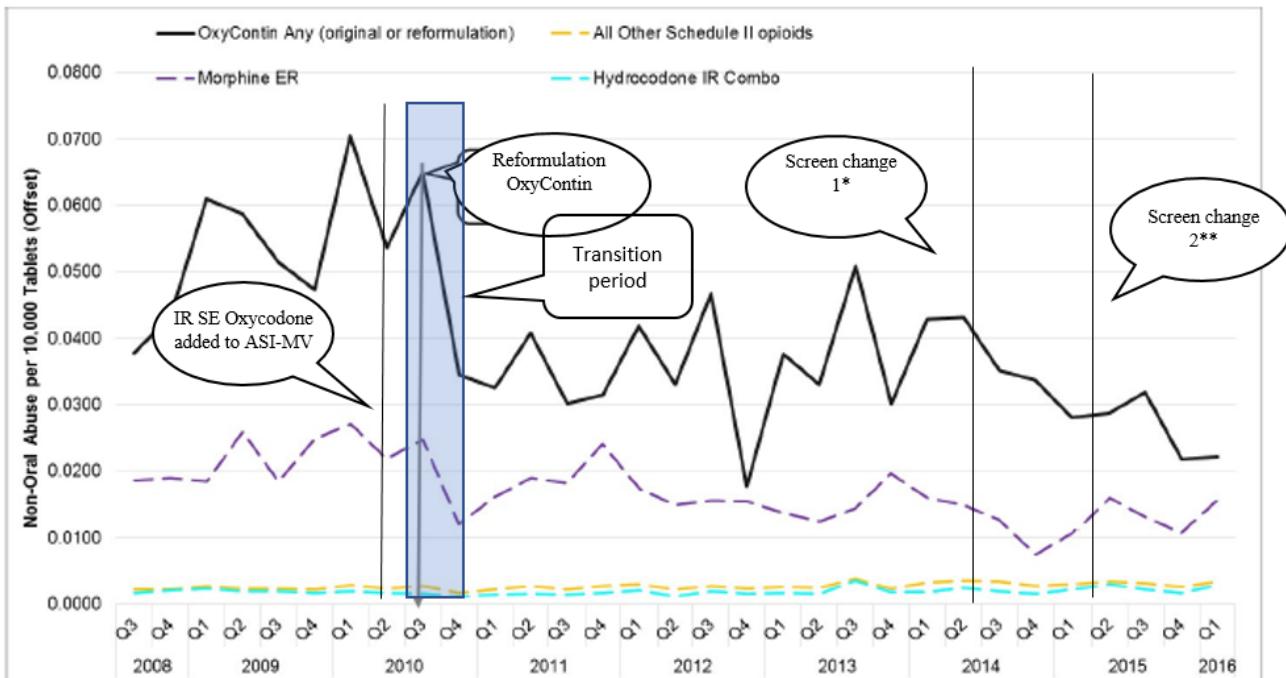
Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 1 models abuse rate per ASI-MV assessments

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Figure 16, which uses the consistent set of sites contributing at least one assessment per quarter, depicts trends in quarterly non-oral abuse rates per 10,000 dosage units dispensed for OxyContin and primary comparators. Quarterly OxyContin non-oral abuse rates show a modest decrease upon reformulation and remain lower in the post-period than in the pre-period. However, in both the pre-and post-periods, OxyContin had higher rates of non-oral abuse than morphine ER, hydrocodone IR combination products, or "other schedule II opioids".

Figure 15: Model 2 estimated rate of <u>non-oral</u> abuse cases <u>per 10,000 dosage units dispensed</u> over time for OxyContin and primary comparator opioids

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Figure 7-10 Model-estimated rate of abuse cases per dosage units dispensed over time for OxyContin and primary comparator opioids. P. 53.)

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2 models abuse rate per tablets dispensed

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Figure 17 below presents trends in utilization-based, quarterly, non-oral abuse for OxyContin (any OxyContin, original OxyContin only, and reformulated OxyContin only), primary comparators, and secondary comparators. Notable here, is the fact that original OxyContin cases remained prevalent well into the post-period despite the fact that dispensing data show an almost complete cessation of original OxyContin dispensing once the reformulated OxyContin became available. Cases endorsing abuse of original OxyContin declined somewhat after the first screen change, in 2014, when original OxyContin was made less prominent as a selection option on the screen.

Figure 16: Model 2 estimated rate of <u>non-oral</u> abuse cases <u>per 10,000 dosage units dispensed</u> over time for OxyContin and all comparator opioids

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 13-2. Model 2: Past 30-day non-oral abuse among sites contributing at least one assessment each quarter from the two-year pre-period to the four-year post-period, prescription tablets dispensed as offset (3Q2008-1Q2016). P. 526.)

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2 models abuse rate per tablets dispensed
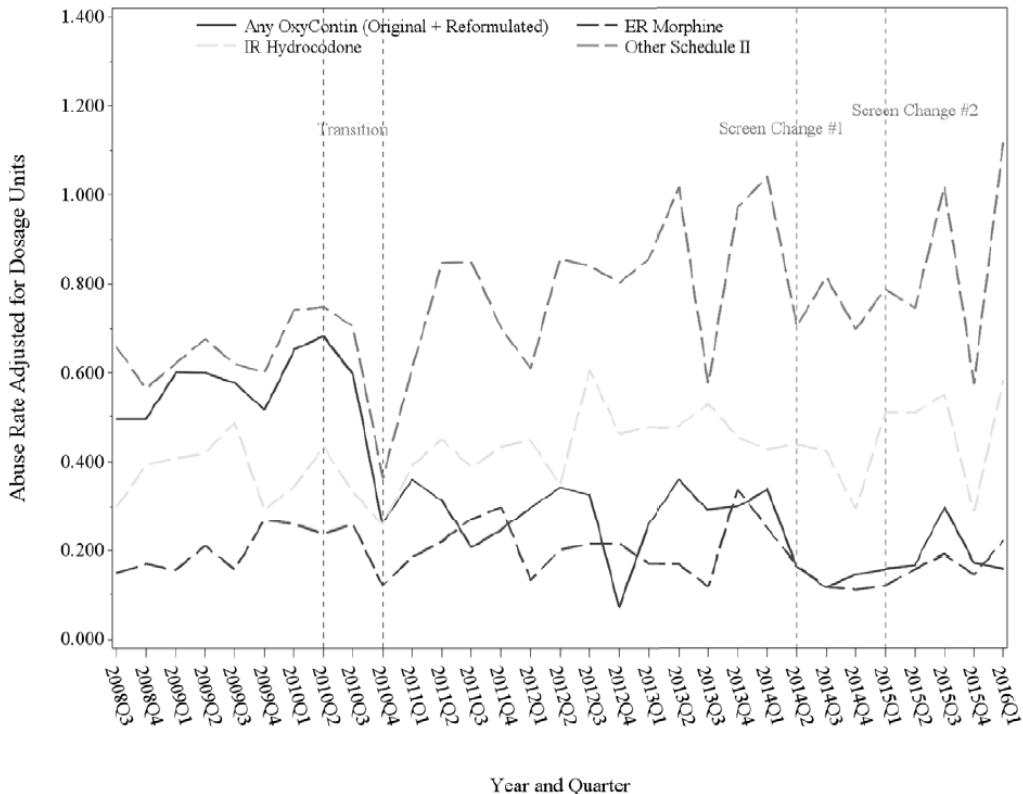
*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Model 2a which adjusts for utilization and total assessments had similar trends to model 2 (appendix 6.3).

Figure 18 depicts quarterly trends in non-oral abuse of OxyContin and primary comparator opioids adjusting for utilization as a covariate in the model. This model shows similar rates of abuse for OxyContin and "other schedule II opioids" in the pre-period, with a sharp decline in both during the transition period. The rates of abuse of "other schedule II opioids" increased subsequently in the post-period, whereas rates of abuse for OxyContin remained at decreased levels, similar to the rates for ER morphine and IR hydrocodone.

Figure 17: Model 3 estimated rate of <u>non-oral</u> abuse cases <u>adjusted for utilization</u> over time for OxyContin and primary comparators

(Source: Purdue Response to FDA information and analyses request on May 30, 2019. Submitted August 2019. Title: Figure 1-1A-5-3. Trend Analysis in Non-oral Abuse Rate Using Sites with at least 1 Assessment per Quarter: Any OxyContin (Original + Reformulated) with Primary Comparator Opioids – Model 3: dosage units dispensed (continuous) as covariate. P. 23.)

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2 models abuse rate adjusted for tablets dispensed as a covariate

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Model 3a estimated quarterly rates of non-oral abuse for OxyContin and comparators are presented in Figure 52 in appendix 6.3. Quarterly trends for these estimates are similar to model 1.

Descriptive trend analyses for non-oral abuse in sites contributing ≥1 assessment/year are provided in appendix 6.3. Quarterly trends for OxyContin abuse in sites contributing ≥1 assessment/year showed a more modest decrease in abuse in the post-period than in sites contributing ≥1 assessment/quarter. Figures 61-62 in appendix 6.3 show unmodeled rates of non-oral abuse, per 100 assessments, and per 10,000 dosage units dispensed, which generally agree with trends from models 1 and 2.
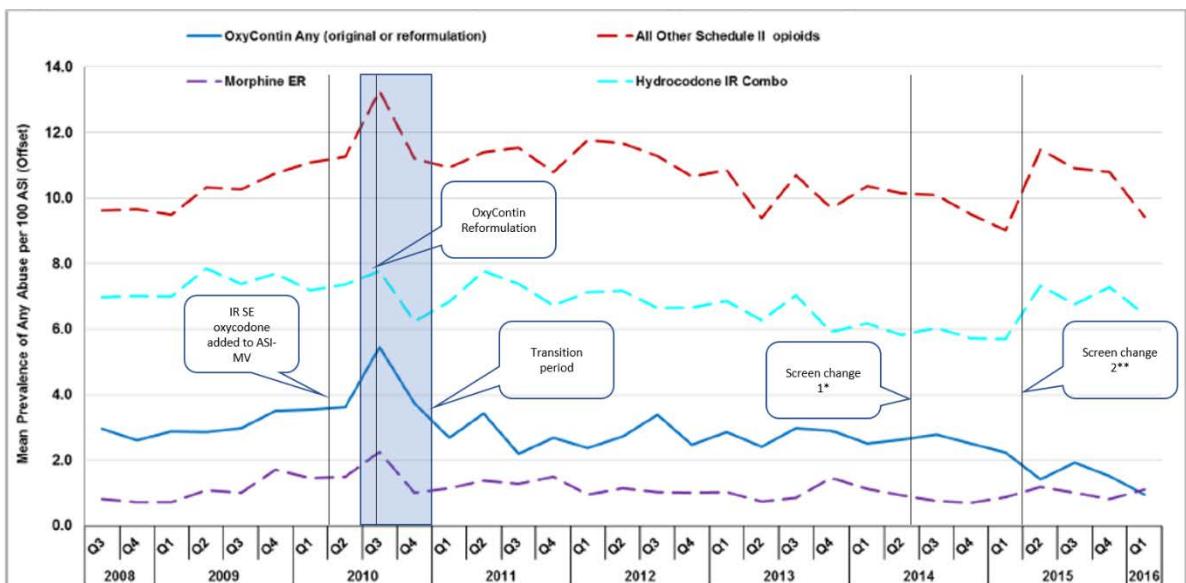
3.4.4 Assessment of Trends in Abuse of OxyContin, Primary, and Secondary Comparator Opioids <u>Via Any Route</u> Using Descriptive Graphs of Quarterly Estimates

Analysis parameters:
- Sites: contributing $\geq$ 1 assessment/quarter
- OxyContin definitions
  - Any OxyContin (original or reformulated)
  - Original pre-period, reformulated post-period
- Unit of analysis: 3-digit ZIP
- Model #1:
  - Offset: Total Assessments
  - Covariates: NA
- Model #2:
  - Offset: Dosage units dispensed
  - Covariate: NA

Figure 19-20 show trends in quarterly prevalence of abuse via any route for OxyContin and primary comparators (figure 19), and OxyContin and all comparators (figure 20) using number ASI-MV assessments as a denominator. The rates of any OxyContin abuse via any route were lower than those for heroin or hydrocodone IR combination products and higher than ER morphine. Here, any OxyContin abuse rates decreased following reformulation, returning to rates fairly similar to those seen in the early pre-period, and then declining further following ASI-MV screen changes. OxyContin abuse rate reductions are greater when only reformulated OxyContin is included in the post-period.

Figure 18: Model 1 descriptive trend analysis figure: <u>any route</u> of abuse for OxyContin and primary comparator opioids <u>per 100 assessments</u>, 3Q2008-1Q2016

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study. OxyContin was reformulated in August 2010.

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 10-1. Model 1 descriptive trend analysis figure: Any route of abuse. P. 351.)

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 1 models abuse rate per ASI-MV assessments

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Figure 19: Model 1 estimated <u>any route</u> abuse rates <u>per 100 assessments</u> over time for OxyContin and all comparator opioids

IR=immediate release; ER=extended release; *Data for oxycodone IR single-entity (SE) is not presented prior to 2Q2010.

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 13-11. Model 1: Past 30-day abuse via any route among sites contributing at least one assessment each quarter from the two-year pre-period to the four-year post-period, ASI-MV® assessments as offset (3Q2008-1Q2016). P. 535.)
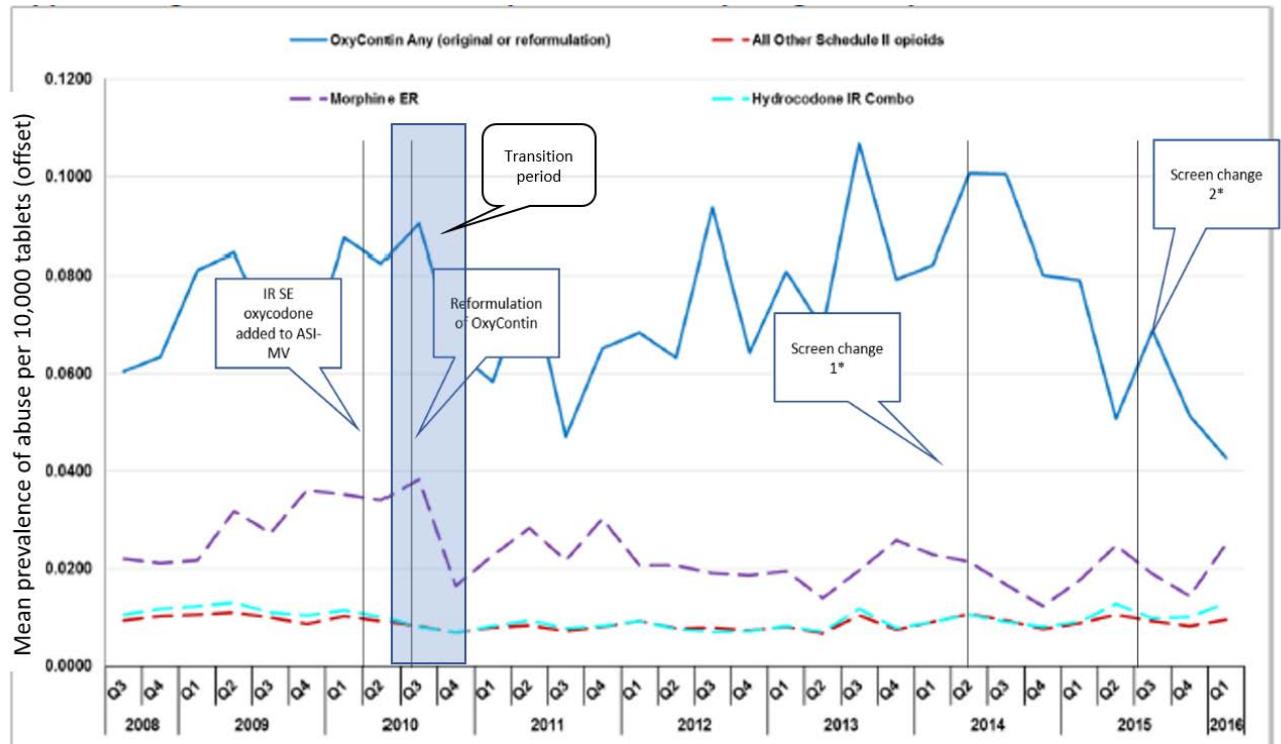
Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 1 models abuse rate per ASI-MV assessments

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Figure 21-22 depict trends in quarterly abuse of any OxyContin and primary comparators (figure 21) and all comparator opioids (figure 22) via any route, per dosage units dispensed. These graphs show the quarterly rates of OxyContin abuse decreasing from 3Q2010-2Q2011, before beginning to rise to rates above those seen in the pre- period and then declining again following ASI-MV screen changes.

Figure 20: Model 2 descriptive trend analysis figure: <u>any route</u> of abuse for OxyContin and primary comparator opioids <u>per 10,000 dosage units dispensed</u>, 3Q2008-1Q2016

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study. OxyContin was reformulated in August 2010.

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 10-2. Model 2 descriptive trend analysis figure: Any route of abuse. P.352.)

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2 models abuse rate per tablets dispensed

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Figure 21: Model 2 estimated <u>any route</u> abuse rates <u>per 10,000 dosage units</u> dispensed over time for OxyContin and all comparator opioids

IR=immediate release; ER=extended release; *Data for oxycodone IR single-entity (SE) is not presented prior to 2Q2010.

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 13-12. Model 2: Past 30-day abuse via any route among sites contributing at least one assessment each quarter from the two-year pre-period to the four-year post-period, prescription tablets dispensed as offset (3Q2008-1Q2016).)

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2 models abuse rate per tablets dispensed

Sensitivity analyses for additional models and quarterly trends for sites contributing ≥1 assessment/year are presented in appendix 6.4. Unmodeled quarterly trends for endorsements via any route are also presented in appendix 6.4.

3.4.5 Pre- and Post-period Mean Non-oral Abuse Rates for OxyContin and Primary Comparators (Descriptive Means Analysis)

Figures below present change in mean quarterly estimated non-oral abuse rate for OxyContin and comparators in the pre- vs. post-periods.

Analysis parameters:
- Sites: contributing ≥ 1 assessment/quarter
- OxyContin definition: any OxyContin (original or reformulated)
- Time period -2y/4y
- Unit of analysis: Respondent 3-digit ZIP code
- Model #1:
  - Offset: Total Assessments
  - Covariates: NA
- Model #2:
  - Offset: Dosage units dispensed
  - Covariates: NA
- Model #3:
  - Offset: NA
  - Covariate: Dosage units dispensed (continuous)

Mean quarterly model-estimated non-oral abuse rates in the pre- and post-period are presented in table 5. Model 1 estimates mean quarterly non-oral abuse cases per 100 assessments, model 2 estimates mean quarterly non-oral abuse cases per 10,000 tablets dispensed, and model 3 estimates mean quarterly non-oral abuse cases adjusted for drug utilization. Estimates produced by all three models demonstrate a decline in mean non-oral abuse rate of OxyContin abuse in the post-period. Model 3 demonstrates the largest decrease. Mean abuse rates for comparators generally either remained constant between the pre- and post-period, or increased slightly, although it should be noted that OxyContin mean quarterly rates were generally still higher than comparators when adjusting for utilization, even in the post-period.

Table 5: Pre and post-period estimates of mean quarterly <u>non-oral</u> abuse cases for OxyContin and primary comparators

	Model 1		Model 2		Model 3	
	Mean quarterly estimated abuse cases/100 respondents		Mean quarterly estimated abuse cases/10,000 dosage units dispensed		Mean quarterly estimated abuse cases adjusted for dosage units dispensed	
	Pre-period Estimate	Post-period Estimate	Pre-period Estimate	Post-period Estimate	Pre-period Estimate	Post-period Estimate
All OxyContin	2.2	1.5	0.05	0.04	0.6	0.3
ER Morphine	0.9	0.8	0.02	0.02	0.2	0.2
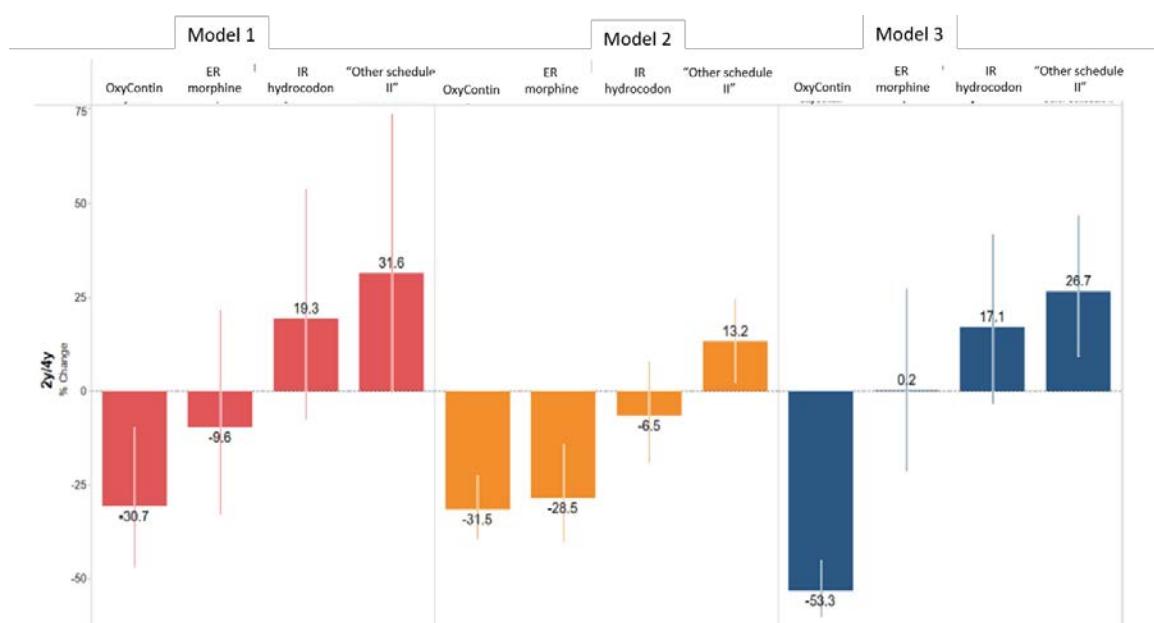
IR hydrocodone	1.4	1.7	0.002	0.002	0.4	0.4
Other schedule II	2.8	3.7	0.003	0.003	0.003	0.003

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Compiled from Appendix 13.)

Key: IR: Immediate Release; ER: Extended Release; Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 3 models abuse rate adjusted for tablets dispensed as a covariate

Figure 23 (and table 22 in appendix 6.5) shows the percent change in non-oral abuse of OxyContin and primary comparator opioids in the pre- vs. post-period. OxyContin consistently showed a decrease in non-oral abuse across all models (range -53.3% to -30.7%), although the largest decrease was observed for model 3. "Other schedule II opioids" consistently showed an increase in non-oral abuse across all models (range +13.2% to +31.6%), while results for IR hydrocodone (range -6.5% to +19.3%) and ER morphine (range -28.5% to +0.2%) were mixed dependent upon the model. The decrease in non-oral abuse of ER morphine was comparable to the decrease observed for OxyContin for model 2, which estimates abuse per dosage units dispensed.

Figure 22: Percent change (95% CI) in <u>non-oral</u> abuse after introduction of reformulated OxyContin, for OxyContin and primary comparator opioids -2y/4y

CI=confidence intervals; IR Hydrocodone=IR hydrocodone combination products; Sites: contributing ≥1 assessment/quarter; OxyContin Definition: Original and Reformulated; Unit of Analysis: Respondent 3-digit ZIP Code; Model 1: Rate of abuse/Assessments. Model 2: Rate of abuse/Dosage units dispensed. Model 3: Abuse count adjusting for dosage units dispensed (continuous).

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Figure 7-6. Percent change (95% CI) in non-oral abuse after introduction of reformulated OxyContin and primary comparator opioids using different modeling approaches -2y/4y. p. 46.)

Key: IR: Immediate Release; ER: Extended Release; Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 3 models abuse rate adjusted for tablets dispensed as a covariate
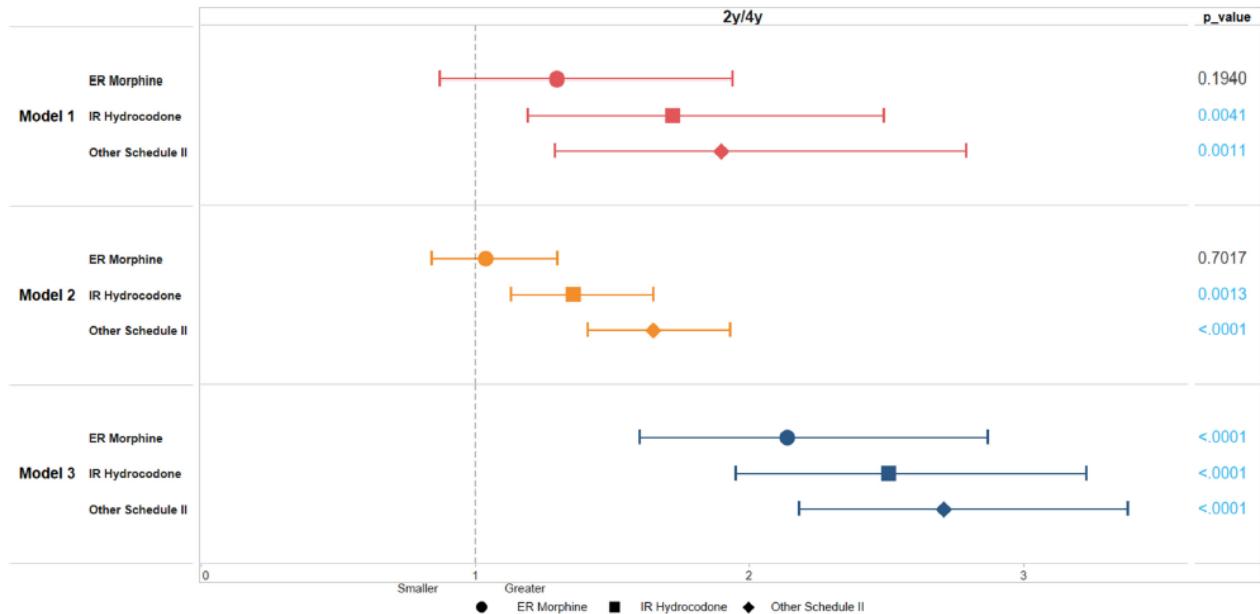
Figure 24 (and table 23 in appendix 6.5) presents ratios of rate ratios (RORRs) comparing the change in rate of non-oral abuse for a comparator opioid in the post- vs. pre-period (numerator) to the change in non-oral abuse for OxyContin in the post- vs. pre-period (denominator). RORR is a type of difference-in-differences model[7] whereby an interaction term tests for a statistically significant relative difference in rate ratios comparing OxyContin's rate ratio to each comparator opioid's rate ratio, further referred to as a ratio of rate ratios (RORR). The RORR parameter can be interpreted as a relative comparison in the rates (null=1) whereby a RORR>1 favors OxyContin with respect to the change in post- to pre-reformulation periods, and a RORR<1 favors the comparator.

RORRs for IR hydrocodone, and "other schedule II opioids" indicate that the decrease in non-oral OxyContin abuse from the pre- to post-period was significantly larger than the decrease for these comparators, regardless of the model. The decrease in non-oral OxyContin abuse from the pre- to the post-period was significantly larger than that for ER morphine abuse only with model #3. Models #1 and #2, which use assessments and dosage units dispensed as offsets, respectively, showed no significant difference for ER morphine vs. OxyContin.

Analyses for percent decrease for OxyContin alone, without comparators is presented in appendix 6.6. These numbers were similar to the percent change decreases presented in analyses above with comparators.

Figure 23: RORR (95% CI) for non-oral abuse after introduction of reformulated OxyContin, primary comparators vs. OxyContin, -2y/4y

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[7] Wing C, Simon K, Bello-Gomez RA. "Designing Difference in Difference Studies: Best Practices for Public Health Policy Research", *Annual Review of Public Health,* 2018;39:453-469.

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: RORR (95% CI) in non-oral abuse after introduction of reformulated OxyContin and primary comparator opioids using different modeling approaches -2y/4y. p. 48.)

Key: IR: Immediate Release; ER: Extended Release; Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 3 models abuse rate adjusted for tablets dispensed as a covariate

3.4.5.1 Sensitivity Analysis: Additional Regression Models

The analyses above present results from the main models used in this study report: models 1, 2, and 3. Further analyses were conducted with the models below to understand how incorporating total assessments as a covariate effected estimated percent changes in abuse of OxyContin and comparators:

- Model 2a: Offset = dosage units dispensed, covariate = total assessments
- Model 3a: Covariates = Dosage units dispensed (continuous) and total assessments

Table 6 below presents percent change estimates for OxyContin and comparators using models 2a and 3a. Overall, these models did not produce substantially different estimates than the main models above. The range for percent change in OxyContin abuse with the main models presented above was -30.7% to -53.3%, and model 2a and model 3a estimated percent change were just above and below that range, respectively. Model 2a estimated percent change in abuse for ER morphine fell within the range for the main models (-28.5%, +0.2%), while model 3a estimated abuse was just above the range. Model 2a and 3a estimated percent change in abuse of IR hydrocodone fell just below

and above estimates produced by main models (-6.5%, +19.3%), respectively, and model 2a and 3a estimated percent changes in abuse of "other schedule II opioids" fell within the range of the main models (13.3%, 31.6%).

Table 6: Percent change (95% CI) in non-oral abuse after introduction of reformulated OxyContin, for OxyContin and primary comparator opioids, -2y/4y

	Model 2a % change (95% CI)	Model 3a % change (95% CI)
All OxyContin	-29.3 (-37.5, -20.1)	-55.6 (-62.3, -47.6)
ER morphine	-24.5 (-37.0, -9.6)	3.7 (-20.4, 35.1)
IR hydrocodone	-8.2 (-20.6, 6.1)	21.2 (-6.5, 56.9)
Other schedule II	14.5 (3.7, 26.4)	15.3 (-2.2, 36.0)

(Source: FDA generated table from information request response.)

Key: IR: Immediate Release; ER: Extended Release; Model 2a models abuse rate per tablets dispensed adjusted for ASI-MV assessments as a covariate; Model 3a models abuse rate adjusted for tablets dispensed and ASI-MV assessments as a covariate

Table 7 below presents RORR estimates from model 2a and 3a for primary comparators vs. OxyContin. All RORRs estimated with models 2a and 3a showed a significantly larger decrease in non-oral OxyContin abuse than comparator, except for ER morphine vs. OxyContin with model 2a.

Table 7: RORR (95% CI) for non-oral abuse after introduction of reformulated OxyContin, primary comparators vs. OxyContin, -2y/4y

	Model 2a RORR (95% CI)	Model 3a RORR (95% CI)
ER morphine	1.07 (0.86, 1.33)	2.33 (1.71, 3.19)
IR hydrocodone	1.30 (1.07, 1.57)	2.73 (2.01, 3.71)
Other schedule II	1.62 (1.38, 1.90)	2.60 (2.06, 3.28)

(Source: FDA generated table from information request response.)

Key: IR: Immediate Release; ER: Extended Release; Model 2a models abuse rate per tablets dispensed adjusted for ASI-MV assessments as a covariate; Model 3a models abuse rate adjusted for tablets dispensed and ASI-MV assessments as a covariate

Results for model 4, which uses dosage units dispensed as a categorical variable covariate, are presented in appendix 6.7. Model 4 estimated percent change in OxyContin abuse and RORRs for all primary comparators fell within the range of main models.

3.4.5.2   Range of estimates for non-oral abuse produced by different models based on

main study variable definitions:

Figure 25 below synthesizes the descriptive means analyses results above. The figure shows the range of percent change values produced for OxyContin and primary comparator opioids for the different models listed below:

- Model 1: Offset = total assessments
- Model 2: Offset = dosage units dispensed
- Model 2a: Offset = dosage units dispensed, covariate = total assessments
- Model 3: Covariate = dosage units dispensed (continuous)
- Model 3a: Covariates = Dosage units dispensed (continuous) and total assessments
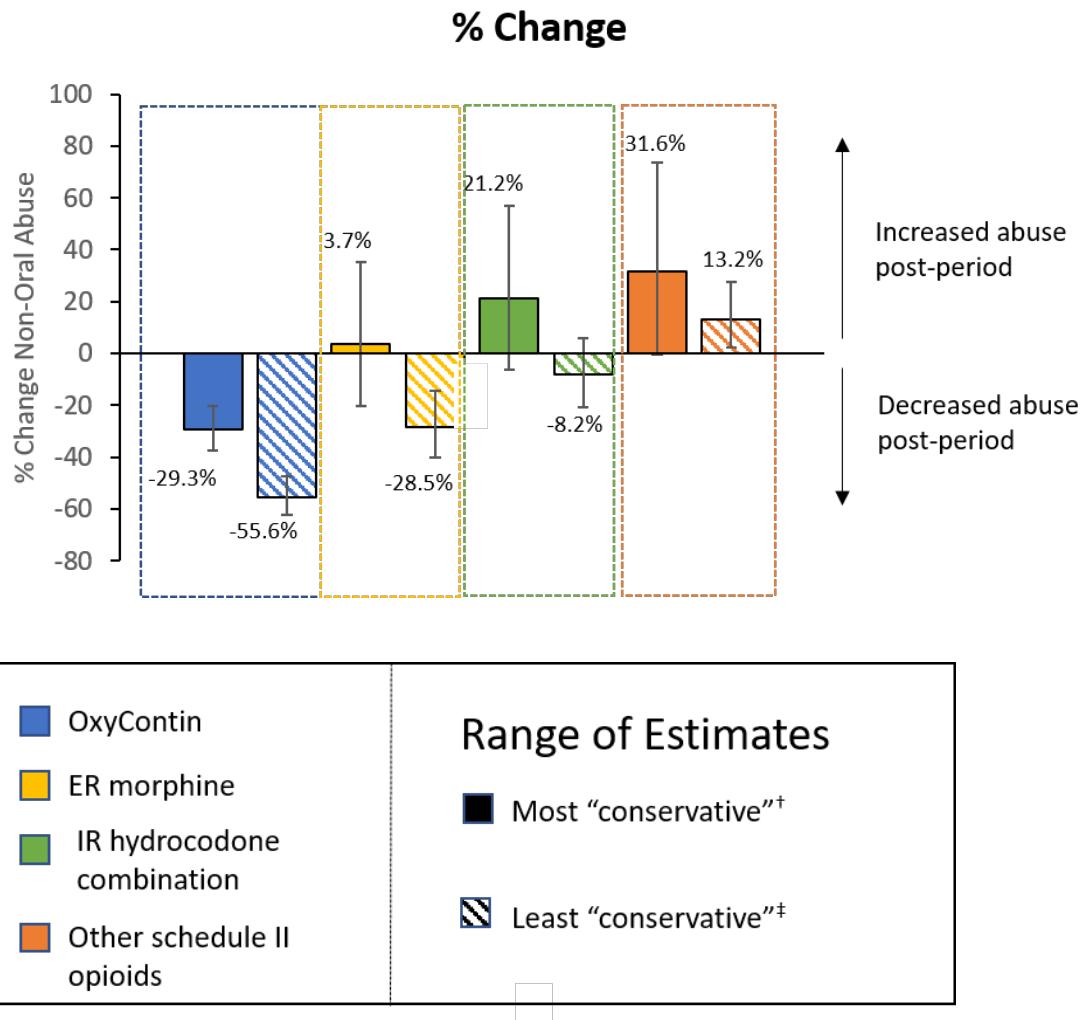
Analysis parameters*:
- OxyContin definition: Any OxyContin (original or reformulated)
- Time period: -2y/4y
- Site inclusion criteria: $\geq$1 assessment/quarter
- Unit of analysis: 3-digit ZIP

*These parameters are considered to be the "main" study variable definitions

This graph demonstrates the most "conservative" estimate of percent decrease (the smallest pre-post reduction, or largest increase, in non-oral abuse rates) in the solid color, and the least "conservative" estimate of percent decrease (the largest pre-post reduction, or smallest increase, in non-oral abuse rates) in striped colors. OxyContin was the only opioid for which all estimates, including the most "conservative" estimate, demonstrated a decrease in non-oral abuse in the post-period. For OxyContin, model 2a, which estimates abuse per 10,000 dosage units dispensed, produced the most "conservative" estimate of decrease, while model 3a, which adjusted for utilization and total assessments as covariates, produced the least "conservative" estimate of decrease. Generally, the opposite was true for comparators, and utilization-based models produced the largest estimates of decrease, while model 3 or 3a, which adjusted for utilization as a covariate, produced the smallest estimates of decrease.

Figure 24: Most and least "conservative" values for percent change in OxyContin and primary comparators mean quarterly <u>non-oral</u> abuse rates with main parameters and all regression models

% Change
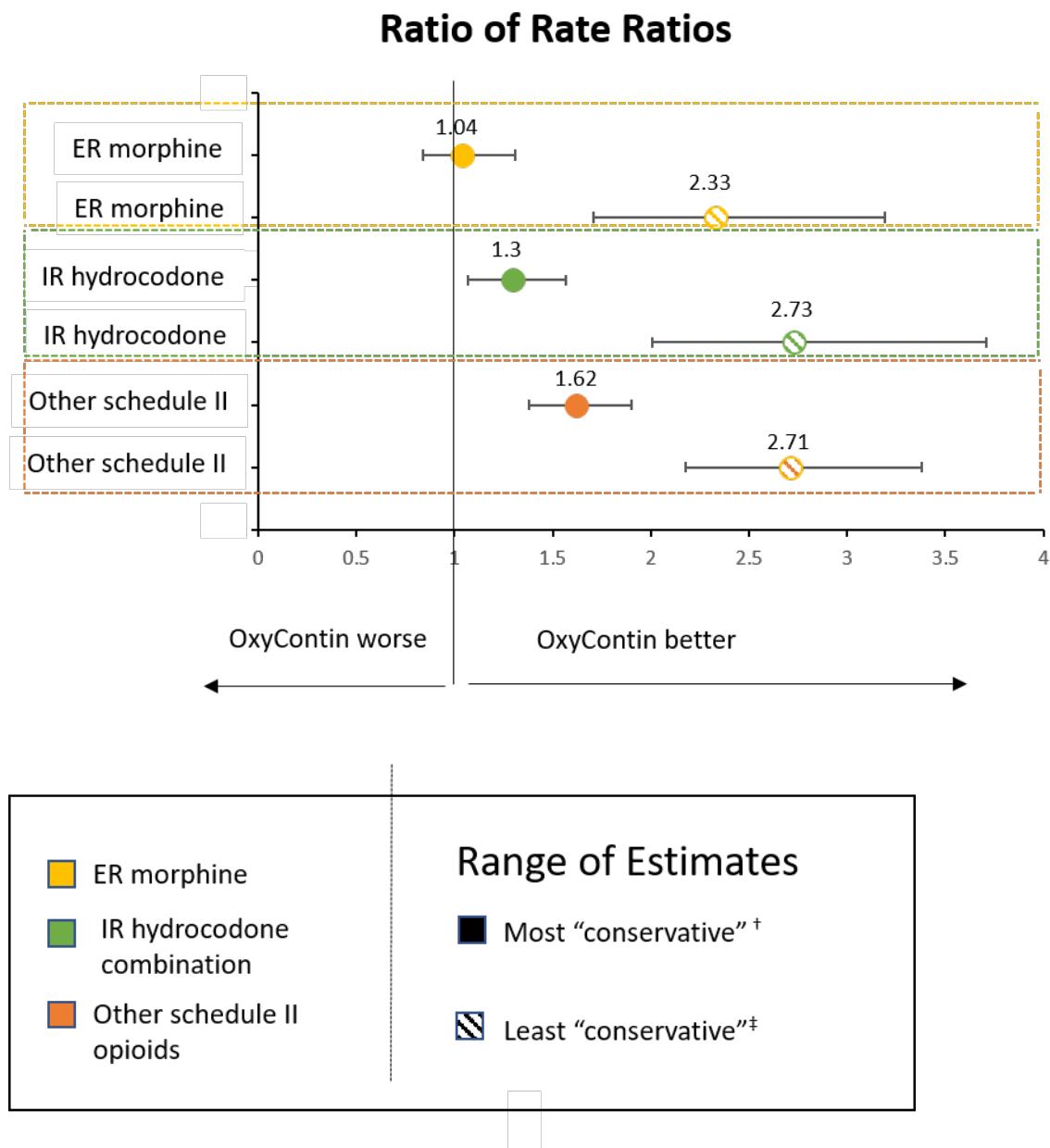
(Source: FDA generated figure from information request response.)

Key: IR: Immediate Release; ER: Extended Release; [†]Most "conservative": smallest pre-post reduction (or largest increase) in non-oral abuse; [‡]Least "conservative": largest pre-post reduction (or smallest increase) in non-oral abuse

Figure 26 below shows the range of values for RORRs for primary comparators vs. OxyContin, with the same parameters listed above. The most and least "conservative" RORR estimates for IR hydrocodone and "other schedule II opioids" showed a significantly larger decrease in OxyContin abuse in the post-period than the decrease observed for the comparator. The least "conservative" RORR for ER morphine showed a significantly larger decrease for OxyContin compared with ER morphine, however the most "conservative" RORR for ER morphine (produced by model 2, which had utilization as an offset) was not statistically significant.

Figure 25: Range of RORRs for <u>non-oral</u> abuse rate for primary comparators vs. OxyContin with main parameters and all regression models

(Source: FDA generated figure from information request response.)

Key: IR: Immediate Release; ER: Extended Release; [†]Most "conservative": smallest pre-post reduction (or largest increase) in OxyContin non-oral abuse relative to comparator's change; [‡]Least "conservative": largest pre-post reduction (or smallest increase) in OxyContin non-oral abuse relative to comparator's change

A table with these least and most conservative model estimates is included in appendix 6.8 with accompanying information on which model produced each respective estimate.

3.4.5.2.1 Sensitivity analysis for <u>time period</u>: Percent change in non-oral abuse of OxyContin and comparators, -1y/3y
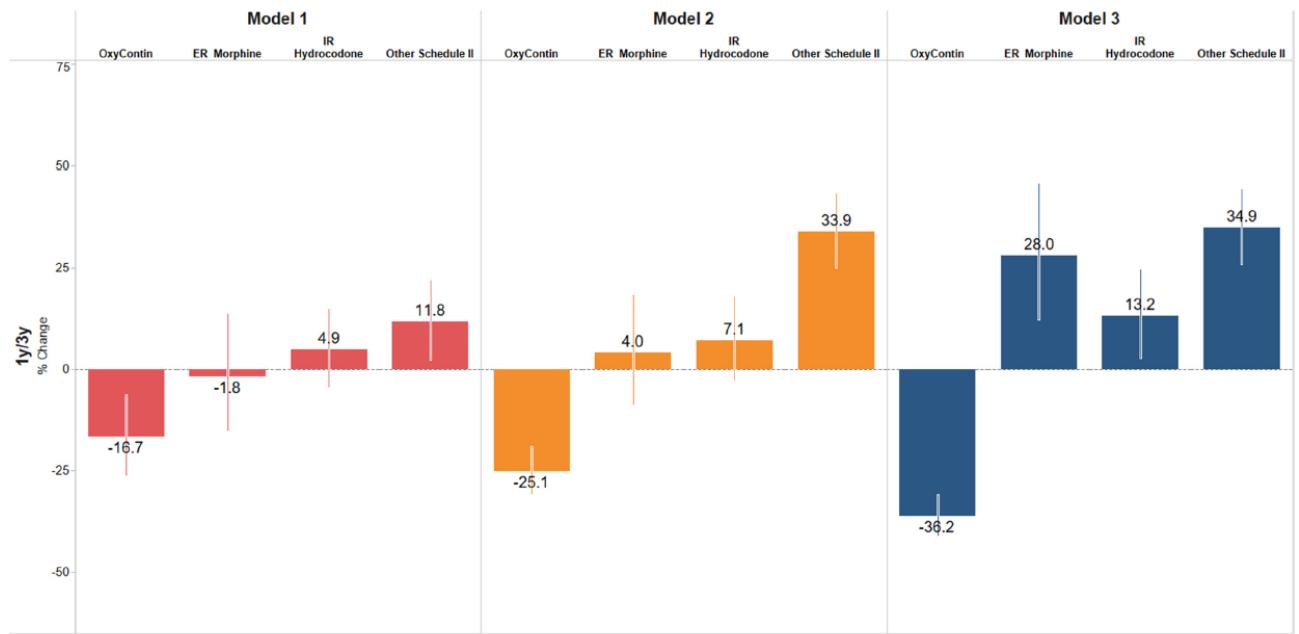
The sensitivity analysis below presents pre-post means analyses for a shortened, -1y/3y time period.

Analysis parameters:

- Sites: contributing ≥1 assessment/quarter
- Time period: -1y/3y
- OxyContin definition: Original and reformulated
- Unit of analysis: Respondent 3-digit ZIP code
- Model #1:
    - Offset: Total assessments
    - Covariates: NA
- Model #2:
    - Offset: Dosage units dispensed
    - Covariate: NA
- Model #3:
    - Offset: NA
    - Covariate: Dosage units dispensed (continuous)

Figure 27 (and table 28 in appendix 6.9) show estimates for percent change in non-oral abuse for a -1y/3y time period. OxyContin showed a consistent decrease across all three models, while IR hydrocodone and "other schedule II opioids" demonstrated an increase. Model 2 and 3 estimated an increase in non-oral ER morphine abuse while model 1 estimated a modest decrease. These estimates of decrease in non-oral OxyContin abuse generally agreed with the estimates produced in the main -2y/4y analyses, although they were modestly attenuated. Decreases were also attenuated for comparators, especially for ER morphine with model 2, where the estimate was -28.5% in the -2y/4y time period, while the estimate here was +4.0%.

Figure 26: Percent change (95% CI) in <u>non-oral</u> abuse for OxyContin and primary comparators after introduction of reformulated OxyContin, -1y/3y

CI=confidence intervals; IR Hydrocodone=IR hydrocodone products; Sites: contributing ≥1 assessment/quarter; OxyContin Definition: Original and Reformulated; Unit of Analysis: Respondent 3-digit ZIP Code; Model 1: Rate of abuse/Assessments. Model 2: Rate of abuse/Dosage units dispensed. Model 3: Abuse count adjusting for dosage units dispensed (continuous). ER=extended release

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 8-2. Percent change (95% CI) in non-oral abuse of reformulated OxyContin and primary comparator opioids using different modeling approaches -1y/3y. p. 338.)

Key: IR: Immediate Release; ER: Extended Release; Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 3 models abuse rate adjusted for tablets dispensed as a covariate

Table 8 (and figure 82 appendix 6.9) shows RORR estimates for non-oral abuse of OxyContin and primary comparators for time period -1y/3y. RORR estimates were significant for all primary comparator opioids except for ER morphine using model #1. RORR estimates for ER morphine in the -1y/3y time period for models 1-3 fell within the range for the -2y/4y time period (1.04-2.14). Model 2 and 3 estimated RORRs for IR hydrocodone for the -1y/3y time period fell within the range for the -2y/4y time period (1.36-2.51), although model 1 estimated RORR fell just below. Model 2 and 3 estimated RORRs for "other schedule II opioids" for the -1y/3y time period fell within the range of -2y/4y RORRs (1.65-2.71), although again, model 1 estimated RORR for the -1y/3y time period fell just below this range.

Table 8: RORR (95% CI) in <u>non-oral</u> abuse after introduction of reformulated OxyContin and primary comparator opioids using different modeling approaches, -1y/3y

	Model 1 RORR (95% CI)	Model 2 RORR (95% CI)	Model 3 RORR (95% CI)
ER Morphine	1.18 (0.97, 1.43)	1.39 (1.19, 1.62)	2.01 (1.72, 2.34)
IR Hydrocodone	1.26 (1.08, 1.47)	1.43 (1.26, 1.62)	1.77 (1.56, 2.01)
Other Schedule II	1.34 (1.16, 1.56)	1.79 (1.61, 1.99)	2.11 (1.90, 2.35)

RORR=ratio of risk ratios; CI=confidence intervals; IR Hydrocodone=IR hydrocodone products; Sites: contributing ≥1 assessment/quarter; OxyContin Definition: Original and Reformulated; Unit of Analysis: Respondent 3-digit ZIP Code; Model 1: Rate of abuse/Assessments. Model 2: Rate of abuse/Dosage units dispensed. Model 3: Abuse count adjusting for dosage units dispensed (continuous). ER=extended release

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Table 8-6. RORR (95% CI) in non-oral abuse after introduction of reformulated OxyContin and primary comparator opioids using different modeling approaches -1y/3y. p. 341.)

Key: IR: Immediate Release; ER: Extended Release; Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 3 models abuse rate adjusted for tablets dispensed as a covariate

Results for OxyContin alone in the -1y/3y time period are presented in appendix 6.10.

3.4.5.2.2 Sensitivity analysis for OxyContin definition

Tables below present percent change estimates using the following definitions of OxyContin:

- Any OxyContin (Original or reformulated)
- Original (pre-period) and Reformulated only (post-period)
- Any OxyContin or generic ER oxycodone

Analysis parameters:
- Sites: contributing ≥ 1 assessment/quarter.
- Unit of analysis: Respondent 3-digit ZIP code.
- Time period: -2y/4y
- Model #1:
  - Offset: Total assessments
  - Covariates: NA
- Model #2:
  - Offset: Dosage units dispensed
  - Covariates: NA
- Model #2a:
  - Offset: Dosage units dispensed
  - Covariate: Total assessments
- Model #3:
  - Offset: NA.
  - Covariate: Dosage units dispensed (continuous)
- Model #3a:
  - Offset: NA
  - Covariate: Dosage units dispensed (continuous), Total assessments

Table 9 shows estimates for percent change in non-oral abuse of OxyContin with the different OxyContin definitions described above. Percent change for original OxyContin in the pre-period compared to reformulated OxyContin only in the post-period ranged from -59.4% to -70.0%. This was considerably higher than the percent change for original OxyContin in the pre-period compared to original OxyContin or reformulated OxyContin in the post-period which ranged from -30.7% to -55.6%, and the OxyContin definition which included generic OxyContin, which ranged from -23.5% to -67.4%.

Table 9: Percent change in mean quarterly past-30 day abuse rate for different OxyContin definitions

OxyContin definition	Model 1 % change (95% CI)	Model 2 % change (95% CI)	Model 2a % change (95% CI)	Model 3 % change (95% CI)	Model 3a % change (95% CI)
Any OxyContin (original or reformulated)	-30.7 (-46.9, -9.5)	-31.5 (-39.4, -22.5)	-29.3 (-37.5, -20.1)	-53.3 (-60.3, -45.0)	-55.6 (-62.3, -47.6)
Original pre-period, Reformulated post-period	-66.0 (-73.2, -56.8)	-60.7 (-65.9, -54.7)	-59.4 (-64.8, -53.2)	-68.9 (-74.2, -62.5)	-70.0 (-75.1, -63.8)
Any OxyContin or generic ER oxycodone	-44.8 (-59.0, -25.9)	-31.6 (-38.1, -24.4)	-23.5 (-30.8, -15.4)	-57.6 (-63.1, -51.3)	-67.4 (-71.8, -62.3)

(Source: FDA generated figure from information request response.)

Key: Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 3 models abuse rate adjusted for tablets dispensed as a covariate

Table 10 below presents RORRs for the different OxyContin definitions described above. RORRs for primary comparators vs. original OxyContin in the pre-period, reformulated only in the post-period showed significantly larger decreases in non-oral OxyContin abuse compared with the decrease for comparators, for all comparators and all models. Using the 'any OxyContin' definition gave RORRs closer to one, but RORRs were significant for all comparator opioids except for ER morphine when using models #1, #2, and #2a. This was also true for the 'original OxyContin or reformulated OxyContin or generic ER oxycodone' definition, which gave significant RORRs for all models and all comparators except for ER morphine for models #2 and 2a.

Table 10: RORR for mean quarterly past-30 day abuse rate of comparators vs. OxyContin for different OxyContin definitions

OxyContin Definition		Model 1 RORR (95% CI)	Model 2 RORR (95% CI)	Model 2a RORR (95% CI)	Model 3 RORR (95% CI)	Model 3a RORR (95% CI)
Any OxyContin						
	ER morphine	1.3 (0.9, 1.9)	1.0 (0.8, 1.3)	1.1 (0.9, 1.3)	2.1 (1.6, 2.9)	2.3 (1.7, 3.2)
	IR hydrocodone	1.7 (1.2, 2.5)	1.4 (1.1, 1.7)	1.3 (1.1, 1.6)	2.5 (2.0, 3.2)	2.7 (2.0, 3.7)
	Other schedule II	1.9 (1.3, 2.8)	1.7 (1.4, 1.9)	1.6 (1.4, 1.9)	2.7 (2.2, 3.4)	2.6 (2.1, 3.3)
Original pre-period, Reformulated post-period						
	ER morphine	2.7 (1.8, 3.9)	1.8 (1.4, 2.3)	1.9 (1.5, 2.3)	3.2 (2.4, 4.4)	3.5 (2.5, 4.8)
	IR hydrocodone	3.5 (2.5, 5.0)	2.4 (1.9, 2.9)	2.3 (1.9, 2.8)	3.8 (2.9, 4.9)	4.0 (2.9, 5.6)
	Other schedule II	3.9 (2.7, 5.6)	2.9 (2.4, 3.4)	2.8 (2.4, 3.4)	4.1 (3.2, 5.2)	3.8 (3.0, 4.9)
Any OxyContin or generic ER oxycodone						
	ER morphine	1.6 (1.1, 2.5)	1.1 (0.9, 1.3)	1.0 (0.8, 1.2)	2.4 (1.8, 3.1)	3.2 (2.3, 4.3)
	IR hydrocodone	2.2 (1.5, 3.2)	1.4 (1.2, 1.6)	1.2 (1.0, 1.4)	2.8 (2.2, 3.5)	3.7 (2.8, 4.9)
	Other schedule II	2.4 (1.6, 3.6)	1.7 (1.4, 1.9)	1.5 (1.3, 1.7)	3.0 (2.4, 3.7)	3.5 (2.8, 4.4)
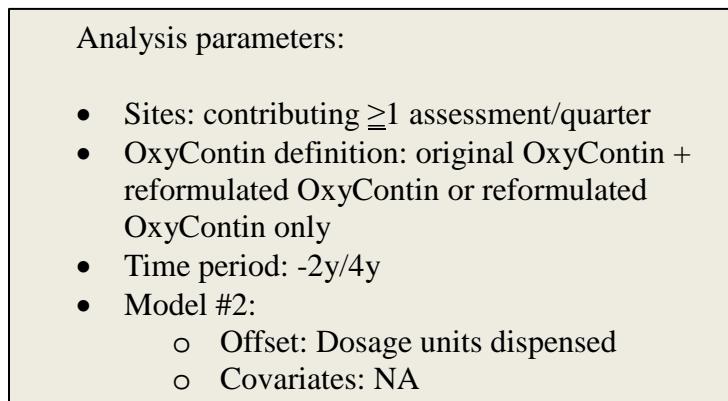
(Source: FDA generated figure from information request response.)

Key: Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablet dispensed adjusted for ASI-MV assessments as covariate; Model 3 models abuse rate adjusted for tablets dispensed as a covariate; Model 3a models abuse rate adjusted for tablets dispensed and ASI-MV assessments as covariates

3.4.5.2.3 Sensitivity analysis using different <u>unit of analysis for dosage units dispensed</u>
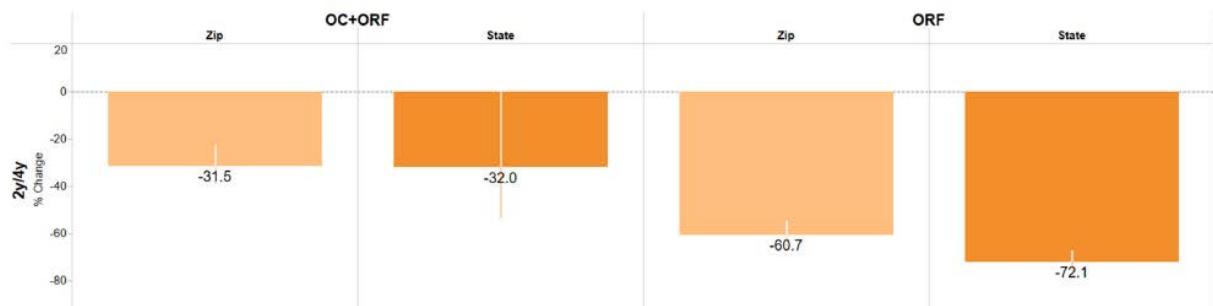
Two different units of analyses were used to estimate dosage units dispensed:

- 3-digit ZIP: Dosage units dispensed estimated from IQVIA for respondent 3-digit ZIP code
- State: Dosage units dispensed estimated from IQVIA in the fixed set of states for the restricted set of fixed sites in each quarter of the study period

> Analysis parameters:
>
> - Sites: contributing ≥1 assessment/quarter
> - OxyContin definition: original OxyContin + reformulated OxyContin or reformulated OxyContin only
> - Time period: -2y/4y
> - Model #2:
>   - Offset: Dosage units dispensed
>   - Covariates: NA

Figures 28 and 29 show percent change in non-oral abuse of OxyContin and primary comparators, using either 3-digit ZIP or the state as the unit of analysis. Percent change in non-oral OxyContin abuse was similar when using 3-digit ZIP or state as the level of analysis.

Figure 27: Percent change in non-oral OxyContin abuse after reformulation using different units of analysis, -2y/4y (model 2)
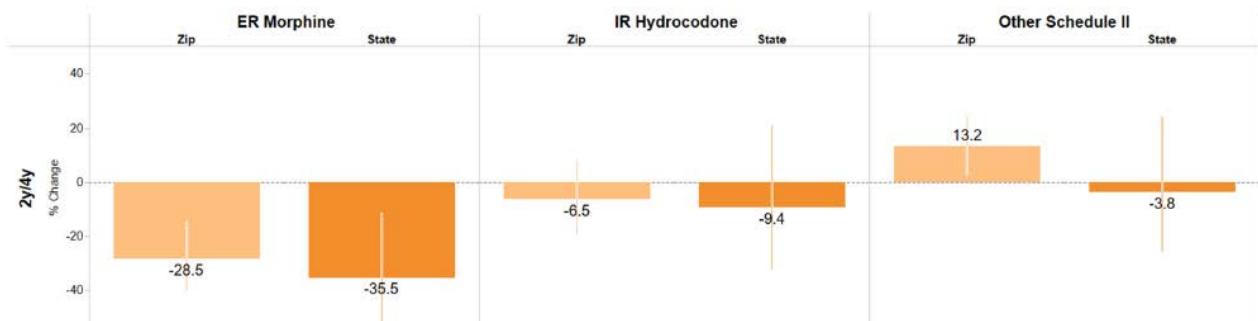
CI=confidence intervals; Sites: contributing ≥1 assessment/quarter; Unit of Analysis: Respondent 3-digit ZIP Code or state; Model 2: Rate of abuse/Dosage units dispensed; Model 3a: Abuse count adjusting for dosage units dispensed (continuous) and assessments. OC=original OxyContin; ORF=reformulated OxyContin

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 7-3. Percent change (95% CI) for unit of analysis sensitivity analysis – OxyContin (Respondent 3-digit ZIP vs state using Model 2 and Model 3a. p. 321.)

Key: OC: Original OxyContin; ORF: Reformulated OxyContin; Model 2 models abuse rate per tablets dispensed

There were considerable differences in estimates for change in utilization-based abuse rates for primary comparators using different units of analysis, especially for "other schedule II opioids" (Figure 29). The state-level analysis estimated a larger percent decrease in utilization-adjusted non-oral abuse for all primary comparators.

Figure 28: Percent change in non-oral abuse of primary comparator opioids after introduction of reformulated OxyContin using different units of analysis, -2y/4y (model 2)

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 7-4. Percent change (95% CI) for unit of analysis sensitivity analysis – primary comparator opioids (respondent 3-digit ZIP vs state using Model 2 and Model 3a. p. 322.)

Key: ER: Extended Release; IR: Immediate Release; Model 2 models abuse rate per tablets dispensed;

3.4.5.2.4 Sensitivity analysis for <u>inclusion of sites</u>

The following site criteria were used to assess percent change in non-oral abuse of OxyContin and comparators:

- ≥1 assessment/quarter
- ≥1 assessment/year
- >1 assessment/year excluding New Mexico[8]

---

[8] Because of the differential contribution of New Mexico sites across the study period due to changes in state laws in Mexico, with complete coverage in the pre-reformulation period and the initial post-reformulation period (through 2012), with little coverage in the remaining post-reformulation study period, New Mexico was excluded as a sensitivity analysis to examine how its exclusion effects the study results.

Analysis parameters:

- Unit of analysis: Respondent 3-digit ZIP code.
- OxyContin definition: Any OxyContin (original or reformulated)
- Time period: -2y/4y
- Model #1:
    - Offset: Total assessments
    - Covariates: NA
- Model #2
    - Offset: Dosage units dispensed
    - Covariate: NA
- Model #2a
    - Offset: Dosage units dispensed
    - Covariate: Total assessments
- Model #3:
    - Offset: NA.
    - Covariate: Dosage units dispensed (continuous)
- Model #3a:
    - Offset: NA
    - Covariate: Dosage units dispensed (continuous), Total assessments

Table 11 shows percent change in non-oral abuse of OxyContin from the pre- to post-periods using the more stringent ≥1 assessment/quarter inclusion criteria or less stringent ≥1 assessment/year inclusion criteria or ≥1 assessment/year excluding New Mexico. Including sites with ≥1 assessment/year (with or without New Mexico) slightly attenuated the decrease in OxyContin non-oral abuse for model 1 and attenuated the decrease to a larger degree for models 2 and 2a.

Table 11: Percent change in non-oral OxyContin abuse using different inclusion criteria for sites, -2y/4y

Site inclusion criteria	Model 1 % change (95% CI)	Model 2 % change (95% CI)	Model 2a % change (95% CI)	Model 3 % change (95% CI)	Model 3a % change (95% CI)
=> 1 assessment/quarter	-30.7 (-46.9, -9.5)	-31.5 (-39.4, -22.5)	-29.3 (-37.5, -20.1)	-53.3 (-60.3, -45.0)	-55.6 (-62.3, -47.6)
=> 1 assessment/year	-27.6 (-40.4, -12.2)	-10.3 (-15.2, -5.2)	-9.5 (-14.4, -4.4)	NA[*]	-29.6 (-34.0, -24.8)
=> 1 assessment/year excluding NM	-26.4 (-39.7, -10.1)	-8.4 (-13.4, -3.1)	-9.4 (-14.3, -4.1)	-31.5 (-35.7, -27.0)	NA[*]

(Source: FDA generated figure from information request response.)

Key: NM: New Mexico; Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablet dispensed adjusted for ASI-MV assessments as covariate; Model 3 models abuse rate adjusted for tablets dispensed as a covariate; Model 3a models abuse rate adjusted for tablets dispensed and ASI-MV assessments as covariates

* We did not incorporate estimates obtained from inadequate models such as those that showed poor model fit and/or convergence issues

Table 12 below presents RORRs for primary comparators using the three site inclusion criteria. Although decreases in non-oral OxyContin abuse were attenuated for the ≥1 assessment/year criteria above, decreases observed in comparators were attenuated as well, and thus RORR was not meaningfully different for comparators vs. OxyContin with the different site inclusion criteria. All RORRs for primary comparators vs. OxyContin demonstrated a larger decrease in non-oral OxyContin abuse in the post-period than comparators, and only one RORR (ER morphine, model 1) was not significant for the ≥1 assessment/year criteria.

Table 12: RORR for change in non-oral abuse of primary comparators vs. OxyContin for different site definitions, -2y/4y

Site inclusion		Model 1 RORR (95% CI)	Model 2 RORR (95% CI)	Model 2a RORR (95% CI)	Model 3 RORR (95% CI)	Model 3a RORR (95% CI)
=> 1 assessment/quarter	ER morphine	1.3 (0.9, 1.9)	1.0 (0.8, 1.3)	1.1 (0.9, 1.3)	2.1 (1.6, 2.9)	2.3 (1.7, 3.2)
	IR hydrocodone	1.7 (1.2, 2.5)	1.4 (1.1, 1.7)	1.3 (1.1, 1.6)	2.5 (2.0, 3.2)	2.7 (2.0, 3.7)
	Other schedule II	1.9 (1.3, 2.8)	1.7 (1.4, 1.9)	1.6 (1.4, 1.9)	2.7 (2.2, 3.4)	2.6 (2.1, 3.3)
=> 1 assessment/year						
	ER morphine	1.4 (1.0, 1.8)	1.2 (1.1, 1.4)	1.3 (1.1, 1.4)	NA[*]	1.2 (1.0, 1.3)
	IR hydrocodone	1.5 (1.2, 1.8)	1.3 (1.2, 1.5)	1.3 (1.2, 1.5)	NA[*]	1.5 (1.3, 1.7)
	Other schedule II	1.5 (1.1, 1.9)	1.7 (1.6, 1.9)	1.8 (1.7, 1.9)	NA[*]	1.8 (1.6, 2.0)
=> 1 assessment/year excluding NM						
	ER morphine	1.4 (1.0, 1.8)	1.2 (1.1, 1.3)	1.2 (1.1, 1.3)	1.3 (1.1, 1.5)	NA[*]
	IR hydrocodone	1.4 (1.1, 1.8)	1.3 (1.2, 1.5)	1.3 (1.2, 1.5)	1.6 (1.4, 1.8)	NA[*]
	Other schedule II	1.5 (1.1, 1.9)	1.7 (1.6, 1.9)	1.8 (1.6, 1.9)	2.0 (1.8, 2.2)	NA[*]

(Source: FDA generated figure from information request response.)

Key: NM: New Mexico; Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablet dispensed adjusted for ASI-MV assessments as covariate; Model 3 models abuse rate adjusted for tablets dispensed as a covariate; Model 3a models abuse rate adjusted for tablets dispensed and ASI-MV assessments as covariates

* We did not incorporate estimates obtained from inadequate models such as those that showed poor model fit and/or convergence issues

3.4.6 Range of Estimates for Change in Non-Oral Abuse Rates from Sensitivity Analyses

Table 13 below presents the range of percent change and RORR estimates generated by sensitivity analyses for OxyContin definition, site inclusion criteria, and model. The most "conservative" estimates for OxyContin as well as comparators were generated by the site inclusion criteria of ≥1 assessment/year, with or without New Mexico. Generally, the least "conservative" estimates were generated by the reformulated only (original in the pre-period, reformulated only in the post-period) definition for OxyContin, while the "any OxyContin" and "OxyContin or ER oxycodone" definitions created the most conservative estimates.

Table 13: Range of estimates for sensitivity analyses for percent change in mean quarterly non-oral abuse and RORR, -2y/4y

	Percent change (95% CI)		RORR (95% CI)	
	Most "conservative"[†]	Least "conservative"[‡]	Most "conservative"[†]	Least "conservative"[‡]
OxyContin	-8.4 (-13.4, -3.1)[1]	-70.0 (-75.1, -63.8)[2]	Ref	Ref
ER morphine	13.5 (3.2, 24.9)[3]	-28.5 (-40.3, -14.3)[4]	1.04 (0.84, 1.30)[9]	3.46 (2.50, 4.78)[10]
IR hydrocodone	22.5 (13.9, 31.6)[5]	-8.2 (-20.6, 6.1)[6]	1.21 (1.01, 1.44)[11]	4.04 (2.94, 5.56)[12]
Other schedule II	60.4 (53.1, 68.1)[7]	13.2 (2.5, 24.9)[8]	1.45 (1.10, 1.90)[13]	4.07 (3.21, 5.16)[14]

(Source: FDA generated figure from information request response.)

1) Model 2; ≥1 assessment/year except NM; any OxyContin; 2) Model 3a; ≥1 assessment/quarter; reformulated OxyContin only; 3) Model 2a; ≥1 assessment/year; 4) Model 2; ≥1 assessment/quarter; 5) Model 2; ≥1 assessment/year excluding NM; 6) Model 2a; ≥1 assessment/quarter; 7) Model 2a; ≥1 assessment/year; 8) Model 2; ≥1 assessment/quarter; 9) Model 2; ≥1 assessment/quarter; any OxyContin; 10) Model 3a; ≥1 assessment/quarter; reformulated OxyContin only; 11) Model 2a; ≥1 assessment/quarter; OxyContin + generic ER oxycodone; 12) Model 3a; ≥1 assessment/quarter; reformulated OxyContin only; 13) Model 1; ≥1

assessment/year except NM; any OxyContin; 14) Model 3; >1 assessment/quarter; reformulated
OxyContin only

Key: Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets
dispensed; Model 2a models abuse rate per tablet dispensed adjusted for ASI-MV assessments as covariate;
Model 3 models abuse rate adjusted for tablets dispensed as a covariate; Model 3a models abuse rate
adjusted for tablets dispensed and ASI-MV assessments as covariates; Most "Conservative" percent
change: Smallest pre-post reduction (or largest increase) in non-oral abuse; Least "Conservative" percent
change: Largest pre-post reduction (or smallest increase) in non-oral abuse; Most "Conservative" RORR:
Smallest pre-post reduction (or largest increase) in OxyContin non-oral abuse relative to comparator's
change; Least "Conservative" RORR: Largest pre-post reduction (or smallest increase) in OxyContin non-
oral abuse relative to comparator's change

3.4.7   Changes in Mean Rates of Past 30-day Non-oral Abuse of OxyContin and Secondary Comparator Opioids from Pre- to Post-reformulation Time Periods (Means Analysis)

Table 14 below describes changes in model-estimated mean rates of abuse by non-oral
routes for OxyContin and secondary comparator opioids.

Analysis parameters:

- Sites: contributing ≥ 1 assessment/quarter
- OxyContin definition: Any OxyContin (original or reformulated)
- Unit of analysis: 3-digit zip code
- Time period: -2y/4y
- Model #1:
  - Offset: Total assessments
  - Covariates: NA
- Model #2:
  - Offset: Dosage units dispensed
  - Covariate: NA
- Model #3:
  - Offset: NA
  - Covariate: Dosage units dispensed (continuous)

These secondary comparators include some of the individual opioids included in the
composite "other schedule II opioids" category, including oxymorphone ER, oxycodone
IR Se, oxycodone IR combination, and oxycodone IR SE and combination, and then
methadone and heroin, which are not included in this composite category. Table 14
shows the percent change in non-oral abuse for OxyContin and secondary comparator
opioids after reformulation of OxyContin. While percent change in OxyContin decreased
from pre- to post-reformulation, ranging from -30.7% to -53.3%, oxymorphone ER,
oxycodone IR SE, and oxycodone IR combination all showed large increases. Although
Oxycodone IR was only collected in ASI-MV beginning 2Q2010, analyses for this

comparator were performed across the -2y/4y time period. Non-oral abuse of methadone did not change substantially, ranging from -1.8% to +4.5%, and percent change in heroin was +6.6% (using Model 1 only since models 2 and 3 are adjusted for prescription dispensing patterns).

Table 14: Percent change (95% CI) in non-oral abuse for OxyContin and secondary comparator opioids, -2y/4y

	Model 1 % Change (95% CI)	Model 2 % Change (95% CI)	Model 3 % Change (95% CI)
All OxyContin	-30.7 (-46.9, -9.5)	-31.5 (-39.4, -22.5)	-53.3 (-60.3, -45.0)
Oxymorphone ER	181.4 (7.9, 633.8)	62.7 (-1.9, 169.8)	286.8 (-12.8, 1,616.2)
Oxycodone IR single-entity	59.8 (3.3, 147.4)	191.7 (38.0, 516.6)	202.6 (17.9, 676.3)
Oxycodone IR combination	56.1 (4.6, 132.9)	41.9 (23.3, 63.3)	47.8 (22.3, 78.6)
Oxycodone IR single-entity and combination	67.7 (20.0, 134.3)	37.6 (20.5, 57.1)	27.6 (6.6, 52.8)
Methadone	0.3 (-21.8, 28.7)	4.5 (-11.6, 23.6)	-1.8 (-22.9, 25.1)
Heroin	6.6 (-6.1, 21.1)	NA	NA

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Table 9-1. Percent change in measures of abuse (95% CI) via non-oral routes for OxyContin versus secondary comparator opioids -2y/4y. P. 344.)

Key: CI: Confidence Interval; ER: Extended Release; IR: Immediate Release; NA: Not Applicable; Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 3 models abuse rate adjusted for tablets dispensed as a covariate;

3.4.8 Changes in Mean Proportion of Past 30-day Abuse of OxyContin and Comparator Opioids Via <u>Specific Routes Among Those Abusing Each Drug</u>; Unmodeled, Descriptive Pre-post Means Analyses

Figures 30-32 below present unmodeled descriptive pre-post means analyses for abuse of OxyContin, ER morphine, and IR hydrocodone by individual routes of abuse.
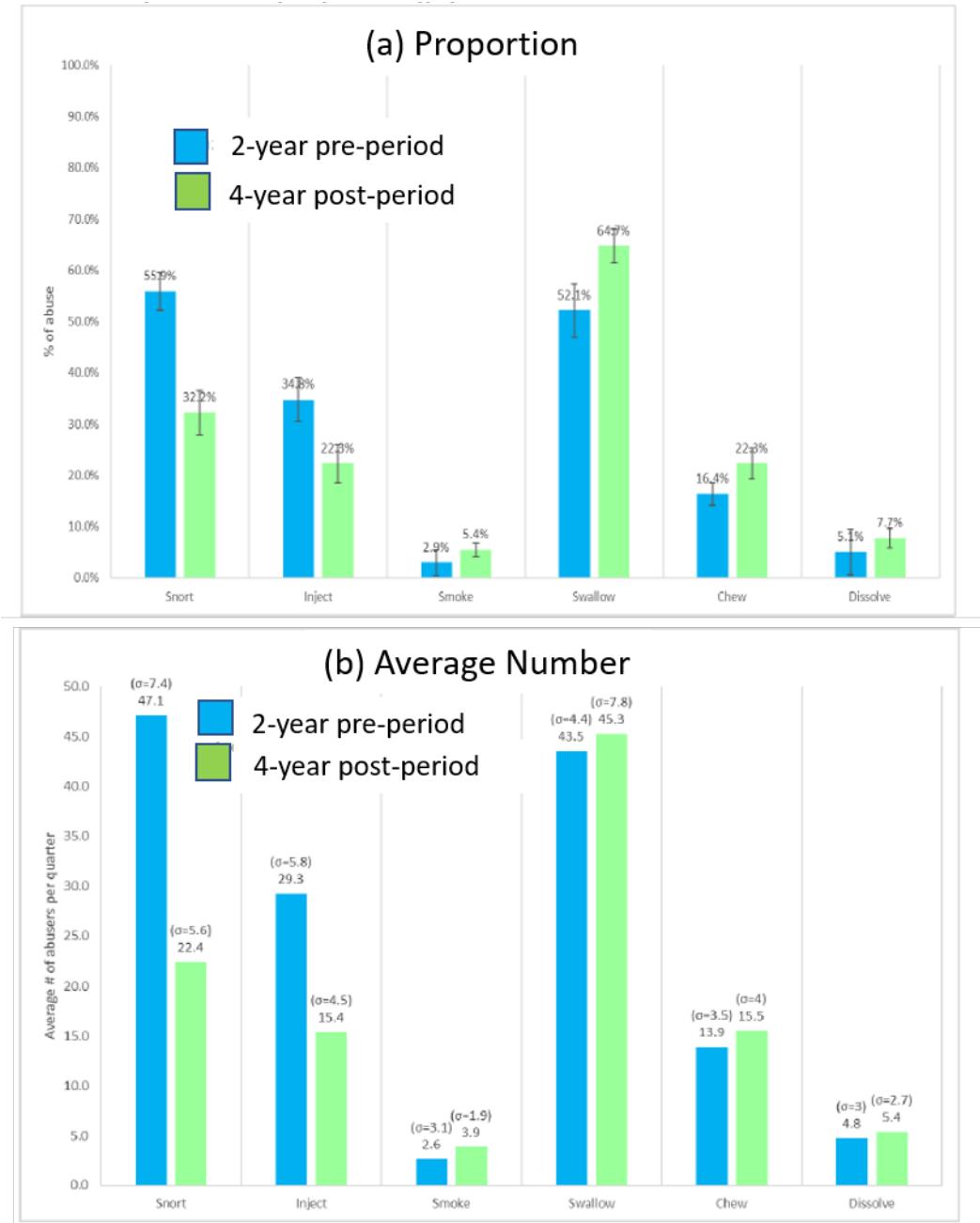
> Analysis parameters:
> - Sites: contributing > 1 assessment/quarter
> - OxyContin definition: any OxyContin (Original or reformulated)

Figure 30 below shows the proportion and average number of individuals abusing OxyContin via specific routes per quarter. These unmodeled data show a decrease in percentage of individuals abusing OxyContin via snort and inject from the pre- to post-period, from 55.9% to 32.2% for snorting and from 34.8% to 22.3% for injection. The average number of individuals endorsing abuse per quarter decreased for these routes as well. These data indicate that a smaller percentage of OxyContin abuse cases reported

snorting and injecting, and that fewer individuals endorsed these routes of abuse for OxyContin in the post-period. In the post-period, the average percent of OxyContin abuse cases via smoking and swallowing increased, as did the average quarterly number of individuals endorsing abuse of OxyContin via smoke, swallow, chew, and dissolve. In the pre-period, the highest average number of individuals abusing OxyContin was via the snorting route, while in the post-period this changed to oral route.

Figure 29: Proportion[*] (a) and average number (b) of individuals reporting abuse of <u>OxyContin</u> (any) via specific routes per quarter, -2y/4y
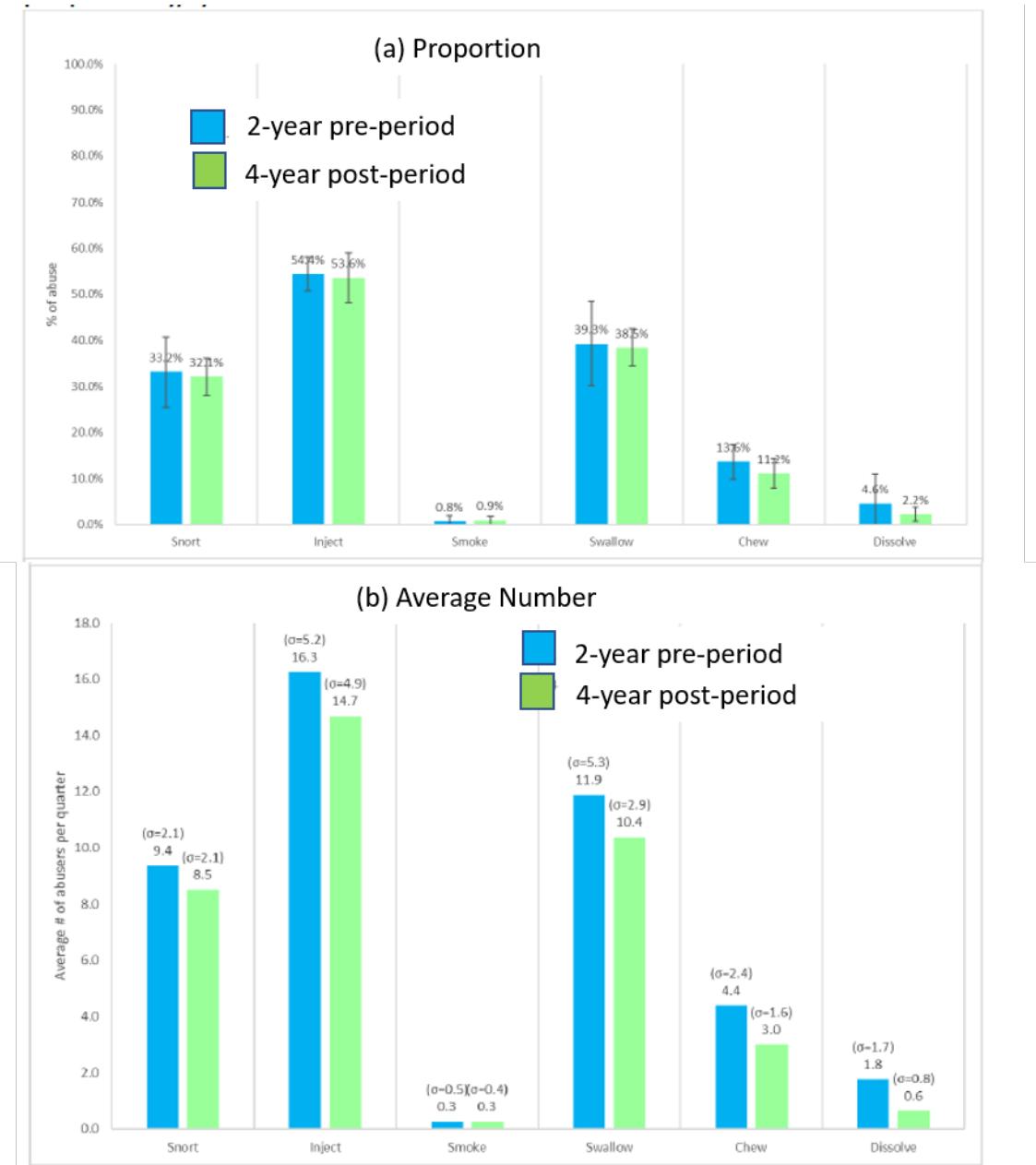
(a) Proportion

(b) Average Number

(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised figure 7-1: Proportion (a) and average number (b) of OxyContin (original and reformulated) abusers via specific routes per quarter -2y/4y. P. 5)

Key: Sigma: Standard Deviation; *Respondents can report more than one route of abuse, so total percentage can equal >100%

Figure 31 shows proportion and average number of individuals abusing ER morphine via specific routes per quarter. These data demonstrate a very small decreased in the percentage of abuse via snort and inject in the post-period, and in the average number of individuals reporting this route of abuse per quarter.

Figure 30: Proportion[*] (a) and average number (b) of individuals reporting abuse of <u>ER morphine</u> via specific routes per quarter -2y/4y
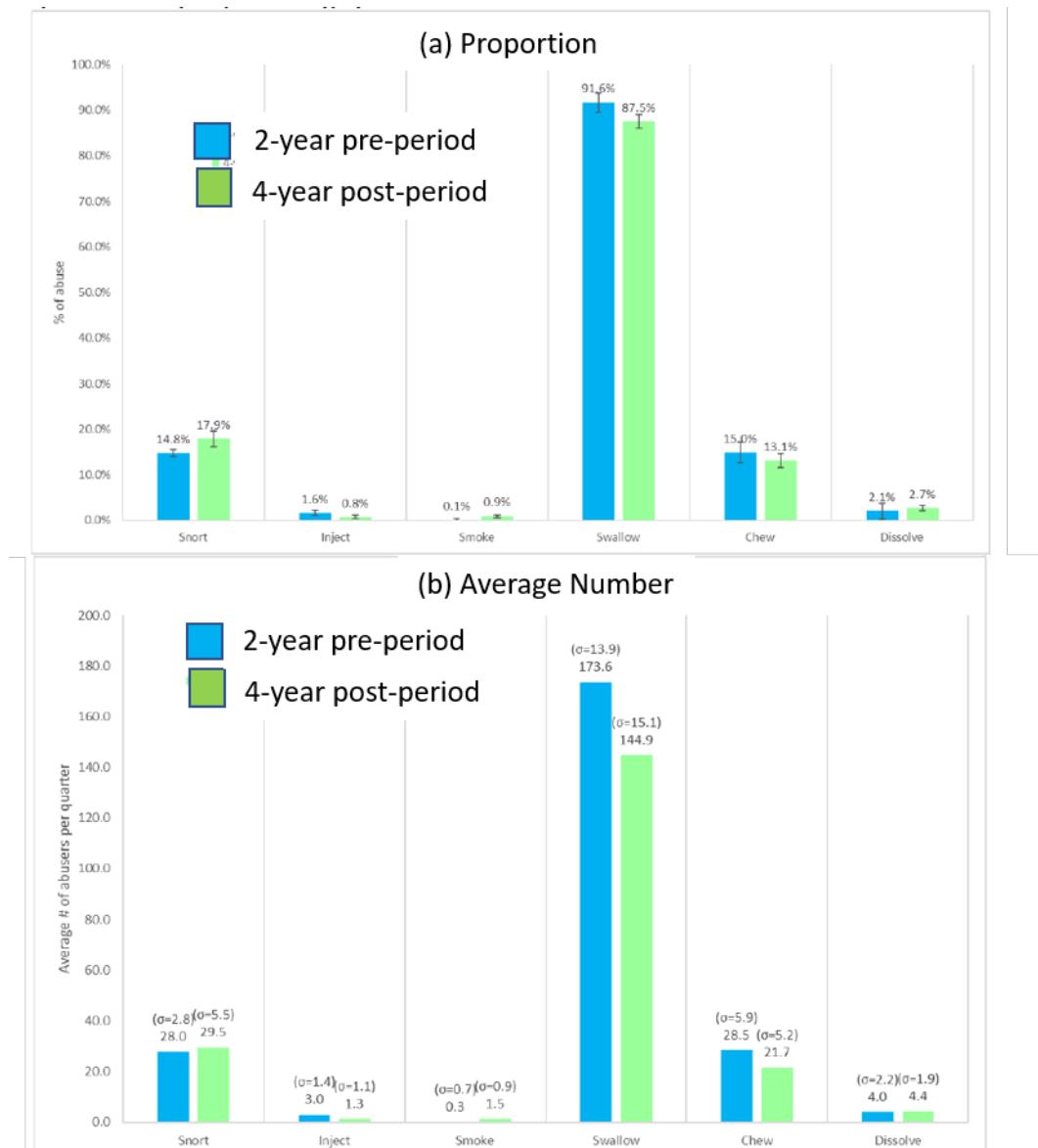
(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised figure 7-2: Proportion (a) and average number (b) of OxyContin (original and reformulated) abusers via specific routes per quarter -2y/4y. P. 6)

Key: Sigma: Standard Deviation; ORF: Reformulation of OxyContin; *Respondents can report more than one route of abuse, so total percentage can equal >100%

Figure 32 below shows the proportion and average number of individuals reporting abuse of IR hydrocodone combination products via specific routes. It is important to note that

injection abuse of IR hydrocodone combination products constituted only a very small percentage of abuse in the pre- and post-periods, 1.6% and 0.8%, respectively. Abuse via snorting increased a small amount, from 14.8% in the pre-period to 17.9% in the post-period, and the average number of individuals endorsing this route of abuse increased slightly in the post-period. Generally, the vast majority of IR hydrocodone abuse was via the oral route.

Figure 31: Proportion[*] (a) and average number (b) of individuals reporting abuse of IR hydrocodone combination products via specific routes per quarter -2y/4y

Error bars: 95% confidence intervals; σ: standard deviation; Sites: contributing ≥ 1 assessment / quarter; ORF=Reformulated OxyContin. Pre-ORF period=3Q2008-2Q2010, post-ORF period=1Q2011-4Q2014.

(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised figure 7-3: Proportion (a) and average number (b) of IR hydrocodone abusers via specific routes per quarter -2y/4y. P. 7)

Key: Sigma: Standard Deviation; ORF: Reformulation of OxyContin

*Respondents can report more than one route of abuse, so total percentage can equal >100%

Sensitivity analyses with changes in site inclusion criteria, OxyContin definition, and time period length are provided for these unmodeled data in appendix 6.11. Generally, similar trends were observed for the OxyContin definition of original in the pre-period, reformulated in the post-period, with a decrease in both percentage of abuse via snort and inject and a decrease in average number individuals endorsing these routes of abuse in the post-period. These data also showed an increase in percentage of abuse via the swallow route, although average number of individuals endorsing this route decreased in the post-period. Site inclusion criteria of ≥1 assessment/year showed similar trends.

3.4.9 Pre- and Post-period Past Month Abuse of OxyContin and Primary Comparators (Descriptive Means Analysis) by <u>Specific Routes of Abuse</u>.

Below are analyses describing changes in abuse of OxyContin and comparator opioids by additional, individual routes of abuse (swallow whole, other oral, snorting, injection, or any route).

3.4.9.1 Changes in abuse via <u>swallowing whole</u> for OxyContin and comparator opioids

Analysis Parameters:
- Sites: contributing ≥1 assessment/quarter
- OxyContin definition: Any OxyContin (original or reformulated)
- Unit of analysis: 3-digit zip code
- Time period: -2y/4
- Model 1:
    - Offset: Total assessments
    - Covariate: NA
- Model 2
    - Offset: Dosage units dispensed
    - Covariate: NA
- Model 2a
    - Offset: Dosage units dispensed
    - Covariate: NA
- Model 3
    - Offset: NA
    - Covariate: Dosage units dispensed (continuous)
- Model 3a
    - Offset: NA
    - Covariate: Dosage units dispensed, total assessments

Table 15 shows the range of estimates for percent change for abuse via swallowing whole for OxyContin and comparator opioids in the pre- vs. post-periods. The range of

estimates reported for change in abuse via swallow whole for OxyContin was +32.8% to -21.4%, which overlapped substantially with the range of estimates for percent change for all comparators.

Table 15: Range of estimates for percent change for abuse via <u>swallow whole</u> route in OxyContin and comparator opioids

	Range: % Pre-post relative change (95% CI)	
	Most "conservative" [†]	Least "Conservative"[‡]
OxyContin	32.8 (16.9, 51.0)[1]	-21.4 (-35.5, -4.3)[2]
ER morphine	-2.3 (-33.3, 43.1)[3]	-31.6 (-46.8, -11.9)[4]
IR hydrocodone	-10.0 (-19.4, 0.4)[5]	-30.7 (-35.1, -25.9)[6]
Other schedule II	-3.0 (-12.7, 7.7)[7]	-22.5 (-26.7, -18.1)[8]

(Source: FDA generated figure from information request response.)

1) Model 2a, 2) Model 3a, 3) Model 3a, 4) Model 2, 5) Model 3a, 6) Model 2a, 7) Model 1, 8) Model 2

Key: CI: Confidence Interval; ER: Extended Release; IR: Immediate Release; Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablet dispensed adjusted for ASI-MV assessments as covariate; Model 3 models abuse rate adjusted for tablets dispensed as a covariate; Model 3a models abuse rate adjusted for tablets dispensed and ASI-MV assessments as covariates; [†]most "conservative": smallest pre-post reduction (or largest increase) in non-oral abuse; [‡]least "conservative": largest pre-post reduction (or smallest increase) in non-oral abuse;

3.4.9.2   Changes in abuse via <u>other-oral (chewed, dissolved, drank)</u> route for OxyContin and comparator opioids

Table 16 shows the range of estimates for percent change and RORR for abuse via other-oral (chewed, dissolved, drank) routes for OxyContin and comparator opioids in the post- vs. pre-periods. Estimates of percent change in abuse via other-oral routes for OxyContin ranged from +57.7% to +33.2%. The range of percent decrease in comparators generally showed a decline in abuse via chewed/swallowed/drank.

Table 16: Range of estimates for percent change for abuse via <u>other-oral (chewed, dissolved, drank)</u> routes in OxyContin and comparator opioids

	Range: Pre-post relative change (95% CI)	
	Most "conservative"[†]	Least "conservative"[‡]

OxyContin	57.7 (27.4, 95.3)[1]	33.2 (6.0, 67.5)[2]
ER morphine	-23.5 (-56.7, 35.3)[3]	-43.0 (-62.1, -14.4)[4]
IR hydrocodone	-7.1 (-29.5, 22.6)[5]	-32.9 (-43.0, -21.1)[6]
Other schedule II	5.2 (-13.9, 28.5)[7]	-14.2 (-24.8, -2.1)[8]

(Source: FDA generated figure from information request response.)
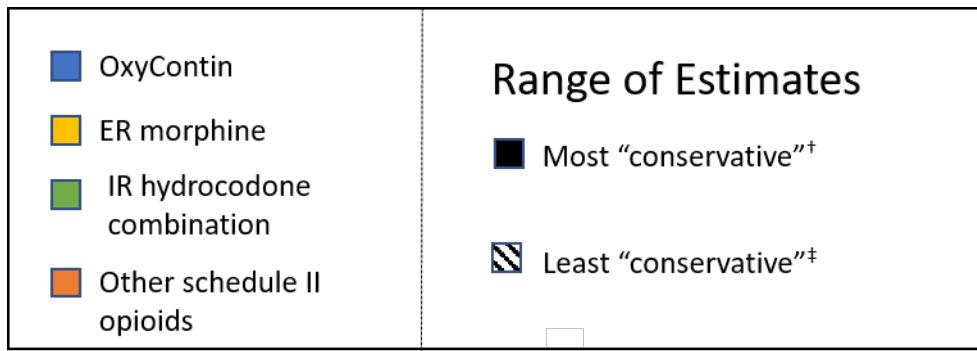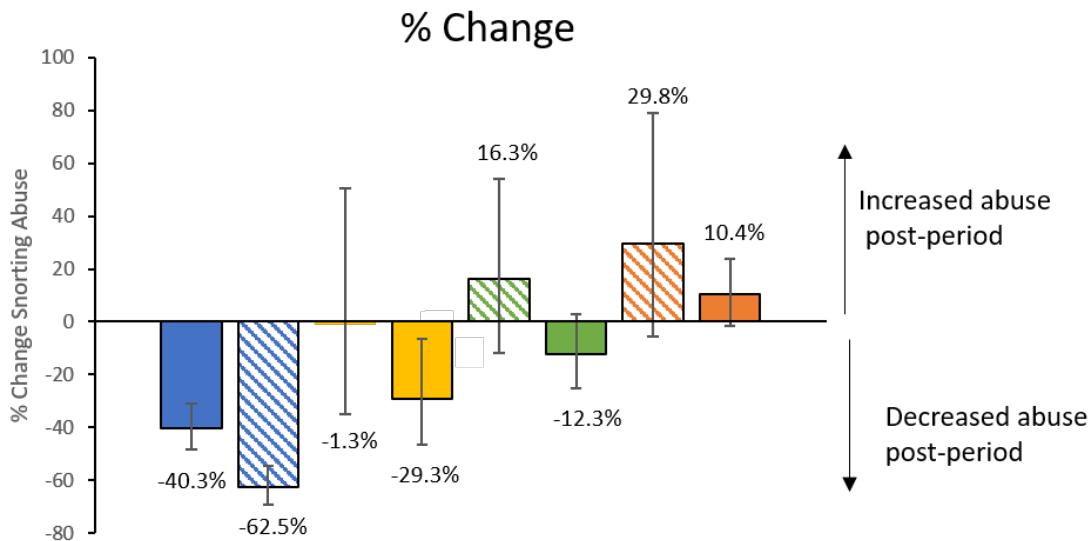
1) Model 2a, 2) Model 1, 3) model 3, 4) model 2, 5) Model 3a, 6) Model 2a, 7) Model 3, 8) Model 2

Key: ER: Extended Release; IR: Immediate Release; Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablet dispensed adjusted for ASI-MV assessments as covariate; Model 3 models abuse rate adjusted for tablets dispensed as a covariate; Model 3a models abuse rate adjusted for tablets dispensed and ASI-MV assessments as covariates; [†]most "conservative": smallest pre-post reduction (or largest increase) in non-oral abuse; [‡]least conservative: largest pre-post reduction (or smallest increase) in non-oral abuse

3.4.9.3 Changes in abuse via <u>snorting</u> for OxyContin and comparator opioids

Figures 33-34 shows the range of estimates for percent change and RORR for abuse via snorting for OxyContin and comparator opioids in the pre- vs. post-periods. Percent change in abuse via snorting ranged from -40.3% to -62.5% for OxyContin. The most and least "conservative" RORR estimates for IR hydrocodone and "other schedule II opioids" showed a significantly larger decrease in snorting abuse for OxyContin than the comparator. For ER morphine, the least "conservative" RORR estimate was significant, however the most "conservative" estimate, while it showed a greater decrease in snorting abuse for OxyContin than ER morphine, was not significant.
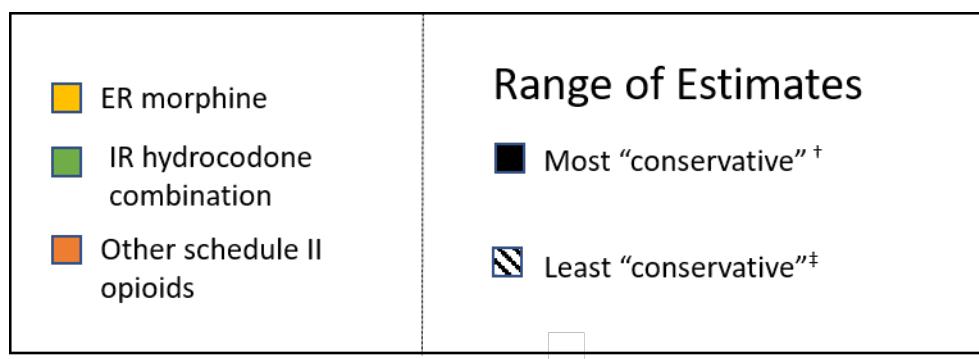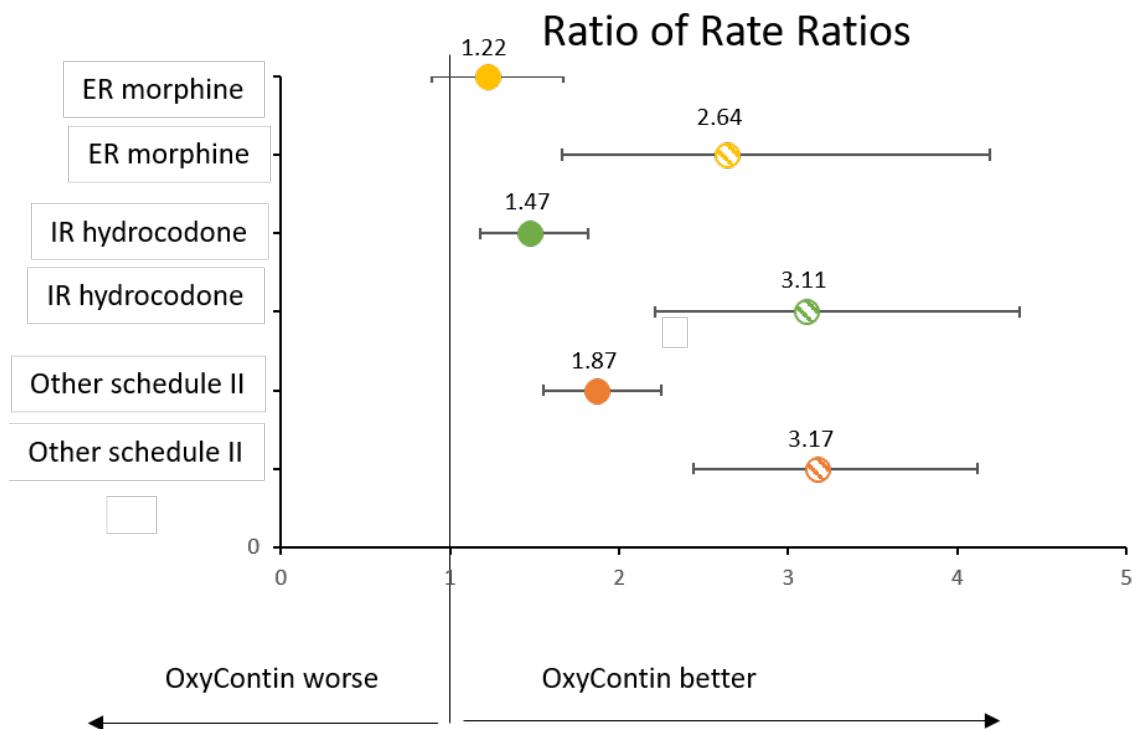
Figure 32: Range of estimates for percent change for abuse via <u>snorting</u> route in OxyContin and comparator opioids

(Source: FDA generated figure from information request response.)

Key: IR: Immediate Release; ER: Extended Release; [†]most "conservative": smallest pre-post reduction (or largest increase) in non-oral abuse; [‡]least conservative: largest pre-post reduction (or smallest increase) in non-oral abuse

Figure 33: Range of estimates for RORR for abuse via <u>snorting</u> route in OxyContin and primary comparators

Ratio of Rate Ratios

ER morphine — 1.22
ER morphine — 2.64
IR hydrocodone — 1.47
IR hydrocodone — 3.11
Other schedule II — 1.87
Other schedule II — 3.17

OxyContin worse   OxyContin better

Range of Estimates

ER morphine

IR hydrocodone combination

Other schedule II opioids

Most "conservative" [†]

Least "conservative" [‡]

(Source: FDA generated figure from information request response.)
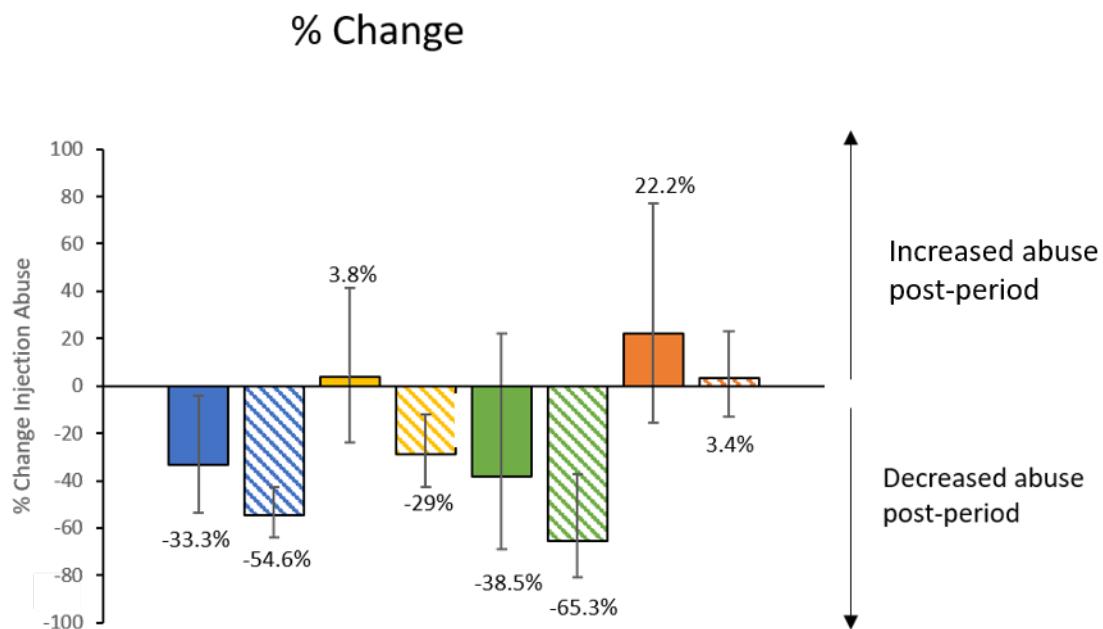
Key: ER: Extended Release; IR: Immediate Release; [†]Most "Conservative": Smallest pre-post reduction (or largest increase) in OxyContin non-oral abuse relative to comparator's change; [‡]Least "Conservative": Largest pre-post reduction (or smallest increase) in OxyContin non-oral abuse relative to comparator's change
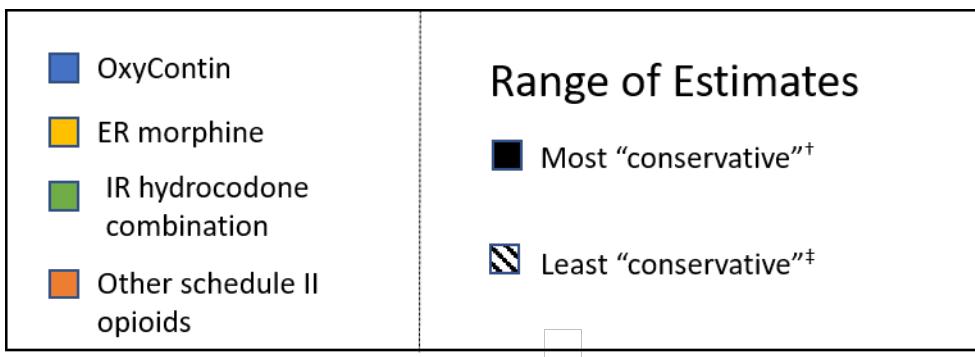
Table 30 in appendix 6.12, presents ranges for percent change and RORR with information on which model produced each respective estimate.

3.4.9.4   Changes in abuse via <u>injection</u> for OxyContin and comparator opioids

Figure 35 shows the range of estimates for percent change and RORR for abuse via injection for OxyContin and comparator opioids in the pre- vs. post-periods. Estimated percent change in abuse of OxyContin via injection in the pre- to post-periods ranged from -33.3% to -54.6%. The most "conservative" estimates of change for ER morphine and "other schedule II opioids" produced positive estimates of change. For "other schedule II opioids", this produced RORR estimates that all showed a decrease in injection route that was significantly larger for OxyContin. For ER morphine, the least "conservative" estimate showed a significantly larger decrease for OxyContin, but while the most "conservative" estimate showed a decrease in OxyContin injection that was slightly larger than ER morphine, it was not significant. For hydrocodone IR the most "conservative" RORR showed a significantly larger decrease in IR hydrocodone injection than OxyContin, and the least "conservative" RORR again showed a larger decrease in IR hydrocodone injection than OxyContin, however it was not significant. *It is important to note*, that IR hydrocodone is not an optimal comparator for this analysis, because IR hydrocodone injection rates were very low in the pre-period (refer to figure 32 section 3.4.8) and therefore a very minor change in abuse via this route led to a large percent decrease.

Figure 34: Range of estimates for percent change and RORR for abuse via <u>injection</u> route in OxyContin and comparator opioids
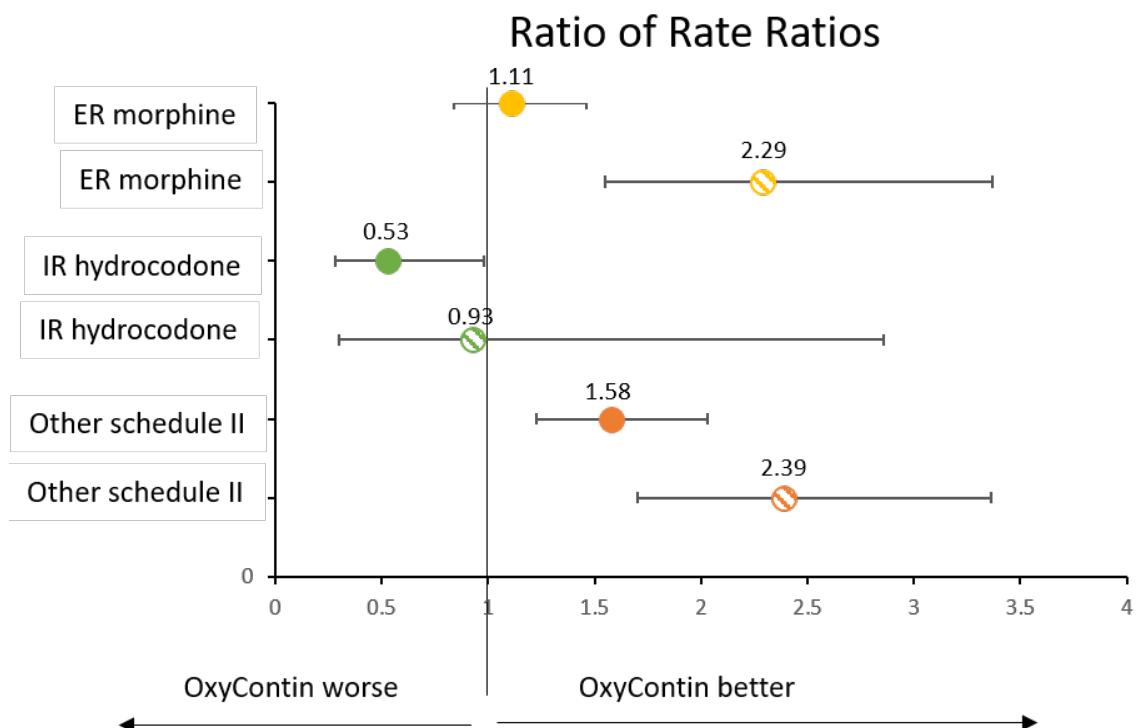
(Source: FDA generated figure from information request response.)

Key: ER: Extended Release; IR: Immediate Release; †Most "Conservative": Smallest pre-post reduction (or largest increase) in non-oral abuse; ‡Least "Conservative": Largest pre-post reduction (or smallest increase) in non-oral abuse

Figure 35: Range of estimates for RORR for abuse via <u>injection </u>route in Oxycontin and primary comparators

ER morphine

IR hydrocodone combination

Other schedule II opioids

Range of Estimates

■ Most "conservative" [†]

▨ Least "conservative"[‡]

(Source: FDA generated figure from information request response.)

Key: ER: Extended Release; IR: Immediate Release; [†]Most "Conservative": Smallest pre-post reduction (or largest increase) in OxyContin non-oral abuse relative to comparator's change; [‡]Least "Conservative": Largest pre-post reduction (or smallest increase) in OxyContin non-oral abuse relative to comparator's change

Table 31 in appendix 6.12 presents ranges for percent change and RORR with information on which model produced each respective estimate.

3.4.9.5   Changes in abuse via <u>any route</u> for OxyContin and comparator opioids

Table 17 shows the range of estimates for percent change and RORR for abuse via any route for OxyContin and comparator opioids in the pre- vs. post-periods. Estimated percent change for OxyContin abuse via any route from the pre- to the post-period ranged from +5.8% to -38.6%. The most "conservative" RORR estimates for each primary comparator showed a significantly greater decrease in abuse via any route for comparator than OxyContin, and a significantly greater decrease in abuse via any route for OxyContin for the least "conservative" RORR estimates.

Table 17: Range of estimates for percent change and RORR for abuse via <u>any route</u> for OxyContin and comparator opioids

	Range: Pre-post relative change (95% CI)		Range: RORR (95% CI)	
	Most "conservative"[†]	Least "conservative"[‡]	Most "conservative" [ψ]	Least "conservative" [ψ]
OxyContin	5.8 (-3.8, 16.5)[1]	-38.6 (-46.5, -29.5)[2]	Ref	Ref
ER morphine	-0.3 (-21.1, 26.0)[3]	-29.0 (-39.4, -16.9)[4]	0.70 (0.58, 0.84)[9]	1.62 (1.24, 2.13)[10]
IR hydrocodone	-2.4 (-15.9, 13.2)[5]	-27.4 (-31.8, -22.7)[6]	0.69 (0.61, 0.77)[11]	1.57 (1.32, 1.87)[12]

| Other schedule II | 3.8 (-4.2, 12.5)[7] | -16.5 (-20.8, -12.0)[8] | 0.80 (0.72, 0.89)[13] | 1.53 (1.30, 1.79)[14] |

(Source: FDA generated figure from information request response.)

1) Model 2a, 2) Model 3a, 3) Model 3a, 4) Model 2, 5) Model 1, 6) Model 2a, 7) Model 3, 8) Model 2, 9) Model 2, 10) Model 3a, 11) Model 2a, 12) Model 3a, 13) Model 2a, 14) Model 3

Key: ER: Extended Release; IR: Immediate Release; Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablet dispensed adjusted for ASI-MV assessments as covariate; Model 3 models abuse rate adjusted for tablets dispensed as a covariate; Model 3a models abuse rate adjusted for tablets dispensed and ASI-MV assessments as covariates; [†]Most "Conservative" percent change: Smallest pre-post reduction (or largest increase) in non-oral abuse; [‡]Least "Conservative" percent change: Largest pre-post reduction (or smallest increase) in non-oral abuse; [Ψ]Most "conservative" RORR: Smallest pre-post reduction (or smallest increase) in OxyContin non-oral abuse relative to comparator's change; [Ψ]Least "Conservative" RORR: Largest pre-post reduction (or smallest increase) in OxyContin non-oral abuse relative to comparator's change

3.4.10 Changes in Prevalence of Past 30-day Abuse of OxyContin Stratified by Treatment Modality, Severity Index, and Geographic Region

Adults being assessed for substance abuse severity and treatment planning with the NAVIPPRO ASI-MV system may be entering a number of different treatment modalities including a residential/inpatient center, outpatient/non-methadone center, methadone center, corrections center, or other types of centers, and these treatment centers are present throughout the US. During the assessment, patients are evaluated for substance abuse problem severity based on a number of different factors, including medical status, employment and support status, drug use and alcohol use, legal status, family and social relationships and psychiatric status.[9]

Tables below present percent change in mean quarterly estimated abuse via any route, oral, and non-oral for OxyContin, stratified by treatment modality, severity index score, and geographic location. Although we consider the definition of ≥1 assessment/quarter to be the main definition for the majority of these analyses, for these more granular analyses presented below, where abuse cases were stratified by treatment modality, severity index, and geographic region (further decreasing the sample sizes of the analyzed groups), we present the analyses for the less restrictive ≥1 assessment/year as the primary analyses, and the ≥1 assessment/quarter as the secondary analyses (appendix 6.13).

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[9] Butler S, Budman SH, Licari A, Cassida TA, Lioy K, Dickinson J, Brownstein JS, Benneyan JC, Green TC, Katz N. National addiction vigilance intervention and prevention program (NAVIPPRO™): a real-time, produt-specific, public health surveillance system for monitoring prescription drug abuse. Pharmacoepidemiology and drug safety 2008;17:1142-1154.

Analysis parameters:
- Sites: contributing ≥1 assessment/year
- OxyContin definition: any Oxycontin (original or reformulated)
- Unit of analysis: 3-digit ZIP code
- Time period -2y/4y
- Model #1:
  - Offset: Total Assessments
  - Covariates: None

Table 18 shows the percent change in mean OxyContin abuse rates, stratified by treatment modality. The rate of OxyContin abuse varied considerably by treatment modality, and non-oral OxyContin abuse in the pre-period was considerably different depending on the treatment modality; the highest rate of endorsement was ~9 endorsements per 100 assessments in individuals in residential/inpatient treatment modalities, as opposed to corrections, which had a rate of <1 endorsement per 100 assessments. Although non-oral abuse rates consistently showed a decrease from pre- to post-reformulation, the magnitude of this decrease varied by treatment modality. Patients being assessed at outpatient/non-methadone facilities showed a -41.9% decrease in non-oral OxyContin abuse from the pre to post-period, while those entering residential/inpatient centers showed a -27% decrease in non-oral OxyContin abuse. Generally, across all treatment modalities, there was a decrease in non-oral abuse, and an increase in oral abuse.

Table 18: Pre-period rate, post-period rate, and percent change in mean abuse rate for any OxyContin per 100 assessments, stratified by treatment modality and route

	Overall (any route)			Oral*			Non-oral		
	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)
Residential/inpatient	11.854 (9.317, 15.083)	10.124 (8.494, 12.067)	-14.6 (-27.1, 0.0)	5.431 (5.026, 5.869)	6.701 (6.419, 6.995)	23.4 (12.9, 34.8)	8.954 (6.714, 11.942)	6.535 (5.186, 8.236)	-27.0 (-39.3, -12.2)
Outpatient/ non-methadone	5.122 (3.818, 6.871)	3.427 (2.591, 4.533)	-33.1 (-44.1, -19.9)	2.310 (2.089, 2.553)	2.386 (2.219, 2.566)	3.3 (-8.7, 16.9)	3.832 (2.705, 5.428)	2.225 (1.423, 3.479)	-41.9 (-54.0, -26.7)
Methadone	10.428 (6.160, 17.653)	8.613 (5.427, 13.671)	-17.4 (-38.6, 11.2)	6.839 (5.777, 8.096)	6.944 (6.024, 8.006)	1.5 (-18.6, 26.6)	7.537 (3.900, 14.569)	4.722 (2.508, 8.891)	-37.4 (-52.6, -17.2)
Corrections	1.429 (1.173, 1.740)	1.481 (1.166, 1.882)	3.7 (-12.4, 22.6)	1.109 (0.989, 1.244)	1.262 (1.170, 1.361)	13.7 (-0.8, 30.5)	0.663 (0.497, 0.884)	0.454 (0.367, 0.561)	-31.5 (-45.1, -14.6)
Other	7.571 (4.906, 11.685)	5.492 (3.874, 7.784)	-27.5 (-45.2, -3.9)	2.970 (2.497, 3.532)	3.836 (3.480, 4.229)	29.2 (5.9, 57.6)	5.457 (3.371, 8.834)	3.269 (2.201, 4.855)	-40.1 (-58.5, -13.6)

*Note Repeated statement was removed from the model as there were following errors when 'repeated' statement was included.
Error: Error in computing the variance function.
Error: Error in parameter estimate covariance computation.

(Source: FDA Postmarketing Requirement Study 3051-1, Purdue Response to FDA Information and Analyses Request on May 30, 2019 Phase 1 Part 2. Title: Table 3: Stratified by treatment modality based on Original + Reformulated OxyContin: sites with ≥1 assessment/year during 2y/4y time period. P. 27.)

Key: CI: Confidence Interval

Table 19 shows the model-estimated percent decrease in overall, oral, and non-oral abuse, stratified by addiction severity index score. The rate of OxyContin abuse varied considerably by severity index score; individuals with no real problem had a mean quarterly abuse rate of <1 OxyContin endorsement per 100 assessments, while those with a considerable to extreme problem had a mean quarterly abuse rate of ~13 OxyContin endorsements per 100 assessments. There was substantial variation in the change in non-oral abuse rates for OxyContin dependent upon the severity index of the patient assessed. Patients assessed as having no real problem to a slight problem did not show a decrease in non-oral OxyContin abuse, showing a modest +6.5% increase in non-oral abuse, while patients having a moderate problem or a considerable to extreme problem showed a -36.2% and -32.8% decrease in non-oral abuse, respectively. While non-oral abuse showed a decrease, oral abuse showed modest, non-significant increases across all severity indices.

Table 19: Pre-period rate, post-period rate, and percent change in mean abuse rate for any OxyContin per 100 assessments, stratified by addiction severity score and route

	Overall (any route)			Oral			Non-oral		
	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)
0-3: No real problem-slight problem	0.529 (0.407, 0.689)	0.546 (0.415, 0.719)	3.2 (-19.4, 32.1)	0.422 (0.314, 0.568)	0.458 (0.344, 0.610)	8.5 (-17.1, 42.1)	0.124 (0.088, 0.174)	0.132 (0.098, 0.177)	6.5 (-27.6, 56.6)
4-5: Moderate problem	2.987 (2.456, 3.631)	2.595 (2.171, 3.102)	-13.1 (-26.9, 3.2)	1.794 (1.463, 2.201)	2.001 (1.675, 2.390)	11.5 (-8.2, 35.4)	1.804 (1.422, 2.289)	1.151 (0.906, 1.463)	-36.2 (-49.1, -20.0)
6-9: Considerable problem-extreme problem	13.367 (10.876, 16.427)	10.614 (9.122, 12.350)	-20.6 (-30.8, -8.9)	6.304 (5.433, 7.316)	7.065 (6.313, 7.907)	12.1 (-0.2, 25.8)	10.622 (8.232, 13.707)	7.137 (5.805, 8.775)	-32.8 (-42.0, -22.2)

(Source: FDA Postmarketing Requirement Study 3051-1, Purdue Response to FDA Information and Analyses Request on May 30, 2019 Phase 1 Part 2. Title: Table 7: Stratified by ASI-MV® score based on Original + Reformulated OxyContin: sites with >1 assessment/year during 2y/4y time period. P. 31.)

Key: CI: Confidence Interval

Table 20 shows percent change in OxyContin abuse stratified by geographic region. While the northeast, south, and midwest regions showed relatively consistent decreases in non-oral abuse, -52.3%, -43.3%, and -50.2%, respectively, the south showed a much smaller decrease (-18.0%). Although the northeast did have sites that contributed to the sample for sites contributing ≥1 assessment/year (shown here), in the more restricted set of sites contributing ≥1 assessment/quarter (appendix 6.13), there was no representation from the Northeast.

Table 20: Pre-period rate, post-period rate, and percent change in mean abuse rate for any OxyContin per 100 assessments, stratified by geographic region

	Overall (any route)			Oral*			Non-oral		
	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)
Northeast	9.707 (5.826, 16.175)	6.567 (4.549, 9.481)	-32.4 (-52.6, -3.5)	5.115 (4.097, 6.386)	4.786 (4.134, 5.541)	-6.4 (-28.3, 22.1)	8.565 (5.418, 13.540)	4.082 (2.823, 5.904)	-52.3 (-64.3, -36.3)
South	7.048 (4.374, 11.356)	5.933 (3.683, 9.556)	-15.8 (-32.6, 5.2)	2.422 (2.261, 2.595)	3.422 (3.294, 3.555)	41.3 (30.6, 52.9)	5.498 (3.088, 9.788)	4.506 (2.432, 8.351)	-18.0 (-35.9, 4.8)
West	3.575 (2.904, 4.401)	2.648 (2.051, 3.420)	-25.9 (-43.6, -2.7)	2.260 (2.024, 2.523)	2.376 (2.184, 2.584)	5.1 (-8.5, 20.7)	2.063 (1.617, 2.633)	1.170 (0.816, 1.680)	-43.3 (-58.4, -22.7)
Midwest	6.857 (5.408, 8.696)	4.679 (3.518, 6.224)	-31.8 (-40.3, -22.1)	3.293 (2.985, 3.633)	3.094 (2.879, 3.325)	-6.0 (-16.8, 6.1)	5.869 (4.683, 7.355)	2.920 (2.212, 3.855)	-50.2 (-55.7, -44.0)

*Note Repeated statement was removed from the model as there were following errors when 'repeated' statement was included.

Error: Error in computing the variance function.

Error: Error in parameter estimate covariance computation.

(Source: FDA Postmarketing Requirement Study 3051-1, Purdue Response to FDA Information and Analyses Request on May 30, 2019 Phase 1 Part 2. Title: Table 11: Stratified by geographic region based on Original + Reformulated OxyContin: sites with >1 assessment/year during 2y/4y time period. P. 35.)

Key: CI: Confidence Interval

Data in appendix 6.13 presents these analyses for the more restricted set of sites (≥1 assessment/quarter). In these analyses, the largest decrease in non-oral OxyContin abuse is also observed for individuals with a moderate to extreme problem.

3.4.11 Interrupted Time Series Analyses

Interrupted time series (ITS) analysis was conducted in order to understand changes in non-oral abuse trends over time, both in terms of the change in slope of non-oral abuse in the pre- and post-periods as well as the immediate shift of non-oral abuse immediately after reformulation. While means analysis can aid our understanding of the change in mean quarterly non-oral abuse rates in pre- and post-periods, ITS can inform our understanding of trends in non-oral abuse of OxyContin and comparators before reformulation, and how reformulation may have affected those trends.
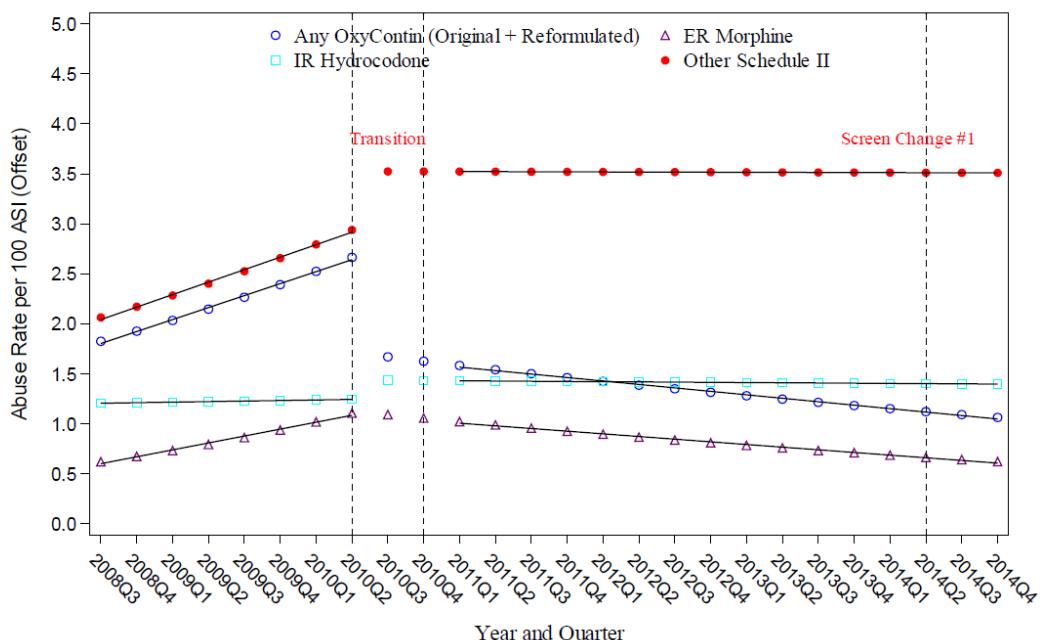
Analysis Parameters:
- Sites: contributing >1 assessment/quarter
- OxyContin definition: any Oxycontin (original or reformulated)
- Unit of analysis: 3-digit ZIP code
- Time period -2y/4y
- Model #1i:
    - Offset: Total assessments
    - Covariates: NA
- Model #2i
    - Offset: Dosage units dispensed
    - Covariate: NA
- Model #3i
    - Offset: NA
    - Covariates: Dosage units dispensed and Total assessments

Visual depictions of ITS trends for OxyContin and comparators for utilization or population adjusted models are shown in figures 37-39 below. Underneath each figure is a table with information on slope, change in slope, and immediate shift (or 'level change')[10] metrics. In population-based analyses (Figure 37), the change in slope and immediate shift metrics are both significant for OxyContin. Change in slope is significant for ER morphine, but immediate shift for this comparator is not significant, and neither change in slope nor immediate shift are significant for IR hydrocodone and "other schedule II opioids". Comparative results show a significant decrease in immediate shift for OxyContin that is larger than immediate shift for IR hydrocodone and "other schedule II opioids", however decrease in slope for OxyContin is not significantly larger than these comparators, and neither immediate shift nor change in slope is significant for ER morphine vs. OxyContin.

Figure 36: Slope and immediate shift for non-oral abuse of OxyContin and primary comparator opioids per 100 assessments, model 1i

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[10] Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomization is not an option: interrupted time series analysis. *BMJ* 2015;350:h2750 doi: 10.1136/bmj.h2750

Abuse Rate per 100 ASI (Offset)

Any OxyContin (Original + Reformulated)   ER Morphine
IR Hydrocodone   Other Schedule II

Transition   Screen Change #1

Year and Quarter

Opioid	Slope in pre	Slope in post	Change in slope (95% CI)	Immediate shift (95% CI)	Comparison: P-value Slope change	Comparison: P-value Immediate shift
OxyContin	0.05	-0.03	-0.08 (-0.15, -0.01)	-0.52 (-0.87, -0.17)	Ref	Ref
ER morphine	0.08	-0.03	-0.12 (-0.23, -0.01)	-0.08 (-0.58, 0.42)	0.6	0.2
IR hydrocodone	0.004	-0.002	-0.006 (-0.095, 0.083)	0.14 (-0.29, 0.57)	0.2	0.02
Other schedule II opioids	0.05	-0.0003	-0.05 (-0.11, 0.01)	0.18 (-0.10, 0.46)	0.5	0.002

(Source: Purdue Response to FDA Information and Analyses Request on May 30, 2019 Postmarketing Requirement Study 3051-1 (received February 2020) Title: Figure 3-1A-1-1. Slopes from Interrupted Time Series Analysis in Non-Oral Abuse Rate Using Sites with at least 1 Assessment per Quarter: Any OxyContin (Original + Reformulated) with Primary Comparator Opioids – Model 1i: assessments as offset. P. 13.)

Key: ER: Extended Release; IR: Immediate Release; CI: Confidence Interval

In utilization-based analyses (Figure 38), immediate shift shows a significant decrease for OxyContin non-oral abuse, however the slope does not change significantly. Immediate shift and slope change were not significant for any comparators when adjusting for utilization. In comparative analyses, neither change in slope nor immediate shift is significant for comparators vs. OxyContin.

Figure 37: Slope and immediate shift for non-oral abuse of OxyContin and primary comparator opioids per 10,000 dosage units dispensed, model 2i

Opioid	Slope in pre	Slope in post	Change in slope (95% CI)	Immediate shift (95% CI)	Comparison: P-value slope change	Comparison: P-value immediate shift
OxyContin	0.04	0.007	-0.04 (-0.14, 0.07)	-0.57 (-1.11, -0.04)	Ref	Ref
ER morphine	0.04	-0.03	-0.07 (-0.24, 0.10)	-0.24 (-1.01, 0.52)	0.8	0.5
IR hydrocodone	-0.02	0.02	0.04 (-0.10, 0.17)	-0.16 (-0.82, 0.50)	0.4	0.3
Other schedule II opioids	0.01	0.02	0.007 (-0.09, 0.10)	-0.06 (-0.49, 0.38)	0.5	0.1

(Source: Purdue Response to FDA Information and Analyses Request on May 30, 2019 Postmarketing Requirement Study 3051-1 (received February 2020) Title: Figure 3-1A-1-2. Slopes from Interrupted Time Series Analysis in Non-Oral Abuse Rate Using Sites with at least 1 Assessment per Quarter: Any OxyContin (Original + Reformulated) with Primary Comparator Opioids – Model 2i: dosage units dispensed as offset. P. 14.)

Key: ER: Extended Release; IR: Immediate Release; CI: Confidence Interval

Figure 39 below presents ITS analyses for model 3i, which adjusts for utilization as a covariate. This model shows a decrease in change in slope and immediate shift for OxyContin, however only the immediate shift shows a significant decrease. No comparators show a significant decrease in slope or immediate shift. In comparative analyses, neither slope change nor immediate shift were significant for comparators vs. OxyContin.

Figure 38: Slope and immediate shift for non-oral abuse of OxyContin and primary comparator opioids adjusted for utilization, model 3i

Opioid	Slope in pre	Slope in post	Change in slope (95% CI)	Immediate shift (95% CI)	P value slope change	P value immediate shift
OxyContin	0.05	-0.02	-0.06 (-0.17, 0.04)	-0.56 (-1.10, -0.03)	Ref	Ref
ER morphine	0.07	-0.02	-0.10 (-0.26, 0.07)	-0.11 (-0.87, 0.66)	0.7	0.3
IR hydrocodone	-0.008	0.01	0.02 (-0.11, 0.16)	-0.02 (-0.68, 0.64)	0.3	0.2
Other schedule II opioids	0.02	0.02	-0.009 (-0.10, 0.09)	-0.01 (-0.45, 0.42)	0.5	0.1

(Source: Purdue Response to FDA Information and Analyses Request on May 30, 2019 Postmarketing Requirement Study 3051-1 (received February 2020) Title: Figure 3-1A-1-3. Slopes from Interrupted Time Series Analysis in Non-Oral Abuse Rate Using Sites with at least 1 Assessment per Quarter: Any OxyContin (Original + Reformulated) with Primary Comparator Opioids – Model 3i: dosage units dispensed (continuous) as covariate. P. 16.)

Key: ER: Extended Release; IR: Immediate Release; CI: Confidence Interval

ITS analyses using additional models can be found in appendix 6.14.

3.4.12 Impact of Screen Changes Made to ASI-MV in 2Q2014 and 1Q2015 on Misclassification of OxyContin Products

A number of screen changes occurred in the ASI-MV tool during and after reformulation of OxyContin.

When reformulated OxyContin was introduced in August 2010, the following changes occurred for the ER oxycodone screen:

1) Additional strengths (15, 30, 40mg) of original OxyContin were included, and pictures were updated to depict truer colors

2) Images of original OxyContin were re-labeled as "old OxyContin" (marked with "OC"). These remained in the first (left-most) position.
3) All strengths of reformulated OxyContin were depicted with true colors, labeled as "OxyContin Reformulated" (marked with "OP"). These were in the second position after original OxyContin.
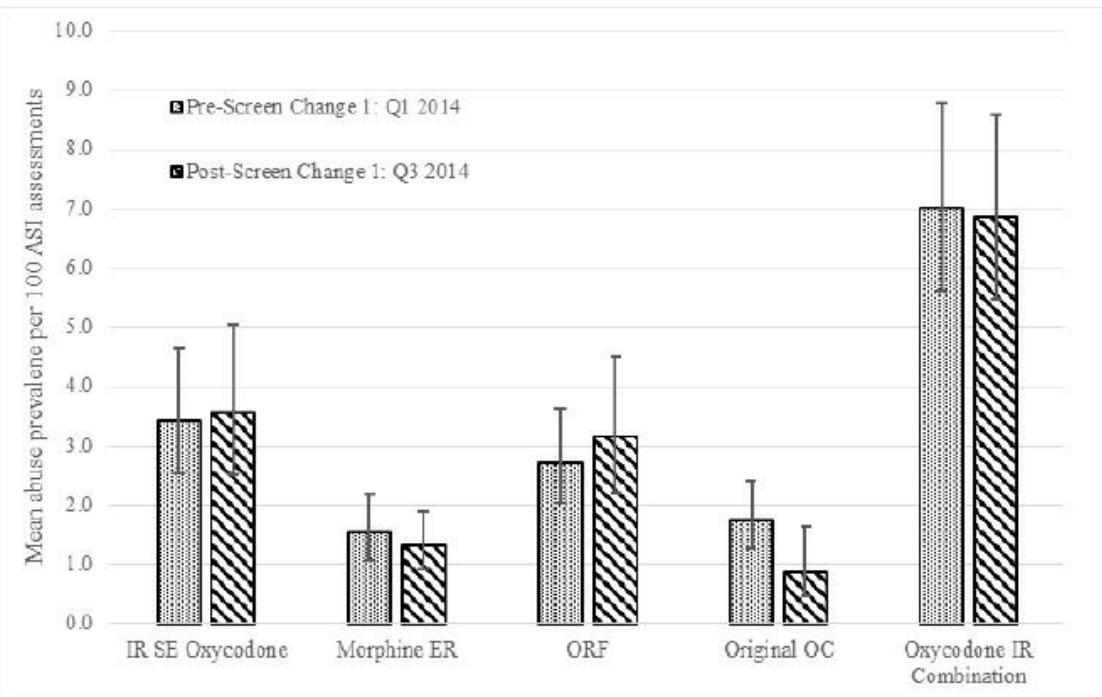
These images were followed by images of OxyContin marked with "EX" (distributed mostly in Mexico), and images of OxyContin marked with "CDN" (distributed mostly in Canada). This was followed by boxes that could be selected, labeled as "other extended release oxycodone not shown" and "None".

In May 2014, images of reformulated OxyContin were moved to the first (left-most) position on the ER oxycodone screen, followed by OxyContin marked with "EX", followed by OxyContin marked with "CDN". The remainder of the screen contained boxes with text reading, "Xartemis XR", "Old OxyContin" (marked with "OC"), "Other extended release non-combination oxycodone not shown", "Other extended-release oxycodone with acetaminophen not shown" and "None."

In March 2015, along with an order change in which Xartemis XR and OxyNeo were added and moved to the second and third products listed from the left, the ER oxycodone screen was moved from the first opioid screen presented to respondents to the fourth, preceded, in order, by hydrocodone products, IR oxycodone combination products, and IR SE oxycodone products.

Figure 40 shows the changes in abuse of OxyContin and comparators after the first screen change in May 2014 when reformulated OxyContin was moved to the first position on the ER oxycodone screen. Immediately following the screen change, there was a decrease in endorsement of original OxyContin by approximately 50% and an increase in endorsement of reformulated OxyContin of approximately 15% per 100 assessments. Endorsement of abuse for comparators remained relatively consistent over the time period.

Figure 39: Change in abuse of OxyContin and comparators before and after the first ASI-MV screen change in 2Q2014 (Model 1)
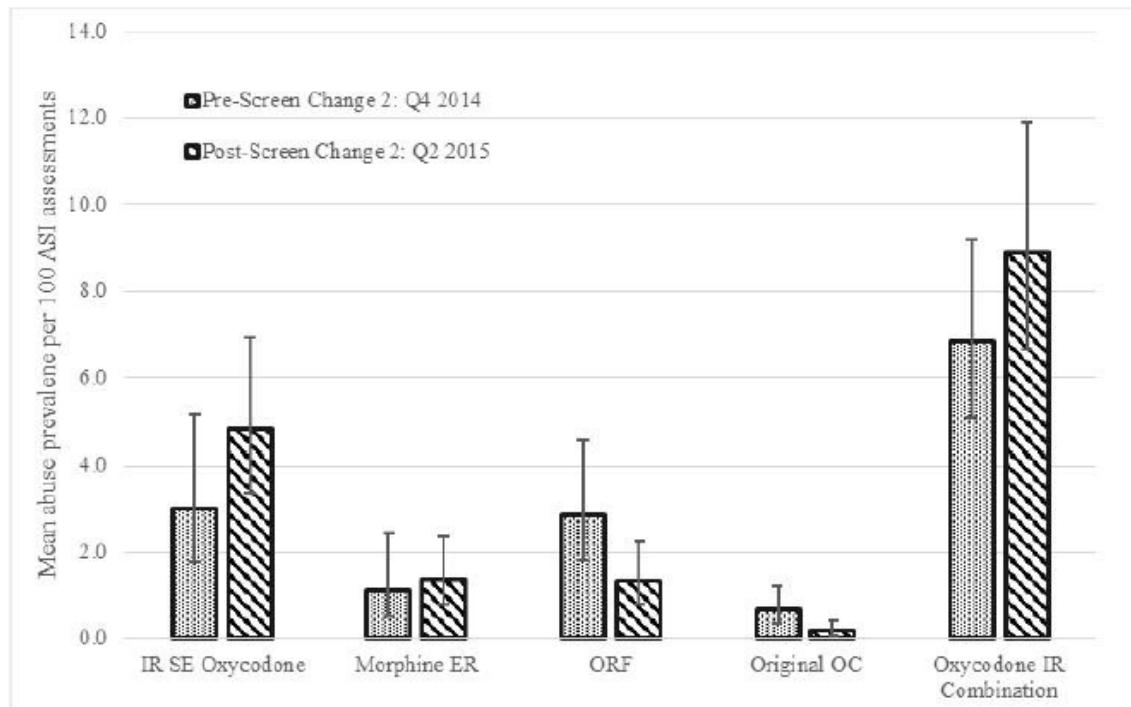
Error bars: 95% confidence intervals; Sites: contributing ≥ 1 assessment/year, 2y/4y; ER=extended release; IR=immediate release; SE=single entity; ORF=reformulated OxyContin; OC=original OxyContin; Q=quarter

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 12-7. Change in abuse of OxyContin and comparators before and after the first ASI-MV® screen change in 2Q2014 (Model 1). P. 377)

Key: ER: Extended Release; IR: Immediate Release; SE: Single Entity; Original OC: Original OxyContin; ORF: Reformulated OxyContin

Figure 41 shows change in endorsement of OxyContin abuse in the quarter before and quarter after the second screen change, occurring in 1Q2015, during which the ER oxycodone screen was moved from first in order to fourth. Mean abuse prevalence of OxyContin products, both original and reformulated, dropped noticeably in the post-screen change 2 time period, while mean prevalence of abuse for comparators remained similar or increased. Mean prevalence of original OxyContin decreased >50%, while mean prevalence of reformulated OxyContin decreased approximately 50%.

Figure 40: Change in abuse of OxyContin and comparators before and after the second ASI-MV screen change in 1Q2015 (Model 1)

Error bars: 95% confidence intervals; Sites: contributing ≥ 1 assessment/year, 2y/4y; ER=extended release; IR=immediate release; SE=single entity; ORF=reformulated OxyContin; OC=original OxyContin; Q=quarter; Legend - pre: shaded bars – post: diagonal line fill

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 12-9. Change in abuse of OxyContin and comparators before and after the second ASI-MV® screen change in 1Q2015 (Model 1). P. 379.)

Key: ER: Extended Release; IR: Immediate Release; SE: Single Entity; Original OC: Original OxyContin; ORF: Reformulated OxyContin

Figures in appendix 6.15 present assessments of screen changes for model 2, and screen changes between a one-year pre-reformulation time period (3Q2009-2Q2010) and a one-year post-screen change period (2Q2015-1Q2016).

3.4.13 Assess the Relationship Between Dosage Units Dispensed and Number of Abuse Cases per Respondent 3-Digit ZIP

Analyses to assess the relationship between dosage units dispensed and number of abuse cases per respondents 3-digit ZIP were included in the SAP. These analyses were proposed by the sponsor in order to assess the appropriateness of the assumptions of models that adjusted for utilization as an offset, where the relationship between utilization and abuse cases is assumed to be linear (which is specifically set at 1), and models that adjust for utilization as a covariate, where the relationship is assumed to be exponential. The sponsor did not ultimately submit the figures from these planned analyses because they were uninterpretable, primarily because four different types of abuse related data were displayed in the same chart using multiple variables and a secondary y-axis to visually represent the information. The sponsor argued that a

thorough model assessment was conducted (presented in appendix 6.16), and therefore these figures were not presented.

3.5   SPONSOR'S STUDY CONCLUSIONS

The sponsor concluded that results of this study in a population of individuals entering a substance abuse disorder treatment program support the hypothesis that the introduction of reformulated OxyContin has resulted in a meaningful and sustained decline in non-oral abuse, primarily via snorting and injecting. This decline is more pronounced than the changes observed for a variety of comparator opioid products, thereby distinguishing the effectiveness of the reformulation of OxyContin from other competing population-based opioid abuse interventions.

4   DISCUSSION

4.1   SUMMARY OF STUDY FINDINGS

Given the potential for both sampling and misclassification bias, as well as differing ways to consider the amount of drug dispensed in the community, this study employed a number of analytic models with differing assumptions. For the most part, these assumptions are not testable, making it difficult to determine the most valid results. Furthermore, several comparator opioids were used as "negative controls," intended to approximate what might have been the expected changes in OxyContin abuse rates had it not been reformulated (i.e., the counterfactual scenario). This is an important consideration when attempting to draw causal inferences from a study, in other words, to conclude that changes seen in OxyContin abuse rates were caused by the reformulation, rather than simply temporally associated with it, particularly given the dynamic nature of this sample and other events (e.g., pill mill-related actions) that occurred around the time of the introduction of reformulated OxyContin. However, there was no ideal comparator for this purpose, and so multiple comparators were used, complicating interpretation of the results. Finally, in a time series analysis such as this study, the selection of pre-, post-, and transition time periods can impact results. Results of trend (ITS) analyses add further information to help interpret means analyses and make causal inferences. Below, we summarize the range of results from the multiple analyses conducted in this study. We believe that the true magnitude of effect may lie within these ranges (but not likely at either extreme), with regard to ADF-related changes in non-oral and overall OxyContin abuse rates in a population of individuals entering or being assessed for substance abuse treatment in the U.S.

4.2   CHANGES IN NON-ORAL ABUSE, AND SPECIFIC ROUTES OF ABUSE

4.2.1   Non-oral Abuse: Descriptive trends in quarterly abuse rates

Descriptive trend figures showing quarterly prevalence of past 30-day abuse for OxyContin and comparator opioids per 100 assessments demonstrated that rate of non-oral abuse of OxyContin decreased from the pre-period to the post-period, and this decrease was sustained in the post-period. Similar sustained decreases were not observed for comparators. Utilization-based analyses demonstrated a more modest decrease in the post-period, but the decrease was again sustained and did not rise to pre-period levels. Again, similar sustained declines were not observed for most comparators, although some decrease was apparent for ER morphine. Utilization-based analyses show that OxyContin abuse was considerably higher than primary comparators in the pre-period and remained higher in the post-period.

4.2.2   Non-oral Abuse: Range of Estimates for Means Analyses (Main)

Estimates for change in non-oral abuse rates for OxyContin in the pre- vs. post-periods for primary variable definitions showed a consistent decrease, ranging from -29.3% to -55.6%. In comparison, the ranges for comparator opioids included both negative and positive estimates of change in non-oral abuse rates: morphine ER (range: +3.7% to -28.5%), hydrocodone IR combination (range: +21.2% to -8.2%), and "other schedule II opioids" (range: +31.6% to +13.2%). The least "conservative" estimates showed a significantly larger decrease in non-oral abuse rates for OxyContin than for any of the primary comparators: RORR for OxyContin compared with morphine ER was 2.33, compared with hydrocodone IR combination products was 2.73, and compared with "other schedule II opioids" was 2.71. The most "conservative" estimates of the decrease in OxyContin across the pre- and post-reformulation time periods included non-significant RORRs for morphine ER (1.04) but remained significant for IR hydrocodone (1.3) and "other schedule II opioids" (1.62). Significant decreases in non-oral OxyContin abuse were observed primarily among those categorized as having moderate to severe addiction, based on addiction severity score.

Within the category of non-oral abuse, the estimates of rates of abuse via snorting showed a consistent decrease for OxyContin (range: -40.3% to -62.5%). The range of RORR for snorting abuse for OxyContin compared with hydrocodone IR combination products and "other schedule II opioids" was significant regardless of the model or variable definitions, ranging from 1.47 to 3.11 for hydrocodone IR combination products, and ranging from 1.87 to 3.17 for "other schedule II opioids". The least conservative estimate of decrease in snorting abuse for OxyContin compared to ER morphine gave an RORR of 2.64, but the most "conservative" estimate gave a non-significant RORR of 1.22.

Within the category of non-oral abuse, the estimates of rate of abuse via injection also showed a consistent decrease for OxyContin (range: -33.3% to -54.6%).The least "conservative" estimates of decrease in injection for OxyContin showed a significant difference between decrease in OxyContin injection for ER morphine (2.29) and "other schedule II opioids" (2.39), however the most "conservative" RORR for ER morphine vs. OxyContin was not significant (1.11). RORR estimates for IR hydrocodone vs. OxyContin showed a larger decrease in injection abuse for hydrocodone than OxyContin, *however it is important to note* that IR hydrocodone injection abuse was very low in the pre- and post-period, and therefore a small change led to a large percent decrease.

Estimates of oral OxyContin abuse via swallowing whole did not show a consistent direction of change across models (+32.8% to -21.4%) while other oral routes (chewed, dissolved, drank) showed a consistent increase (+57.7% to +33.2%).

4.2.3 Specific Route of Abuse Profile: Change in Route of Abuse Among Those Reporting Abuse of OxyContin and Comparators

Supportive of the main analyses of non-oral abuse rates, descriptive, unmodeled analyses showed reductions in the percent of OxyContin abuse via snorting and injection among those reporting abuse of any OxyContin. Similar reductions were not seen for comparators. From the pre- to post-period, the percent of individuals endorsing abuse of OxyContin who reported they snorted the drug decreased from 55.2% to 33.4%, and the percent who reported injecting the drug decreased from 31.5% to 19.8%. These descriptive analyses did not formally test for statistical significance, but the estimate for the post-period did lie outside the 95% confidence interval for the pre-period estimate. In analyses looking only at those who reported abuse of original OxyContin in the pre-period or reformulated OxyContin in the post- period, the percent reporting abuse via snorting decreased from 57.3% to 27.3%, and from 30.9% to 25.4% for injection. By contrast, the percent of individuals endorsing ER morphine who reported snorting the drug increased from 22.4% to 28.1%, and the percent who reported injecting increased from 40.4% to 49.1%. For the smaller subset of sites contributing $\geq$1 assessment per quarter, the percentage of those abusing IR hydrocodone combination products who reported snorting decreased slightly from 17.2% to 14.4%, and the percent injecting remained very low, decreasing from 1.6% to 0.2%. The results from the larger set of sites contributing $\geq$1 assessment/year were qualitatively different, and showed a small increase in proportion of IR hydrocodone cases via injection reported (Figure 89, appendix 6.11).

4.2.4 Non-oral Abuse: Interrupted Time Series Analysis

ITS analysis results provide some additional support for the hypothesis that the reformulation reduced non-oral abuse of OxyContin in this population as the results were qualitatively consistent with the findings of the means analyses, although ITS findings

were mixed with regard to statistical significance. The ITS findings demonstrated a significant decrease in slope and in immediate shift of non-oral OxyContin abuse in population-based analyses, and a significant immediate shift in non-oral OxyContin abuse in utilization-based analyses supporting the hypothesis that the reformulation had an immediate impact on the level of OxyContin non-oral abuse, and, at least for population adjusted analyses, an impact on the slope of non-oral OxyContin abuse. In population-based analyses, ER morphine showed a significant decrease in slope but not in immediate shift. No other comparator showed a significant decrease in slope or immediate shift for any other main analyses. In comparative analyses, OxyContin showed a larger decrease for immediate shift than IR hydrocodone and "other schedule II opioids" in population-based analyses, but no other comparative results showed a significantly larger decrease for OxyContin than comparators.

4.3   CHANGES IN OVERALL ABUSE (VIA ANY ROUTE)

4.3.1   Overall Abuse: Range of Estimates for Means Analyses

Estimates of percent change in overall OxyContin abuse (via any route) were mixed, ranging from +5.8% to -38.6%. Ranges of estimates for relative change in abuse for primary comparator opioids were -0.3% to -29.0% for Morphine ER, -2.4% to -26.4% for hydrocodone IR combination products, and +3.8% to -16.5% for "other schedule II opioids". Generally, the modeled rates per tablets dispensed produced the largest decrease in abuse for comparators, while models that adjusted for tablets dispensed as a covariate produced the largest decrease in abuse for OxyContin. RORR results were mixed as well, with the least conservative estimates demonstrating a significantly larger decrease in OxyContin abuse than comparators, and the most conservative RORR estimates demonstrating a significantly larger decrease in comparators abuse than OxyContin.

4.3.2   Overall Abuse: Descriptive Trends in Quarterly Abuse Rates

Descriptive trend figures of quarterly prevalence of abuse via any route for OxyContin and comparator opioids showed little change in overall abuse rates for OxyContin in the pre- vs. post-periods. While the overall rate of OxyContin abuse demonstrated a modest decrease in the post-period, it returned to levels similar to the pre-period. Graphs of proportion and average number of individuals endorsing OxyContin via specific routes per quarter showed that this increase was likely coming from a slight increase in the average number of individuals endorsing abuse of OxyContin per quarter via swallow, chew, dissolve, and smoke.

4.4   METHODOLOGICAL CONSIDERATIONS AND SENSITIVITY ANALYSIS RESULTS

A large number of parameters were included in these analyses in part due to the complicated nature of the ASI-MV data source. There is no single, standard scientifically agreed-upon denominator or modeling approach to estimate abuse rates. Therefore, the study generated estimates using a population-based model (Model 1: number of ASI-MV assessments used as the denominator [i.e., offset]), a utilization-based model (Model 2: dosage units dispensed used as the denominator), and utilization-adjusted (Model 3: dosage units dispensed included as a covariate), with additional models adjusting for assessments as a covariate. In addition, due to the inherent uncertainties associated with these data and this design (e.g., potential for bias due to product misclassification, use of a dynamic study sample, confounding secular trends), a number of sensitivity analyses were conducted, including varying the time period, definition of an OxyContin abuse case (e.g., any OxyContin, any ER oxycodone, original/reformulated OxyContin), and site inclusion criteria (with main analyses using a smaller, consistent sample of sites and sensitivity analyses using a larger sample that changed over time). Together, these different models and sensitivity analyses were used to estimate a range of possible effect sizes and assess robustness of the overall study findings with regard to the effect of reformulation on abuse rates in this population. The results of sensitivity analyses, described below, were largely consistent with the main study findings, although the exact estimates varied (refer to section 3.4.6).

4.4.1   Misclassification Bias and OxyContin Definition

Misclassification can occur in a survey setting when a respondent is unsure of which product he or she abused, and instead endorses another product, either because it looks or sounds similar to the abused product, or because of misunderstanding of questions, survey fatigue, or careless response. In this analysis, there was a high number of endorsements of original OxyContin after the reformulation and discontinuation of original OxyContin. There was also endorsement of generic ER oxycodone throughout the post-period, although dispensing of generic ER oxycodone fell dramatically in January 2011 and was negligible throughout the remainder of the post-period. The endorsements of both generic ER oxycodone and original OxyContin in the post-period likely include some misclassified abuse of reformulated OxyContin or another oxycodone product.

Sensitivity analyses using different OxyContin definitions showed smaller changes in abuse rates including "any ER oxycodone" (range: -23.5% to -67.4%) compared to including "any OxyContin" (range: -29.3% to -55.6%), whereas the definition including "original OxyContin (pre-period) versus reformulated OxyContin only (post-period)" showed the largest decrease in abuse rates (range: -59.4% to -70.0%). Analyses of opioid abuse endorsements after screen changes 1 and 2 provide some information about potential misclassification bias. When the ER oxycodone screen was changed such that

reformulated OxyContin was listed first, and original Oxycontin was moved to a less prominent position and the image removed, endorsement of reformulated OxyContin increased and endorsement of original OxyContin decreased. This suggests that some misclassification of reformulated OxyContin as original OxyContin likely did occur. It is also possible that other oxycodone products, such as IR SE oxycodone were misclassified as original OxyContin; however, this likely occurred throughout the study period, and excluding original OxyContin cases during the post-period would also bias results away from the null. To avoid such bias away from the null, models using the "any OxyContin" definition were considered as main definition by the agency as the definition of OxyContin would be appropriate in order to minimize this bias, recognizing that estimates of change using this definition may be overly conservative. Because it is not possible to measure the degree or direction of misclassification, we are again left with a range of possible estimates, with the "true" result unlikely to lie at either extreme.

Assessment of screen changes in 1Q2015 show that when the oxycodone ER screen was moved from the first position to the fourth position, endorsement of all OxyContin products decreased noticeably, indicating again that there may be a primacy effect. Although time periods used to assess changes in OxyContin abuse should not include quarters after this screen change due to this trend break, the apparent impact of the screen order change illustrates the challenges making comparisons of abuse rates across time periods and drug products using these data

4.4.2   Time Period

This study used two timeframes to compare abuse rates in the pre- vs. post-periods for OxyContin and comparators: a 1-year baseline with a 3-year post-reformulation time period, and a 2-year baseline with a 4-year post-reformulation time period. The 2-year baseline represents a more stable estimate of baseline abuse of OxyContin prior to reformulation, and the 4-year post-period maximizes the available data for estimating post-reformulation abuse rates and examining maintenance of effect (but avoids potential bias from screen order changes in 2Q2015). However, the -2y/4y time-frame limits the number of sites included in the consistent sampling population of ≥ 1 assessment/quarter to 34 sites, whereas the consistent set of sites that submitted ≥ 1 assessment/quarter for the -1y/3y time-frame included 91 sites. Therefore, -2y/4y time-frame allowed for a longer baseline and follow-up periods but estimates from the -1y/3y provide a larger and more geographically diverse sample. Decreases in non-oral abuse of OxyContin were attenuated using the -1y/3y time period compared to the -2y/4y time period. Although the decrease in OxyContin was attenuated in the shorter time period, the decrease in OxyContin non-oral abuse rates were still generally larger than comparators.

4.4.3 Study Analytic Sample

One of the major limitations of ASI-MV is the non-representative and dynamic nature of the sample. Furthermore, it is a heterogeneous sample of sites with widely varying patterns of substance abuse (e.g., assessments occurring at correctional facilities versus inpatient treatment settings), so changes in site participation and distribution have the potential to affect overall abuse rates substantially. Very few sites that are originally enrolled in the ASI-MV sample remain enrolled for a long period of time, and many of the sites that remain enrolled for a long period of time do not consistently report data. To capture a consistent study sample and increase internal validity, the main analyses were restricted to ASI-MV sites that contributed >1 assessment per quarter during the pre- and post-periods. This limited the study population to only 34 assessment sites (out of a total 847 sites that participated at some point in the study period throughout 38 states): Twelve sites in four western states (California, Wyoming, Colorado, and New Mexico), ten sites in two midwestern states (Michigan and Nebraska), and twelve sites in four southern states (Oklahoma, Florida, North Carolina and Maryland), with no sites in northeastern states represented. This lack of representation in the northeast was particularly problematic, as this area represents one that has experienced severe problems with both prescription opioid and heroin abuse, addiction, and overdose. As a sensitivity analysis, sites were included if they contributed ≥1 assessment per year. In this larger and more geographically diverse but less stable sample (consisting of 175 sites), reductions in OxyContin abuse rates were generally of smaller magnitude that in the more restricted sample of site contributing data every quarter. However, the percent decrease was generally attenuated for primary comparators in this larger sample, and therefore relative reductions (RORRs) were not substantially affected.

4.4.4 Comparators

The study included m ultiple comparators, allowing a broad view of the opioid utilization and abuse landscape. The primary comparators, in particular, are included to improve the ability to assess causality (i.e., the amount of change in OxyContin abuse rates that can be attributed to the reformulation, versus other factors impacting abuse trends more broadly). These comparator opioids, however, do not serve as perfect negative controls, as none had prescribing and abuse trends exactly reflecting those of OxyContin in the pre-period, and external factors may impact OxyContin and other opioids differently. The characteristics of each of the comparator groups, including their strengths and limitations as comparators, are discussed in more detail in appendix 6.17. In addition, trends in comparators may not necessarily be independent of the reformulation of OxyContin, given the prevalence of polysubstance abuse and potential for substitution effects. Results from PMR 3051-3 ([ref PMR 3051-3](#)) suggest that abuse of OxyContin was not

independent of abuse of comparators, and it is possible that changes in OxyContin abuse could result in both substitution and also concurrent reduction in other opioids that are commonly used in addition to OxyContin. All of this complicates the interpretation of the comparative analyses and making it virtually impossible to precisely estimate the causal effect of the reformulation.

4.4.5 Polysubstance Abuse and Substitution Effects

Individuals reporting abuse of OxyContin endorsed abusing a median of six different opioids during the past 30 days during both the pre- and post-reformulation period, illustrating the polysubstance nature of opioid abuse and addiction. Although this study was not designed to examine the impact of OxyContin's reformulation on the abuse of other opioids, either prescription or illicit (heroin), it is useful to examine the change in rates of abuse for other opioids across the study period to better understand overall changes in the landscape of opioid abuse. There was a relatively small, +6.6% increase reported in non-oral abuse of heroin in the post-period in sites contributing ≥ 1 assessment/quarter. It is important to keep in mind that there was no representation in the sample from sites in the Northeast region of the U.S. (and minimal representation in the ASI-MV network overall), and this is an area with a high prevalence of heroin use. Descriptive trends of non-oral abuse of heroin in the ≥ 1 assessment/year sample suggested steady increases in heroin endorsement in the post-period that were not seen in the more restricted sample.

There was a sharp increase in IR oxycodone endorsements starting in 2Q2010 (before the reformulation), and this is likely due, at least in part, to the addition of IR SE oxycodone to the ASI-MV survey in this quarter. This increase in IR oxycodone endorsements largely drives the increase seen in the "other schedule II opioids" group, and it is difficult to determine how much of the increase was due to better ascertainment versus individuals shifting to these products after OxyContin's reformulation. A large increase in ER oxymorphone endorsements was also evident after OxyContin's reformulation. In addition, this study did not evaluate frequency of use, so it is possible that there were shifts in the relative frequency of use across different opioids among individuals who were already abusing those opioids to some extent (e.g., decreased frequency of use of OxyContin and increased frequency of heroin or other opioids). Finally, it is important to keep in mind that individuals were included in this sample because they had or were deemed to have some need to be assessed for substance use disorders, and therefore, overall trends cannot be interpreted as representing those in the general population.

4.5 STUDY STRENGTHS AND LIMITATIONS:

The conclusions that can be drawn from this study are impacted by its methodological strengths and limitations.

Strengths:

- Provides product-specific and route of abuse-specific reporting.
- Assessment is integrated into clinical care, resulting in high participation rate.
- Demographic, clinical, and substance abuse characteristics are captured and can be used to assess for potential bias and confounding.
- The abuse outcome used in the ASI-MV surveillance program is generally consistent with the definition of abuse used by the FDA – "the nonmedical use of a drug, repeatedly, or even sporadically, for the positive psychoactive effects it produces." Although, it is possible that some cases of misuse (considered by FDA as "the use of a drug outside label directions or in a way other than prescribed or directed by a healthcare practitioner") could be captured and classified as abuse, particularly among those in whom prescription opioids were not the primary substance of abuse or among those assessed and found not to require treatment.
- Uses an enriched, sentinel population with a relatively high prevalence of prescription opioid abuse via alternate routes of administration.
- Availability of multiple comparators provides contextual information to help interpret changes in OxyContin abuse patterns.
- Data source has information covering time period before and after OxyContin reformulation without trend breaks.

Limitations:

- The study sample is dynamic due to sites dropping in and out of the surveillance program. When only sites contributing ≥1 assessment/quarter in the pre- and post-reformulation time periods were included, the sample size dropped to 34 assessment sites. Twelve of these sites were in four western states (California, Wyoming, Colorado, and New Mexico), ten sites were in two midwestern states (Michigan and Nebraska), and twelve sites were in four southern states (Oklahoma, Florida, North Carolina and Maryland). No sites located in Northeastern states were represented.
- Patterns observed in the ASI-MV sample may not be generalizable to individuals abusing drugs but not entering or being assessed for treatment. Factors that may influence the number of individuals being assessed for treatment in the ASI-MV system include limited treatment program capacity, law enforcement and judicial practices, and other political, social, geographic, and economic factors not directly related to the prevalence of prescription opioid abuse in the community. Geographic areas with high rates of abuse but limited access to treatment might not be represented in this sample.
- Although demographic characteristics of the study population appeared to be similar in the pre- and post-periods, changes in the types of settings and geographic locations in which assessments take place may differentially affect the abuse estimates for different drugs and create bias, the direction of which is

difficult to predict. This bias should be mitigated by the restriction to sites contributing ≥1 assessment in each quarter.

- Self-report of abused products is subject to misclassification that may substantially affect prevalence estimates. Notable in this data source is the persistent prevalence of reported original OxyContin abuse years after the product was removed from the market. The degree of misclassification may vary across products and across time in ways that are difficult to quantify and are influenced by changes in design of the ASI-MV assessment tool. For instance, original OxyContin remaining in the prominent, left-most position on the screen until 2Q2014 likely led to increased levels of endorsement of the original product over the reformulated product, or misclassification of other oxycodone products as abuse of original OxyContin. Distinguishing among different oxycodone products may be particularly challenging for respondents. Sensitivity analyses undertaken to assess misclassification bias show that prevalence of reformulated OxyContin increased, and original OxyContin decreased, after the ASI-MV survey page for oxycodone products was changed to feature the reformulated OxyContin product as the first option. Therefore, it is clear that there was misclassification of reformulated OxyContin as original OxyContin.
- The ASI-MV does not assess the prevalence of clinical outcomes consequent to abuse of specific drug products, including overdose, addiction, or death.

4.6   FINDINGS FROM THE PUBLISHED LITERATURE

A number of papers have been published in the scientific literature describing the changes in abuse for OxyContin and comparators during the time of OxyContin reformulation. Six of these papers analyzed NAVIPPRO ASI-MV assessments; these articles are abstracted in a table in appendix 6.18 and are summarized below. Generally, these studies (most co-authored or supported by the sponsor) found a decrease in snorting and injection of OxyContin, which agrees with PMR 3051-1 study results, although the magnitude of the decreases reported in the literature are larger. Unlike PMR 3051-1, some of the studies in the published literature also showed a decrease in both oral and overall abuse of OxyContin in the post-period. These discrepancies appear to be due to differences in the definition of OxyContin and whether or not utilization was included in the model. In agreement with findings from study PMR 3051-1 where we see an increase in oral abuse of OxyContin, Butler et al. 2018, also described an increase in oral abuse of crush resistant tablets.

Three studies (Butler *et al*. 2013,[11] Coplan *et al*., 2016,[12] and Cassidy *et al*., 2017[13]) analyzed the change in OxyContin abuse rates after the reformulation, while three other studies (Butler *et al*. 2011,[14] Butler *et al*. 2018,[15] and Cassidy *et al.*, 2014[16]) analyzed comparator opioids during the reformulation time period to better understand the landscape of abuse during this time frame. Butler *et al*. 2013 estimated unadjusted and prescription-based rates of OxyContin, ER morphine, and ER oxymorphone abuse in the pre- vs. post-reformulation periods. This study found a -41% decrease in overall OxyContin abuse and a -66% decrease in non-oral OxyContin abuse. In utilization-based analyses, OxyContin showed a -33% decrease among all ASI-MV assessments, which is similar to results of PMR 3051-1. Injection of OxyContin among those abusing the drug decreased from 36% in the pre-reformulation period to 16% in the post-reformulation period. During this same time period, overall ER morphine abuse increased +2% and ER oxymorphone abuse increased +246%, while in prescription-based analyses, abuse of ER morphine and ER oxymorphone increased +0.9% and +111%, respectively.

The decreases reported in Butler et al., 2013 are larger than those reported in the final study report for PMR 3051-1. There are a number of differences in the analysis parameters for these two studies that could lead to these differences. The largest difference between the two studies is the definition of OxyContin that was used in the two studies: the Butler study defined OxyContin as original OxyContin in the pre-period and "reformulated OxyContin only" in the post-period, whereas PMR 3051-1 explored multiple definitions of OxyContin, the main definition being "any OxyContin (original or reformulated)" throughout the entire time period. Another difference was the time period explored in the study: Butler *et al.* analyzed data from June 1, 2009 to March 31, 2012 while the main time period for PMR 3051-1 was July 1, 2008 to December 31, 2014. A final difference between the two studies was that the abuse rate in the Butler *et al.* study was per 10,000 prescriptions dispensed, while the abuse rate in PMR 3051-1 was per 10,000 tablets dispensed.

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[11] Butler SF, Cassidy TA, Chilcoat H, Black RA, Landau C, Budman SH, Coplan PM. Abuse Rates and Routes of Administration of Reformulated Extended-Release Oxycodone: Initial Findings From a Sentinel Surveillance Sample of Individuals Assessed for Substance Abuse Treatment. *The Journal of Pain*. 2013;14(4):351-358.

[12] Coplan PM, Chilcoat HD, Butler SF, Sellers EM, Kadakia A, Harikrishnan V, Haddox JD, Dart RC. The Effect of an Abuse-Deterrent Opioid Formulation (OxyContin) on Opioid Abuse-Related Outcomes in the Postmarketing Setting. *Clinical Pharmacology & Therapeutics*. 2016;100(3):275-286.

[13] Cassidy TA, Thorley E, Black RA, DeVaugh-Geiss A, Butler SF, Coplan P. Abuse of Reformulated OxyContin: Updated findings from a sentinel surveillance sample of individuals assessed for substance use disorder. *Journal of Opioid Management*. 2017;13(6):425-440.

[14] Butler SF, Black RA, Cassidy TA, Dailey TM, Budman, SH. Abuse risks and routes of administration of different prescription opioid compounds and formulations. *Harm Reduction Journal*. 2011;8(29).

[15] Butler SF, Black RA, Fleming AB. Relative Abuse of Crush-Resistant Prescription Opioid Tablets via Alternative Oral Modes of Administration. *Pain Medicine*. 2018;19:1613-1627.

[16] Cassidy TA, DasMahapatra P, Black RA, Wieman MS, Butler SF. Changes in Prevalence of Prescription Opioid Abuse after Introduction of an Abuse-Deterrent Opioid Formulation. *Pain Medicine*. 2014;15:440-451.

Coplan *et al.*, 2016 presented selected, high level results from ten different investigations using multiple data sources to assess changes in OxyContin abuse post-reformulation, including poison control data, information from individuals entering substance abuse treatment, diversion reports from law enforcement, and claims data, and fatality reports. In ASI-MV data, OxyContin abuse decreased -48% overall in population-based analyses. In prescription-based analyses, OxyContin abuse decreased -34%. In this same analysis, abuse of "other schedule II opioids" decreased -3% in population-based analyses, and 0% in prescription-based analyses. Using population-based rates, OxyContin non-oral abuse decreased -69%. These decreases are considerably larger than the decreases reported in PMR 3051-1. One of the main reasons for this difference is likely the definition of OxyContin abuse in the two studies: in the published article, OxyContin cases are defined as original OxyContin in the pre-period, and "reformulated OxyContin only" in the post-period, whereas the OxyContin definition in PMR 3051-1 is any OxyContin, original or reformulated, for both time periods. Another difference is that the rates in the Coplan article were prescription-based while rates were dosage unit dispensed-based dispensed in PMR 3051-1.

Cassidy *et al.*, 2017, analyzed ASI-MV assessments for abuse via any route for OxyContin and comparators (ER oxymorphone, ER morphine, and IR oxycodone SE and combination products) from January 2009-December 2015 utilizing two post-periods: January 2011-December 2011 (a 1-year post-period directly after reformulation) and April 2015-December 2015 (a 9-month post-period 5 years after reformulation). The study analyzed two definitions of OxyContin: original OxyContin in the pre-period and reformulated OxyContin in the post-period, and original OxyContin in the pre-period and brand and generic OxyContin in the post-period (any OxyContin plus ER oxycodone). Using the "any OxyContin" definition, OxyContin showed a -41% decrease in post-period 1, and a -52% decrease in post-period 2. The outpatient/non-methadone treatment modality showed the largest decrease in post-period 1: -56%, and in post-period 2: -67%. The largest decrease in abuse for OxyContin was observed in the Midwest (-47%) in post-period 1, and the West in post-period 2: -59%. There are two major differences between this study and PMR 3051-1. This study assessed two shortened post-periods: one single-year post-period after reformulation and a second nine-month post-period five years after reformulation. OxyContin showed a sharp decline in the transition period, a less steep decline from 1Q2011-4Q2011, and an evening out of slope and a slight increase from 1Q2012-2Q2015. At 2Q2015 (the start of the second post-period in this study), there was a sharp decline seen in any OxyContin abuse, likely due to a screen change at the end of 1Q2015 in which the oxycodone screen was moved from the first opioid screen presented to respondents to the fourth. Both of the shortened post-periods analyzed in this study showed declines that were greater than the rest of the 1Q2012-1Q2015 post-period not analyzed. The second parameter that is different between this study and PMR 3051-1 is the denominators used in the model. This study analyzed abuse

prevalence per 100 individuals endorsing abuse of a prescription opioid using the ASI-MV tool but did not incorporate prescription or volume of dosage units dispensed into estimates.

The three other studies captured in the literature review that utilized ASI-MV data provide context for comparator opioids during the pre- and post-periods, but do not analyze non-oral abuse of OxyContin in the context of comparators specifically. Butler *et al.*, 2011 presented unadjusted and prescription-based rates of abuse for hydrocodone, IR and ER oxycodone, methadone, IR and ER morphine, hydromorphone, IR and ER fentanyl, and ER oxymorphone in 2009, the year before OxyContin reformulation. This study found that unadjusted abuse was highest for hydrocodone, IR oxycodone, and ER oxycodone, while prescription-based abuse rates were highest for methadone, ER oxycodone, and IR morphine. Butler et al., 2018 presented data on oral abuse of crush resistant tablets versus non-crush resistant tablets. This study presented two categories: crush resistant tablets, which consisted of reformulated oxycodone ER and reformulated oxymorphone ER, and non-crush resistant tablets which included the original formulation of oxycodone ER, oxymorphone ER, morphine ER, and oxycodone IR SE. This study found that crush resistant tablets were abused by an alternate oral route including chewed and swallowed, dissolved in mouth, or dissolved in liquid and drank 1.4 times more often than non-crush resistant tablets, as a proportion of overall abuse of the specified product. Finally, Cassidy et al., 2014 studied comparator opioids to determine if reformulation of OxyContin led to any changes in abuse prevalence of comparators during the pre- to post-period, from January 1, 2008 to December 31, 2011. This study showed an +8.3% increase in abuse of all prescription opioids, and a -2.0% decrease in abuse of all prescription opioids in prescription-based analyses. Of these prescription opioids, the increase in abuse of buprenorphine and oxymorphone ER was larger in those reporting injection only or snorting only than in those reporting oral only. The increase in buprenorphine and ER oxymorphone began before the reformulation of OxyContin in 3Q2010, however an inflection point does occur at the time of reformulation.

4.7 OVERALL SYNTHESIS OF FINDINGS

Overall, the data showed that non-oral OxyContin abuse rates decreased after reformulation among individuals being assessed for treatment at substance abuse centers using the NAVIPPRO ASI-MV system. This decrease was observed using multiple different analytic methods, and in most analyses was significantly larger than for comparator opioids, supporting the hypothesis that OxyContin's reformulation at least partially caused the observed reduction in non-oral abuse rates. The wide range of estimates in both absolute decreases and decreases relative to different comparators make it difficult to determine the magnitude of this effect. The reduction in non-oral abuse appears to have occurred primarily in those with a moderate to severe addiction severity

index score, where OxyContin abuse rates were far higher than in individuals assessed and found to have no or only a mild problem.

Interrupted time series analysis was used to evaluate the impact of a population-level intervention in the context of pre-existing trends. These analyses attempted to answer two questions: 1) did the intervention change the trajectory, or slope, of the quarterly rates from that observed in the pre-period (i.e., did the intervention "bend the curve"), and 2) did the intervention cause an immediate shift in the level of the outcome measure just after the intervention (here, after the transition period)? For the purposes of causal inference, ITS assumes that there were no other interventions happening around the same time as the intervention of interest. Because this assumption may not be valid in this case, comparators were added to the ITS as well, asking whether any changes in the slope or level following the reformulation were different for Oxycontin versus comparators. In these analyses, population-based rates of OxyContin abuse showed a significant decrease both in slope and immediate shift, while utilization-based analyses demonstrated a significant decrease in immediate shift, but not slope. The statistically significant immediate shift was not seen in any of the comparators, including ER morphine. This demonstrates that the intervention likely did cause an immediate decrease in the level of OxyContin abuse via non-oral routes among individuals being assessed for substance use disorder treatment in the post-period. Comparative analyses showed a significant difference in population-based analyses for immediate shift for IR hydrocodone vs. OxyContin and "other schedule II opioids" vs. OxyContin. All other analyses were not significant.

In means analyses, OxyContin showed a significantly greater decrease than primary comparator opioids, except for ER morphine, where there was still a larger decrease in abuse for OxyContin, but the difference was not statistically significant. When OxyContin non-oral abuse was further stratified by abuse via snorting and injection, OxyContin showed a significantly greater decrease via snorting compared to IR hydrocodone and "other schedule II opioids". The decrease for OxyContin abuse via snorting was also larger than that for ER morphine, although this was not significant for the most "conservative" estimates of decrease, which assessed abuse per unit of utilization. For injection, the percent decrease was larger for OxyContin compared to "other schedule II opioids", and for the least "conservative" estimate of decrease against ER morphine, however the decrease in abuse via injection for OxyContin was not significant against ER morphine for the most "conservative" estimate, which was utilization-based. Due to very low rates of injection abuse in the pre-period for IR hydrocodone, a very small change in the post-period led to a large overall percent change for this comparator, and the percent decrease in IR hydrocodone abuse was larger than the decrease for OxyContin.

In general, population-based rates demonstrated a larger decrease in mean non-oral abuse than utilization-based estimates for OxyContin, and comparative analyses for primary comparators vs. OxyContin were more favorable toward OxyContin with population-based analyses. This is reflective of some of these comparators having increasing trends in utilization during the study period, while OxyContin dispensing was decreasing. Making causal inferences based on these findings requires consideration of several possible reasons for the decline in OxyContin dispensing. The first reason lies within the causal pathway from the ADF to a reduction in abuse rates: OxyContin dispensing decreased due to the reformulation and the subsequent decrease in desirability of this drug for abuse purposes. The second reason does not lie within the causal pathway but is instead a confounder of the causal association between the ADF and changes in abuse rates: OxyContin dispensing decreased due to reasons other than the reformulation, for example changes in formularies, insurance coverage, or prescriber or patient preference unrelated to abuse of the drug. The third, and most likely, explanation is that some combination of both of these scenarios led to decreases in OxyContin dispensing (and possibly changes in utilization trends for comparator opioids). The relative contribution of these two causal pathways is unknown, which makes it difficult to determine which estimate—population or utilization-based—lies closer to the true effect of the reformulation. In interpreting the means analysis results, it is important to keep in mind that the most "conservative" estimates, in which reductions for OxyContin were not statistically significantly different from those seen for ER morphine, are expected to underestimate the effect of the reformulation by some unquantifiable amount, due to use of the "any OxyContin" definition (i.e., includes both original and reformulated OxyContin endorsements in the post-period), full adjustment for reductions in utilization, and the use of the most restricted, consistent set of sites, which reduces sampling bias but also reduces study power.

Unmodeled proportion and average number of individuals endorsing abuse of OxyContin and primary comparators who reported using the drugs via specific routes showed a substantial decrease in snorting and injection abuse of OxyContin that was not present for ER morphine, although abuse of OxyContin by these routes did still occur in the post-reformulation period. OxyContin abuse via snorting decreased from 55.3% to 33.4%, and abuse via injection decreased from 31.5% in the pre-period to 19.9% in the post-period. The average number of individuals abusing OxyContin via snorting per quarter decreased from 47.1 to 22.4, and average number of individuals abusing OxyContin via injection decreased from 29.3 to 15.4. For ER morphine, percent abuse via snorting increased from 22.4% to 28.1%, and injection increased from 40.4% to 49.1%. Average number of individuals endorsing abuse via snorting and injection did decrease modestly, from 9.4 to 8.5 for snorting and from 16.3 to 14.7 for injection. The percent of hydrocodone abuse via snorting and injection did decrease, but the level of injection was minimal, at less than 2%. These data are generally consistent with the main analyses in suggesting a

reduction in non-oral OxyContin abuse attributable to the reformulation, and, importantly, they do not suggest any shift from snorting to injection of OxyContin following its reformulation.

It is important to keep in mind, however, that although utilization-based rates of OxyContin did decrease post-reformulation, OxyContin abuse rate per dosage unit dispensed remained higher than all primary comparators. This was true for both overall and non-oral abuse rates.

Analyses for change in abuse of OxyContin via any route among patients being assessed for substance use disorder treatment were mixed, and therefore did not provide robust evidence for a decrease in overall abuse of OxyContin that was substantially different from comparators. The range of estimated percent change for OxyContin abuse via any route was +5.8% to -38.6%, and RORRs showed a significantly greater decrease for comparators vs. OxyContin for the most "conservative" estimates, and a significantly greater decrease for OxyContin vs. comparators for the least "conservative" estimates. This likely reflects the consistently high, and slightly increased, rates of oral OxyContin abuse that occurred in conjunction with the decrease in non-oral routes (snorting and injecting) following reformulation.

Summary Interpretation of Study Findings

This study provided reasonably compelling evidence that the reformulation decreased non-oral abuse of OxyContin in people who are entering or being assessed for treatment, although it is difficult to quantify the size of this effect. Although results varied depending on the specific parameters, analyses were largely consistent in demonstrating a reduction in non-oral abuse rates for OxyContin in this study population that differed from the changes in non-oral abuse rates observed in comparator opioids. These findings appear to have been driven primarily by a reduction in non-oral abuse among people assessed to have moderate to severe addiction. Among individuals abusing OxyContin, the proportions who reported snorting and injecting the product both declined, and the proportion who reported abusing it orally slightly increased. Similar changes were not observed for comparator opioids. Results of published studies analyzing ASI-MV data were qualitatively consistent with this main finding, although decreases reported in the literature were larger.

The evidence for the reformulation leading to a reduction in overall OxyContin abuse (via any route) in this population was weaker. Although some analyses indicated an overall decline in OxyContin abuse that was greater than that of comparators, findings were inconsistent across the various models. This lack of strong evidence for a reduction in overall abuse of OxyContin was likely due to ongoing oral abuse in this population, which remained the most common route reported throughout the study period.

After reformulation, utilization-based abuse rates of non-oral abuse of OxyContin remained relatively high among the opioids examined; however, such cross-sectional comparisons between drugs must be made cautiously as data from treatment centers are not a nationally representative sample of all persons abusing opioids, or even all persons with substance use disorders or entering treatment, and relative abuse rates may be substantially affected by design of the assessment tool, order in which products are presented, and other sources of product misclassification.
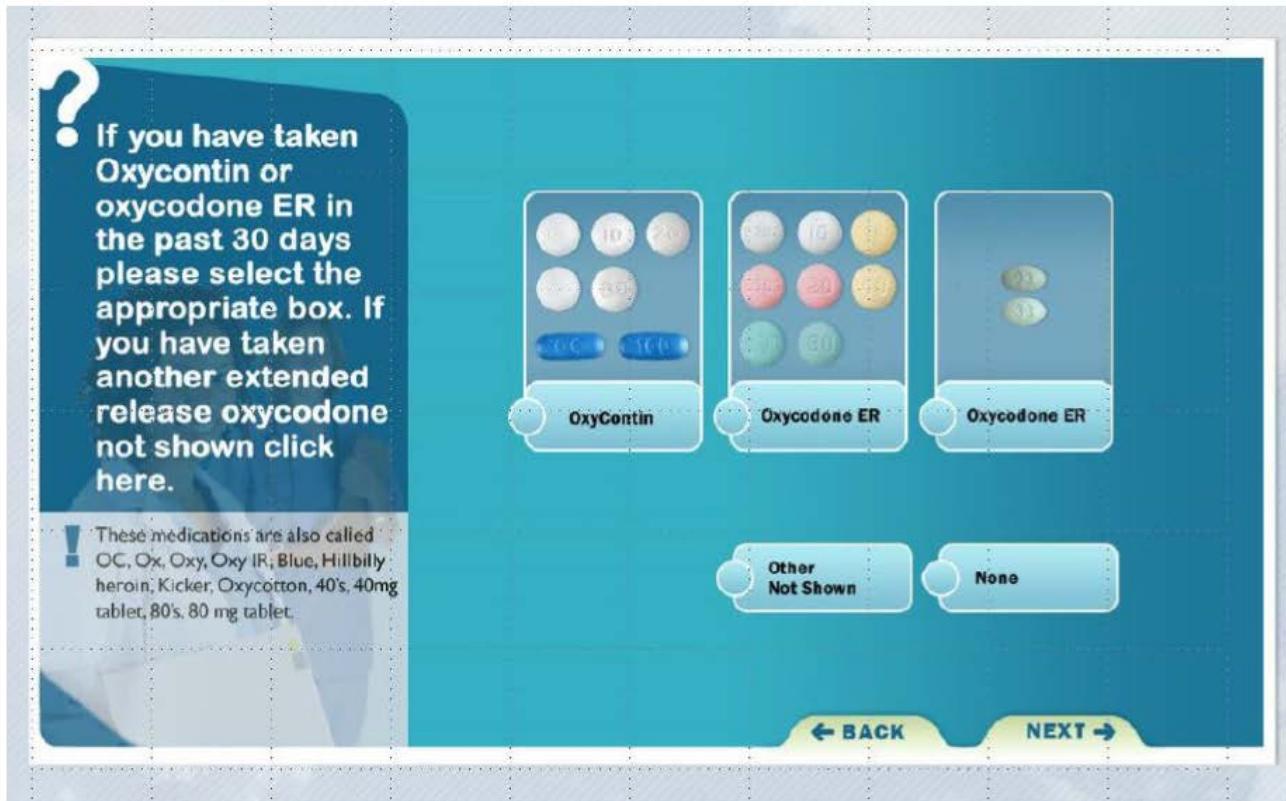
5   CONCLUSIONS

PMR study 3051-1 provides reasonably compelling evidence that reformulation decreased non-oral abuse of OxyContin in people who are entering or being assessed for treatment, although it is not possible to quantify the size of this effect. This reduction appears to have occurred predominantly among people assessed to have moderate to severe addiction. Oral abuse of OxyContin was common in this population both before and after reformulation, and this study did not provide compelling evidence that the reformulation reduced overall OxyContin abuse (via any route) in this population. After reformulation, utilization-based overall and non-oral abuse rates (per 10,000 tablets dispensed) for OxyContin remained high relative to most other opioid analgesic examined.

6   APPENDICES

6.1   SCREEN CHANGES IN THE ASI-MV ASSESSMENT TOOL

Figure 41: Sample screen shot of a prescription opioid question on the ASI-MV in 2007

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 12-1. Sample screen shot of a prescription opioid question on the ASI-MV® in 2007. P. 372.)

Figure 42: Sample screen shot of a prescription opioid question on the ASI-MV in 2013

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 12-3. Sample screen shot of a prescription opioid question on the ASI-MV® in 2013. P. 373.)

Figure 43: Sample screen shot of a prescription opioid question on the ASI-MV in May 2014

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 12-4. Sample screen shot of a prescription opioid question on the ASI-MV® in May 2014. P. 374.)

Figure 44: Sample screen shot of a prescription opioid question on the ASI-MV in 2015

If you have taken OxyContin®, Xartemis™ XR, OxyContin from Canada or Latin America, or oxycodone ER (extended-release) **in the past 30 days** please select the appropriate box below. If possible, select the pictures you recognize of the mediation you used. The images may not be the same as their actual size.

These medications are also called OC, new OC, OP, OG, Oxy, Oxy ER, Hillbilly heroin, Oxycotton, oxyNeos.
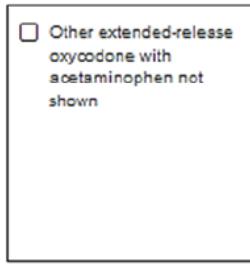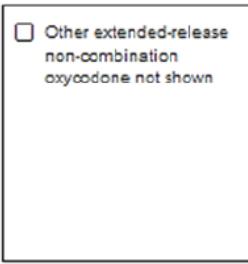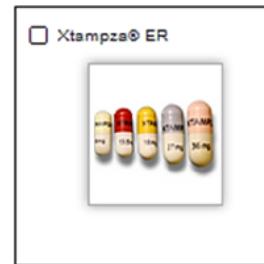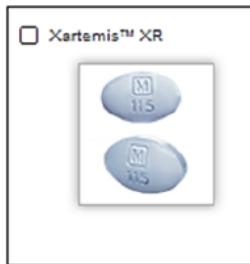
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 12-5. Sample screen shot of a prescription opioid question on the ASI-MV® in 2015. P. 375.)

Figure 45: Sample screen shot of a prescription opioid question on the ASI-MV in 2016

Alcohol and Drugs

If you have taken OxyContin®, Xartemis™ XR, Xtampza® ER, or other oxycodone ER (extended-release) **in the past 30 days** please select the appropriate box below. If possible, select the pictures you recognize of the medication you used. The images may not be the same as their actual size.
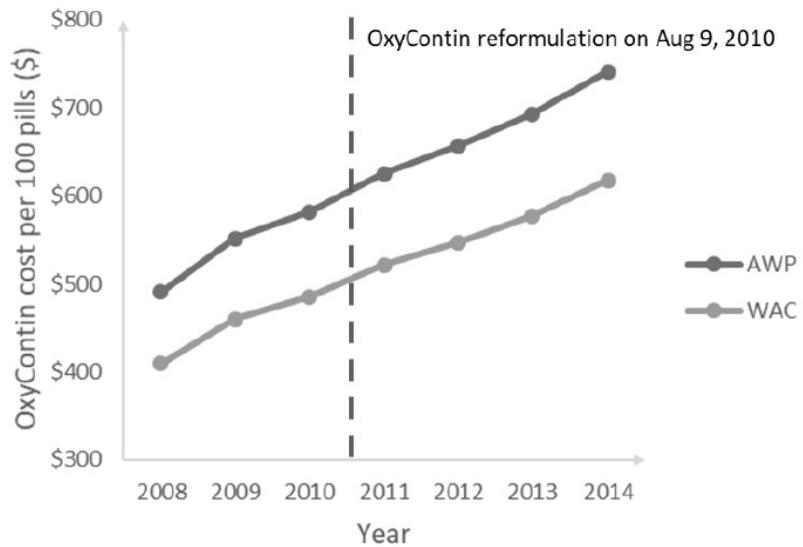
These medications are also called new OC, OP, Oxy, Oxy ER, Hillbilly heroin and Oxycotton.

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 12-6. Sample screen shot of a prescription opioid question on the ASI-MV® in 2016. P. 376.)

6.2   OXYCONTIN WHOLESALE ACQUISITION PRICE

Figure 46: OxyContin average wholesale price (AWP) and wholesale acquisition cost (WAC) for a package of 100 pills over time, 2008-2014

(Source: FDA Postmarketing Requirement Study 3051-1 IR Response Document. Figure 1: OxyContin costs* for a package of 100 pills over time, 2008-2014. *Costs depicted are based on 30mg OxyContin P. 154.)

Key: AWP: Average Wholesale Price; WAC: Wholesale Acquisition Price; Dashed vertical line denotes OxyContin reformulation

6.3 SENSITIVITY ANALYSES FOR QUARTERLY TREND ANALYSES, NON-ORAL ABUSE
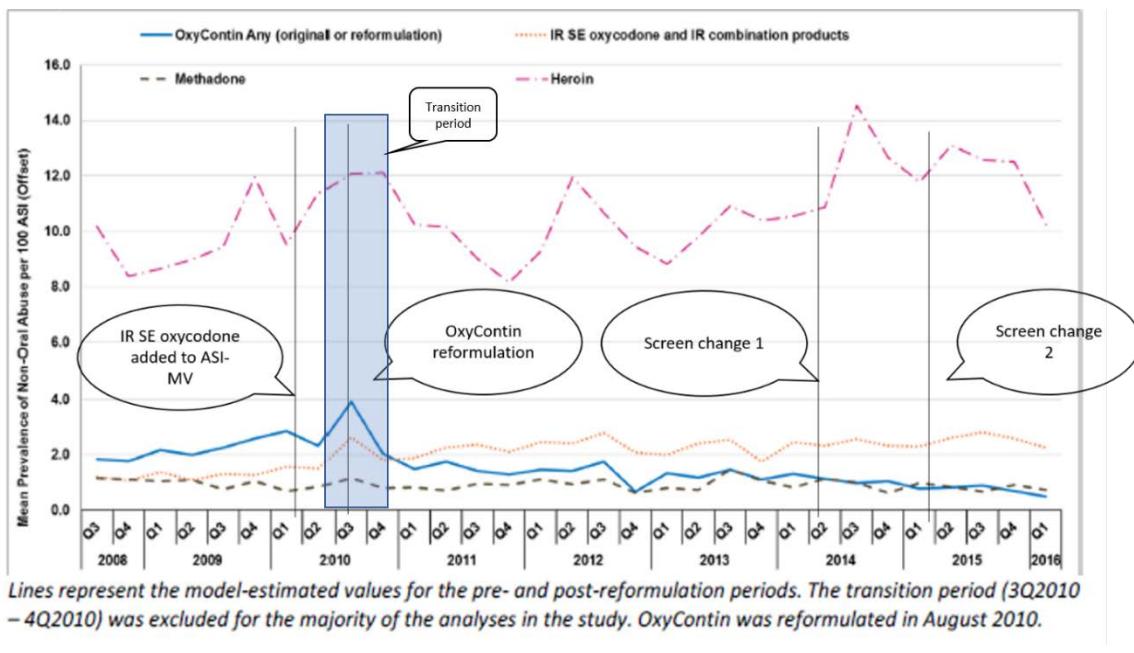
Analysis parameters:
- Abuse: Non-oral
- Sites: contributing ≥ 1 assessment/quarter
- OxyContin definition: Reformulated OxyContin, Original and reformulated OxyContin, and all oxycodone ER.
- Unit of analysis: 3-digit ZIP
- Model #1:
    - Offset: Total assessments.
    - Covariates: NA.
- Model #2:
    - Offset: Dosage units dispensed
    - Covariate: NA
- Model #2a:
    - Offset: Dosage units dispensed
    - Covariate: Total assessments
- Model #3a:
    - Offset: NA
    - Covariate: Dosage units dispensed (continuous), Total assessments
- Model #4a:
    - Offset: NA
    - Covariate: Dosage units dispensed (categorical)

Table 21: Overlap in OxyContin and "other schedule II opioid" non-oral abuse cases

	Quarter	Total Assessments (N)	Other Schedule II Opioids (n)	Any OxyContin (n)	Overlap (n)	% Overlap Other Schedule II Opioids	% Overlap Any OxyContin
Pre-reformulation	2008Q3	2,433	55	45	28	50.9	62.2
	2008Q4	2,806	56	50	25	44.6	50.0
	2009Q1	2,956	71	64	40	56.3	62.5
	2009Q2	2,766	60	55	29	48.3	52.7
	2009Q3	2,754	66	62	34	51.5	54.8
	2009Q4	2,465	69	64	35	50.7	54.7
	2010Q1	2,743	84	78	45	53.6	57.7
	2010Q2	2,804	78	65	35	44.9	53.8
Transition	2010Q3	1,638	71	64	41	57.7	64.1
	2010Q4	1,877	53	37	24	45.3	64.9
Post-reformulation	2011Q1	2,538	76	38	27	35.5	71.1
	2011Q2	2,694	100	47	33	33.0	70.2
	2011Q3	2,585	93	37	22	23.7	59.5
	2011Q4	2,323	82	30	21	25.6	70.0
	2012Q1	2,611	97	38	29	29.9	76.3
	2012Q2	2,455	85	35	22	25.9	62.9
	2012Q3	2,447	97	43	33	34.0	76.7
	2012Q4	2,357	78	16	10	12.8	62.5
	2013Q1	2,622	91	35	24	26.4	68.6
	2013Q2	2,694	92	32	21	22.8	65.6
	2013Q3	2,720	104	40	27	26.0	67.5
	2013Q4	2,623	84	29	19	22.6	65.5
	2014Q1	2,682	98	35	24	24.5	68.6
	2014Q2	2,928	99	33	26	26.3	78.8
	2014Q3	2,776	102	27	18	17.6	66.7
	2014Q4	2,570	85	27	19	22.4	70.4
	2015Q1	2,654	87	21	15	17.2	71.4
	2015Q2	2,690	98	22	20	20.4	90.9
	2015Q3	2,665	101	24	20	19.8	83.3
	2015Q4	2,327	77	16	13	16.9	81.3
	2016Q1	2,429	79	12	11	13.9	91.7

(Source: FDA Postmarketing Requirement Study 3051-1, Purdue Response to FDA Information and Analyses Request on October 2019 Phase 1 Part 2. Title: Overlap in OxyContin and other schedule II opioid non-oral abuse cases for PMR 3051-1. p. 38.)

Figure 47: Model 1 estimated rate of non-oral abuse cases per 100 assessments over time for OxyContin and secondary comparators
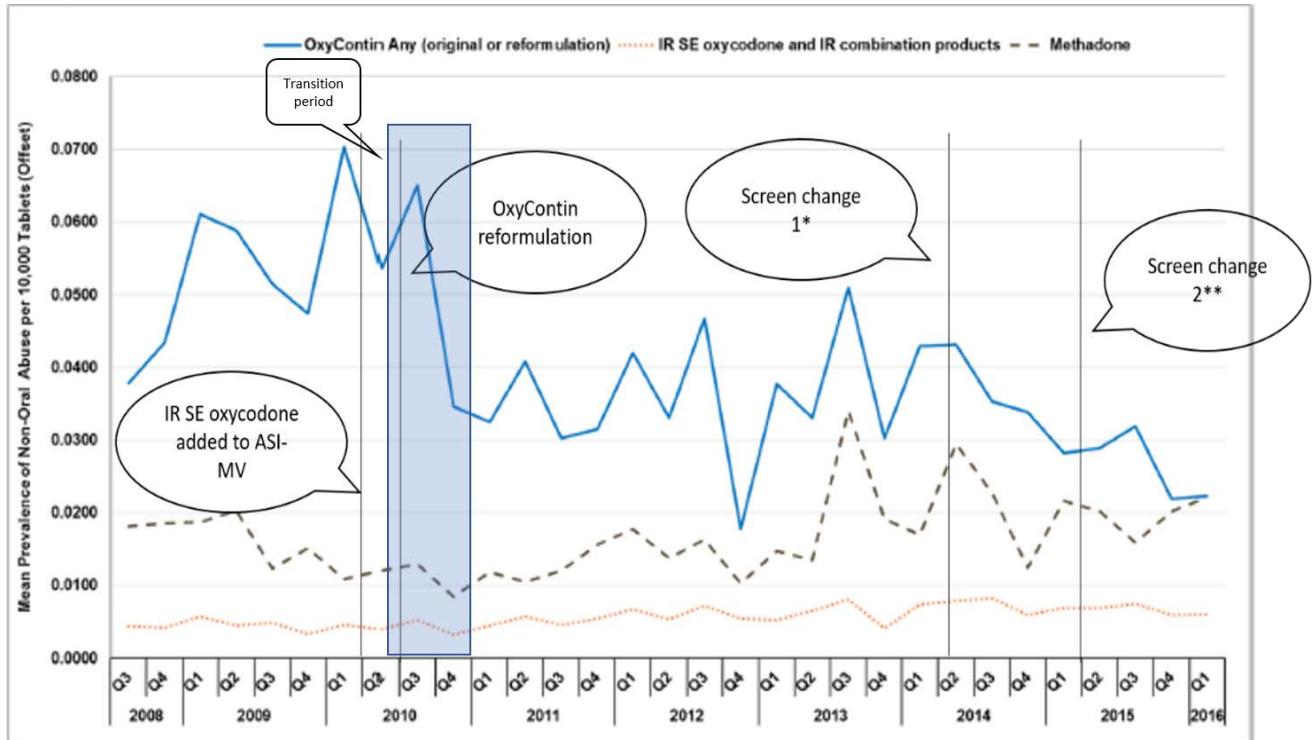
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 11-1. Model 1 descriptive trend analysis figure: Non-oral abuse, secondary comparators. P. 358.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 1 models abuse rate per ASI-MV assessments; ER oxymorphone was not included in this graph

Figure 48: Model 2 estimated rate of non-oral abuse cases per 10,000 tablets over time for OxyContin and secondary comparator opioids

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study. OxyContin was reformulated in August 2010.
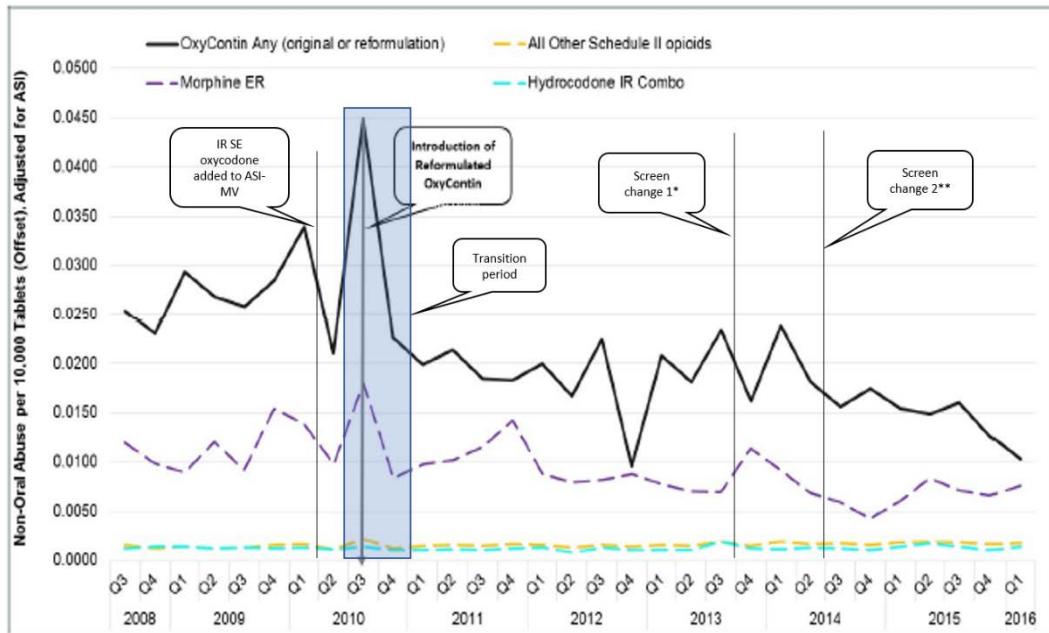
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 11-2. Model 2 descriptive trend analysis figure: Non-oral abuse, secondary comparators. P. 359.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2 models abuse rate per tablets dispensed; ER oxymorphone was not included in this graph

Figure 49: Model 2a estimated rate of <u>non-oral abuse cases per dosage units dispensed over time, adjusted for assessments as a covariate,</u> for OxyContin and primary comparator opioids

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study.
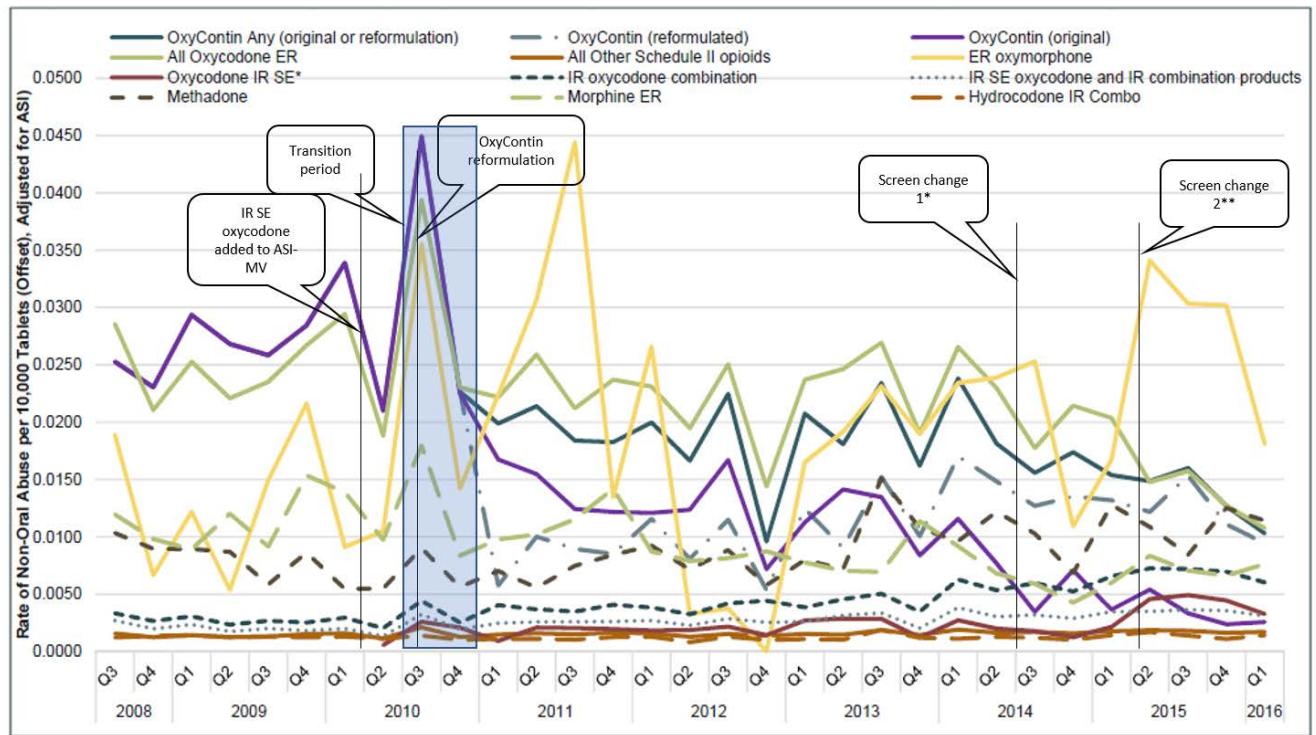
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Figure 7-11. Model-estimated rate of abuse cases per dosage units dispensed over time for OxyContin and primary comparator opioids (Model 2a). P. 53.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2a models abuse rate per tablets dispensed adjusted for ASI-MV assessments as a covariate

Figure 50: Model 2a estimated rate of <u>non-oral abuse cases per 10,000 dosage units dispensed, adjusted for assessments as a covariate</u>, for OxyContin and <u>all comparators</u>

IR=immediate release; ER=extended release; *Data for oxycodone IR single-entity (SE) is not presented prior to 2Q2010.
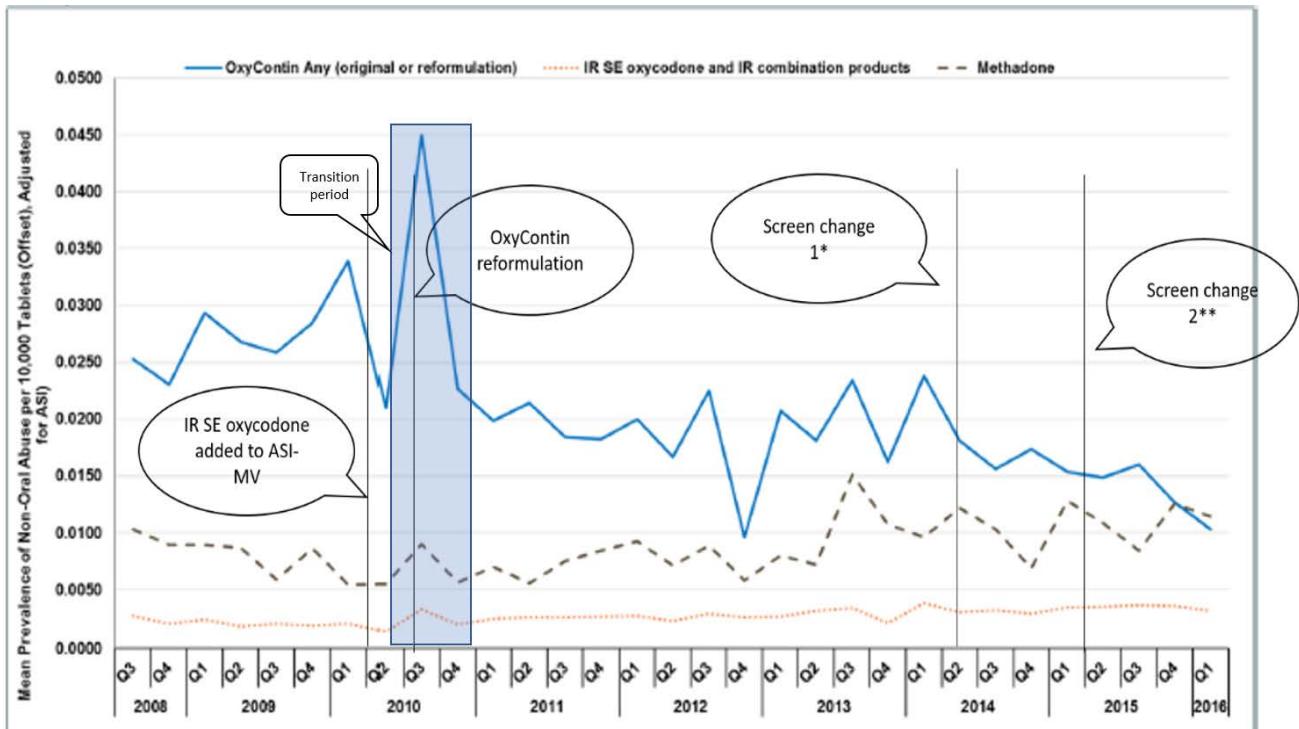
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 13-3. Model 2a: past 30-day non-oral abuse among sites contributing at least one assessment for each quarter from the two-year pre-period to the four-year post-period, prescription tablets dispensed as offset and ASI as covariate (3Q2008-1Q2016). P. 527.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2a models abuse rate per tablets dispensed adjusted for ASI-MV assessments as a covariate;

Figure 51: Model 2a estimated rate of non-oral abuse cases per 10,000 dosage units dispensed over time, adjusted for assessments as covariate, OxyContin and secondary comparators

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study. OxyContin was reformulated in August 2010.
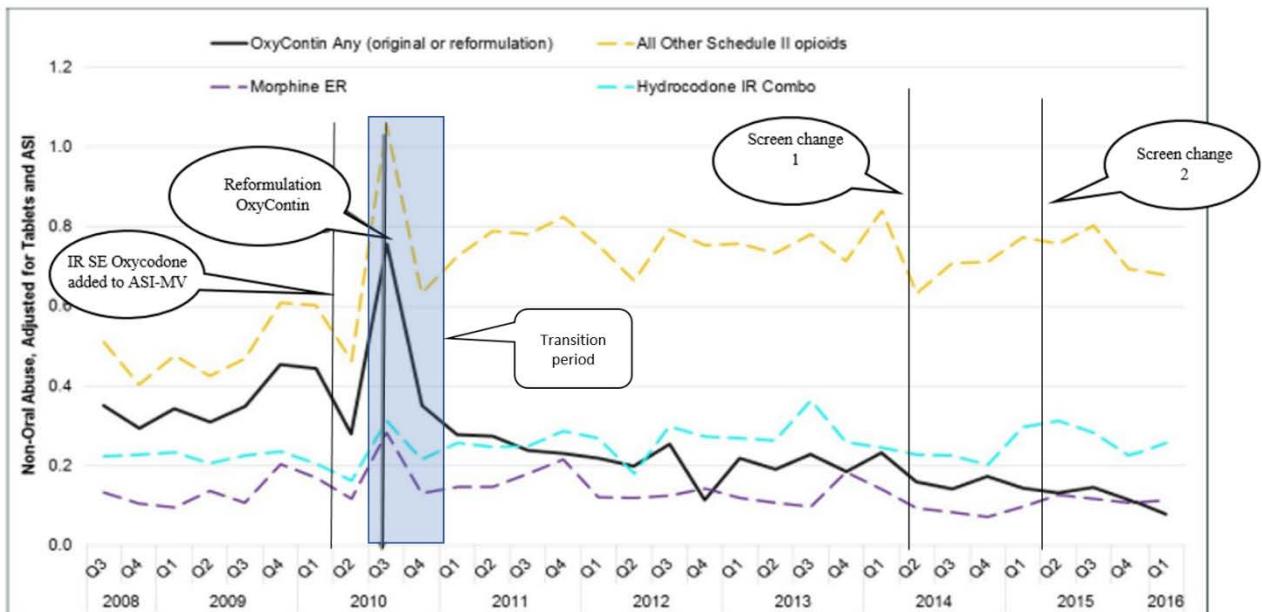
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 11-3. Model 2a descriptive trend analysis figure: Non-oral abuse, secondary comparators. P. 359.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2a models abuse rate per tablets dispensed adjusted for ASI-MV assessments as a covariate; ER oxymorphone was excluded here

Figure 52: Model 3a estimated non-oral abuse rates, adjusted for dosage units dispensed (continuous) and assessments as covariates, over time for OxyContin and primary comparator opioids

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study.
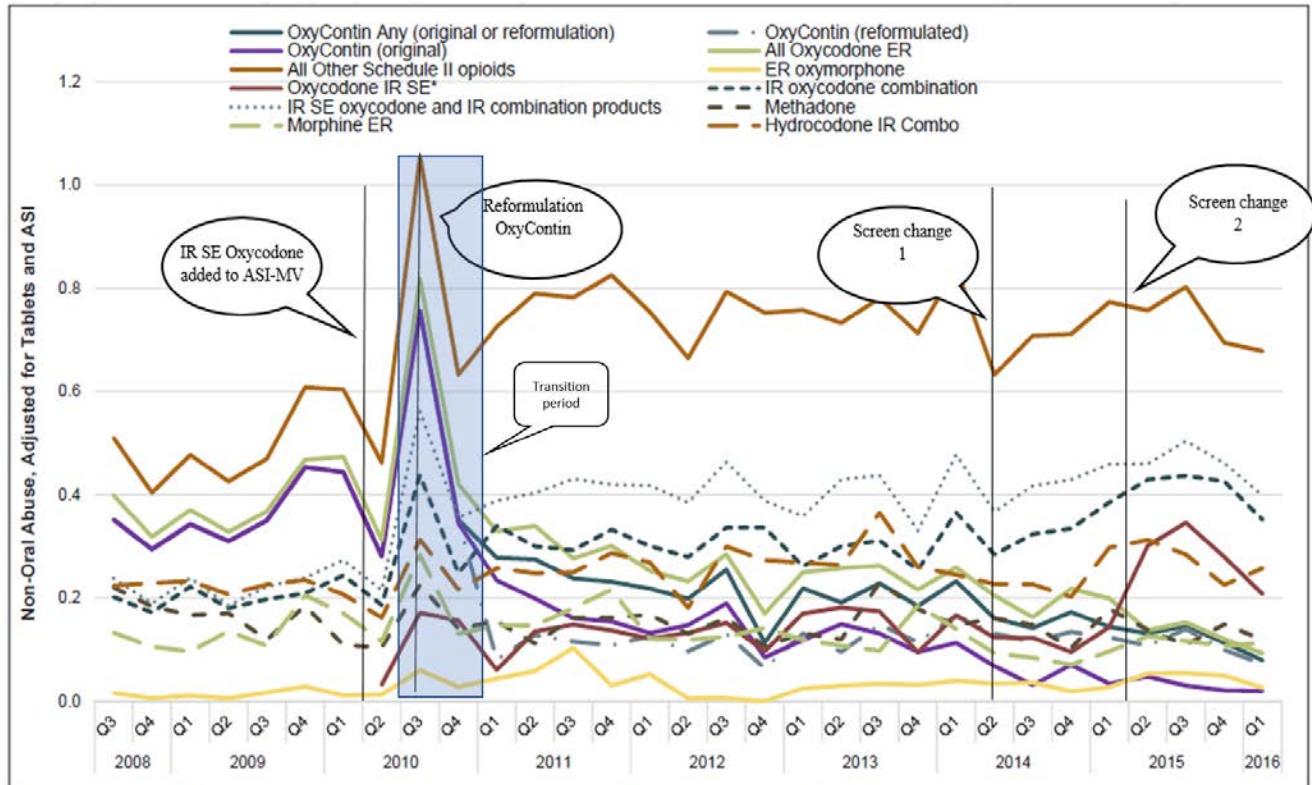
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Figure 7-12. Model-estimated adjusted abuse cases over time for OxyContin and primary comparator opioids (Model 3a). p. 54.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 3a models abuse rate adjusted for tablets dispensed and ASI-MV assessments as a covariate

Figure 53: Model 3a estimated non-oral abuse rates, adjusted for dosage units dispensed (continuous) and assessments as covariates, over time for OxyContin and all comparator opioids
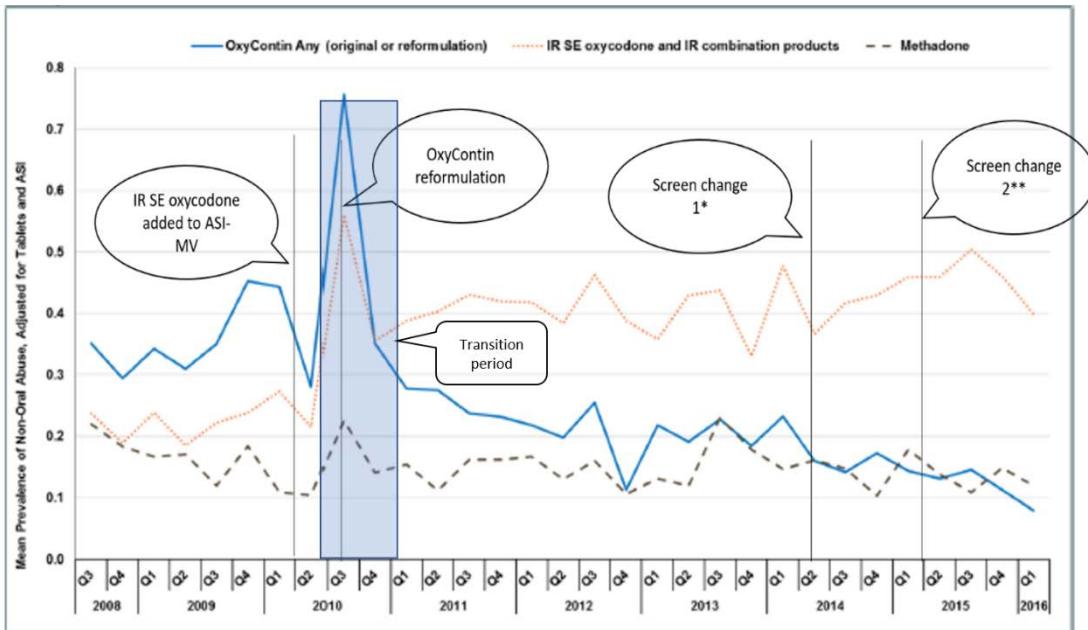
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 13-4. Model 3a: Past 30-day non-oral abuse among sites contributing at least one assessment each quarter from the two-year pre-period to the four-year post-period, tablets dispensed as continuous covariate and ASI as covariate (3Q2008-1Q2016). P. 528.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 3a models abuse rate adjusted for tablets dispensed and ASI-MV assessments as a covariate

Figure 54: Model 3a estimated non-oral abuse rates, adjusted for dosage units dispensed (continuous) and assessments as covariates, over time for OxyContin and secondary comparator opioids

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study. OxyContin was reformulated in August 2010.
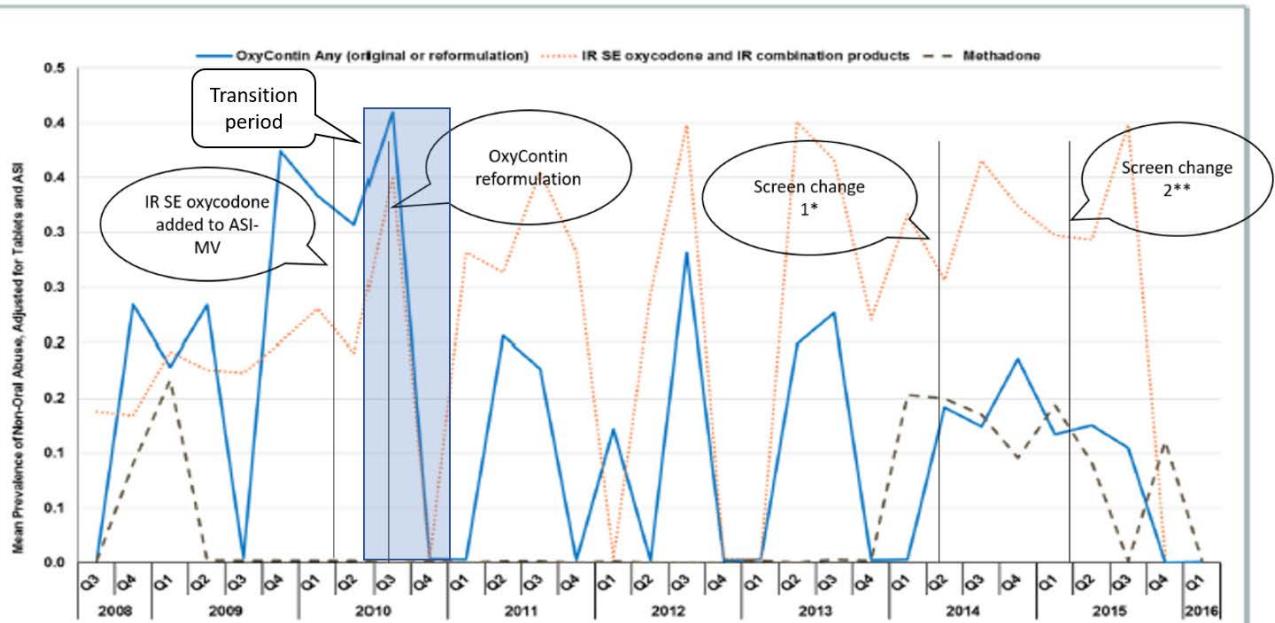
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 11-4. Model 3a descriptive trend analysis figure: Non-oral abuse, secondary comparators. P. 360.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 3a models abuse rate adjusted for tablets dispensed and ASI-MV assessments as a covariate; ER oxymorphone is not included here

Figure 55: Model 4a estimated non-oral abuse rates, adjusted for dosage units dispensed (categorical) and assessments as covariates, over time for OxyContin and secondary comparators

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study. OxyContin was reformulated in August 2010.
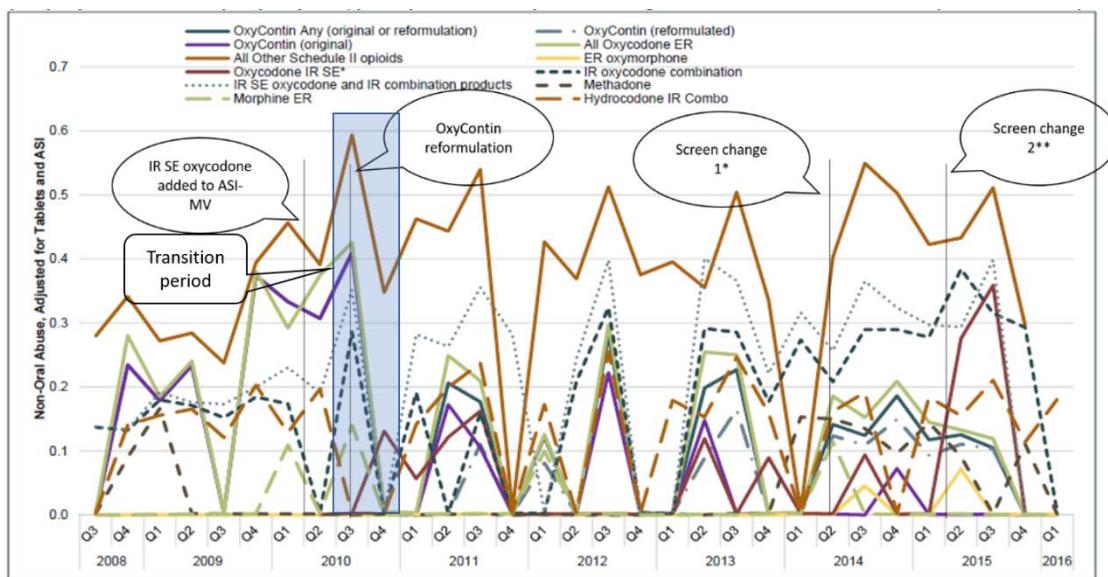
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 11-5. Model 4a descriptive trend analysis figure: Non-oral abuse, secondary comparators. P. 360.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 4a models abuse rate adjusted for tablets dispensed (categorical) and ASI-MV assessments as a covariate; ER oxymorphone is not included here

Figure 56: Model 4a estimated non-oral abuse cases, adjusted for dosage units dispensed (categorical) and assessments, over time for OxyContin and all comparator opioids

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 13-5. Model 4a: Past 30-day non-oral abuse among sites contributing at least one assessment each quarter from the two-year pre-period to the four-year post-period, prescription tablets dispensed as categorical covariate and ASI as covariate (3Q2008-1Q2016). P. 529.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 4a models abuse rate adjusted for tablets dispensed (categorical) and ASI-MV assessments as a covariate;

Analysis parameters:
- Abuse: <u>Non-oral abuse</u>
- Sites: <u>contributing > 1 assessment/year</u>
- OxyContin definition: Reformulated OxyContin, Original and reformulated OxyContin, and all oxycodone ER.
- Unit of analysis: 3-digit ZIP
- Model #1:
  - Offset: Total assessments.
  - Covariates: NA.
- Model #2:
  - Offset: Dosage units dispensed
  - Covariate: NA
- Model #2a:
  - Offset: Dosage units dispensed
  - Covariate: Total assessments
- Model #3a:
  - Offset: NA
  - Covariate: Dosage units dispensed (continuous), Total assessments
- Model #4a:
  - Offset: NA
  - Covariate: Dosage units dispensed (categorical)

Figure 57: Model 2 estimated non-oral abuse cases per 10,000 dosage units dispensed for OxyContin and all comparator opioids

IR=immediate release; ER=extended release; *Data for oxycodone IR single-entity (SE) is not presented prior to 2Q2010.
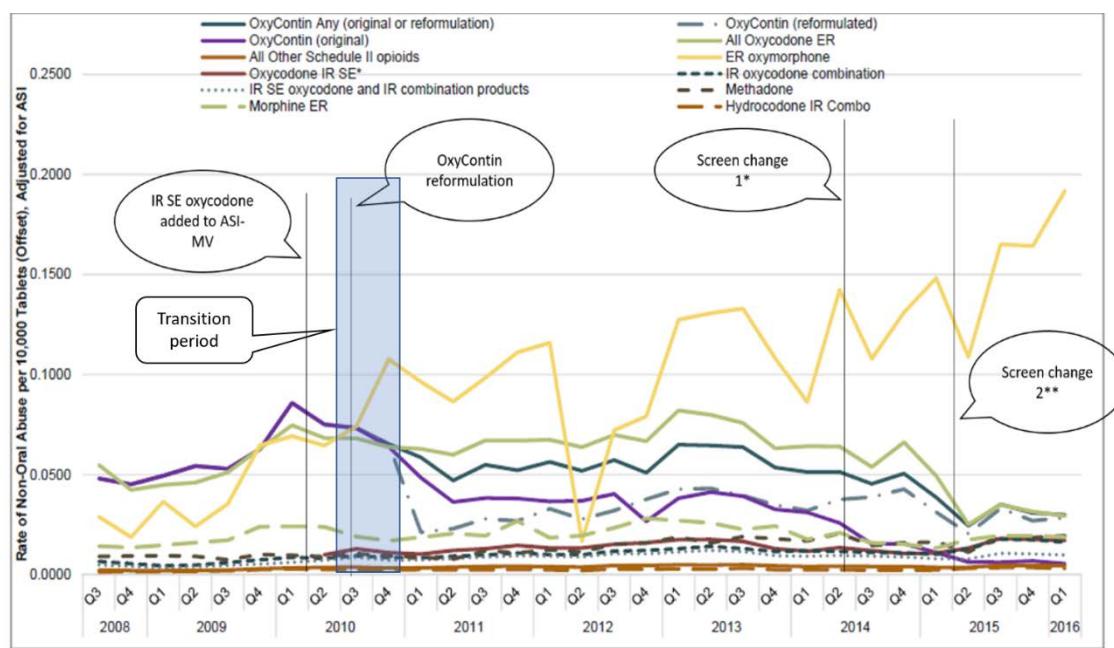
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 13-7. Model 2: Past 30-day non-oral abuse among sites contributing at least one assessment each year from the two-year pre-period to the four-year post-period, prescription tablets dispensed as an offset (3Q2008-1Q2016). P. 531.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2 models abuse rate per tablets dispensed; ER oxymorphone was not included in this graph

Figure 58: Model 2a estimated non-oral abuse cases per 10,000 dosage units dispensed, adjusted for assessments, for OxyContin and all comparator opioids

IR=immediate release; ER=extended release; *Data for oxycodone IR single-entity (SE) is not presented prior to 2Q2010.
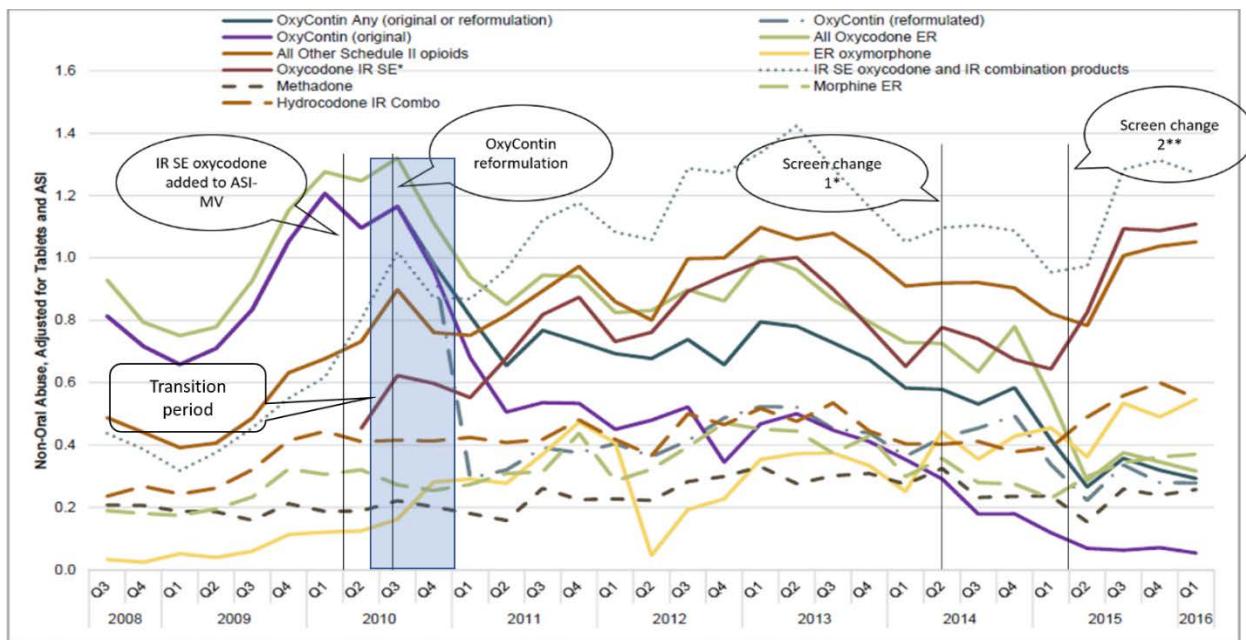
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 13-8. Model 2a: Past 30-day non-oral abuse among sites contributing at least one assessment each year from the two-year pre-period to the four-year post-period, prescription tablets dispensed as offset and ASI as covariate (3Q2008-1Q2016). P. 532.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2a models abuse rate per tablets dispensed adjusted for ASI-MV assessments as a covariate

Figure 59: Model 3a estimated non-oral abuse cases, adjusted for assessments and dosage units dispensed (continuous) for OxyContin and all comparator opioids
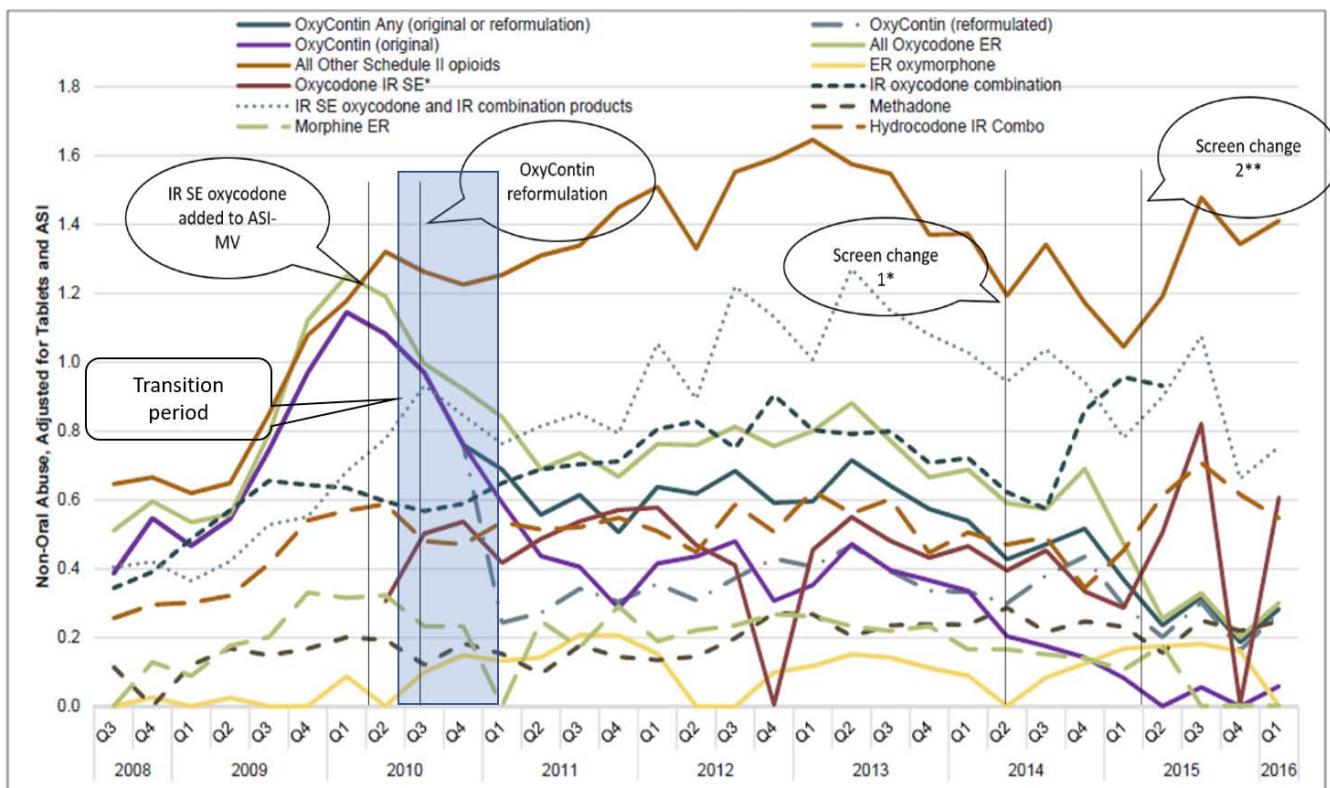
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 13-9. Model 3a: Past 30-day non-oral abuse among sites contributing at least one assessment each year from the two-year pre-period to the four-year post-period, prescription tablets dispensed as continuous covariate and ASI as covariate (3Q2008-1Q2016). P. 533.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 3a models abuse rate adjusted for tablets dispensed and ASI-MV assessments as a covariate

Figure 60: Model 4a estimated non-oral abuse cases, adjusted for dosage units dispensed (categorical) and assessments as covariates, over time for OxyContin and all comparator opioids

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 13-10. Model 4a: Past 30-day non-oral abuse among sites contributing at least one assessment each year from the two-year pre-period to the four-year post-period, prescription tablets dispensed as categorical covariate and ASI as covariate (3Q2008-1Q2016). P. 534.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.
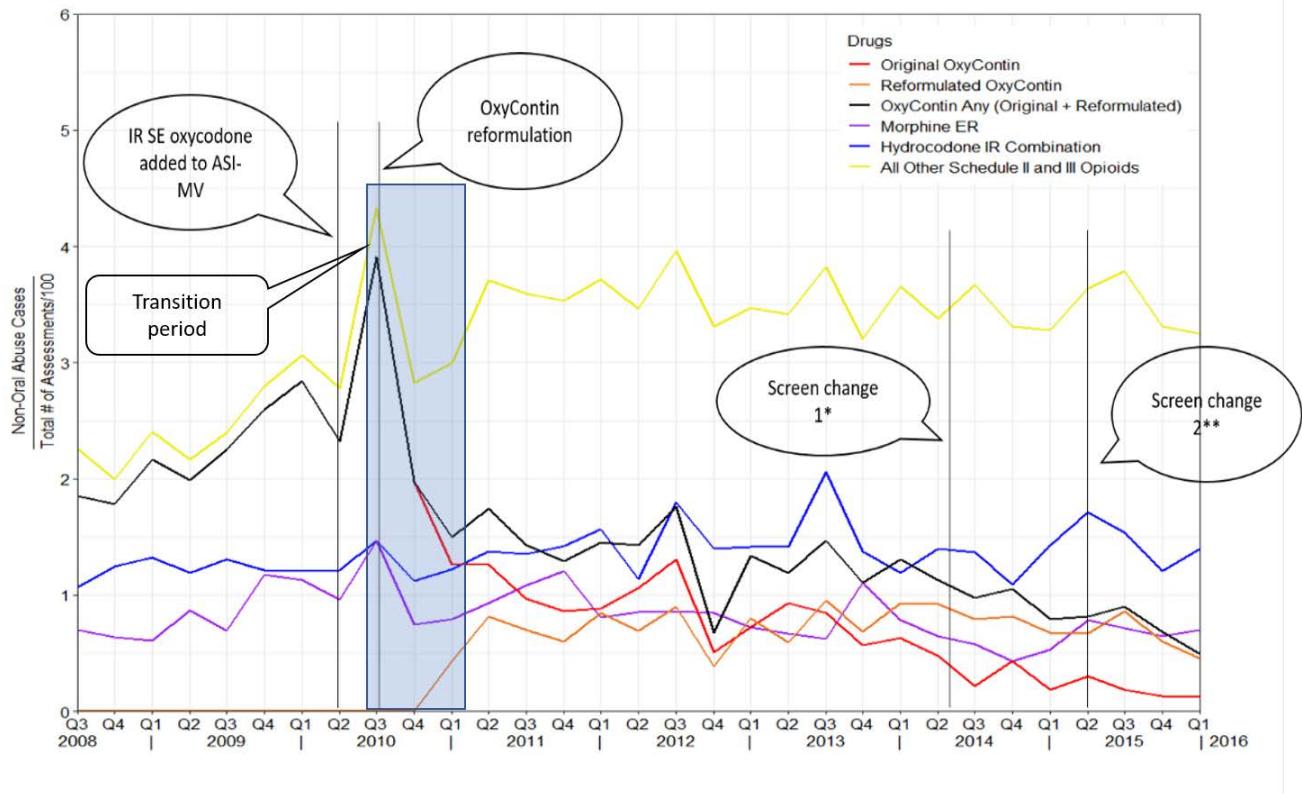
**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 4a models abuse rate adjusted for tablets dispensed (categorical) and ASI-MV assessments as a covariate; ER oxymorphone is not included here

Analysis parameters:
- Sites: ≥1 assessment/quarter
- OxyContin definitions:
  - Any OxyContin (original or reformulated)
  - Original pre-period, Reformulated post-period

Figure 61: Observed quarterly rates of non-oral abuse cases for OxyContin and primary comparators per 100 assessments
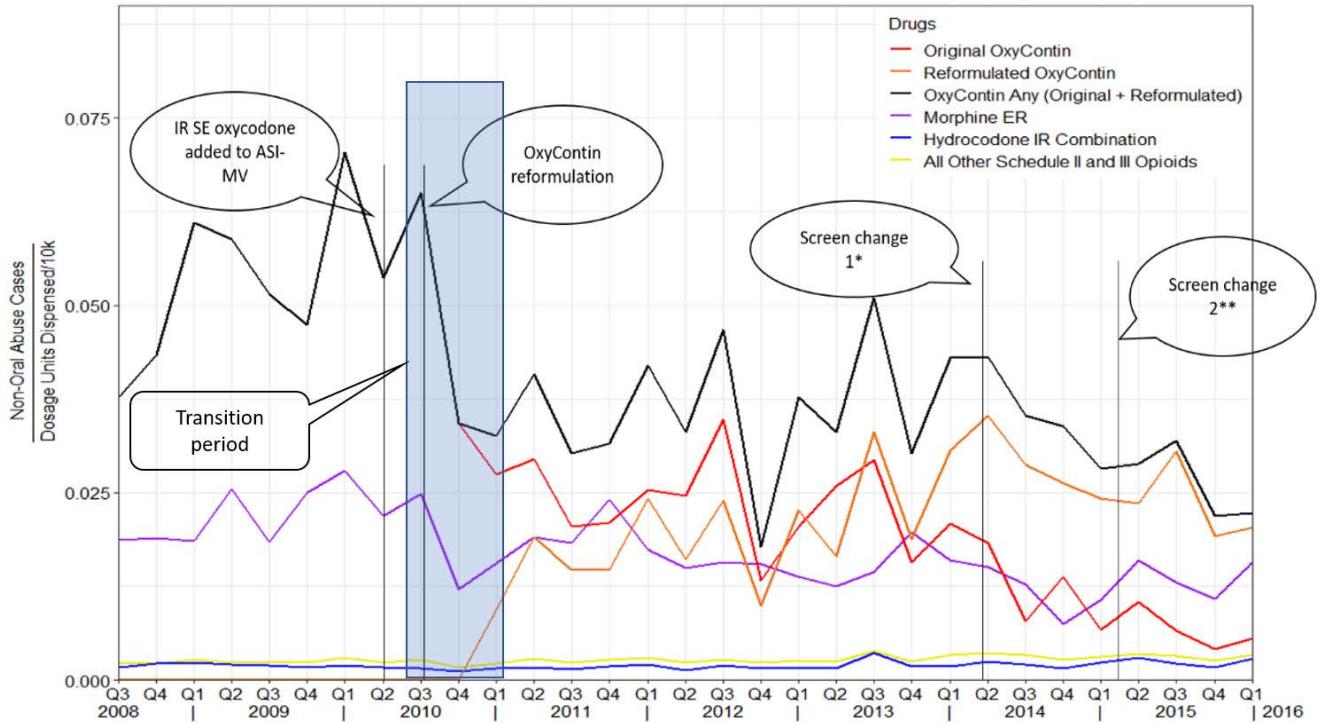
(Source: FDA generated graphs from sponsor information request response)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity

Figure 62: Observed quarterly rates of endorsements for non-oral abuse of OxyContin and primary comparators per 10,000 dosage units dispensed

(Source: FDA generated figures based on sponsor information request response)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.
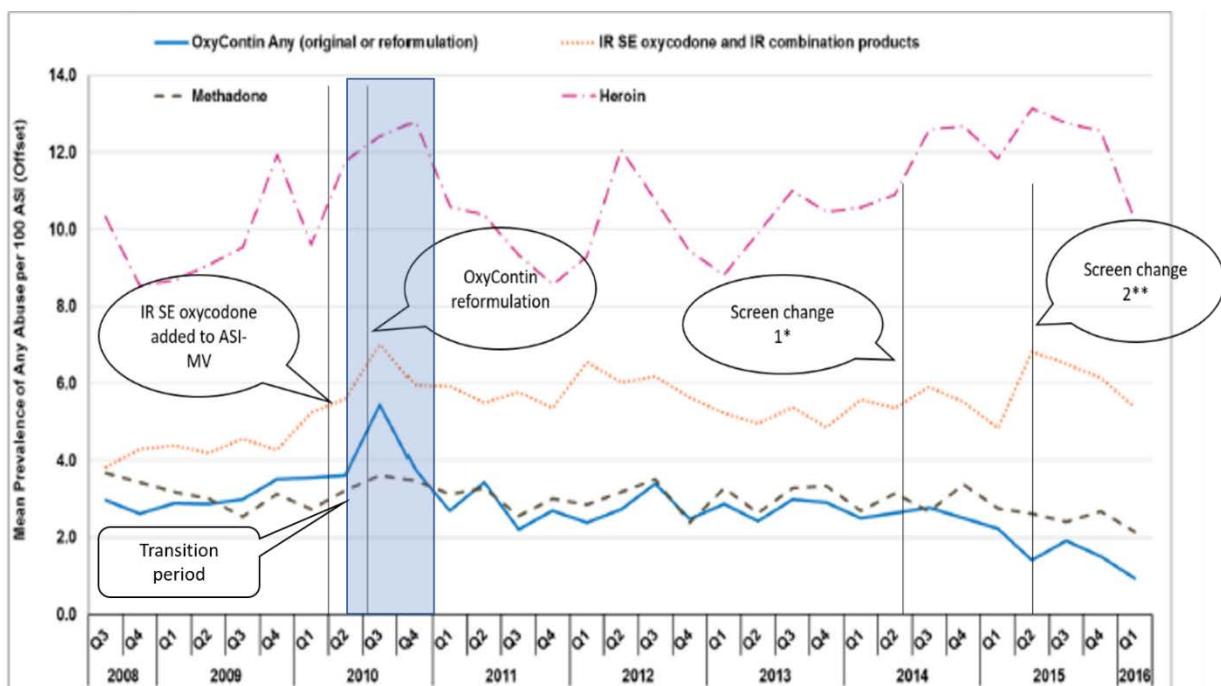
Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity

6.4 SENSITIVITY ANALYSES FOR QUARTERLY TREND ANALYSES, ANY ROUTE OF ABUSE

Analysis parameters:
- Abuse: <u>Any route of abuse</u>
- Sites: contributing $\geq$ 1 assessment/quarter
- OxyContin definition: Reformulated OxyContin, Original and reformulated OxyContin, and all oxycodone ER.
- Unit of analysis: 3-digit ZIP
- Model #1:
  - Offset: Total assessments.
  - Covariates: NA.
- Model #2:
  - Offset: Dosage units dispensed
  - Covariate: NA
- Model #2a:
  - Offset: Dosage units dispensed
  - Covariate: Total assessments
- Model #3a:
  - Offset: NA
  - Covariate: Dosage units dispensed (continuous), Total assessments
- Model #4a:
  - Offset: NA
  - Covariate: Dosage units dispensed (categorical)

Figure 63: Model 1 estimated rate of abuse via any route per 100 assessments over time for OxyContin and secondary comparators

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study.
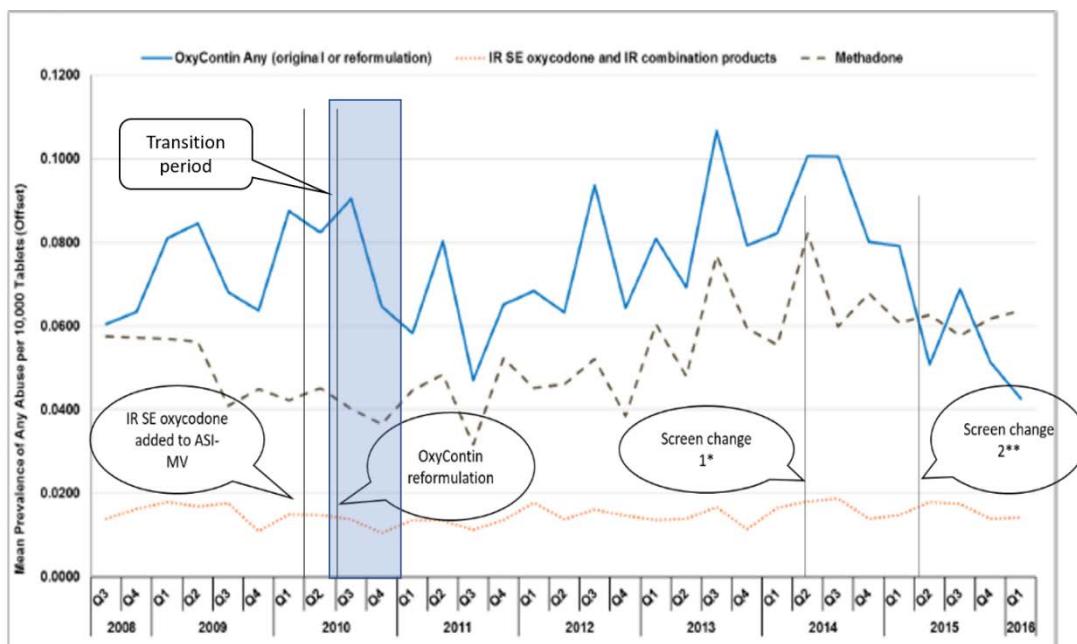
(Source: FDA Postmarketing Requirements Study 3051-1 Final Report. Title: Appendix Table 11-6. Model 1 descriptive trend analysis figure: Any route of abuse, secondary comparators. P. 363.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 1 models abuse rate per ASI-MV assessments; ER oxymorphone was not included in this graph

Figure 64: Model 2 estimated rate of abuse via any route per 10,000 tablets over time for OxyContin and secondary comparators

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study.
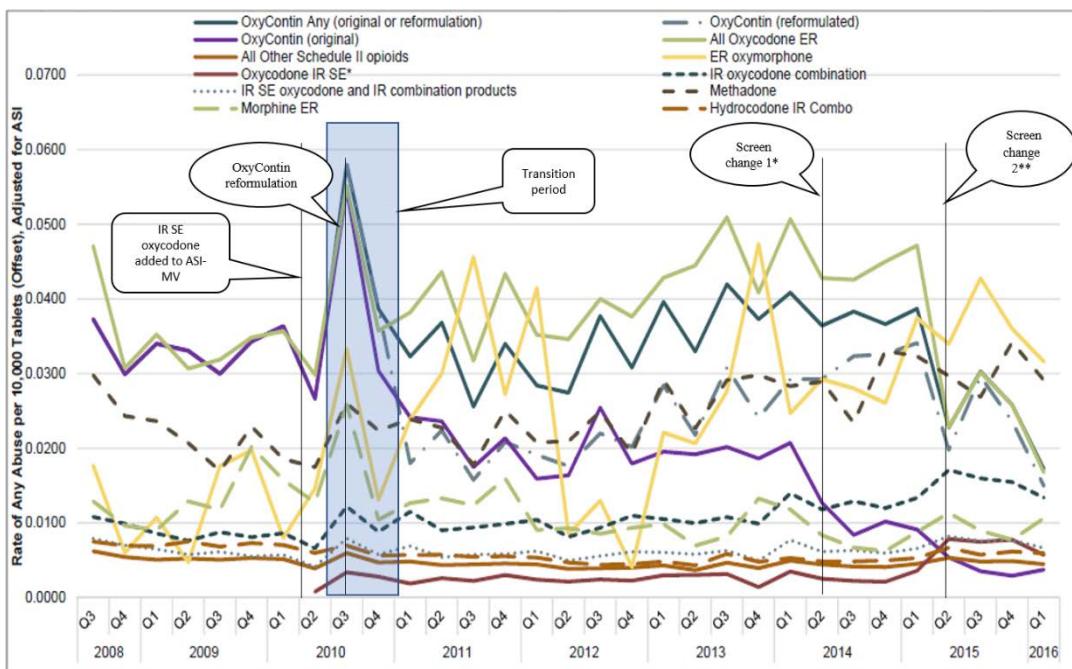
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 11-7. Model 2 descriptive trend analysis figure: Any route of abuse, secondary comparators. P. 363.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2 models abuse rate per tablets dispensed; ER oxymorphone was not included in this graph

Figure 65: Model 2a estimated rate of abuse via any route per dosage units dispensed over time, adjusted for assessments as a covariate, for OxyContin and all comparators.
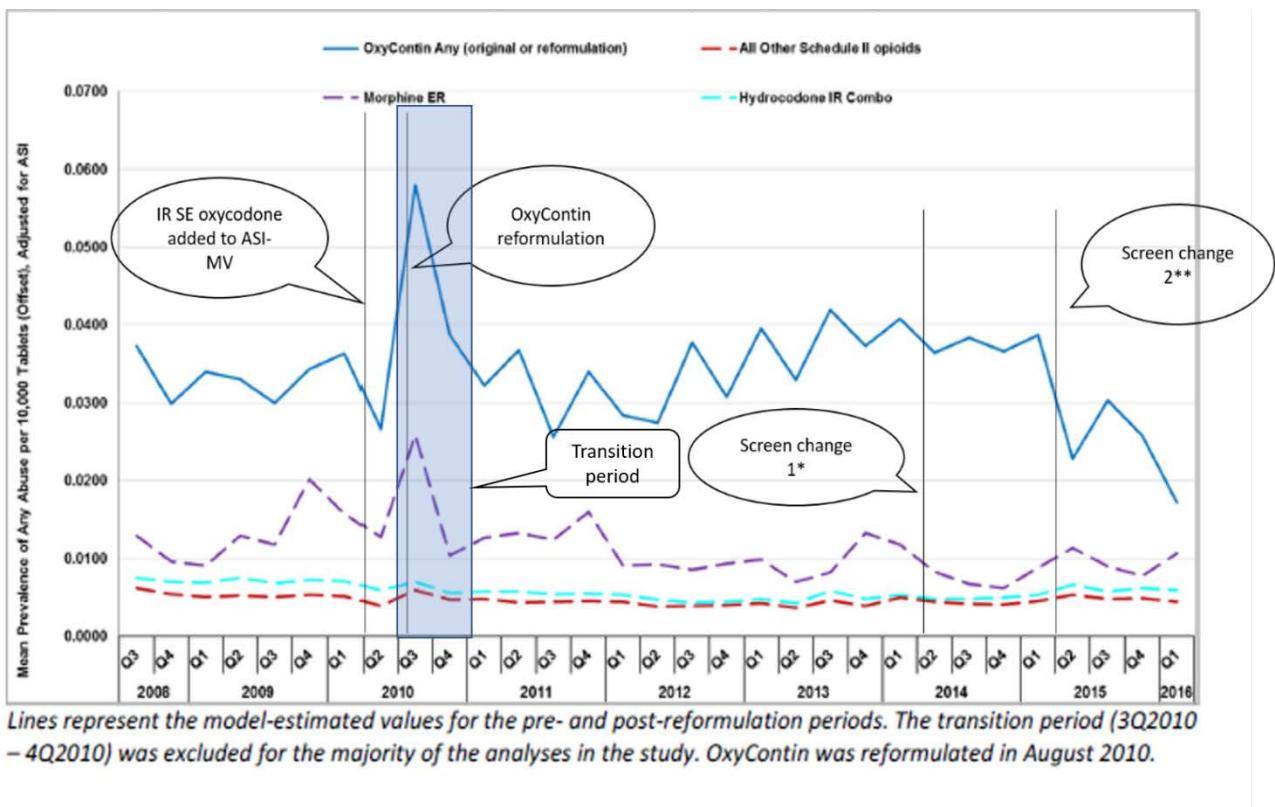
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 13-13. Model 2a: Past 30-day abuse via any route among sites contributing at least one assessment each quarter from the two-year pre-period to the four-year post-period, prescription tablets dispensed as offset and ASI covariate (3Q2008-1Q2016). P. 537)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2a models abuse rate per tablets dispensed adjusted for ASI-MV assessments as a covariate

Figure 66: Model 2a estimated rate of abuse via any route per 10,000 dosage units dispensed adjusted for assessments over time for OxyContin and primary comparators

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study. OxyContin was reformulated in August 2010.
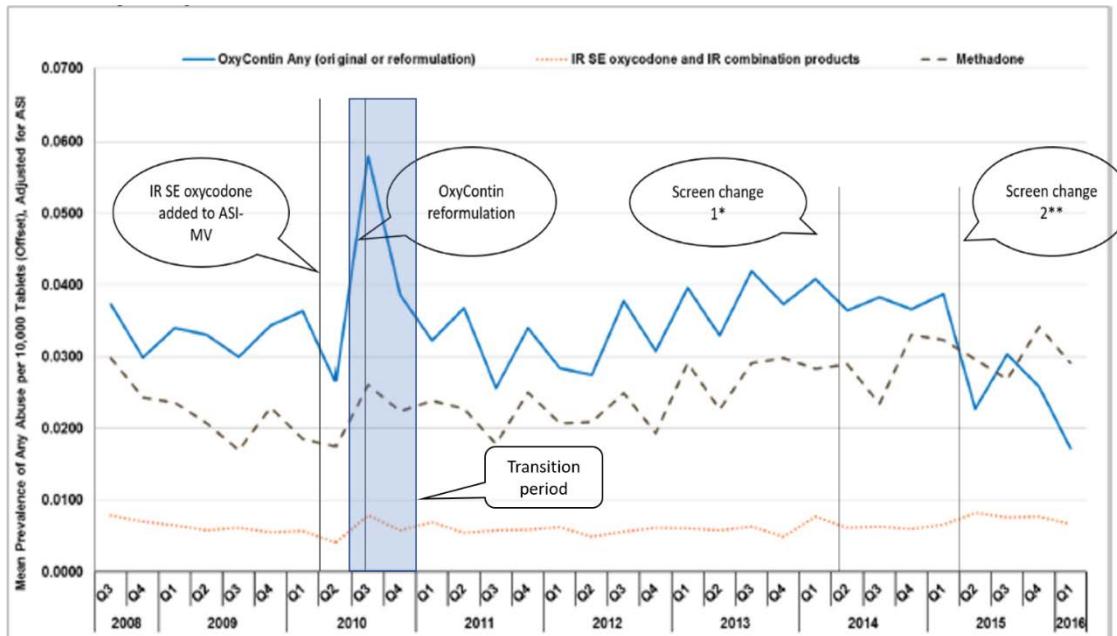
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 10-3. Model 2a descriptive trend analysis figure: any route of abuse. P.352.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2a models abuse rate per tablets dispensed adjusted for ASI-MV assessments as a covariate

Figure 67: Model 2a estimated rate of abuse via any route per 10,000 dosage units dispensed, adjusted for assessments as covariate, for OxyContin and secondary comparators

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study.
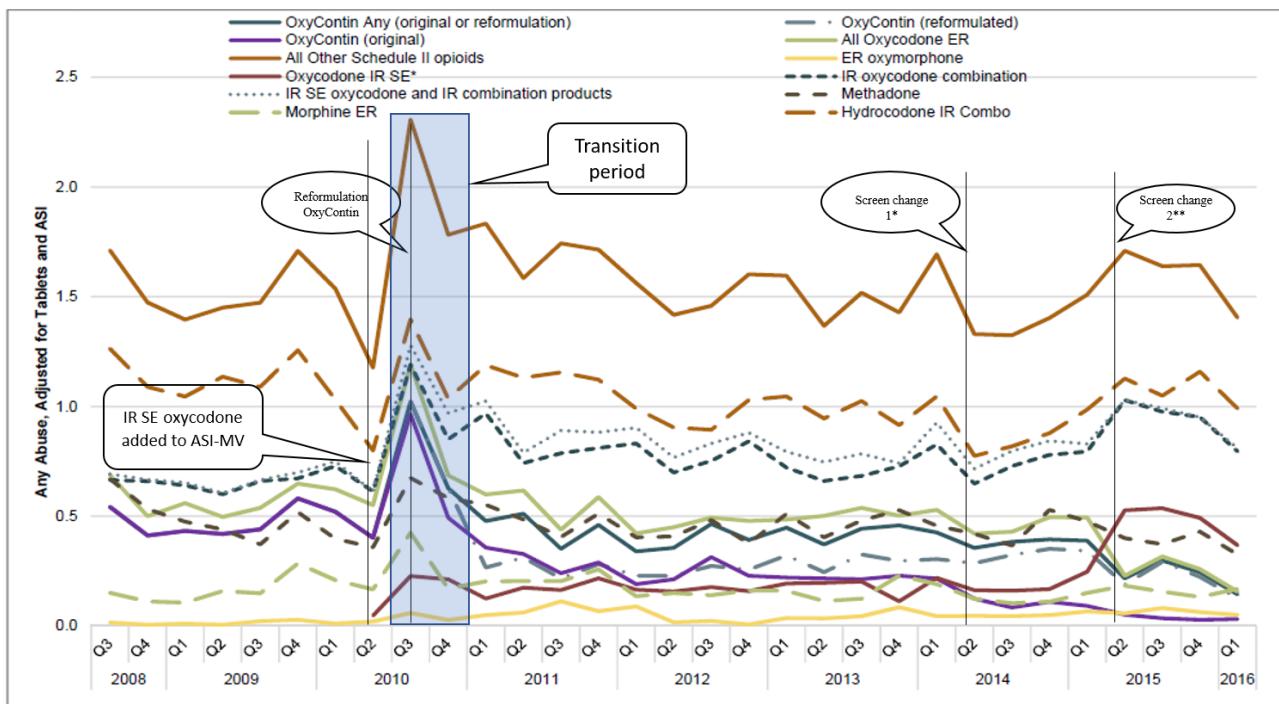
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 11-8. Model 2a descriptive trend analysis figure: Any route of abuse, secondary comparators. P. 364.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2a models abuse rate per tablets dispensed adjusted for ASI-MV assessments as a covariate; ER oxymorphone was not included in this graph

Figure 68: Model 3a estimated rate of abuse via any route, <u>adjusted for dosage units dispensed (continuous) and assessments as covariates</u>, for OxyContin and <u>all comparator opioids</u>

IR=immediate release; ER=extended release; *Data for oxycodone IR single-entity (SE) is not presented prior to 2Q2010.
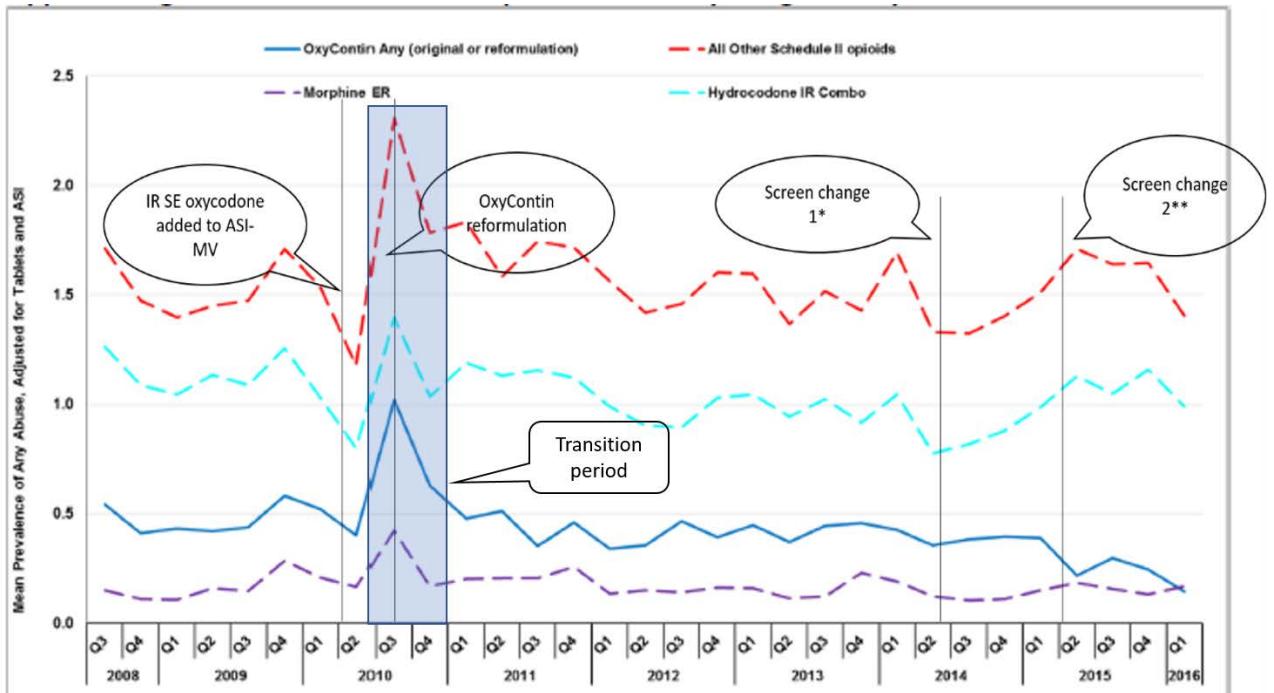
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 13-14. Model 3a: Past 30-day abuse via any route among sites contributing at least one assessment each quarter form the two-year pre-period to the four-year post-period, prescription tablets dispensed as continuous covariate and ASI as covariate (3Q2008-1Q2016). P. 538.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 3a models abuse rate adjusted for tablets dispensed and ASI-MV assessments as a covariate

Figure 69: Model 3a estimated rate of abuse via any route, adjusted for dosage units dispensed (continuous) and assessments as covariates, for OxyContin and primary comparator opioids

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study. OxyContin was reformulated in August 2010.
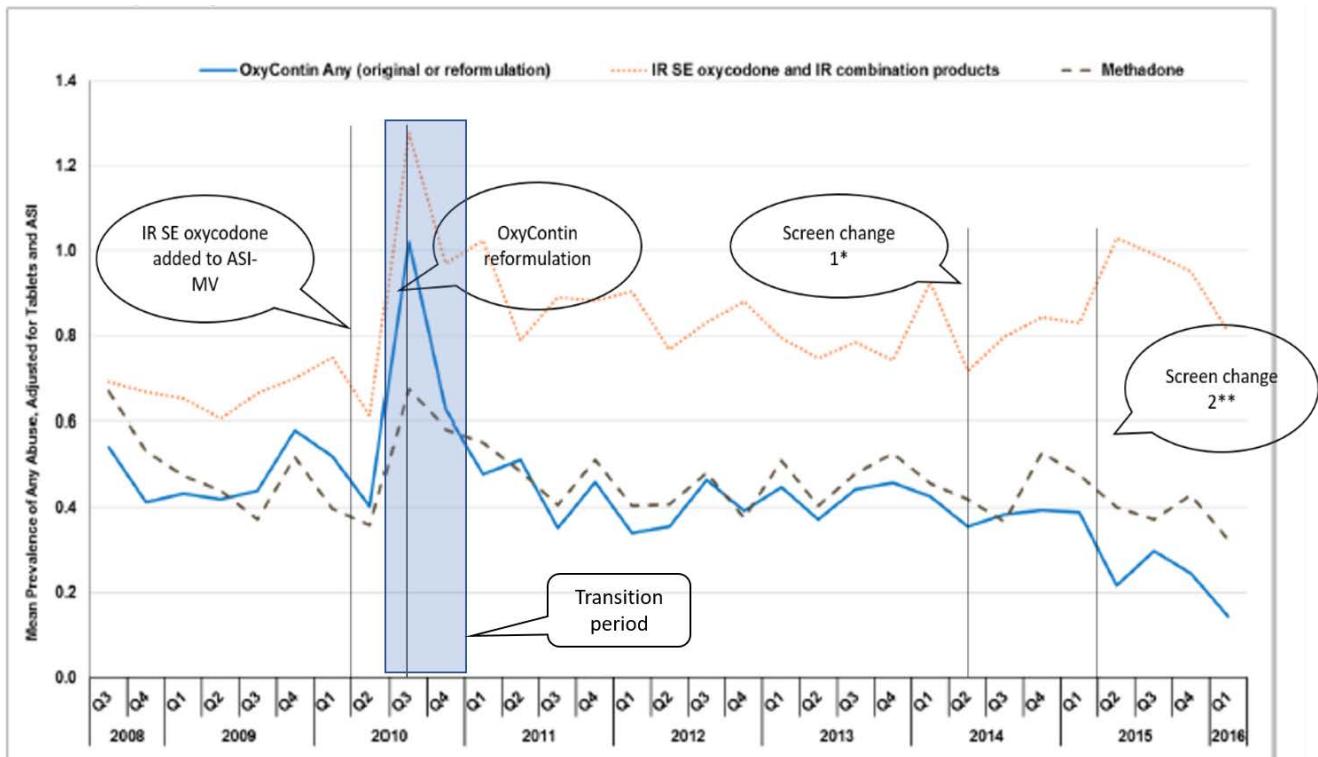
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 10-4. Model 3 descriptive trend analysis figure: any route of abuse. P.353.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 3a models abuse rate adjusted for tablets dispensed and ASI-MV assessments as a covariate

Figure 70: Model 3a estimated rate of abuse via any route, adjusted for dosage units dispensed (continuous) and assessments as covariates, over time for OxyContin and secondary comparator opioids

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study.
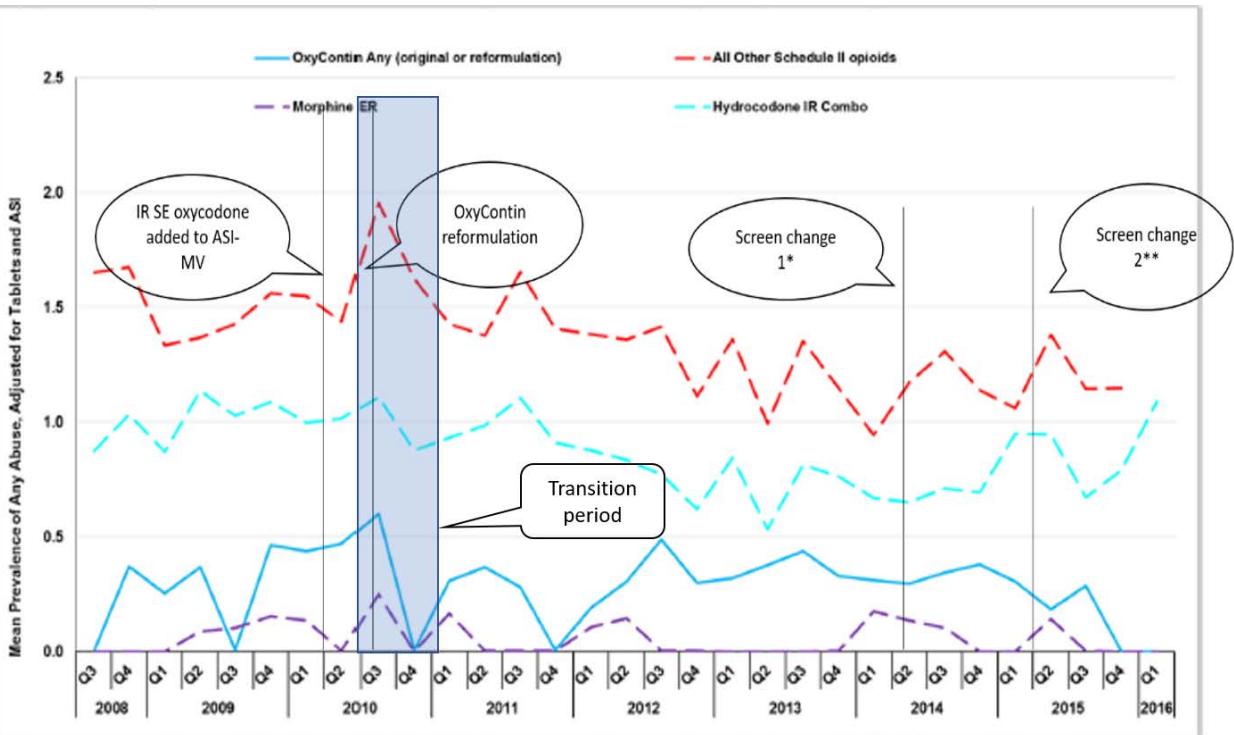
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 11-9. Model 3a descriptive trend analysis figure: Any route of abuse, secondary comparators. P. 364.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 3a models abuse rate adjusted for tablets dispensed and ASI-MV assessments as a covariate; ER oxymorphone is not included here

Figure 71: Model 4a estimated rate of abuse via any route, adjusted for dosage units dispensed (categorical) and assessments as covariates, over time for OxyContin and primary comparators

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study. OxyContin was reformulated in August 2010.
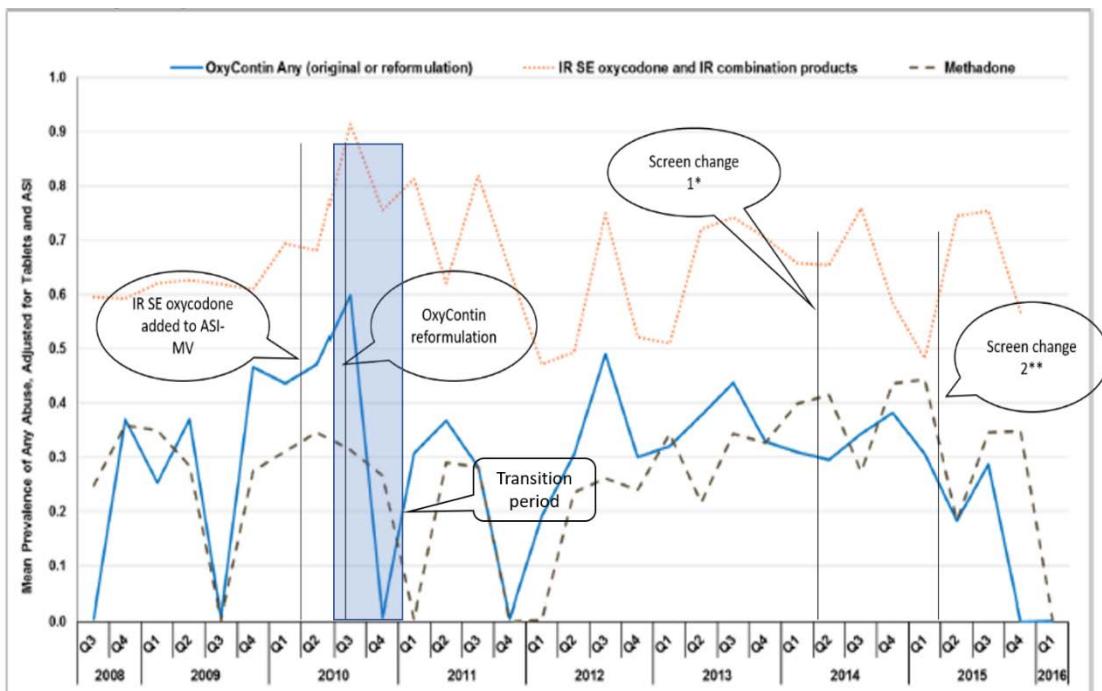
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 10-5. Model 4a descriptive trend analysis figure: any route of abuse. P.353.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 4a models abuse rate adjusted for tablets dispensed (categorical) and ASI-MV assessments as a covariate

Figure 72: Model 4a estimated rate of abuse via any route, adjusted for dosage units dispensed (categorical) and assessments, over time for OxyContin and secondary comparator opioids

Lines represent the model-estimated values for the pre- and post-reformulation periods. The transition period (3Q2010 – 4Q2010) was excluded for the majority of the analyses in the study.
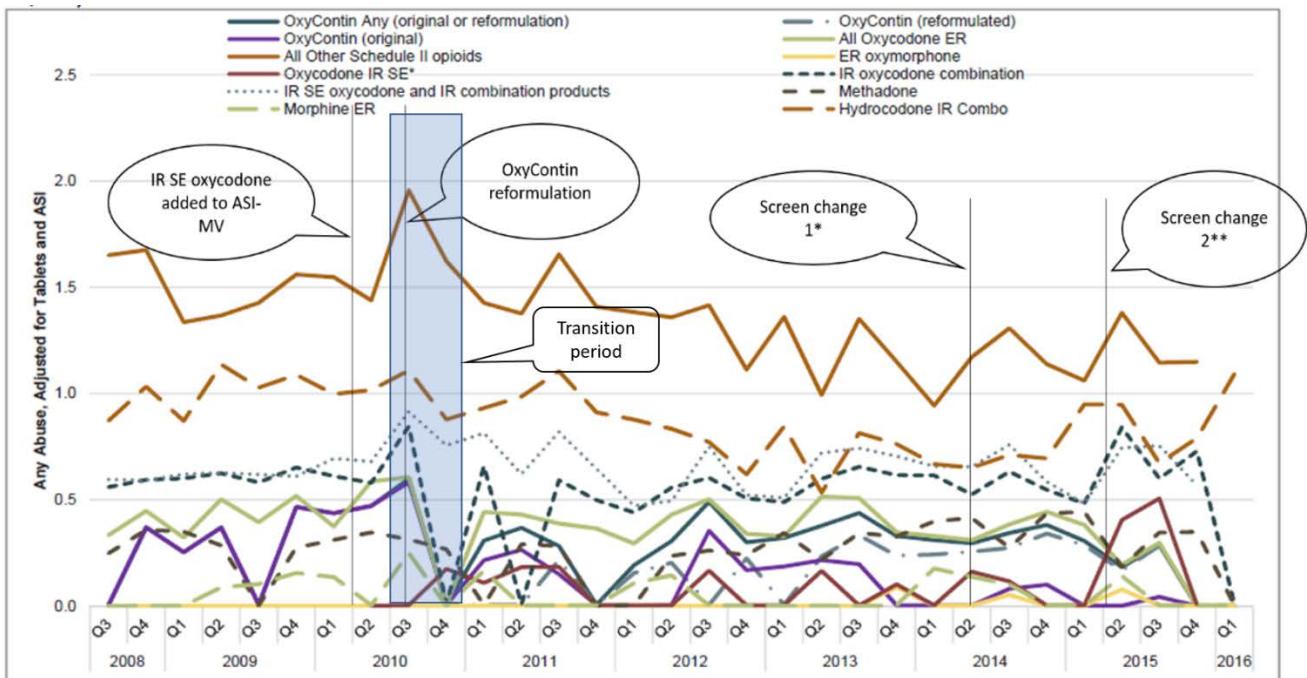
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 11-10. Model 4a descriptive trend analysis figure: Any route of abuse, secondary comparators. P. 365.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 4a models abuse rate adjusted for tablets dispensed (categorical) and ASI-MV assessments as a covariate; ER oxymorphone is not included here

Figure 73: Model 4a estimated rate of abuse via any route, adjusted for dosage units dispensed (categorical) and assessments, for OxyContin and all comparator opioids

IR=immediate release; ER=extended release; *Data for oxycodone IR single-entity (SE) is not presented prior to 2Q2010.
Note: The measures of abuse adjusted for tablets dispensed as a categorical covariate and ASI as a covariate was non-estimable for oxycodone IR SE, oxycodone IR SE and combination, and all other schedule II opioids during 1Q2016.

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 13-15. Model 4a: Past 30-day abuse via any route among sites contributing at least one assessment each quarter from the two-year pre-period to the four-year post-period, prescription tablets dispensed as categorical covariate and ASI as covariate (3Q2008-1Q2016). P. 539.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 4a models abuse rate adjusted for tablets dispensed (categorical) and ASI-MV assessments as a covariate;

Analysis parameters:
- Abuse: <u>Any route of abuse</u>
- Sites: contributing <u>> 1 assessment/year</u>
- OxyContin definition: Reformulated OxyContin, Original and reformulated OxyContin, and all oxycodone ER.
- Unit of analysis: 3-digit ZIP
- Model #1:
  - Offset: Total assessments.
  - Covariates: NA.
- Model #2:
  - Offset: Dosage units dispensed
  - Covariate: NA
- Model #2a:
  - Offset: Dosage units dispensed
  - Covariate: Total assessments
- Model #3a:
  - Offset: NA
  - Covariate: Dosage units dispensed (continuous), Total assessments
- Model #4a:
  - Offset: NA
  - Covariate: Dosage units dispensed (categorical)

Figure 74: Model 1 estimated rate of abuse via any route per 100 assessments over time for OxyContin and all comparator opioids

IR=immediate release; ER=extended release; *Data for oxycodone IR single-entity (SE) is not presented prior to 2Q2010.

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 1 models abuse rate per ASI-MV assessments;

Figure 75: Model 2 estimated rate of abuse via any route per 10,000 dosage units dispensed over time for OxyContin and all comparator opioids

IR=immediate release; ER=extended release; *Data for oxycodone IR single-entity (SE) is not presented prior to 2Q2010.

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2 models abuse rate per tablets dispensed

Figure 76: Model 2a estimated rate of abuse via any route per 10,000 dosage units dispensed over time, adjusted for assessments for OxyContin and all comparator opioids
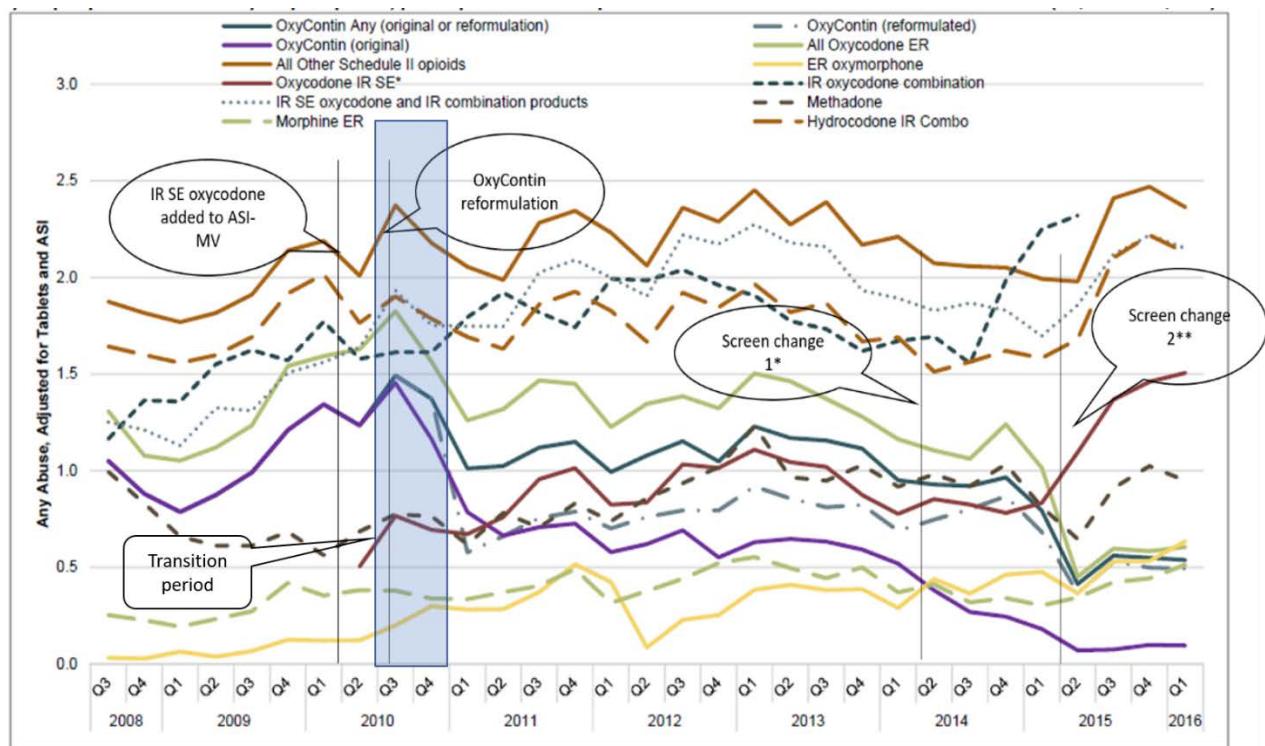
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 13-18. Model 2a: Past 30-day abuse via any route among sites contributing at least one assessment each year from the two-year pre-period to the four-year post-period, prescription tablets dispensed as offset and ASI as covariate (3Q2008-1Q2016). P. 542.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 2a models abuse rate per tablets dispensed adjusted for ASI-MV assessments as a covariate

Figure 77: Model 3a estimated rate of abuse via any route, adjusted for assessments and dosage units dispensed (continuous), over time for OxyContin and all comparator opioids
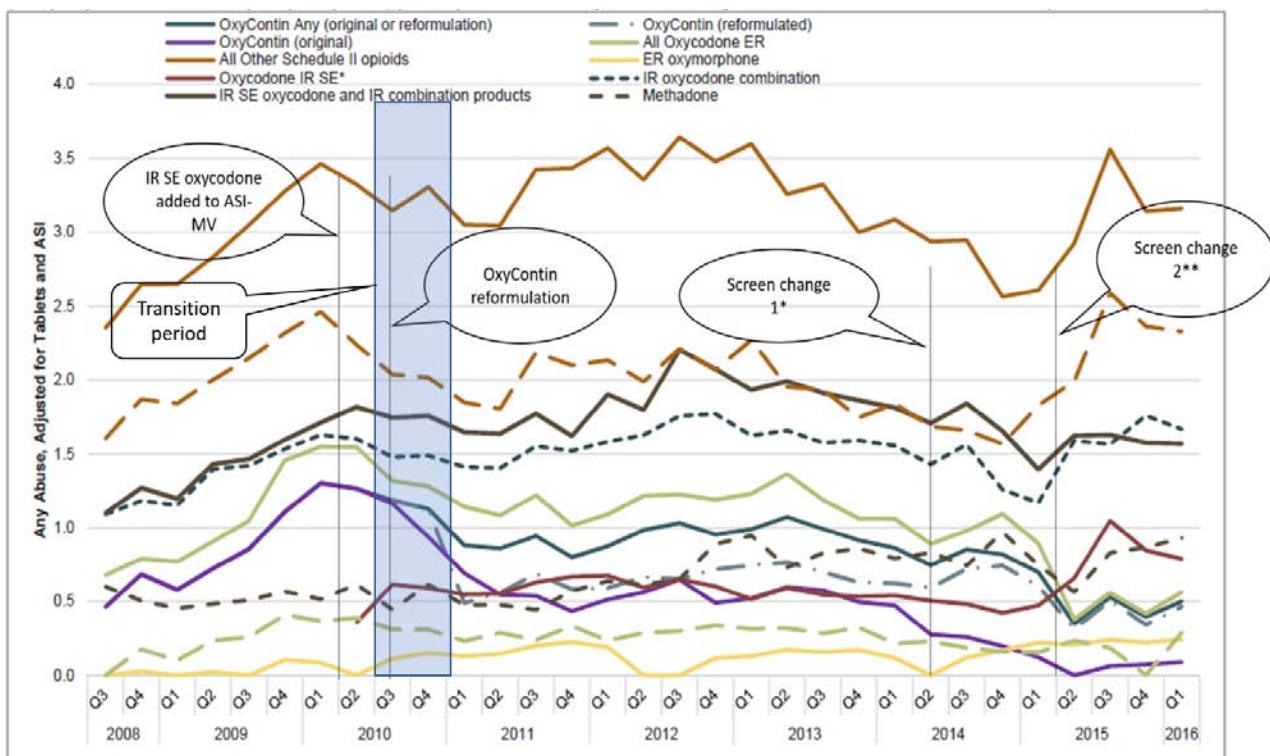
(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 13-19. Model 3a: Past 30-day abuse via any route among sites contributing at least one assessment each year from the two-year pre-period to the four-year post-period, prescription tablets dispensed as continuous covariate and ASI as covariate (3Q2008-1Q2016). P. 543.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 3a models abuse rate adjusted for tablets dispensed and ASI-MV assessments as a covariate

Figure 78: Model 4a estimated rate of abuse via any route, adjusted for assessments and dosage units dispensed (categorical), over time for OxyContin and all comparator opioids

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 13-20. Model 4a: Past 30-day abuse via any route among sites contributing at least one assessment each year from the two-year pre-period to the four-year post-period, prescription tablets dispensed as categorical covariate and ASI as covariate (3Q2008-1Q2016). P. 544.)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity; Model 4a models abuse rate adjusted for tablets dispensed (categorical) and ASI-MV assessments as a covariate;

Analysis parameters:
- Sites: ≥1 assessment/quarter
- OxyContin definitions:
  - Any OxyContin (original or reformulated)
  - Original pre-period, Reformulated post-period

Figure 79: Observed quarterly rates of endorsement for abuse of OxyContin and primary comparators via any route per 100 assessments
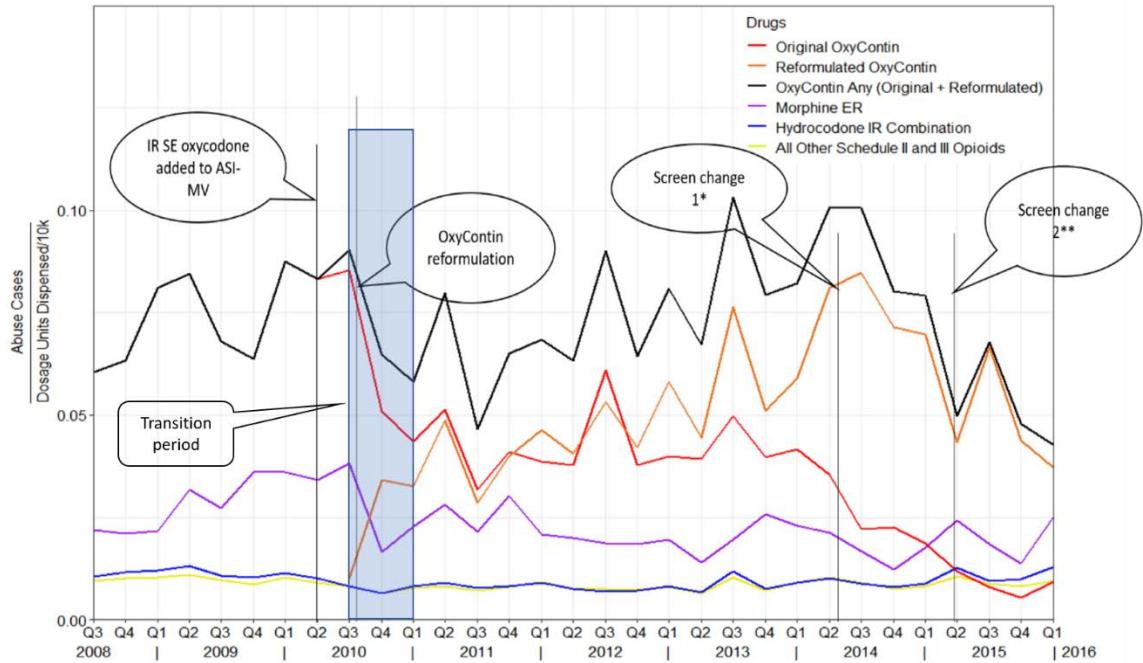
(Source: FDA generated figure from sponsor information request response)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity

Figure 80: Observed quarterly rates of endorsements for abuse of OxyContin and primary comparators via any route per 10,000 dosage units dispensed

(Source: FDA generated figure from sponsor information request response)

*Screen change 1: Reformulated OxyContin image moved to the first (left-most) position on the ER oxycodone screen. Original OxyContin moved to text box. May 2014.

**Screen change 2: ER oxycodone screen moved from the first opioid screen presented to respondents to the fourth. March 2015.

Key: IR: Immediate Release; ER: Extended Release; SE: Single Entity

6.5 PRE- AND POST-PERIOD MEAN NON-ORAL ABUSE RATES FOR OXYCONTIN AND PRIMARY COMPARATORS (DESCRIPTIVE MEANS ANALYSIS)

Table 22: Percent change (95% CI) in non-oral abuse after introduction of reformulated OxyContin and primary comparator opioids -2y/4y

	Model 1 % change (95% CI)	Model 2 % change (95% CI)	Model 3 % change (95% CI)
All OxyContin	-30.7 (-46.9, -9.5)	-31.5 (-39.4, -22.5)	-53.3 (-60.3, -45.0)
ER Morphine	-9.6 (-32.9, 21.7)	-28.5 (-40.3, -14.3)	+0.2 (-21.3, 27.5)
IR Hydrocodone	+19.3 (-7.7, 54.3)	-6.5 (-19.1, 8.1)	+17.1 (-3.5, 42.0)
Other Schedule II	+31.6 (-0.3, 73.7)	+13.2 (2.5, 24.9)	+26.7 (9.3, 46.9)

CI=confidence intervals; ER=extended release; IR Hydrocodone=IR hydrocodone combination products; Sites: contributing ≥1 assessment/quarter; OxyContin Definition: Original and Reformulated; Unit of Analysis: Respondent 3-digit ZIP Code; Model 1: Rate of abuse/Assessments. Model 2: Rate of abuse/Dosage units dispensed. Model 3: Abuse count adjusting for dosage units dispensed (continuous).

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Table 7-3. Percent change (95% CI) in non-oral abuse after introduction of reformulated OxyContin and primary comparator opioids using different modeling approaches -2y/4y. p. 47.)

Key: IR: Immediate Release; ER: Extended Release; Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 3 models abuse rate adjusted for tablets dispensed as a covariate

Table 23: RORR (95% CI) in non-oral abuse after introduction of reformulated OxyContin, primary comparators vs. OxyContin, -2y/4y

	Model 1 RORR (95% CI)	Model 2 RORR (95% CI)	Model 3 RORR (95% CI)
ER Morphine	1.30 (0.87, 1.94)	1.04 (0.84, 1.30)	2.14 (1.60, 2.87)
IR Hydrocodone	1.72 (1.19, 2.49)	1.36 (1.13, 1.65)	2.51 (1.95, 3.23)
Other Schedule II	1.90 (1.29, 2.79)	1.65 (1.41, 1.93)	2.71 (2.18, 3.38)

RORR=ratio of risk ratios; CI=confidence intervals; IR Hydrocodone=IR hydrocodone combination products; Sites: contributing ≥1 assessment/quarter; OxyContin Definition: Original and Reformulated; Unit of Analysis: Respondent 3-digit ZIP Code; Model 1: Rate of abuse/Assessments. Model 2: Rate of abuse/Dosage units dispensed. Model 3: Abuse count adjusting for dosage units dispensed (continuous).

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: RORR (95% CI) in non-oral abuse after introduction of reformulated OxyContin and primary comparator opioids using different modeling approaches -2y/4y. p. 49.)
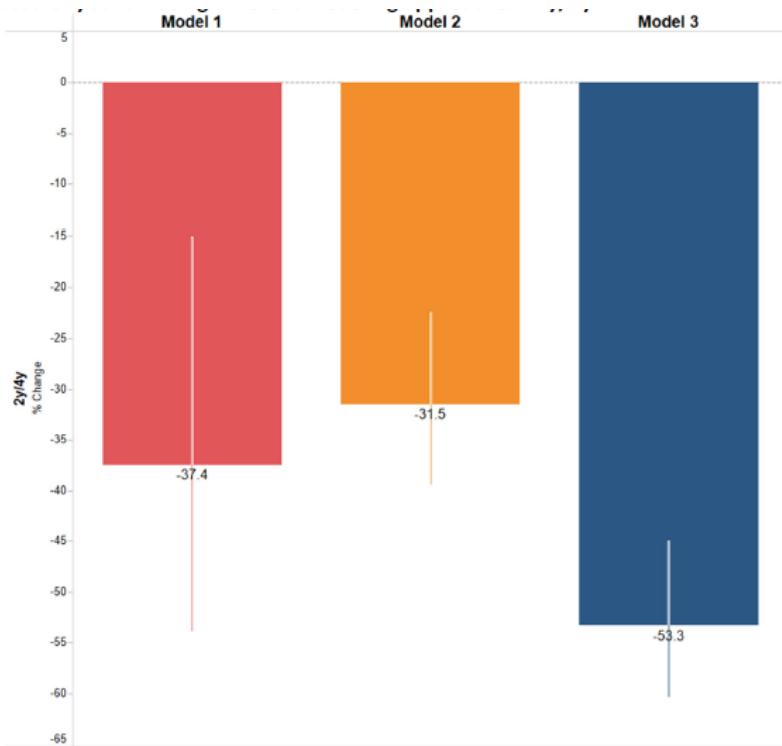
Key: IR: Immediate Release; ER: Extended Release; Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 3 models abuse rate adjusted for tablets dispensed as a covariate

6.6   PRE- AND POST-PERIOD MEAN NON-ORAL ABUSE RATES FOR OXYCONTIN ONLY (DESCRIPTIVE MEANS ANALYSIS)

Analysis parameters:
- Sites: Contributing ≥1 assessment per quarter
- OxyContin definition: All OxyContin including original and reformulated
- Unit of analysis: Respondent 3-digit ZIP code
- Model #1:
  - Offset: Total assessments
  - Covariates: NA
- Model #2:
  - Offset: Dosage units dispensed
  - Covariates: NA
- Model #3:
  - Offset: NA
  - Covariate: Dosage units dispensed (continuous)

Figure 81: Percent change (95% CI) in non-oral OxyContin abuse after introduction of reformulated OxyContin, (-2y/4y)

CI=confidence intervals; Sites: contributing ≥1 assessment/quarter; OxyContin Definition: Original and Reformulated; Unit of Analysis: Respondent 3-digit ZIP Code; Model 1: Rate of abuse/Assessments. Model 2: Rate of abuse/Dosage units dispensed. Model 3: Abuse count adjusting for dosage units dispensed (continuous).

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Figure 7-5. Percent change (95% CI) in non-oral OxyContin abuse after introduction of reformulated OxyContin using different modeling approaches -2y/4y. p. 42)

Key: Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 3 models abuse rate adjusted for tablets dispensed as a covariate

Table 24: Percent change (95% CI) in non-oral OxyContin abuse after introduction of reformulated OxyContin, -2y/4y

	Model 1 % change (95% CI)	Model 2 % change (95% CI)	Model 3 % change (95% CI)
All OxyContin	-37.4 (-53.9, -15.1)	-31.5 (-39.4, -22.5)	-53.3 (-60.3, -45.0)

CI=confidence intervals; Sites: contributing ≥1 assessment/quarter; OxyContin Definition: Original and Reformulated; Unit of Analysis: Respondent 3-digit ZIP Code; Model 1: Rate of abuse/Assessments. Model 2: Rate of abuse/Dosage units dispensed. Model 3: Abuse count adjusting for dosage units dispensed (continuous).

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Table 7-2. Percent change (95% CI) in non-oral OxyContin abuse after introduction of reformulated OxyContin using different modeling approaches -2y/4y. p. 42.)

Key: Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 3 models abuse rate adjusted for tablets dispensed as a covariate

6.7 SENSITIVITY ANALYSIS: INCLUDING DOSAGE UNITS DISPENSED AS A CATEGORICAL VARIABLE IN REGRESSION MODEL (SENSITIVITY FOR MEANS ANALYSIS)

Analysis parameters:
- Sites: contributing $\geq$ 1 assessment/quarter
- Unit of analysis: Respondent 3-digit ZIP code
- OxyContin definition: original OxyContin + reformulated OxyContin
- Model #4:
  - Offset: NA
  - Covariate: Dosage units dispensed (categorical)

Table 25: Percent change (95% CI) in non-oral abuse after introduction of reformulated OxyContin using Model 4, -2y/4y

	Model 4
All OxyContin	-34.2 (-46.2, -19.5)

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Table 7-1. Percent change (95% CI) in non-oral abuse after introduction of reformulated OxyContin using Model 3a and Model 4, -2y/4y. p. 328.)

Key: Model 4 models abuse rate adjusted for tablets dispensed (categorical) as a covariate

Table 26: RORR (95% CI) in non-oral abuse after introduction of reformulated OxyContin and primary comparator opioids using different modeling approaches, -2y/4y

	Model 4
ER morphine	1.43 (0.91, 2.23)
IR hydrocodone	1.75 (1.29, 2.36)
Other schedule II	1.67 (1.30, 2.14)

Key: ER: Extended Release; IR: Immediate Release; Model 4 models abuse rate adjusted for tablets dispensed (categorical) as a covariate

6.8 RANGE OF ESTIMATES FOR OXYCONTIN MEANS ANALYSES

Table 27: Most and least "conservative" values for percent change in OxyContin and primary comparators mean quarterly non-oral abuse rates with main parameters and all regression models

	Range % Change		Range RORR	
	Most "conservative"[†]	Least "conservative"[‡]	Most "conservative"[ɣ]	Least "conservative"[x]
OxyContin	-29.3	-55.6	Reference	Reference

	(-37.5, -20.1)[a]	(-62.3, -47.6)[b]		
ER Morphine	3.7 (-20.4, 35.1)[c]	-28.5 (-40.3, -14.3)[d]	1.04 (0.84, 1.30)[i]	2.33 (1.71, 3.19)[j]
IR Hydrocodone	21.2 (-6.5, 56.9)[e]	-8.2 (-20.6, 6.1)[f]	1.30 (1.07-1.57)[k]	2.73 (2.01, 3.71)[l]
Other Schedule II opioids	31.6 (-0.3, 73.7)[g]	13.2 (2.5, 24.9)[h]	1.62 (1.38, 1.90)[m]	2.71 (2.18, 3.38)[n]

(Source: FDA generated figure from information request response.)

A: Model 2a, B: Model 3a, C: Model 3a, D: Model 2, E: Model 3a, F: Model 2a, G: Model 1, H: Model 2, I: Model 2, J: Model 3a, K: Model 2a, L: Model 3a, M: Model 2a, N: Model 3

Key: IR: Immediate Release; ER: Extended Release; [†]Most "conservative": smallest pre-post reduction (or largest increase) in non-oral abuse; [‡]Least "conservative": largest pre-post reduction (or smallest increase) in non-oral abuse; [ϒ]Most "conservative": smallest pre-post reduction (or largest increase) in OxyContin non-oral abuse relative to comparator's change; [Ƶ]Least "conservative": largest pre-post reduction (or smallest increase) in OxyContin non-oral abuse relative to comparator's change

6.9   SENSITIVITY ANALYSES FOR TIME PERIOD (-1Y/3Y) (SENSITIVITY FOR MEANS ANALYSIS)

Table 28: Percent change (95% CI) in non-oral abuse after introduction of reformulated OxyContin and primary comparator opioids, -1y/3y
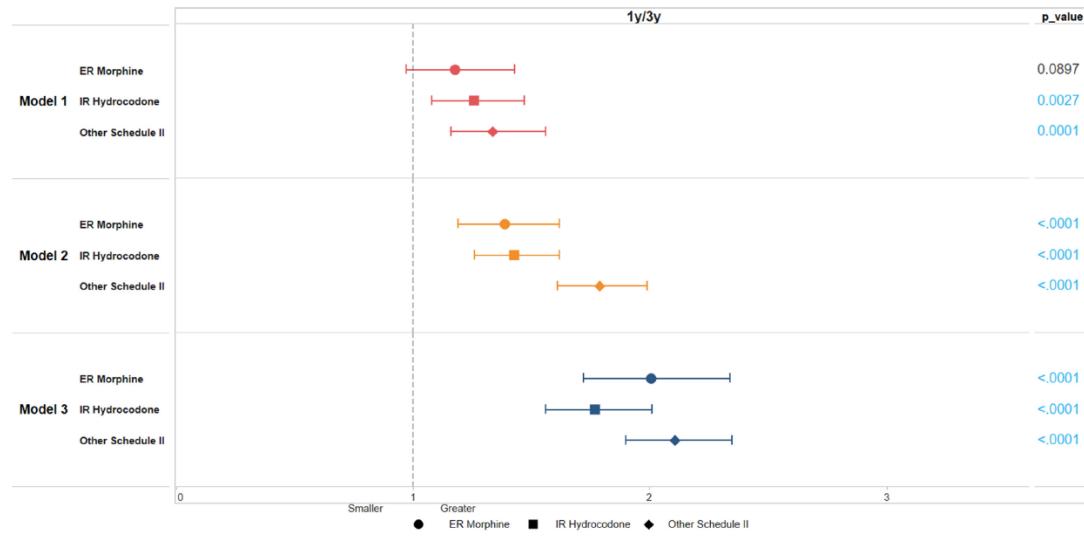
	Model 1 % Change (95% CI)	Model 2 % Change (95% CI)	Model 3 % Change (95% CI)
OxyContin	-16.7 (-26.1, -6.2)	-25.1 (-30.8, -18.9)	-36.2 (-41.0, -30.9)
ER Morphine	-1.8 (-15.3, 13.9)	+4.0 (-8.8, 18.5)	+28.0 (12.3, 46.0)
IR Hydrocodone	+4.9 (-4.4, 15.1)	+7.1 (-2.9, 18.1)	+13.2 (2.6, 24.8)
Other Schedule II	+11.8 (2.2, 22.2)	+33.9 (25.1, 43.4)	+34.9 (25.9, 44.5)

CI=confidence intervals; IR Hydrocodone=IR hydrocodone products; Sites: contributing ≥1 assessment/quarter; OxyContin Definition: Original and Reformulated; Unit of Analysis: Respondent 3-digit ZIP Code; Model 1: Rate of abuse/Assessments. Model 2: Rate of abuse/Dosage units dispensed. Model 3: Abuse count adjusting for dosage units dispensed (continuous). ER=extended release

Key: IR: Immediate Release; ER: Extended Release; Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 3 models abuse rate adjusted for tablets dispensed as a covariate

Figure 82: RORR (95% CI) in non-oral abuse after introduction of reformulated OxyContin and primary comparator opioids, -1y/3y

RORR=ratio of risk ratios; CI=confidence intervals; IR Hydrocodone=IR hydrocodone products; Sites: contributing ≥1 assessment/quarter; OxyContin Definition: Original and Reformulated; Unit of Analysis: Respondent 3-digit ZIP Code; Model 1: Rate of abuse/Assessments. Model 2: Rate of abuse/Dosage units dispensed. Model 3: Abuse count adjusting for dosage units dispensed (continuous). ER=extended release

Key: IR: Immediate Release; ER: Extended Release; Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 3 models abuse rate adjusted for tablets dispensed as a covariate

6.10 SENSITIVITY ANALYSES FOR TIME PERIOD (-1Y/3Y), OXYCONTIN ALONE (SENSITIVITY FOR MEANS ANALYSIS)

Analysis parameters:
- Sites: contributing $\geq$ 1 assessment/quarter
- Time period: -1y/3y
- OxyContin definition: Original and reformulated
- Unit of analysis: Respondent 3-digit ZIP code
- Model #1:
  - Offset: Total assessments
  - Covariates: NA
- Model #2:
  - Offset: Dosage units dispensed
  - Covariate: NA
- Model #3:
  - Offset: NA
  - Covariate: Dosage units dispensed (continuous)

Figure 83: Percent change (95% CI) in non-oral abuse after introduction of reformulated OxyContin, for OxyContin, -1y/3y

CI=confidence intervals; IR Hydrocodone=immediate release hydrocodone products; Sites: contributing ≥1 assessment/quarter; OxyContin Definition: Original and Reformulated; Unit of Analysis: Respondent 3-digit ZIP Code; Model 1: Rate of abuse/Assessments. Model 2: Rate of abuse/Dosage units dispensed. Model 3: Abuse count adjusting for dosage units dispensed (continuous).

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 8-1. Percent change (95% CI) in non-oral abuse after introduction of reformulated OxyContin using different modeling approaches -1y/3y. p. 336.)

Key: Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 3 models abuse rate adjusted for tablets dispensed as a covariate

Table 29: Percent change (95% CI) in non-oral abuse after introduction of reformulated OxyContin, for OxyContin, -1y/3y

	Model 1 % Change (95% CI)	Model 2 % Change (95% CI)	Model 3 % Change (95% CI)
OxyContin	-25.3 (-34.6, -14.6)	-25.1 (-30.8, -18.9)	-29.9 (-35.3, -24.0)

CI=confidence intervals; IR Hydrocodone=immediate release hydrocodone products; Sites: contributing ≥1 assessment/quarter; OxyContin Definition: Original and Reformulated; Unit of Analysis: Respondent 3-digit ZIP Code; Model 1: Rate of abuse/Assessments. Model 2: Rate of abuse/Dosage units dispensed. Model 3: Abuse count adjusting for dosage units dispensed (continuous).

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Table 8-4. Percent change (95% CI) in non-oral abuse after introduction of reformulated OxyContin using different modeling approaches -1y/3y. p. 336.)
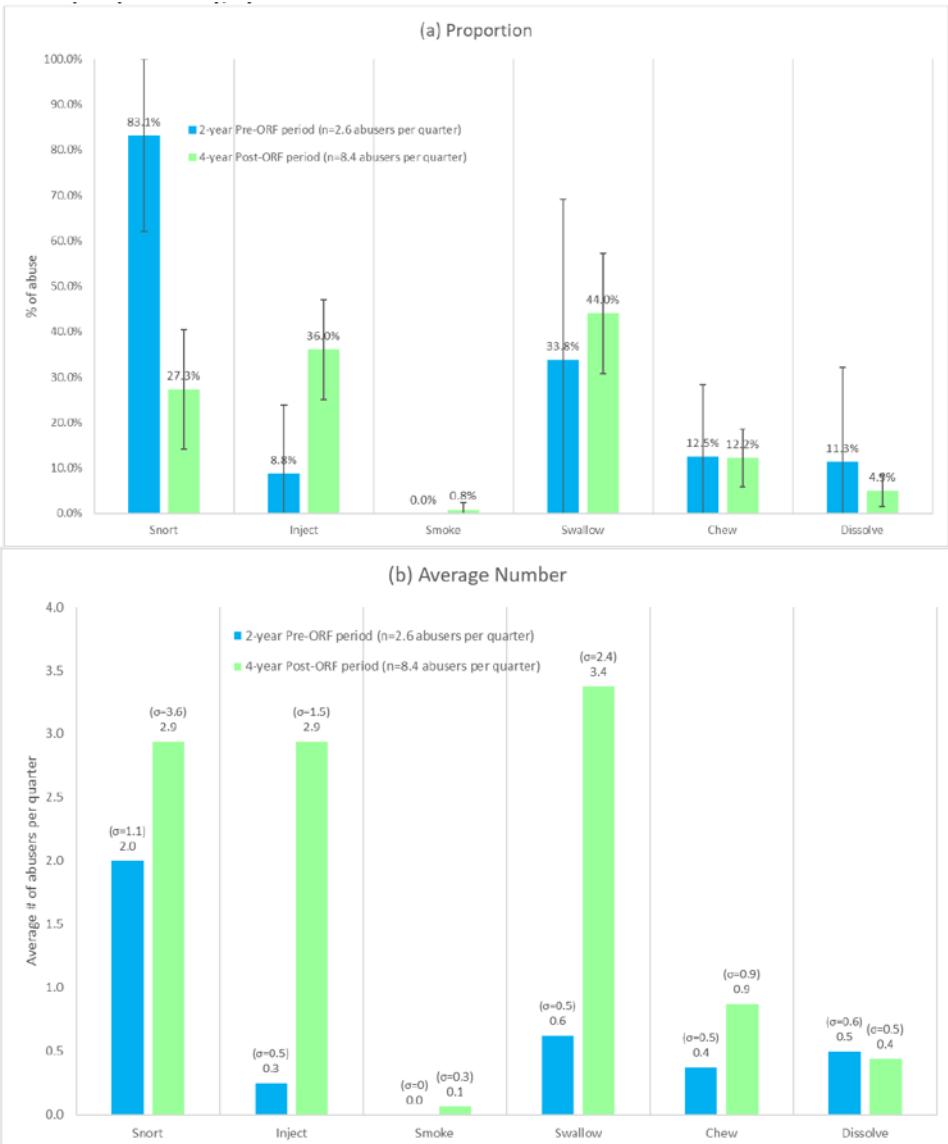
Key: Model 1 models abuse rate per ASI-MV assessments; Model 2 models abuse rate per tablets dispensed; Model 3 models abuse rate adjusted for tablets dispensed as a covariate

6.11 SENSITIVITY ANALYSES FOR CHANGES IN MEAN PROPORTION OF PAST 30-DAY ABUSE OF OXYCONTIN AND COMPARATOR OPIOIDS VIA SPECIFIC ROUTES AMONG THOSE ABUSING EACH DRUG: UNMODELED, DESCRIPTIVE PRE-POST MEANS ANALYSES

Analysis parameters:
- Sites: contributing ≥ 1 assessment/quarter
- OxyContin definition: Original or Reformulated

Figure 84: Proportion* (a) and average number (b) of individuals reporting abuse of <u>ER oxymorphone combination products</u> via specific routes per quarter -2y/4y

(a) Proportion

(b) Average Number

Error bars: 95% confidence intervals; σ: standard deviation; Sites: contributing ≥ 1 assessment / quarter; ORF=Reformulated OxyContin. Pre-ORF period=3Q2008-2Q2010, post-ORF period=1Q2011-4Q2014.
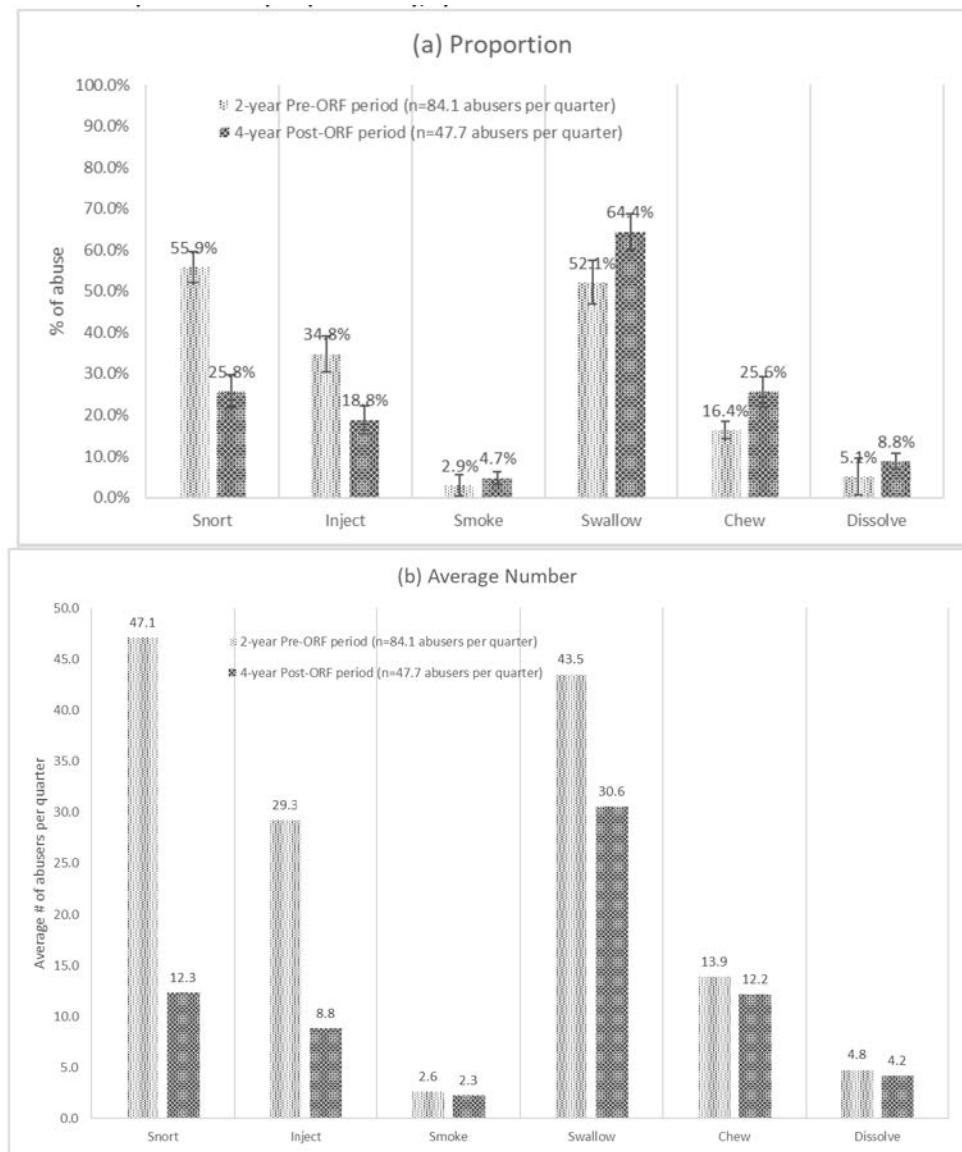
(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised figure 7-4: Proportion (a) and average number (b) of ER oxymorphone abusers via specific routes per quarter -2y/4y. P. 8)

Key: Sigma: Standard Deviation; ORF: Reformulation of OxyContin; *Respondents can report more than one route of abuse, so total percentage can equal >100%

Analysis parameters:
- Sites: contributing > 1 assessment/quarter
- OxyContin definition: Reformulated only

Figure 85: Proportion* (above) and average number (below) of individuals reporting abuse of OxyContin (reformulated only) via specific routes, >1 assessment per quarter, -2y/4y

(a) Proportion

(b) Average Number

* Using sites contributing ≥ 1 assessment per quarter; Error bars: 95% confidence intervals;
ORF=Reformulated OxyContin. Pre-ORF period=3Q2008-2Q2010, post-ORF period=1Q2011-4Q2014.
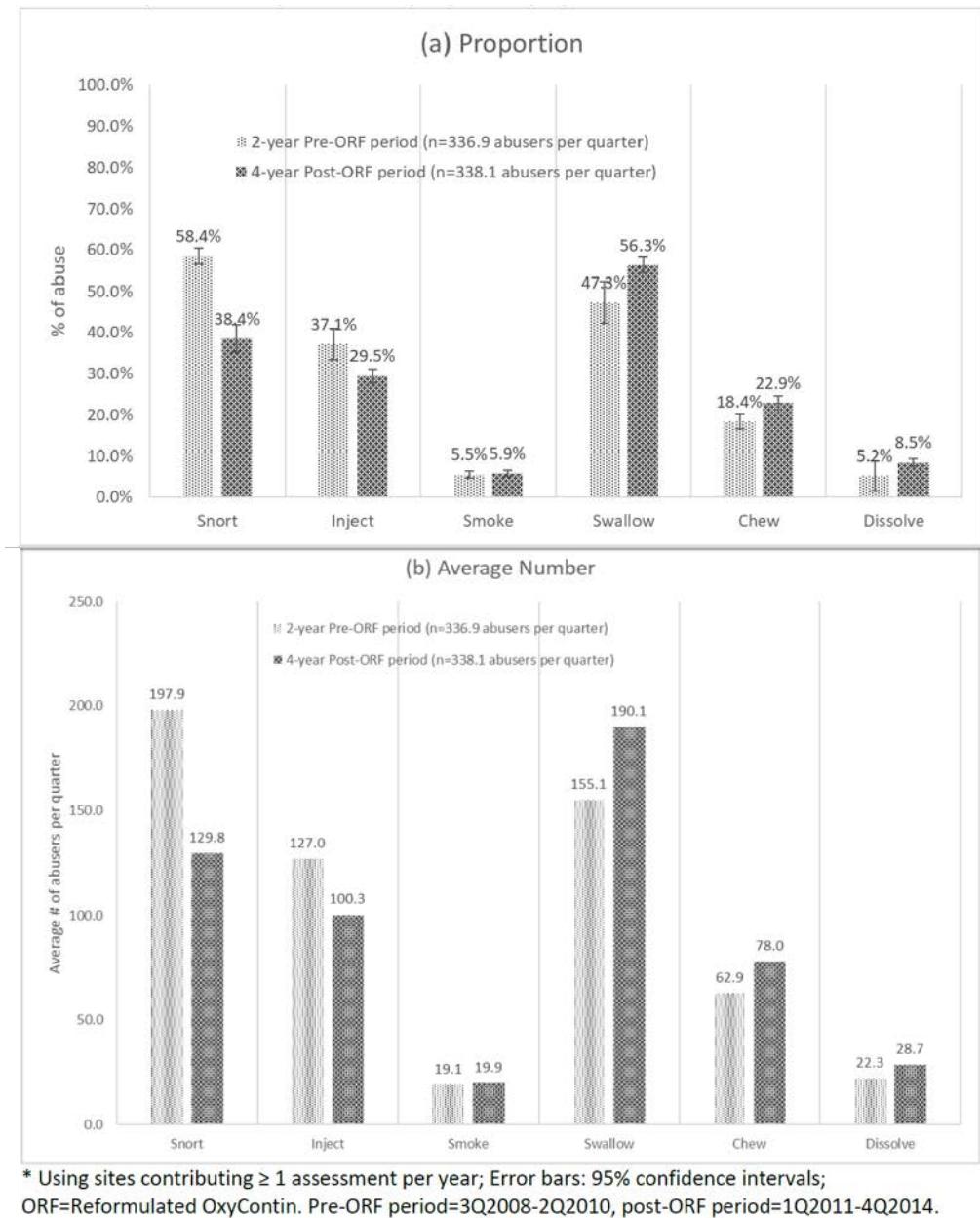
(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 5-1: Proportion (a) and average number (b) of OxyContin (reformulated only) abusers via specific routes per quarter -2y/4y. P. 8)

Key: Sigma: Standard Deviation; ORF: Reformulation of OxyContin; *Respondents can report more than one route of abuse, so total percentage can equal >100%

> Analysis parameters:
> - Sites: contributing > 1 assessment/year
> - OxyContin definition: Original and reformulated

Figure 86: Proportion* (above) and average number (below) of individuals reporting abuse of OxyContin (original and reformulated) via specific routes, >1 assessment per year, -2y/4y

(a) Proportion

- 2-year Pre-ORF period (n=336.9 abusers per quarter)
- 4-year Post-ORF period (n=338.1 abusers per quarter)

Snort: 58.4%, 38.4%
Inject: 37.1%, 29.5%
Smoke: 5.5%, 5.9%
Swallow: 47.3%, 56.3%
Chew: 18.4%, 22.9%
Dissolve: 5.2%, 8.5%

(b) Average Number

- 2-year Pre-ORF period (n=336.9 abusers per quarter)
- 4-year Post-ORF period (n=338.1 abusers per quarter)

Snort: 197.9, 129.8
Inject: 127.0, 100.3
Smoke: 19.1, 19.9
Swallow: 155.1, 190.1
Chew: 62.9, 78.0
Dissolve: 22.3, 28.7

* Using sites contributing ≥ 1 assessment per year; Error bars: 95% confidence intervals;
ORF=Reformulated OxyContin. Pre-ORF period=3Q2008-2Q2010, post-ORF period=1Q2011-4Q2014.
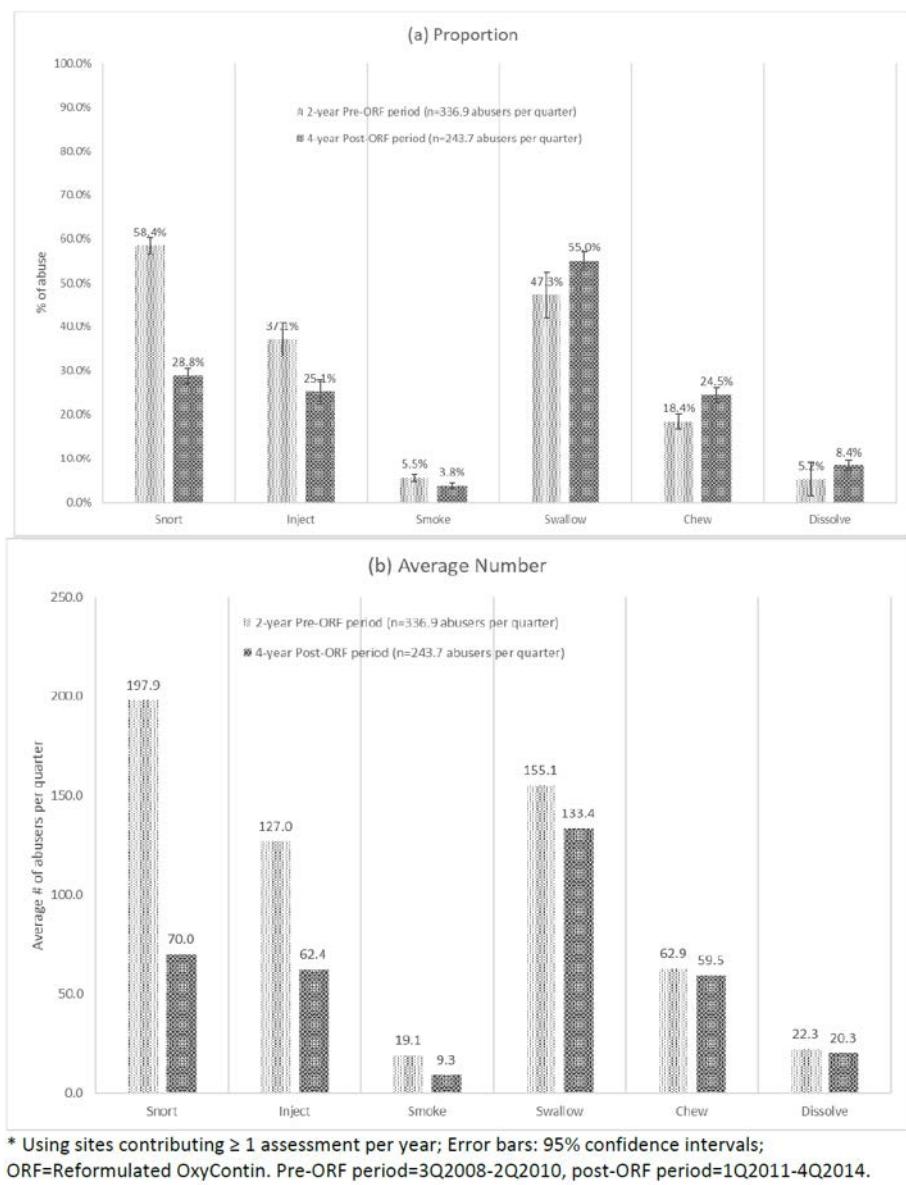
(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 5-2. Proportion (a) and average number (b) of OxyContin (original and reformulated) abusers via specific routes per year. P. 10.)

Key: Sigma: Standard Deviation; ORF: Reformulation of OxyContin; *Respondents can report more than one route of abuse, so total percentage can equal >100%

Analysis parameters:
- Sites: contributing ≥ 1 assessment/year
- OxyContin definition: Reformulated only

Figure 87: Proportion* (above) and average number (below) of individuals endorsing abuse of OxyContin (original and reformulated) via specific routes, ≥1 assessment per year, -2y/4y

* Using sites contributing ≥ 1 assessment per year; Error bars: 95% confidence intervals;
ORF=Reformulated OxyContin. Pre-ORF period=3Q2008-2Q2010, post-ORF period=1Q2011-4Q2014.
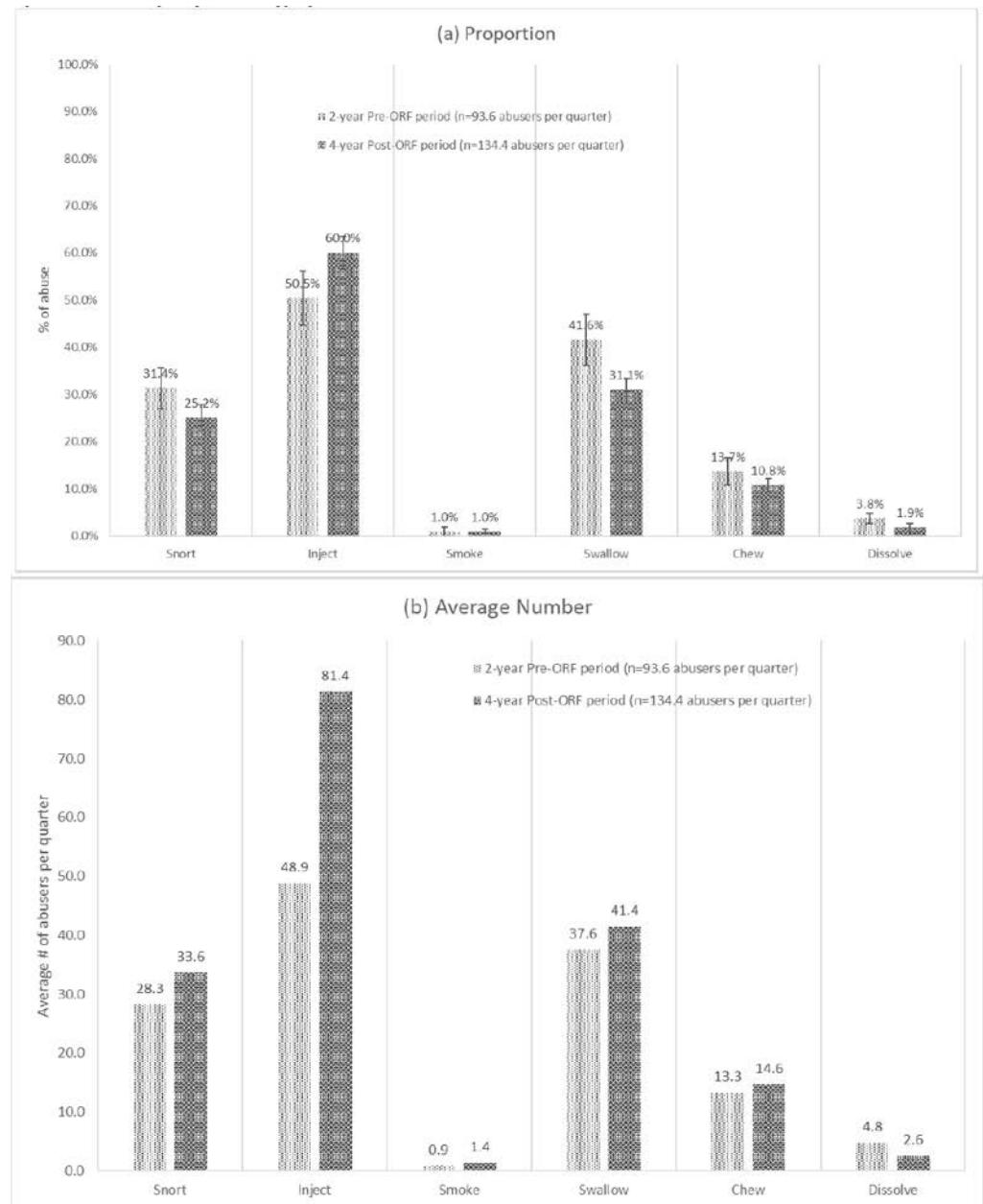
(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 5-3. Proportion (a) and average number (b) of OxyContin (reformulated only) abusers via specific routes per year. P. 11.)

Key: Sigma: Standard Deviation; ORF: Reformulation of OxyContin; *Respondents can report more than one route of abuse, so total percentage can equal >100%

Analysis parameters:
- Sites: contributing > 1 assessment/year
- Drug: ER morphine

Figure 88: Proportion[*] (above) and average number (below) of individuals endorsing abuse of ER morphine via specific routes, >1 assessment per year, -2y/4y

* Using sites contributing ≥ 1 assessment per year; Error bars: 95% confidence intervals;
ORF=Reformulated OxyContin. Pre-ORF period=3Q2008-2Q2010, post-ORF period=1Q2011-4Q2014.

(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 5-4. Proportion (a) and average number (b) of ER morphine abusers via specific routes per year -2y/4y. P.12.)*
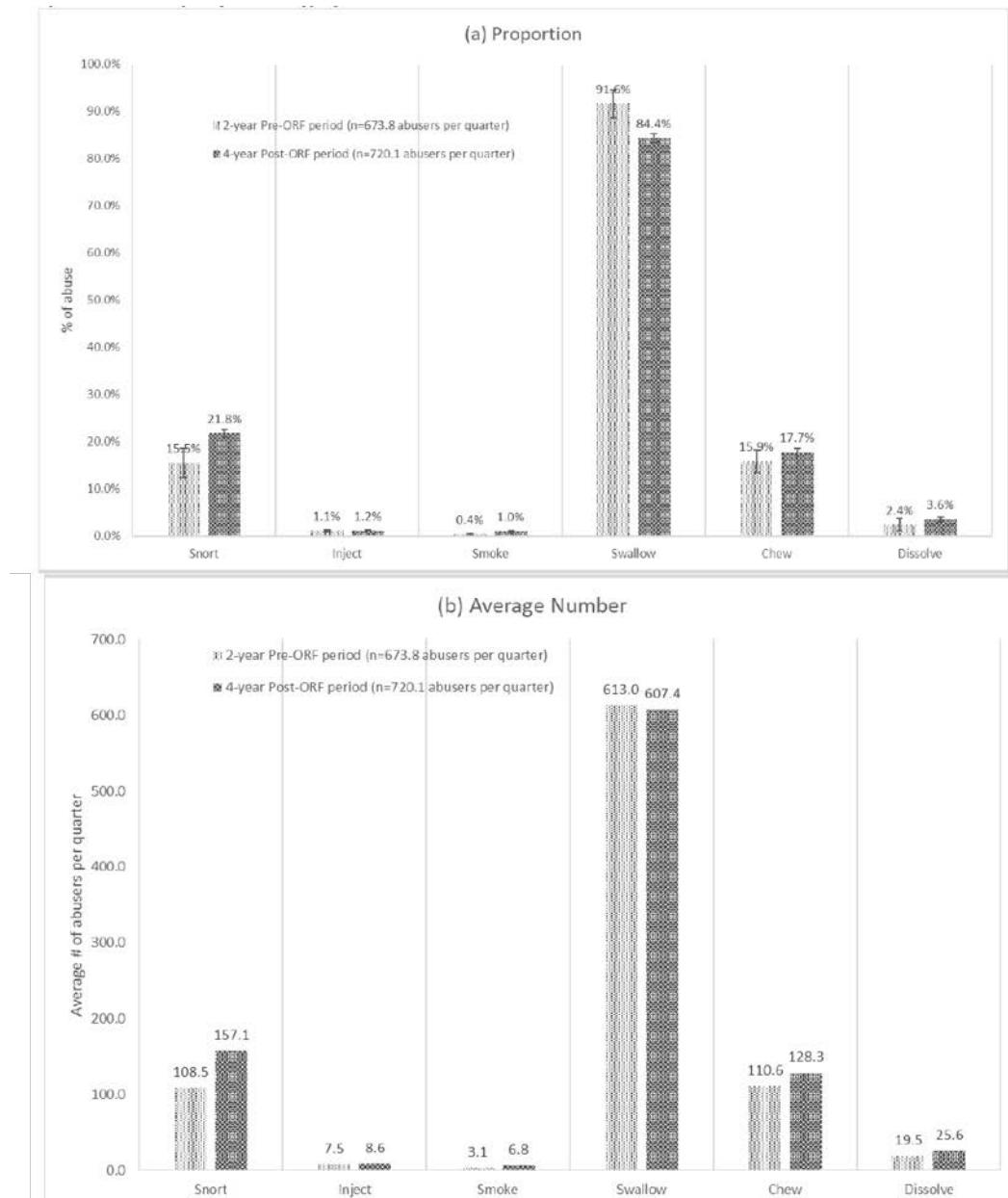
Key: ER: Extended Release; Sigma: Standard Deviation; ORF: Reformulation of OxyContin;
*Respondents can report more than one route of abuse, so total percentage can equal >100%

Analysis parameters:
- Sites: contributing $\geq$ 1 assessment/year
- Drug: IR hydrocodone combination products

Figure 89: Proportion* (above) and average number (below) of individuals endorsing abuse of IR hydrocodone combination products via specific routes, $\geq$1 assessment per year, -2y/4y

* Using sites contributing $\geq$ 1 assessment per year; Error bars: 95% confidence intervals; ORF=Reformulated OxyContin. Pre-ORF period=3Q2008-2Q2010, post-ORF period=1Q2011-4Q2014.

Key: IR: Immediate Release; Sigma: Standard Deviation; ORF: Reformulation of OxyContin;
*Respondents can report more than one route of abuse, so total percentage can equal >100%

Analysis parameters:
- Sites: contributing > 1 assessment/year.
- Drug: ER Oxymorphone

Figure 90: Proportion[*] (above) and average number (below) of individuals endorsing abuse of ER oxymorphone via specific routes, >1 assessment per year, -2y/4y

(a) Proportion

2-year Pre-ORF period (n=24.1 abusers per quarter)
4-year Post-ORF period (n=107.1 abusers per quarter)

Route	Pre-ORF	Post-ORF
Snort	76.4%	55.6%
Inject	12.0%	35.6%
Smoke	0.0%	1.1%
Swallow	25.1%	22.7%
Chew	12.6%	8.0%
Dissolve	1.2%	2.6%

(b) Average Number

2-year Pre-ORF period (n=24.1 abusers per quarter)
4-year Post-ORF period (n=107.1 abusers per quarter)

Route	Pre-ORF	Post-ORF
Snort	18.8	60.8
Inject	3.0	39.1
Smoke	0.0	1.2
Swallow	5.6	22.3
Chew	3.5	7.7
Dissolve	0.5	2.7

* Using sites contributing ≥ 1 assessment per year; Error bars: 95% confidence intervals;
ORF=Reformulated OxyContin. Pre-ORF period=3Q2008-2Q2010, post-ORF period=1Q2011-4Q2014.

(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Appendix Figure 5-6. Proportion (a) and average number (b) of ER oxymorphone abusers via specific routes per year* -2y/4y. P. 14.)
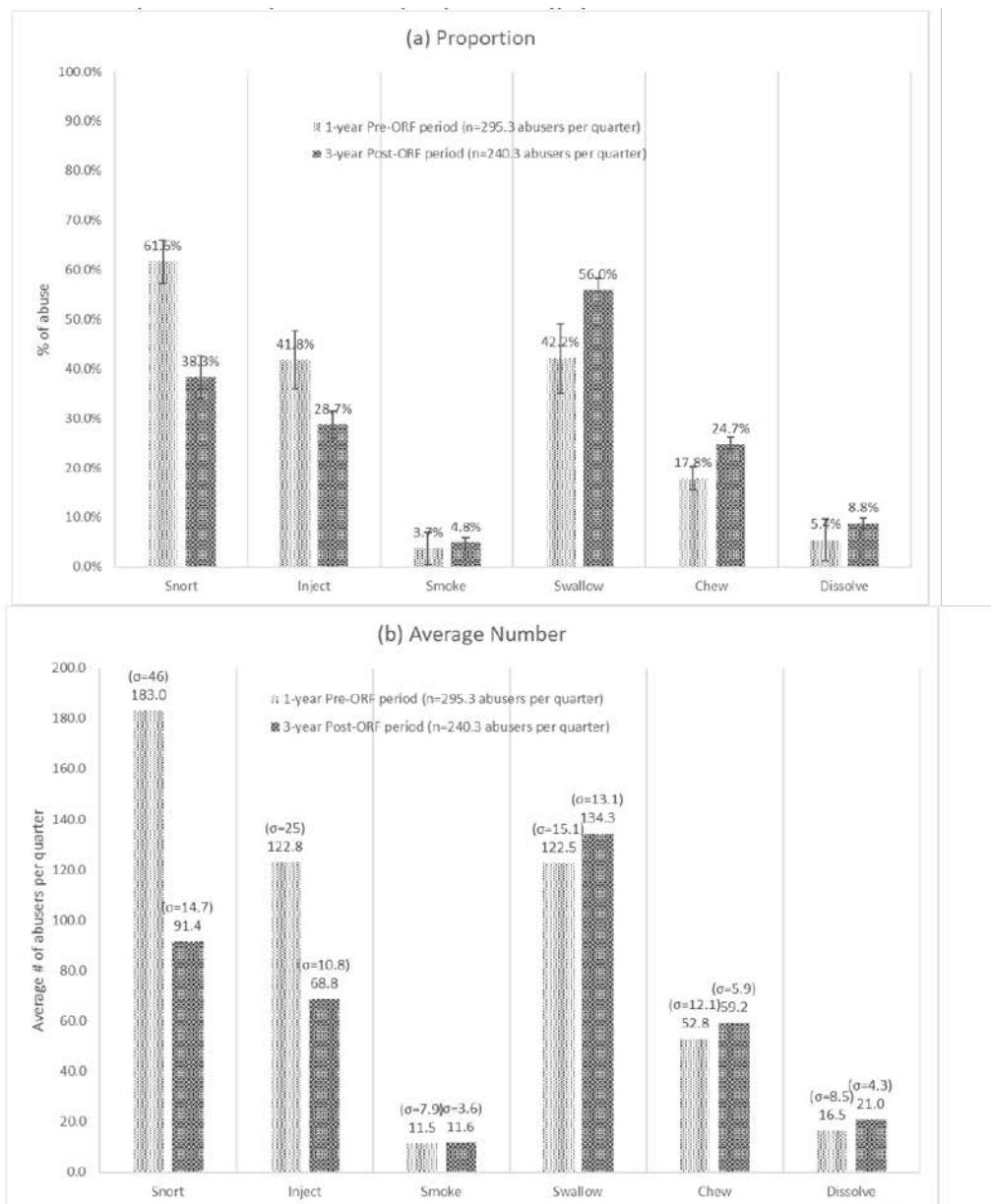
Key: ER: Extended Release; Sigma: Standard Deviation; ORF: Reformulation of OxyContin;
*Respondents can report more than one route of abuse, so total percentage can equal >100%

Analysis parameters:
- Sites: contributing ≥ 1 assessment/quarter
- OxyContin definition: any OxyContin (original or reformulated)

Figure 91: Proportion* (above) and average number (below) of individuals reporting abuse of any OxyContin (original or reformulated) via specific routes, ≥1 assessment per quarter, -1y/3y

* Using sites contributing ≥ 1 assessment per quarter; Error bars: 95% confidence intervals; σ: standard deviation; ORF=Reformulated OxyContin. Pre-ORF period=3Q2009-2Q2010, post-ORF period=1Q2011-4Q2013.
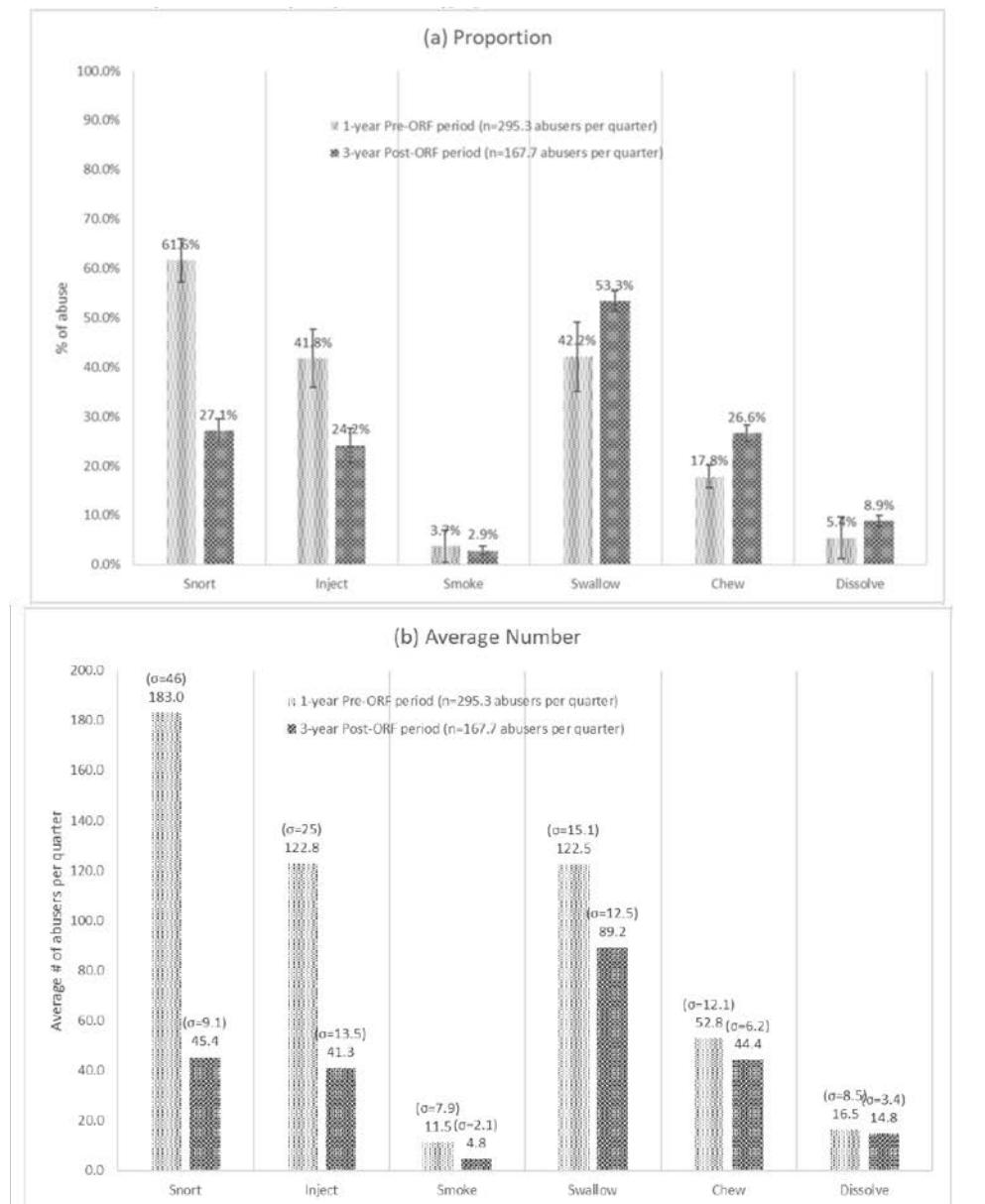
(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 5-7. Proportion (a) and average number (b) of OxyContin (original and reformulated) abusers via specific routes per quarter* -1y/3y. P. 15.)

Key: Sigma: Standard Deviation; ORF: Reformulation of OxyContin; *Respondents can report more than one route of abuse, so total percentage can equal >100%

Analysis parameters:
- Sites: contributing $\geq$ 1 assessment/quarter
- OxyContin definition: Reformulated only

Figure 92: Proportion (above) and average number (below) of individuals reporting abuse of OxyContin (reformulated only) via specific routes, ≥1 assessment per quarter, -1y/3y

* Using sites contributing ≥ 1 assessment per quarter; Error bars: 95% confidence intervals; σ: standard deviation; ORF=Reformulated OxyContin. Pre-ORF period=3Q2009-2Q2010, post-ORF period=1Q2011-4Q2013.
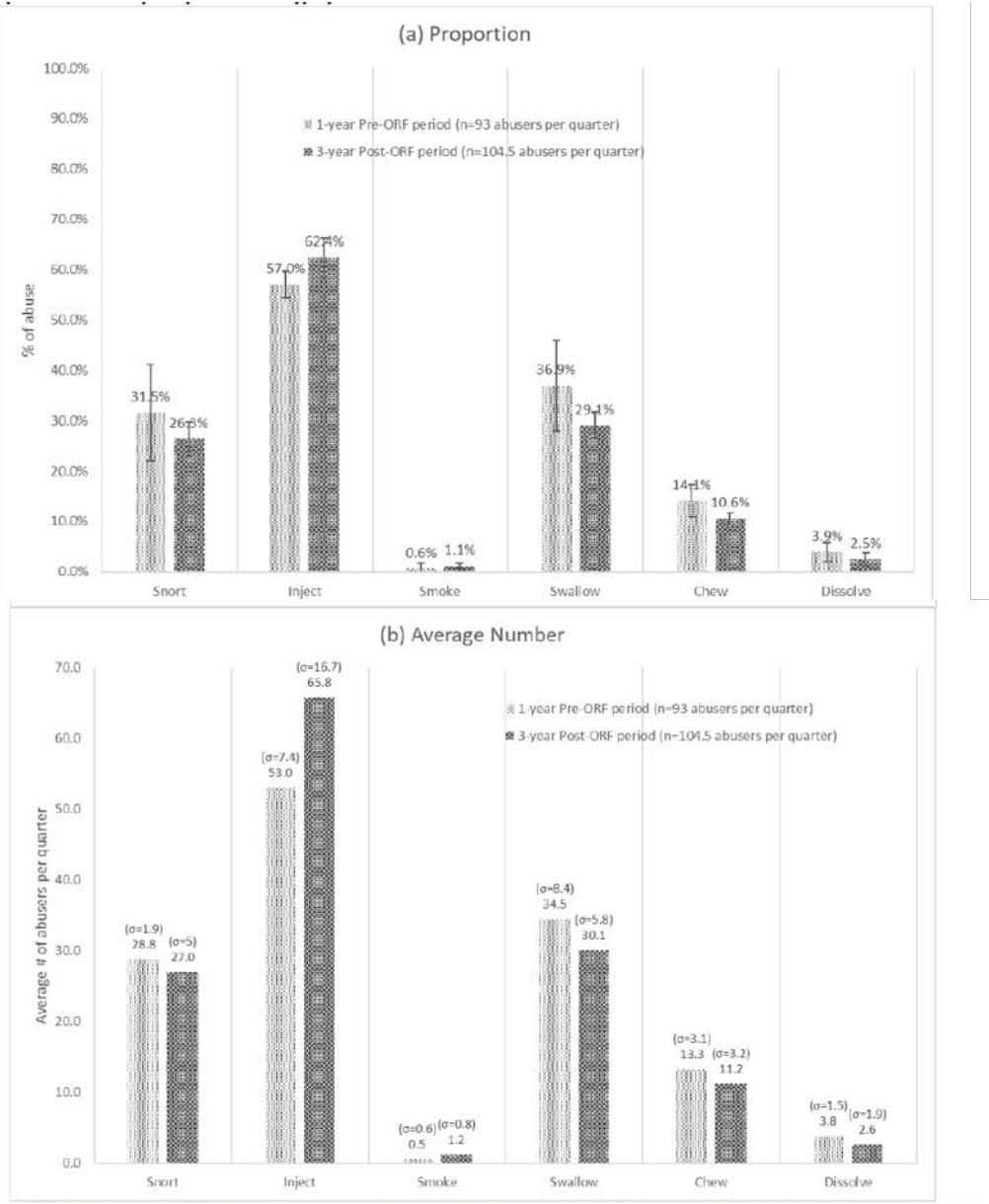
(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 5-8. Proportion (a) and average number (b) of all OxyContin (reformulated only) abusers via specific routes per quarter -1y/3y. P. 16.)*

Key: Sigma: Standard Deviation; ORF: Reformulation of OxyContin; *Respondents can report more than one route of abuse, so total percentage can equal >100%

Analysis parameters:
- Sites: contributing > 1 assessment/quarter
- Drug: ER morphine

Figure 93: Proportion[*] (above) and average number (below) of individuals endorsing abuse of ER morphine via specific routes, >1 assessment per quarter, -1y/3y

(a) Proportion

(b) Average Number

* Using sites contributing ≥ 1 assessment per quarter; Error bars: 95% confidence intervals; σ: standard deviation; ORF=Reformulated OxyContin. Pre-ORF period=3Q2009-2Q2010, post-ORF period=1Q2011-4Q2013.
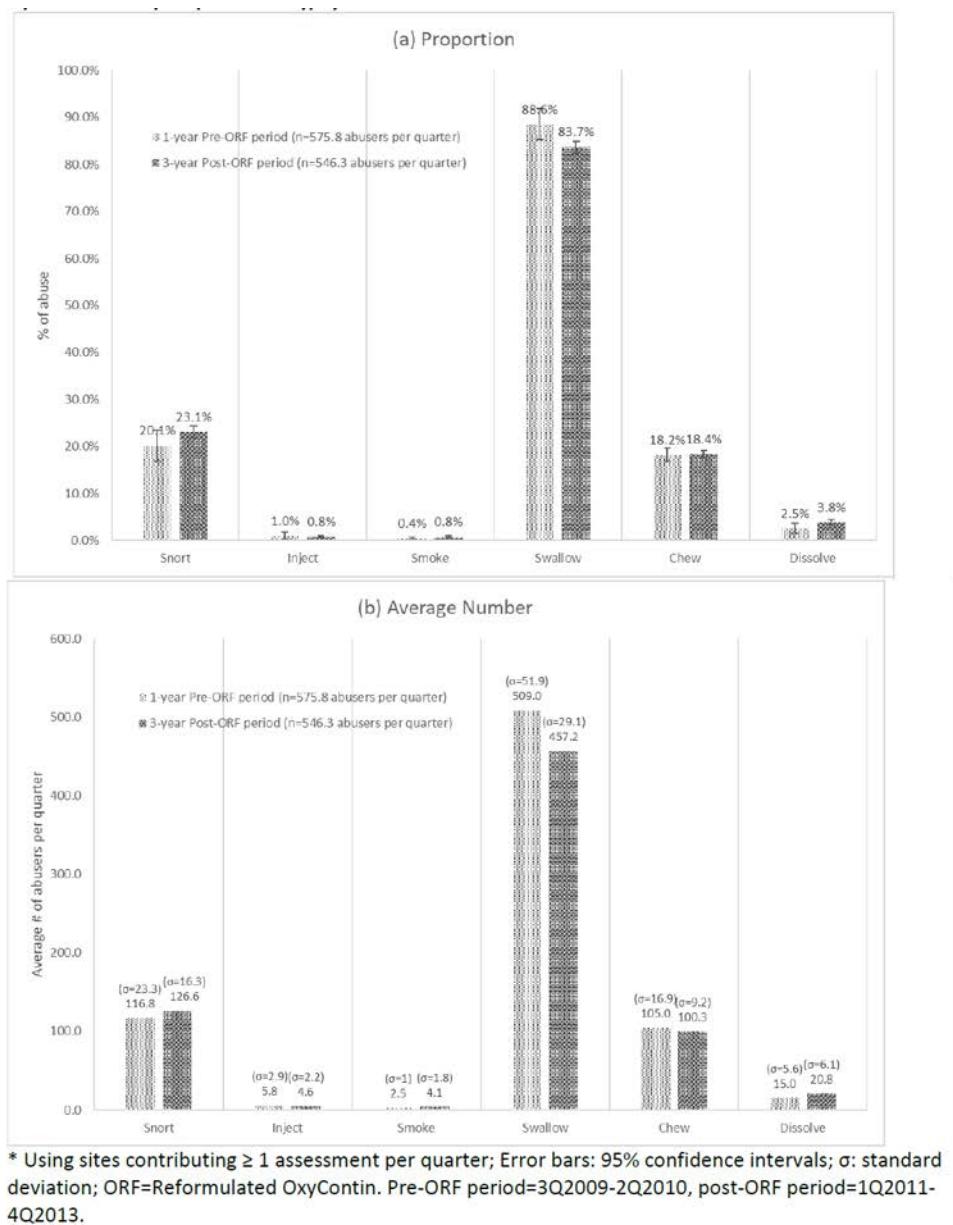
(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 5-9. Proportion (a) and average number (b) of ER morphine abusers via specific routes per quarter* -1y/3y. P. 17.)

Key: ER: Extended Release; Sigma: Standard Deviation; ORF: Reformulation of OxyContin;
*Respondents can report more than one route of abuse, so total percentage can equal >100%

Analysis parameters:
- Sites: contributing ≥ 1 assessment/quarter
- Drug: IR hydrocodone combination products

Figure 94: Proportion* (above) and average number (below) of individuals endorsing abuse of IR hydrocodone combination products via specific routes, >1 assessment per quarter, -1y/3y

* Using sites contributing ≥ 1 assessment per quarter; Error bars: 95% confidence intervals; σ: standard deviation; ORF=Reformulated OxyContin. Pre-ORF period=3Q2009-2Q2010, post-ORF period=1Q2011-4Q2013.

(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 5-10. Proportion (a) and average number (b) of IR hydrocodone combination products abusers via specific routes per quarter* -1y/3y. P. 18.)
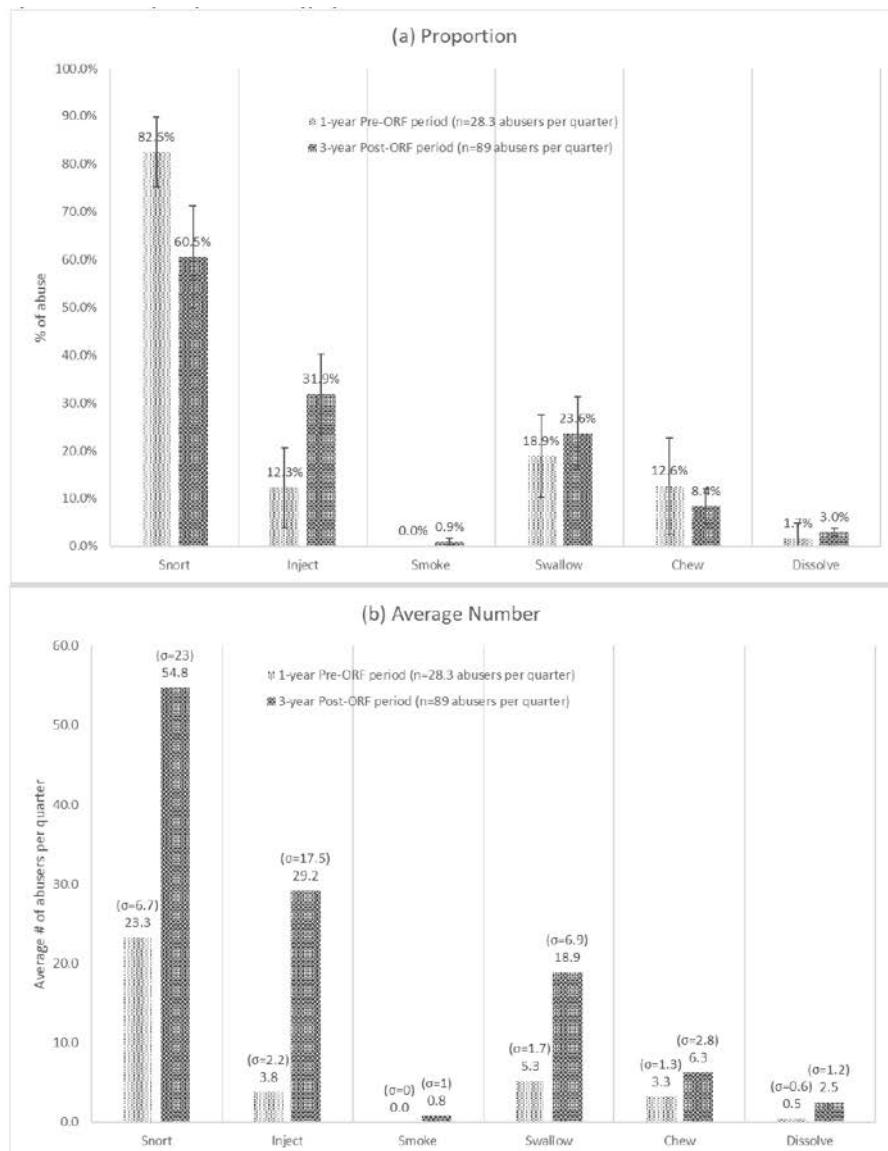
Key: IR: Immediate Release; Sigma: Standard Deviation; ORF: Reformulation of OxyContin;
*Respondents can report more than one route of abuse, so total percentage can equal >100%

Analysis parameters:
- Sites: contributing ≥ 1 assessment/quarter
- Drug: ER oxymorphone

Figure 95: Proportion[*] (above) and average number (below) or individuals endorsing abuse of ER oxymorphone via specific routes, >1 assessment per quarter, -1y/3y

* Using sites contributing ≥ 1 assessment per quarter; Error bars: 95% confidence intervals; σ: standard deviation; ORF=Reformulated OxyContin. Pre-ORF period=3Q2009-2Q2010, post-ORF period=1Q2011-4Q2013.

(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 5-11. Proportion (a) and average number (b) of ER morphine abusers via specific routes per quarter -1y/3y. P. 19.)*
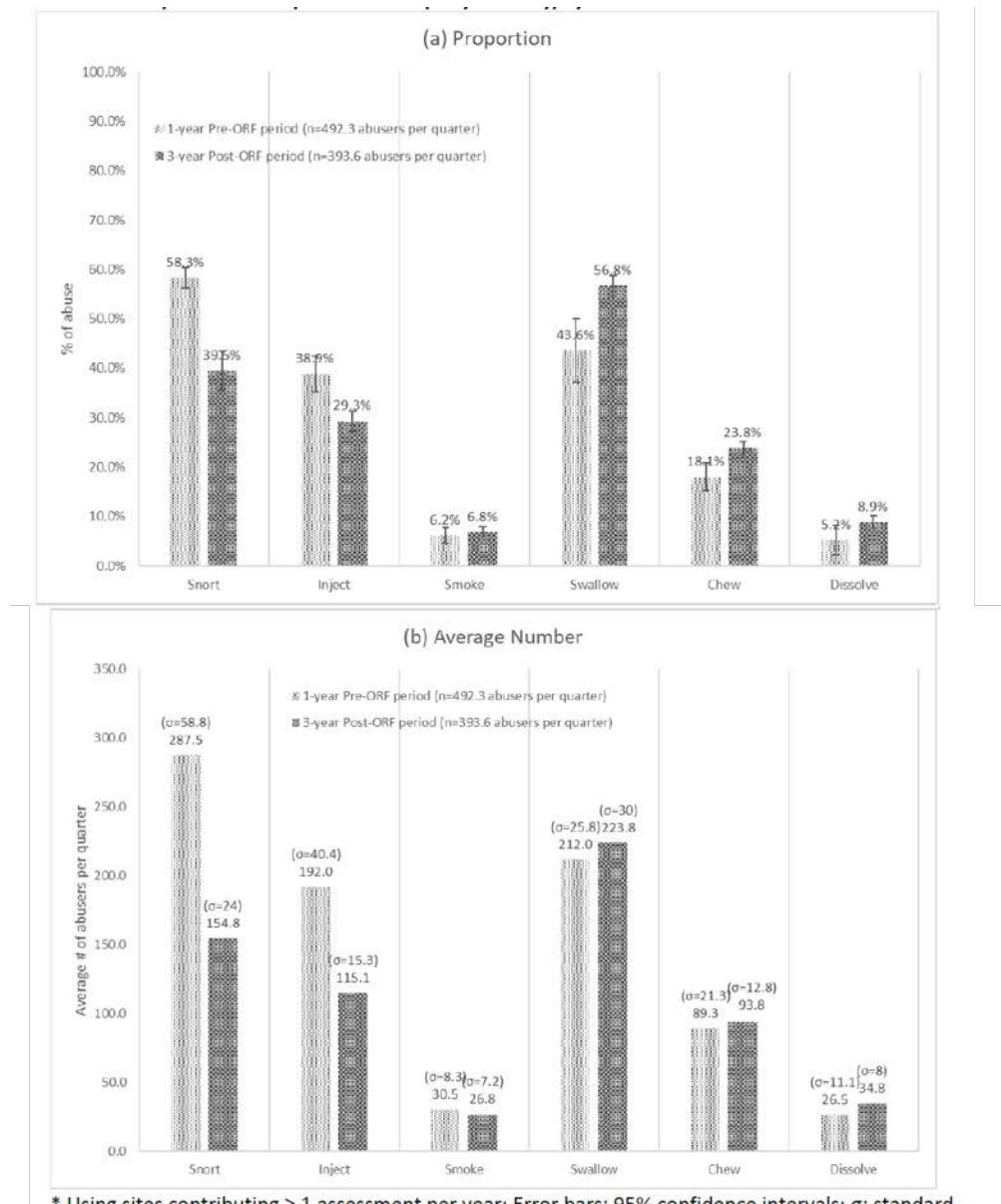
Key: ER: Extended Release; Sigma: Standard Deviation; ORF: Reformulation of OxyContin;
*Respondents can report more than one route of abuse, so total percentage can equal >100%

Analysis parameters:
- Sites: contributing $\geq$ 1 assessment/year
- OxyContin definition: original and reformulated

Figure 96: Proportion* (above) and average number (below) of individuals endorsing abuse of OxyContin (original and reformulated) via specific routes, $\geq$1 assessment per year, -1y/3y

* Using sites contributing $\geq$ 1 assessment per year; Error bars: 95% confidence intervals; σ: standard deviation; ORF=Reformulated OxyContin. Pre-ORF period=3Q2009-2Q2010, post-ORF period=1Q2011-4Q2013.
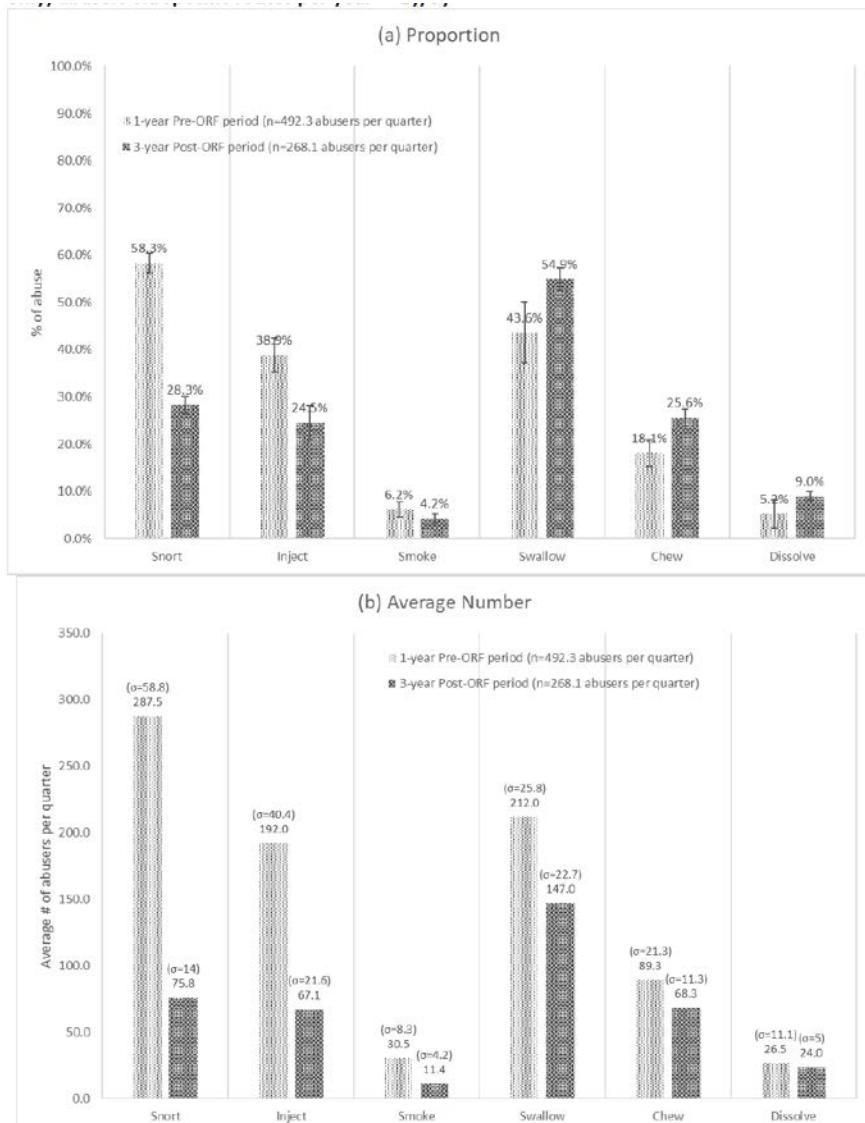
(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 5-12. Proportion (a) and average number (b) of OxyContin (original and reformulated) abusers via specific routes per year* -1y/3y. P. 20.)

Key: Sigma: Standard Deviation; ORF: Reformulation of OxyContin; *Respondents can report more than one route of abuse, so total percentage can equal >100%

Analysis parameters:
- Sites: contributing ≥ 1 assessment/year
- OxyContin definition: Reformulated only

Figure 97: Proportion* (above) and average number (below) of individuals endorsing abuse of OxyContin (reformulated only) via specific routes, ≥ 1 assessment per year, -1y/3y

* Using sites contributing ≥ 1 assessment per year; Error bars: 95% confidence intervals; σ: standard deviation; ORF=Reformulated OxyContin. Pre-ORF period=3Q2009-2Q2010, post-ORF period=1Q2011-4Q2013.

Key: Sigma: Standard Deviation; ORF: Reformulation of OxyContin; *Respondents can report more than one route of abuse, so total percentage can equal >100%

Analysis parameters:
- Sites: contributing $\geq$ 1 assessment/year
- Drug: ER morphine

Figure 98: Proportion* (above) and average number (below) of individuals endorsing abuse of ER morphine via specific routes, >1 assessment per year, -1y/3y

* Using sites contributing ≥ 1 assessment per year; Error bars: 95% confidence intervals; σ: standard deviation; ORF=Reformulated OxyContin. Pre-ORF period=3Q2009-2Q2010, post-ORF period=1Q2011-4Q2013.

Key: ER: Extended Release; Sigma: Standard Deviation; ORF: Reformulation of OxyContin;
*Respondents can report more than one route of abuse, so total percentage can equal >100%

Analysis parameters:
- Sites: contributing > 1 assessment/year
- Drug: IR hydrocodone combination products

Figure 99: Proportion* (above) and average number (below) of individuals endorsing abuse of IR hydrocodone combination products via specific routes, >1 assessment per year, -1y/3y

* Using sites contributing ≥ 1 assessment per year; Error bars: 95% confidence intervals; σ: standard deviation; ORF=Reformulated OxyContin. Pre-ORF period=3Q2009-2Q2010, post-ORF period=1Q2011-4Q2013.

(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 5-15. Proportion (a) and average number (b) of IR hydrocodone combination products abusers via specific routes per year* -1y/3y. P. 23.)
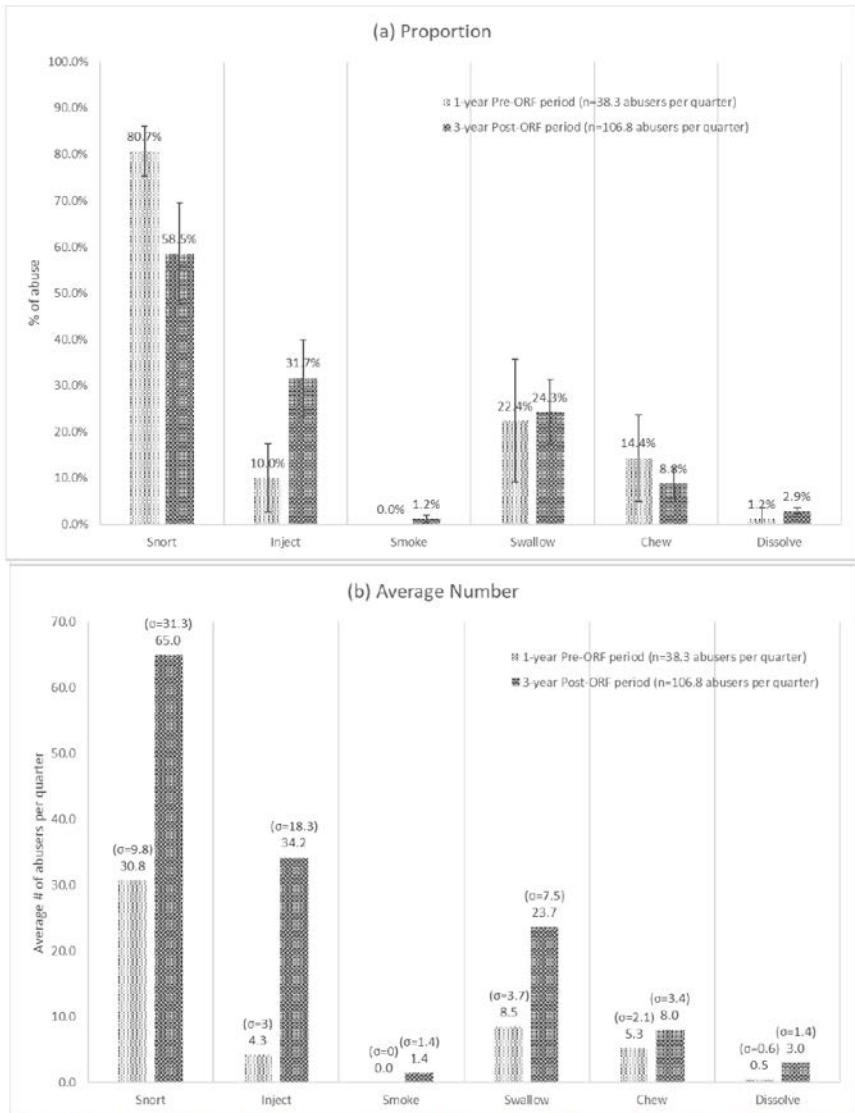
Key: IR: Immediate Release; Sigma: Standard Deviation; ORF: Reformulation of OxyContin;
*Respondents can report more than one route of abuse, so total percentage can equal >100%

Analysis parameters:
- Sites: contributing ≥ 1 assessment/year
- Drug: ER oxymorphone

Figure 100: Proportion* (above) and average number (below) of individuals endorsing abuse of ER oxymorphone via specific routes, ≥ 1 assessment per year, -1y/3y

* Using sites contributing ≥ 1 assessment per year; Error bars: 95% confidence intervals; σ: standard deviation; ORF=Reformulated OxyContin. Pre-ORF period=3Q2009-2Q2010, post-ORF period=1Q2011-4Q2013.

Key: ER: Extended Release; Sigma: Standard Deviation; ORF: Reformulation of OxyContin;
*Respondents can report more than one route of abuse, so total percentage can equal >100%

6.12 RANGE OF ESTIMATES FOR PRE- AND POST-PERIOD PAST MONTH ABUSE OF OXYCONTIN AND PRIMARY COMPARATORS BY SPECIFIC ROUTES OF ABUSE (MEANS ANALYSIS)

Table 30: Range of estimates for percent change and RORR for abuse via snorting route in OxyContin and comparator opioids

	Range: Pre-post relative change (95% CI)		Range: RORR (95% CI)	
	Most "conservative"[†]	Least "Conservative"[‡]	Most "Conservative"[ᵛ]	Least "Conservative"[ˣ]
OxyContin	-40.3 (-48.3, -31.0)[1]	-62.5 (-69.2, -54.4)[2]	Ref	Ref
ER morphine	-1.3 (-35.1, 50.3)[3]	-29.3 (-46.7, -6.3)[4]	1.22 (0.89, 1.67)[9]	2.64 (1.66, 4.19)[10]
IR hydrocodone	16.3 (-12.0, 53.9)[5]	-12.3 (-25.2, 2.8)[6]	1.47 (1.18, 1.82)[11]	3.11 (2.21, 4.37)[12]
Other schedule II	29.8 (-5.8, 78.9)[7]	10.4 (-1.8, 24.0)[8]	1.87 (1.55, 2.25)[13]	3.17 (2.44, 4.12)[14]

(Source: FDA generated table from information request response)

1) Model 2a, 2) Model 3a, 3) Model 3a, 4) Model 2, 5) Model 3a, 6) Model 2a, 7) Model 1, 8) Model 2, 9) Model 2, 10) Model 3a, 11) Model 2a, 12) Model 3a, 13) Model 2a, 14) Model 3

Key: CI: Confidence Interval; ER: Extended Release; IR: Immediate Release; [†]most "conservative": smallest pre-post reduction (or largest increase) in non-oral abuse; [‡]least "conservative": largest pre-post reduction (or smallest increase) in non-oral abuse; [ᵛ]most "conservative": smallest pre-post reduction (or largest increase) in non-oral OxyContin abuse relative to comparator; [ˣ]least "conservative": largest pre-post reduction (or smallest increase) in non-oral OxyContin abuse relative to comparator

Table 31: Range of estimates for percent change and RORR for abuse via injection route in OxyContin and comparator opioids

	Range: Pre-post relative change (95% CI)		Range: RORR (95% CI)	
	Most "conservative"[†]	Least "Conservative"[‡]	Most "Conservative"[ᵛ]	Least "Conservative"[ˣ]
OxyContin	-33.3 (-53.7, -4.0)[1]	-54.6 (-64.0, -42.8)[2]	Ref	Ref
ER morphine	3.8 (-23.8, 41.5)[3]	-29.0 (-42.7, -12.0)[4]	1.11 (0.84, 1.46)[9]	2.29 (1.55, 3.37)[10]
IR hydrocodone	-38.5 (-69.1, 22.2)[5]	-65.3 (-80.8, -37.2)[6]	0.53 (0.28, 0.98)[11]	0.93 (0.30, 2.86)[12]
Other schedule II	22.2 (-12.6, 44.8)[7]	3.4 (-12.9, 22.9)[8]	1.58 (1.23, 2.03)[13]	2.39 (1.70, 3.36)[14]

(Source: FDA generated table from information request response)

1) Model 1, 2) Model 3a, 3) Model 3a, 4) Model 2, 5) Model 1, 6) Model 2a, 7) Model 1, 8) Model 2, 9) Model 2, 10) Model 3a, 11) Model 2a, 12) Model 3a, 13) Model 2a, 14) Model 3

Key: CI: Confidence Interval; ER: Extended Release; IR: Immediate Release; †most "conservative": smallest pre-post reduction (or largest increase) in non-oral abuse; ‡least "conservative": largest pre-post reduction (or smallest increase) in non-oral abuse; ᵞmost "conservative": smallest pre-post reduction (or largest increase) in non-oral OxyContin abuse relative to comparator; ˣleast "conservative": largest pre-post reduction (or smallest increase) in non-oral OxyContin abuse relative to comparator

6.13 SENSITIVITY ANALYSIS FOR CHANGES IN PREVALENCE OF PAST 30-DAY ABUSE OF OXYCONTIN STRATIFIED BY TREATMENT MODALITY, SEVERITY INDEX, AND GEOGRAPHIC REGION, FOR THE MORE RESTRICTED SET OF SITES ≥1 ASSESSMENT/QUARTER

Analysis parameters:
- Sites: contributing ≥1 assessment/quarter
- OxyContin definition: any Oxycontin (original or reformulated)
- Unit of analysis: 3-digit ZIP code
- Time period -2y/4y
- Model #1:
  - Offset: Total Assessments
  - Covariates: None

Table 32: Pre-period rate, post-period rate, and percent change in mean abuse rate for any OxyContin per 100 assessments, stratified by treatment modality and route, -2y/4y

	Overall* (any route)			Oral*			Non-oral*		
	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)
Residential/ Inpatient	7.989 (7.228, 8.831)	7.881 (7.310, 8.496)	-1.4 (-13.0, 11.8)	4.526 (3.963, 5.171)	6.058 (5.560, 6.601)	33.8 (14.2, 56.8)	5.569 (4.940, 6.279)	3.610 (3.230, 4.034)	-35.2 (-45.0, -23.7)
Outpatient/ non-methadone	2.729 (2.381, 3.129)	2.337 (2.081, 2.624)	-14.4 (-28.4, 2.4)	1.550 (1.293, 1.858)	1.814 (1.590, 2.069)	17.0 (-6.5, 46.4)	1.908 (1.620, 2.246)	1.087 (0.917, 1.288)	-43.0 (-55.0, -27.9)
Methadone	7.025 (5.019, 9.831)	9.929 (8.017, 12.297)	41.3 (-5.1, 110.5)	4.545 (2.993, 6.903)	7.920 (6.233, 10.062)	74.2 (7.6, 182.0)	3.719 (2.343, 5.903)	4.374 (3.169, 6.036)	17.6 (-33.0, 106.5)
Corrections	1.058 (0.854, 1.310)	0.554 (0.452, 0.680)	-47.6 (-61.0, -29.6)	0.768 (0.598, 0.987)	0.470 (0.376, 0.586)	-38.8 (-56.3, -14.5)	0.567 (0.423, 0.759)	0.211 (0.151, 0.294)	-62.8 (-76.1, -42.1)
Other	1.360 (0.790, 2.342)	1.719 (1.326, 2.228)	26.4 (-30.8, 130.9)	0.628 (0.282, 1.397)	1.387 (1.039, 1.852)	121.0 (-5.6, 417.5)	1.046 (0.563, 1.944)	0.814 (0.558, 1.187)	-22.2 (-62.3, 60.8)

*Note: Repeated statement was removed from the model as there were the following errors when the 'repeated' statement was included.
Error: Error in computing the variance function.
Error: Error in parameter estimate covariance computation.

(Source: FDA Postmarketing Requirement Study 3051-1, Purdue Response to FDA Information and Analyses Request on May 30, 2019 Phase 1 Part 2. Title: Table 1: Stratified by treatment modality based on Original + Reformulated OxyContin: sites with >1 assessment/year during 2y/4y time period. P. 25.)

Key: CI: Confidence Interval

Table 33: Pre-period rate, post-period rate, and percent change in mean abuse rate for any OxyContin per 100 assessments, stratified by ASI-MV severity index, -2y/4y

	Overall (any route)			Oral*			Non-oral		
	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)
0-3: No real problem-slight problem	0.353 (0.227, 0.551)	0.363 (0.171, 0.770)	2.8 (-43.3, 86.3)	0.292 (0.211, 0.405)	0.306 (0.244, 0.384)	4.8 (-29.5, 56.0)	0.075 (0.036, 0.155)	0.063 (0.032, 0.121)	-16.0 (-66.6, 110.9)
4-5: Moderate problem	2.235 (1.708, 2.925)	2.062 (1.297, 3.279)	-7.7 (-41.3, 45.0)	1.376 (0.997, 1.899)	1.835 (1.489, 2.261)	33.3 (-9.2, 95.8)	1.349 (0.968, 1.879)	0.751 (0.494, 1.142)	-44.3 (-67.3, -5.2)
6-9: Considerable problem-extreme problem	8.934 (6.641, 12.017)	8.327 (6.877, 10.083)	-6.8 (-28.4, 21.3)	5.131 (4.601, 5.724)	6.221 (5.784, 6.691)	21.2 (6.3, 38.2)	6.354 (3.680, 10.973)	4.363 (3.042, 6.258)	-31.3 (-47.4, -10.4)

*Note Repeated statement was removed from the model as there were following errors when 'repeated' statement was included.
Error: Error in computing the variance function.
Error: Error in parameter estimate covariance computation.

(Source: FDA Postmarketing Requirement Study 3051-1, Purdue Response to FDA Information and Analyses Request on May 30, 2019 Phase 1 Part 2. Title: Table 5: Stratified by ASI-MV® score based on Original + Reformulated OxyContin: sites with >1 assessment/year during 2y/4y time period. P. 29.)

Key: CI: Confidence Interval

Table 34: Pre-period rate, post-period rate, and percent change in mean abuse rate for any OxyContin per 100 assessments, stratified by geographic region, -2y/4y

	Overall** (any route)			Oral**			Non-oral**		
	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)	Pre-period (95% CI)	Post-period (95% CI)	% change (95% CI)
Northeast	NA*	NA*	NA*	NA*	NA*	NA*	NA*	NA*	NA*
South	2.386 (2.118, 2.687)	2.744 (2.539, 2.966)	15.0 (-0.2, 32.6)	1.849 (1.615, 2.116)	2.325 (2.136, 2.530)	25.8 (7.2, 47.5)	1.109 (0.931, 1.321)	0.916 (0.801, 1.048)	-17.4 (-33.7, 3.0)
West	2.619 (2.198, 3.121)	3.006 (2.656, 3.403)	14.8 (-7.4, 42.3)	1.739 (1.402, 2.156)	2.525 (2.206, 2.891)	45.2 (12.6, 87.2)	1.488 (1.179, 1.877)	1.203 (0.988, 1.463)	-19.2 (-40.4, 9.6)
Midwest	5.903 (5.300, 6.576)	3.295 (2.960, 3.667)	-44.2 (-52.1, -35.0)	2.433 (2.057, 2.878)	2.055 (1.795, 2.354)	-15.5 (-31.9, 4.8)	5.134 (4.573, 5.764)	2.272 (1.997, 2.585)	-55.8 (-62.8, -47.4)

*NA: Data not available for northeast region because no sites in that region met the inclusion criteria of $\geq$1 assessment/quarter.

**Note Repeated statement was removed from the model as there were following errors when 'repeated' statement was included.
Error: Error in computing the variance function.
Error: Error in parameter estimate covariance computation.

(Source: FDA Postmarketing Requirement Study 3051-1, Purdue Response to FDA Information and Analyses Request on May 30, 2019 Phase 1 Part 2. Title: Table 9: Stratified by geographic region based on Original + Reformulated OxyContin: sites with >1 assessment/year during 2y/4y time period. P. 33.)

Key: CI: Confidence Interval

6.14 ITS ANALYSES WITH ADDITIONAL MODELS

Table 35 Slope and immediate shift for non-oral abuse of OxyContin and primary comparator opioids per 10,000 dosage units dispensed, adjusted for respondents, model 2ai

Opioid	Slope in pre	Slope in Post	Change in slope (95% CI)	Immediate shift (95% CI)	Comparison: P-value Slope change	Comparison: P-value Immediate shift
OxyContin	0.004	-0.005	-0.01 (-0.10, 0.08)	-0.3 (-0.8, 0.1)	Ref	Ref
ER morphine	0.02	-0.04	-0.06 (-0.20, 0.08)	-0.07 (-0.71, 0.58)	0.6	0.5
IR hydrocodone	-0.02	0.008	0.03 (-0.09, 0.1)	-0.09 (-0.65, 0.47)	0.6	0.5
Other schedule II opioids	-0.009	0.009	0.02 (-0.06, 0.10)	0.1 (-0.3, 0.5)	0.7	0.2

(Source: FDA produced table from information request response)

Key: ER: Extended Release; IR: Immediate Release; CI: Confidence Interval

Table 36: Slope and immediate shift for non-oral abuse of OxyContin and primary comparator opioids adjusted for utilization and respondents, model 3ai

Opioid	Slope in pre	Slope in Post	Change in slope (95% CI)	Immediate shift (95% CI)	Comparison: P-value Slope change	Comparison: P-value Immediate shift

OxyContin	0.02	-0.03	-0.05 (-0.11, 0.02)	-0.34 (-0.66, -0.02)	Ref	Ref
ER morphine	0.04	-0.04	-0.08 (-0.18, 0.02)	0.12 (-0.34, 0.58)	0.6	0.1
IR hydrocodone	-0.03	-0.005	0.03 (-0.05, 0.11)	0.35 (-0.05, 0.74)	0.2	0.008
Other schedule II opioids	0.03	-0.006	-0.03 (-0.09, 0.02)	0.37 (0.11, 0.63)	0.8	0.0007

(Source: FDA produced table from information request response)

Key: ER: Extended Release; IR: Immediate Release; CI: Confidence Interval

6.15 ASSESSING SCREEN CHANGES

Figure 101: Change in abuse of OxyContin and comparators before and after the first ASI-MV screen change in 2Q2014 (Model 2)
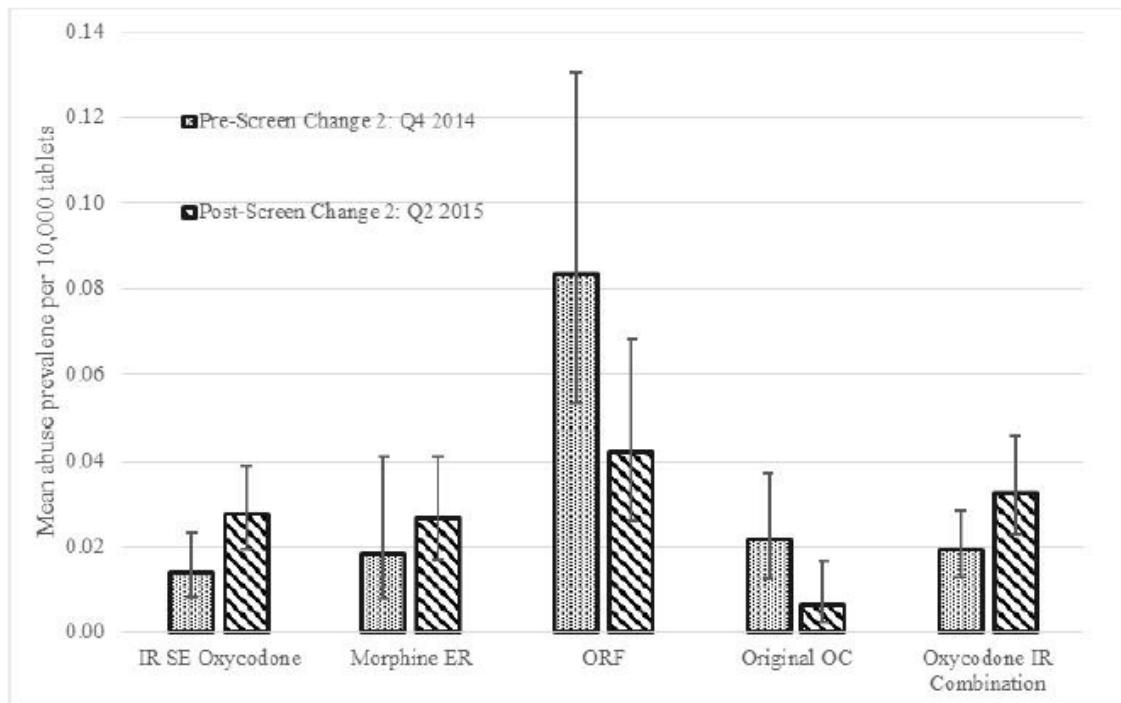
Error bars: 95% confidence intervals; Sites: contributing ≥ 1 assessment/year, 2y/4y; ER=extended release; IR=immediate release; SE=single entity; ORF=reformulated OxyContin; OC=original OxyContin; Q=quarter

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 12-8. Change in abuse of OxyContin and comparators before and after the first ASI-MV® screen change in 2Q2014 (Model 2). P. 377.)

Key: ER: Extended Release; IR: Immediate Release; SE: Single Entity; ORF: Reformulated OxyContin; OC: OxyContin; Model 2 models abuse rate per tablets dispensed

Figure 102: Change in abuse of OxyContin and comparators before and after the second ASI-MV screen change in 1Q2015 (Model 2)
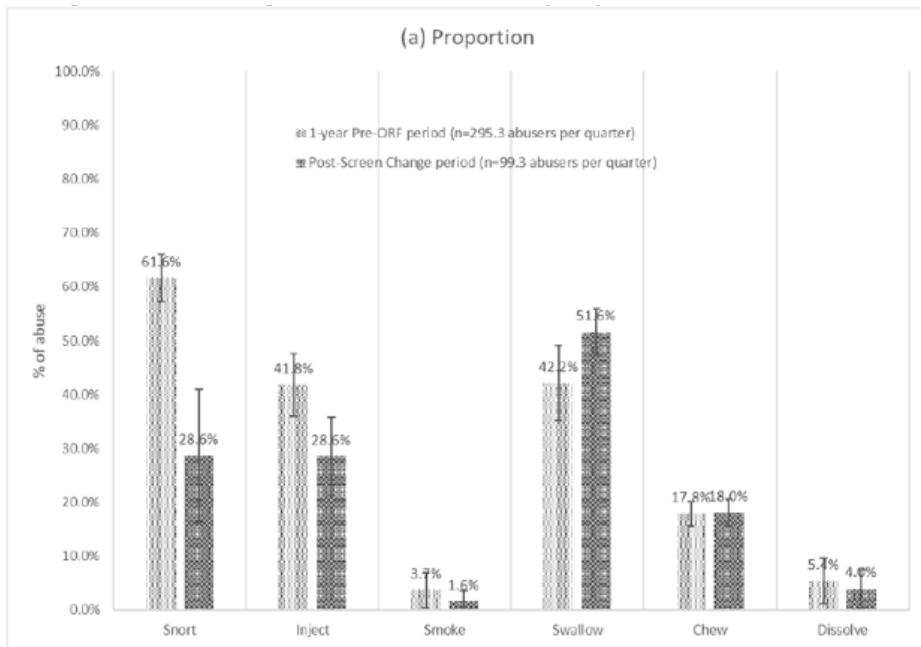
Error bars: 95% confidence intervals; Sites: contributing ≥ 1 assessment/year, 2y/4y; ER=extended release; IR=immediate release; SE=single entity; ORF=reformulated OxyContin; OC=original OxyContin; Q=quarter; Legend - pre: shaded bars – post: diagonal line fill

(Source: FDA Postmarketing Requirement Study 3051-1 Final Report. Title: Appendix Figure 12-10. Change in abuse of OxyContin and comparators before and after the second ASI-MV® screen change in 1Q2015 (Model 2). P. 380.)

Key: ER: Extended Release; IR: Immediate Release; SE: Single Entity; ORF: Reformulated OxyContin; OC: OxyContin; Model 2 models abuse rate per tablets dispensed
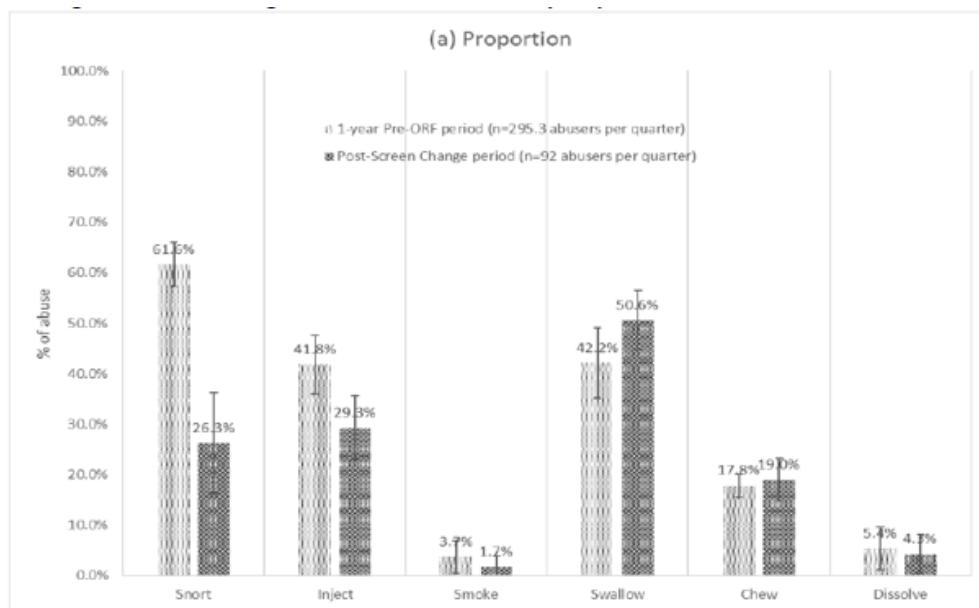
Figure 103: Proportion of abuse via specific routes among individuals endorsing abuse of OxyContin (original and reformulated) in the one-year pre-reformulation period (3Q2009-2Q2010) and one-year post-screen change period (2Q2015-1Q2016) among sites contributing at least one assessment per quarter

(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 12-11. Proportion of abuse via specific routes among OxyContin (original and reformulated) abusers, and average number of abusers per quarter in the one-year pre-reformulation period and one-year post-screen change period (2Q2015-1Q2016) among sites contributing at least on assessment per quarter. P. 31.)

Key: ORF: OxyContin reformulation

Figure 104: Proportion of abuse via specific routes among those endorsing abuse of OxyContin (reformulated only) in the one-year pre-reformulation period (3Q2009-2Q2010) and one-year post-screen change period (2Q2015-1Q2016) among sites contributing at least one assessment per quarter
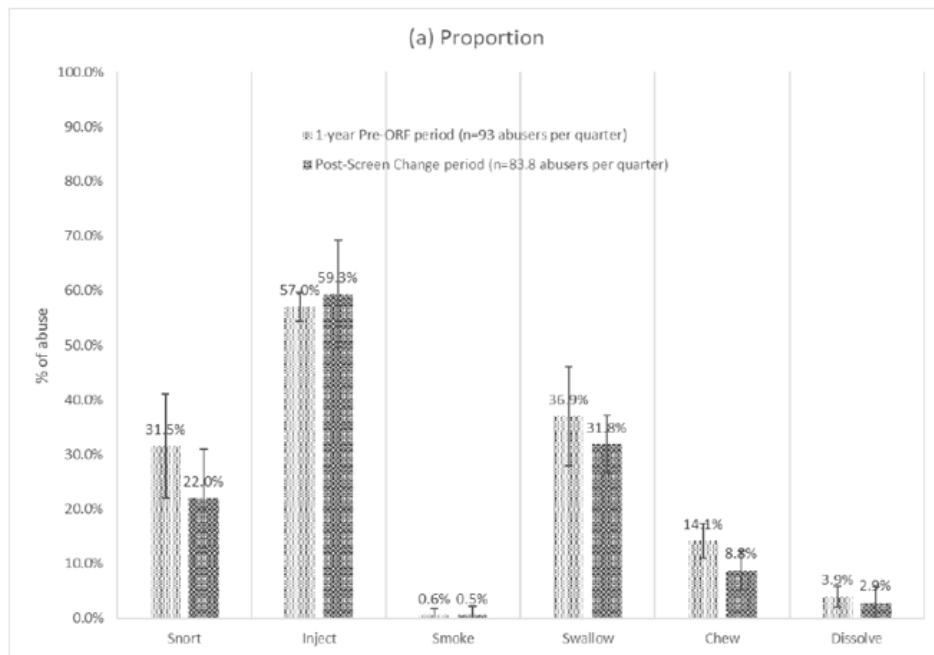
(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 12-12. Proportion of abuse via specific routes among OxyContin (reformulated only) abusers, and average number

of abusers per quarter in the one-year pre-reformulation period and one-year post-screen change period (2Q2015-1Q2016) among sites contributing at least one assessment per quarter. P. 32.)

Key: ORF: OxyContin reformulation
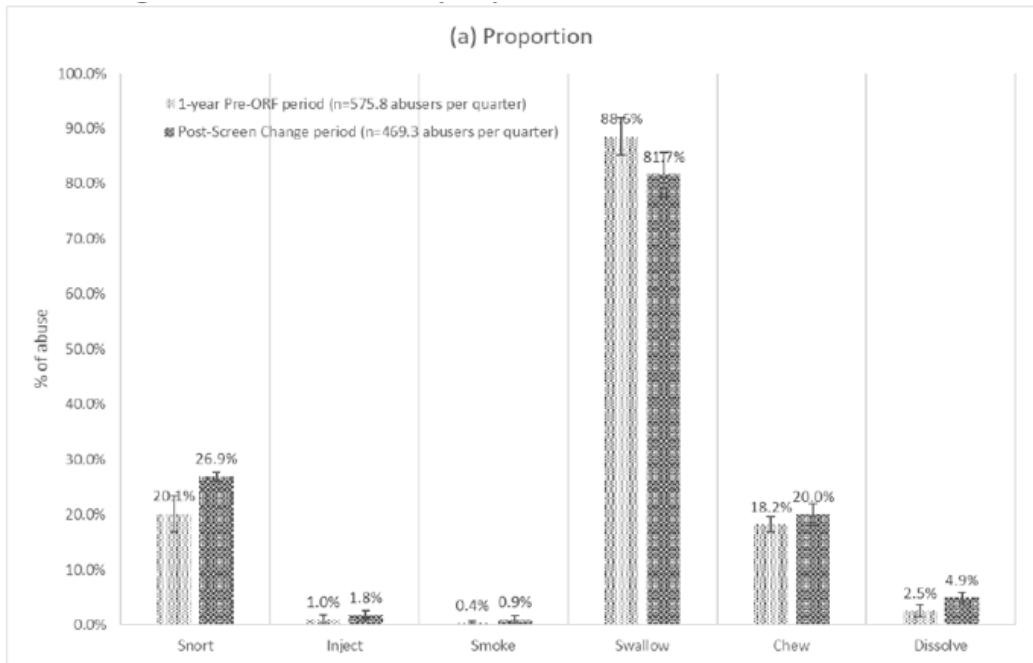
Figure 105: Proportion of abuse via specific routes among those endorsing abuse of ER Morphine in the one-year pre-reformulation period (3Q2009-2Q2010) and one-year post-screen change period (2Q2015-1Q2016) among sites contributing at least one assessment per quarter


(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 12-13. Proportion of abuse via specific routes among ER Morphine abusers, and average number of abusers per quarter in the one-year pre-reformulation period and one-year post-screen change period (2Q2015-1Q2016) among sites contributing at least one assessment per quarter. P. 33.)

Key: ER: Extended Release; ORF: OxyContin reformulation
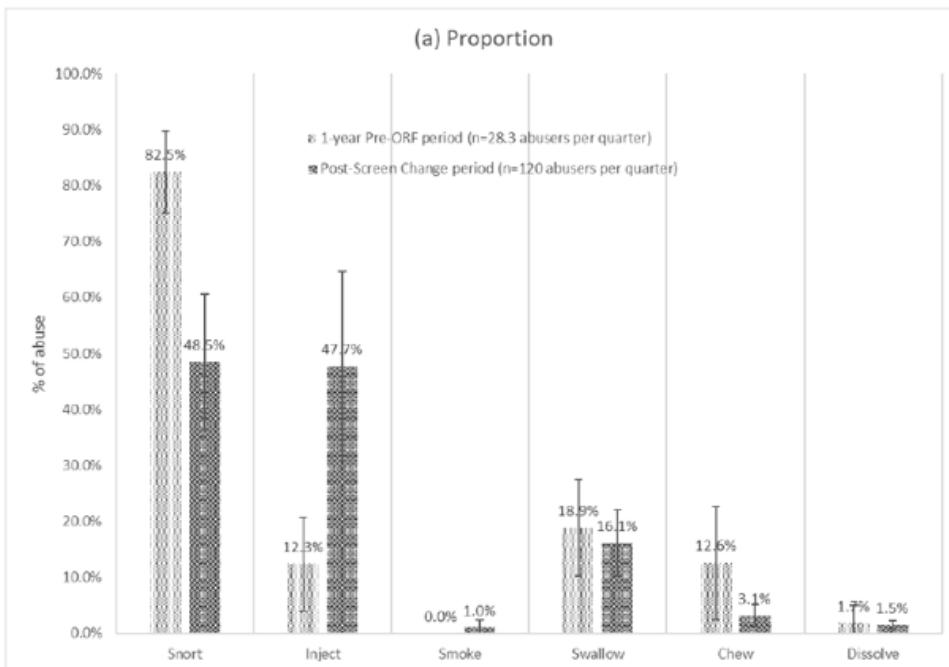
Figure 106: Proportion of abuse via specific routes among those endorsing abuse of IR Hydrocodone in the one-year pre-reformulation period (3Q2009-2Q2010) and one-year post-screen change period (2Q2015-1Q2016) among sites contributing at least one assessment per quarter

(a) Proportion

(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 12-14. Proportion of abuse via specific routes among IR Hydrocodone abusers, and average number of abusers per quarter in the one-year pre-reformulation period and one-year post-screen change period (2Q2015-1Q2016) among sites contributing at least one assessment per quarter. P. 34.)

Key: IR: Immediate Release; ORF: OxyContin reformulation

Figure 107: Proportion of abuse via specific routes among those endorsing abuse of ER oxymorphone in the one-year pre-reformulation period (3Q2009-2Q2010) and one-year post-screen change period (2Q2015-1Q2016) among sites contributing at least one assessment per quarter

(a) Proportion

(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 12-15. Proportion of abuse via specific routes among ER oxymorphone abusers, and average number of abusers per quarter in the one-year pre-reformulation period and one-year post-screen change period (2Q2015-1Q2016) among sites contributing at least one assessment per quarter. P. 35.)

Key: ER: Extended Release; ORF: OxyContin reformulation
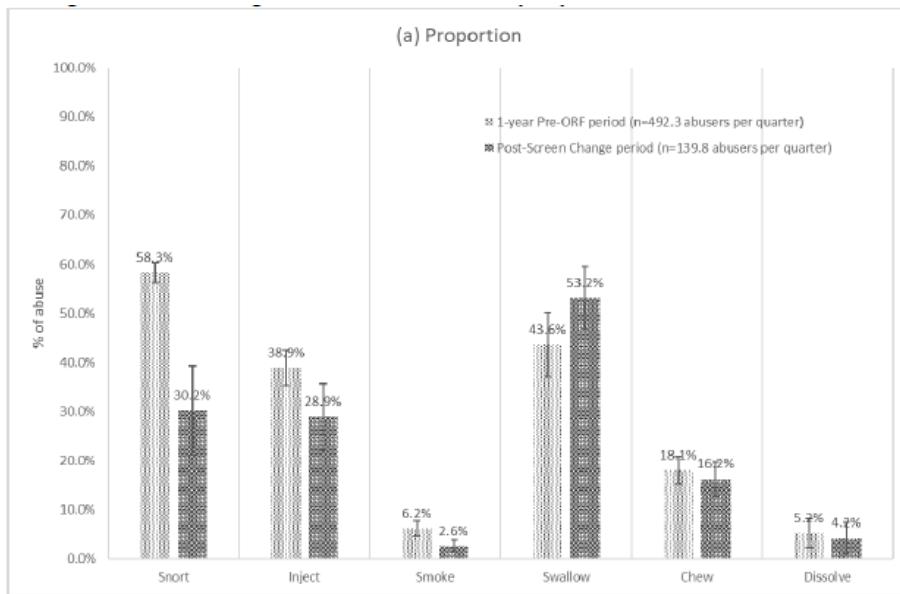
Table 37: Proportion of abuse via specific routes of administration, 1-year pre-reformulation period (3Q2009-2Q2010) compared to 1-year post-reformulation period compared to 1-year post-screen change period (2Q2015-1Q2016), among sites contributing at least one assessment per quarter

	1-Year Pre-Reformulation Period			1-Year Post-Screen Change Period		
	Percentage of Abusers	95% CI		Percentage of Abusers	95% CI	
SWALLOWED WHOLE						
OxyContin†	42.16	35.16	49.16	51.55	47.27	55.83
ER Morphine	36.93	27.87	45.99	31.82	26.57	37.08
IR Hydrocodone	88.56	85.22	91.91	81.69	77.70	85.67
Oxymorphone ER	18.85	10.21	27.49	16.12	10.21	22.03
CHEW						
OxyContin†	17.85	15.56	20.13	18.04	15.47	20.61
ER Morphine	14.15	11.00	17.29	8.78	5.27	12.29
IR Hydrocodone	18.17	16.73	19.61	20.05	18.11	21.99
Oxymorphone ER	12.57	2.45	22.70	3.13	1.20	5.06
DISSOLVE						
OxyContin†	5.41	1.22	9.60	3.96	0.39	7.53
ER Morphine	3.94	2.01	5.87	2.90	0.14	5.67
IR Hydrocodone	2.55	1.42	3.67	4.88	3.91	5.86
Oxymorphone ER	1.72	0.00	4.92	1.48	0.71	2.26
SNORT						
OxyContin†	61.61	57.19	66.03	28.62	16.28	40.97
ER Morphine	31.55	21.98	41.11	21.97	12.97	30.96
IR Hydrocodone	20.15	16.83	23.47	26.94	26.14	27.73
Oxymorphone ER	82.45	75.12	89.78	48.48	36.35	60.61
SMOKE						
OxyContin†	3.70	0.41	6.99	1.58	0.00	3.65
ER Morphine	0.60	0.00	1.72	0.53	0.00	2.22
IR Hydrocodone	0.43	0.22	0.64	0.92	0.18	1.65
Oxymorphone ER	N/A	N/A	N/A	0.97	0.00	2.34
INJECT						
OxyContin†	41.76	35.88	47.64	28.56	21.33	35.80
ER Morphine	57.05	54.36	59.73	59.34	49.48	69.19
IR Hydrocodone	1.01	0.26	1.76	1.79	1.03	2.55
Oxymorphone ER	12.29	3.91	20.67	47.70	30.81	64.60

(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Table 12-3. Proportion of abuse via specific routes of administration, 1-year pre-reformulation period compared to 1-year post-screen change period (2Q2015-1Q2016), among sites contributing at least one assessment per quarter. P. 41.)

Key: ER: Extended Release; IR: Immediate Release
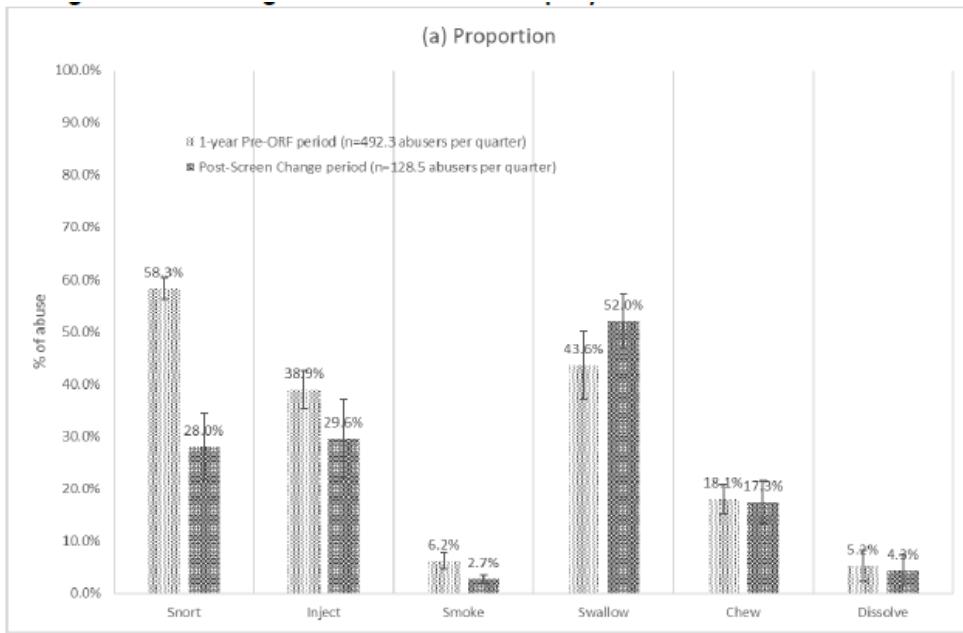
Figure 108: Proportion of abuse via specific routes among those endorsing abuse of OxyContin (original and reformulated), in the one-year pre-reformulation (3Q2009-2Q2010) and one-year post-screen change period (2Q2015-1Q2016) among sites contributing at least one assessment per year

(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 12-16. Proportion of abuse via specific routes among OxyContin (original and reformulated) abusers, and average number of abusers per quarter in the one-year pre-reformulation period and one-year post-screen change period (Q2 2015- Q1 2016) among sites contributing at least one assessment per year p. 36)

Key: ORF: OxyContin reformulation
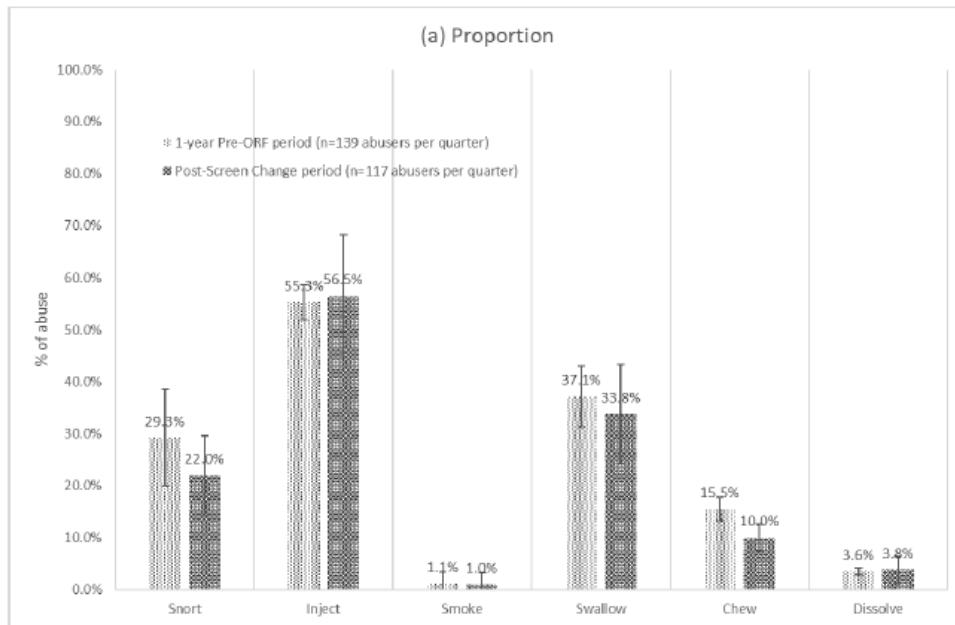
Figure 109: Proportion of abuse via specific routes among those endorsing abuse of OxyContin (reformulated only) in the one-year pre-reformulation period (3Q2009-2Q2010) and one-year post-screen change period (Q2 2015- Q1 2016) among sites contributing at least one assessment per year

(a) Proportion

(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Appendix Figure 12-17. Proportion of abuse via specific routes among OxyContin (reformulation only) abusers, and average number of abusers per quarter in the one-year pre-reformulation period and one-year post-screen change period (Q2 2015-Q1 2016) among sites contributing at least one assessment per year. P. 37.)

Key: ORF: OxyContin reformulation

Figure 110: Proportion of abuse via specific routes among those endorsing abuse of ER morphine in the one-year pre-reformulation period (3Q2009-2Q2010) and one-year post-screen change period (Q2 2015-Q1 2016) among sites contributing at least one assessment per year
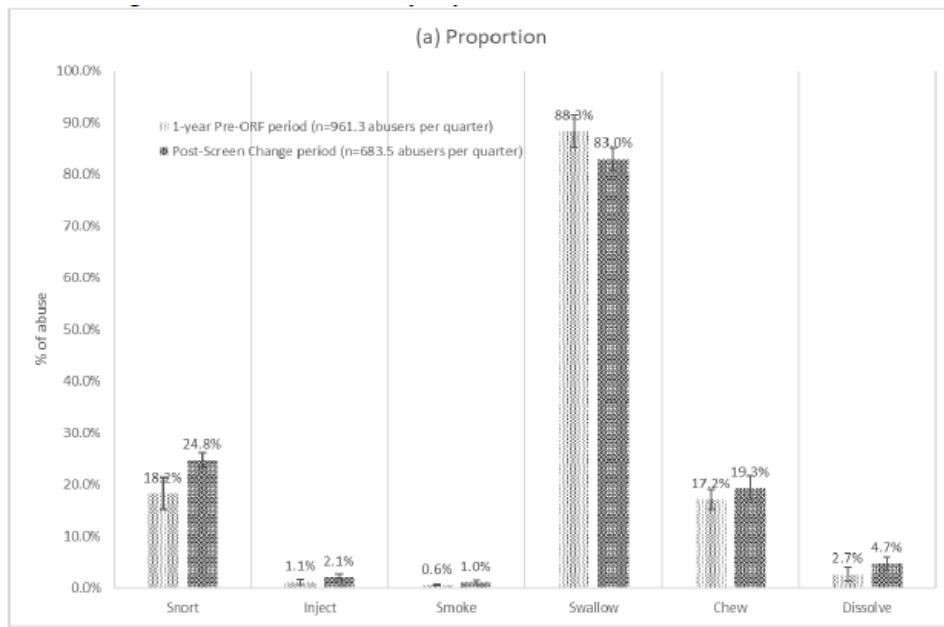
(a) Proportion

(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 12-18. Proportion of abuse via specific routes among ER Morphine abusers, and average number of abusers per

quarter in the one-year pre-reformulation period and one-year post-screen change period (Q2 2015-Q1 2016) among sites contributing at least one assessment per year. P. 38.)

Key: ER: Extended Release; ORF: OxyContin reformulation
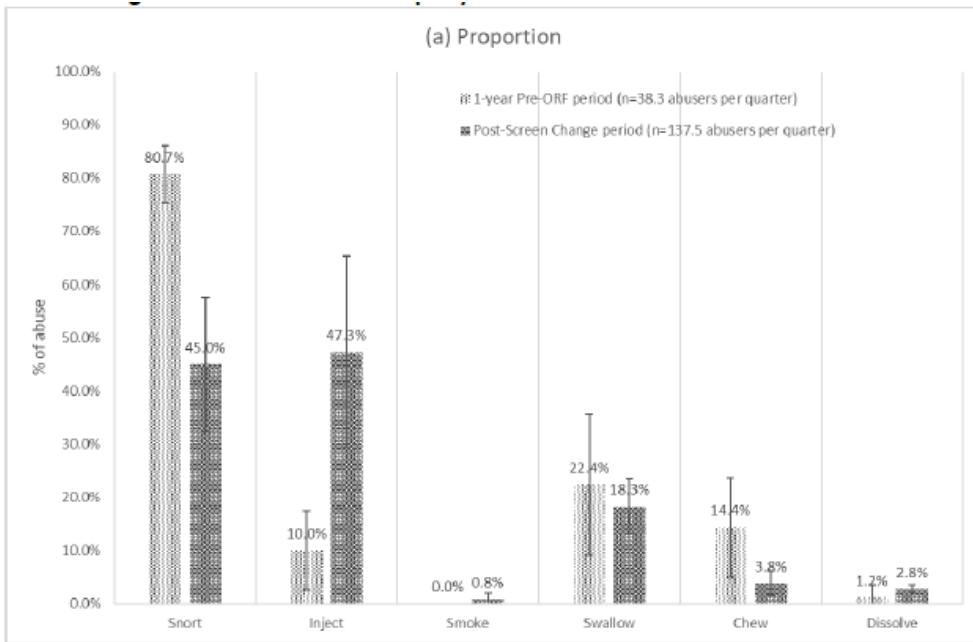
Figure 111: Proportion of abuse via specific routes among those endorsing abuse of IR Hydrocodone in the one-year pre-reformulation period (3Q2009-2Q2010) and one-year post-screen change period (Q2 2015-Q1 2016) among sites contributing at least one assessment per year

(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Revised Appendix Figure 12-19. Proportion of abuse via specific routes among IR Hydrocodone abusers, and average number of abusers per quarter in the one-year pre-reformulation period and one-year post-screen change period (Q2 2015-Q1 2016) among sites contributing at least one assessment per year. P. 39.)

Key: IR: Immediate Release; ORF: OxyContin reformulation

Figure 112: Proportion of abuse via specific routes among those endorsing abuse of ER oxymorphone in the one-year pre-reformulation period (3Q2009-2Q2010) and one-year post-screen change period (Q2 2015-Q1 2016) among sites contributing at least one assessment per year

(a) Proportion

(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Appendix Figure 12-20. Proportion of abuse via specific routes among ER oxymorphone abusers, and average number of abusers per quarter in the one-year pre-reformulation period and one-year post-screen change period (Q2 2015 – Q1 2016) among sites contributing at least one assessment per year. P. 40.)

Key: IR: Immediate Release; ORF: OxyContin reformulation

Table 38: Proportion of abuse via specific routes of administration, 1-year pre-reformulation period (3Q2009-2Q2010) compared to 1-year post-screen change period (2Q2015-1Q2016), among sites contributing at least one assessment per year

	1-Year Pre-Reformulation Period			1-Year Post-Screen Change Period		
	Percentage of Abusers	95% CI		Percentage of Abusers	95% CI	
SWALLOWED WHOLE						
OxyContin†	43.59	37.08	50.11	53.16	46.78	59.54
ER Morphine	37.13	31.28	42.99	33.81	24.33	43.30
IR Hydrocodone	88.31	85.26	91.36	82.97	80.79	85.15
Oxymorphone ER	22.40	9.19	35.60	18.26	13.09	23.43
CHEW						
OxyContin†	18.05	15.23	20.88	16.23	12.79	19.67
ER Morphine	15.46	13.23	17.68	9.97	7.45	12.49
IR Hydrocodone	17.17	15.24	19.10	19.35	17.05	21.64
Oxymorphone ER	14.35	4.98	23.72	3.83	1.49	6.17
DISSOLVE						
OxyContin†	5.24	2.26	8.21	4.22	0.99	7.44
ER Morphine	3.56	2.93	4.19	3.76	1.20	6.33
IR Hydrocodone	2.66	1.38	3.95	4.73	3.36	6.10
Oxymorphone ER	1.20	0.00	3.49	2.76	2.07	3.44
SNORT						
OxyContin†	58.30	56.24	60.37	30.20	21.22	39.19
ER Morphine	29.25	19.95	38.55	21.99	14.36	29.62
IR Hydrocodone	18.24	15.16	21.33	24.77	23.41	26.13
Oxymorphone ER	80.68	75.35	86.01	44.98	32.44	57.51
SMOKE						
OxyContin†	6.19	4.58	7.79	2.62	1.45	3.80
ER Morphine	1.10	0.00	3.30	0.99	0.00	3.25
IR Hydrocodone	0.62	0.43	0.81	1.00	0.54	1.47
Oxymorphone ER	N/A	N/A	N/A	0.83	0.00	1.99
INJECT						
OxyContin†	38.88	35.30	42.47	28.90	22.10	35.70
ER Morphine	55.26	51.96	58.57	56.47	44.72	68.23
IR Hydrocodone	1.12	0.60	1.63	2.13	1.47	2.79
Oxymorphone ER	9.98	2.55	17.41	47.27	29.19	65.36

ER=extended release; IR Hydrocodone=immediate release hydrocodone combination products; CI=confidence interval;†OxyContin represents original OxyContin in the pre-reformulation period and both original and reformulated OxyContin in the post-reformulation period.

(Source: PMR 3051-1: Response to FDA question received via email March 12, 2020. Received July 17, 2020. Title: Appendix Table 12-4. Proportion of abuse via specific routes of administration, 1-year pre-reformulation period compared to 1-year post-screen change period (2Q2015-1Q2016), among sites contributing at least one assessment per year. P. 42.)

Key: ER: Extended Release; IR: Immediate Release

6.16 MODEL ASSESSMENTS

Table 39: AIC model fit statistic values for changes in overall abuse for OxyContin relative to primary comparators, -2y/4y

Model	AIC value
Model 1	39489

Model 2	49048
Model 2a	35924
Model 3	48556
Model 3a	29214

(Source: Response to FDA Information Request, received 8/27/2019. Table 1-1A.)

6.17 COMPARATORS

The strengths and limitations for each primary and secondary comparator are addressed below:

ER Morphine: During the study period, ER morphine had a large and relatively stable market share, was subject to ER/LA opioid analgesic regulatory actions such as the ER/LA opioid analgesic REMS, and is classified as a Schedule II product, as is OxyContin. It is also commonly abused via non-oral routes. The ASI-MV® assessment instrument did not undergo any major changes in the ascertainment of ER morphine abuse during the study period. Dosage units dispensed were increasing for ER morphine in the post-period, while dosage units dispensed for OxyContin were decreasing, making it imperative to compare changes in abuse rates of these two products both with and without adjusting for the number of dosage units dispensed over time.

IR hydrocodone combination products: During the study period, IR hydrocodone combination products had a large and relatively stable market share; however, unlike OxyContin, this category is composed of immediate release products. The ASI-MV® assessment instrument did not undergo any major changes in the ascertainment of IR hydrocodone combination product abuse during the study period. For the majority of the study period these products were categorized as schedule III, however in October 2014, hydrocodone combination products were changed to schedule II. The most frequently dispensed IR hydrocodone combination product contains acetaminophen, and reports of non-oral abuse in both the pre- and post-period were low, particularly for injection, with percentage of injection cases at 1.6% in the pre-period, and 0.2% in the post-period, and levels of snorting abuse at 17.2% in the pre-period, and 14.4% in the post-period. These low proportions of injection and snorting, relative to OxyContin, make IR hydrocodone combination products a less useful comparator in terms of assessing changes in route of abuse, but this comparator remains valuable in evaluating change in overall abuse.

All other schedule II opioids: This is a composite category combining ER and IR formulations of hydrocodone combination products, ER and IR oxymorphone, ER and IR hydromorphone, ER and IR morphine, and IR oxycodone. The advantage of this composite category is that the large number of products included create a more stable drug utilization pattern, and therefore allows for an adjusted rate that is not affected by fluctuations in utilization. However, composite categories like this one include drugs that vary widely with respect to market share, length of time on the market, and trends in

utilization and abuse. This composite category is more heavily influenced by products with relatively larger market shares and higher numbers of abuse reports, and changes in rates of abuse for products with smaller market shares or lower numbers of abuse reports will be obscured. In addition, several opioids in this composite category underwent specific changes that affected their market share, screen order, and rates of abuse in ASI-MV®. Most importantly, the IR oxycodone screen in ASI-MV® assessment tool was changed in April 2010 to include the addition of IR oxycodone single-entity product response options. Also, of note, in April 2012, the oxymorphone screen was changed to include images of the reformulated Opana ER product.

Methadone: Methadone is used both for pain management and for treatment of opioid addiction and is therefore difficult to interpret as a comparator. Only the methadone that is prescribed and dispensed for pain is captured in drug utilization databases and counted as part of the denominator in utilization-adjusted analyses; however, methadone dispensed at opioid treatment centers may also be diverted and abused, and therefore captured as part of the numerator but not the denominator in these studies.

IR oxycodone: Although IR oxycodone, particularly SE oxycodone, has potential value as a comparator for OxyContin® because it contains the same opioid molecule as OxyContin®, IR oxycodone was a problematic comparator in this study because IR oxycodone SE was not included as an option in the ASI-MV® assessment tool during most of the pre-period.

ER Oxymorphone: ER oxymorphone is an appealing comparator, as it is a high potency, single-entity, extended-release opioid that is commonly abused via non-oral routes. ER oxymorphone trends are difficult to interpret, however, because it was relatively new to the market at the beginning of the study period and had a small and rapidly increasing market share, followed by introduction of a reformulated product (designed to deter non-oral abuse not approved by FDA to be labeled as abuse-deterrent) as well as generics during the study period.

Heroin: Heroin is another drug that is commonly abused via non-oral routes; however, it is an illicit opioid with complex and multifactorial drivers of availability and abuse. This drug can, however, help us understand the context of changes in OxyContin abuse following reformulation. Concerns have been raised about the reformulation of OxyContin having a substitution effect, resulting in a shift to heroin and an increase in heroin overdoses. This study was not designed to evaluate this phenomenon or assess the impact of OxyContin's reformulation on heroin abuse.

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6.18 SUMMARY TABLE OF PUBLISHED LITERATURE RELATED TO PMR 3051-1

Author, Publication Year (Funding source)	Study Design, Data Source	Study Period, Sites	Methods	Results	Strengths and limitations
Butler, 2011 (King Pharmaceuticals /Pfizer)	Observational, cross-sectional NAVIPPRO® ASI-MV®	Study period: 2009 Sites: Only assessments with prescription opioid abuse - 354 unique 3-digit zip codes	Estimated unadjusted and prescription volume-based risk of abuse from ASI-MV® assessments for prescription opioid abuse. 1) Log binomial regression to estimate unadjusted risk of abuse and prescription-adjusted risk of abuse of each IR and ER compound 2) Random effects binary logistic regression model to estimate the predicted probabilities of abusing each IR and ER compound by one of five ROAs: intended ROA, inhalation and snorting, injection, chewing and swallowing, and other.	Rank of unadjusted abuse for 2009: 1) Hydrocodone, 2) IR oxycodone, 3) ER oxycodone, 4) methadone, 5) ER morphine, 6) IR hydromorphone, 7) IR morphine, 8) ER fentanyl, 9) ER oxymorphone, 10) IR fentanyl, 11) IR oxymorphone. Rank of abuse per 100,000 prescriptions for 2009: 1) methadone, 2) ER oxycodone, 3) IR morphine, 4) ER oxymorphone, 5) IR oxymorphone, 6) IR hydromorphone, 7) IR fentanyl, 8) ER morphine, 9) ER fentanyl, 10) IR oxycodone, 11) hydrocodone Predominant ROA: Hydrocodone: Intended ROA Oxycodone: Intended ROA Fentanyl: Other Hydromorphone: Injection Methadone: No information Morphine: Injection Oxymorphone: Inhalation	(+) Presents abuse in 2009, pre-OxyContin reformulation, for many APIs, contextual data (+) Presents both unadjusted and prescription-adjusted rates (-) Uses prescription number, not tablets (-) Retail pharmacy data would not captured methadone OTP dispensing (-) API level rather than product level

Author, Publication Year (Funding source)	Study Design, Data Source	Study Period, Sites	Methods	Results	Strengths and limitations
Butler, 2013 (Purdue)	Observational, cross-sectional NAVIPPRO® ASI-MV®	Study period: June 1, 2009-March 31, 2012 Sites: 357 centers in US - common subset of assessment sites that provided data during both the pre and post-ORF introduction and included comparator opioids (mention that same conclusions are reached with no limits on study sites). 140,496 individuals assessed for substance abuse treatment.	Estimated unadjusted and prescription volume-based risk of abuse from ASI-MV® assessments overall and for prescription opioid abuse. Generalized estimating equation log-binary regression models to estimate: 1) quarterly unadjusted percentages of past 30 day abuse of OC, ORF, and any ER oxycodone, 2) the pre- to post-ORF changes in unadjusted and prescription volume adjusted percentages of past 30 day abuse of ER oxycodone and comparator products	Pre-post percent change in abuse rate (unadjusted) among all ASI-MV assessments: OC vs. ORF: -41% overall , -66% non-oral ER morphine: +2% overall ER oxymorphone: +246% Pre-post percent change in prescription-based abuse rate among all ASI-MV assessments: OC vs. ORF: -33% ER morphine: +0.9% ER oxymorphone: +111% Pre-post percent change in abuse rate (unadjusted) among ASI-MV assessments endorsing Rx opioids: OC vs. ORF: -49% overall, -71% non-oral ER morphine: -12% ER oxymorphone: +196% Pre-post percent change in prescription-based abuse rate among ASI-MV assessments endorsing Rx opioids: OC vs. ORF: -42% ER morphine: -13% ER oxymorphone: +80% Injection: OC: 36%, ORF: 16% Snorting: OC: 53%, ORF: 25% Oral: OC: 55%, ORF: 76% Frequency of abuse: 10.8 days for OC, 7.5 days for ORF	(+) Presents both unadjusted and prescription-based abuse estimates (-) OxyContin is defined as reformulated only in the post-period - least conservative estimate. (-) Uses prescription volume, not tablets dispensed

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Author, Publication Year (Funding source)	Study Design, Data Source	Study Period, Sites	Methods	Results	Strengths and limitations
Butler, 2018 (Collegium Pharmaceuticals)	Observational, cross-sectional NAVIPPRO® ASI-MV®	Study period: January 1 2009 - March 31, 2015 Sites: 1,008 sites in 44 states	Logistic regression models among those reporting past 30-day abuse of one of the specified Rx opioids via an oral route in ASI-MV® data. Overall abuse for the specified product was used as an offset for prevalence of abuse by alternate oral mode of administration (MOAs) by product. Estimated probabilities and 95% CIs for 1) any oral MOA that involved manipulation among those who abused any of the target products 2) any oral MOA that involved manipulation among any individuals indicating oral abuse of the specific product and 3) each oral MOA separately among any individuals indicating oral abuse.	Crush resistant tablets (CRTs) were abused by an alternative oral MOA (chewed and swallowed, dissolved in mouth, or dissolved in liquid and drank) 1.40 times more often than non-CRTs. Biggest difference was for chewing and dissolving in mouth. Abuse by swallow whole route was not different between CRTs and non-CRTs.	(+) Deeper analysis of oral manipulation and abuse of CRTs and non-CRTs (-) Does not differentiate between different products for CRTs

Author, Publication Year (Funding source)	Study Design, Data Source	Study Period, Sites	Methods	Results	Strengths and limitations
Cassidy, 2014 (Endo pharmaceuticals)	Observational, cross-sectional NAVIPPRO® ASI-MV®	Study period: January 1 2008-December 31, 2011 Sites: 437 sites	Time-series analysis using logistic regression to estimate quarterly prevalence of past 30-day abuse (adjusted for covariate and prescription volume) and changes in abuse for pre- and post-ADF OxyContin introduction in ASI-MV®. Time series analysis of quarterly data using joinpoint regression. Generalized estimating equations were employed to estimate unadjusted prevalence of quarterly abuse for each compound, and a generalized estimating equation Poisson regression model was used to estimate prescription adjusted abuse prevalence. Prescription information at the state level.	Percent change in abuse rates (any route) per 100 assessments: All Rx opioids: +8.3% IR opioids: +2.5% ER opioids: +10.5% Buprenorphine: +84.7% Oxymorphone: +190.9% Percent change in abuse rates (any route) per 100,000 prescriptions: All Rx opioids: -2.0% IR opioids: -11.1% ER opioids: -14.9% Buprenorphine: +18.7% Oxymorphone: +45.0% Increase in abuse of buprenorphine and oxymorphone ER was larger in those reporting injection only or snorting only. Increase began before 3Q2010, but an inflection point for that increase does occur at 3Q2010. Increase in oxycodone IR SE as well (however this is difficult to interpret due to this moiety being introduced to the ASI-MV® tool 2Q2010. Decline in heroin abuse, increase in amphetamine use.	(+) Unadjusted and prescription-based abuse rates (-) API level only (-) Uses prescriptions not tablets (-) Unclear if changes in abuse prevalence of comparators related to reformulation of OxyContin

Author, Publication Year (Funding source)	Study Design, Data Source	Study Period, Sites	Methods	Results	Strengths and limitations
Coplan, 2016 (Purdue)	Observational, cross-sectional NAVIPPRO® ASI-MV®	Study period: 3Q2009-4Q2013 (transition period: 3Q2010-4Q2010) Sites: Not specified	Used endorsements from SKIP and OTP to estimate population adjusted and prescription adjusted abuse rate for OxyContin and comparators. Poisson regression and model utilizing abuse cases as the dependent variable, with time, opioid groups, and opioid group by time as the covariates, and log census population, or prescription numbers as offset.	OxyContin abuse decreased -48% in the pre to post-period in ASI-MV® assessments when adjusted for population rates. Other schedule II opioids decreased -3% in the post-period when adjusted for population rates. OxyContin abuse decreased -34% in the post-period when adjusting for prescription rates, and other schedule II opioid abuse decreased 0% when adjusting for prescription rates. Using population-adjusted rates, OxyContin non-oral abuse decreased -69%.	(+) Includes results from multiple surveillance systems (-) Unclear which sites were included and how changed over time (-) OxyContin definition for ASI-MV® analysis was ORF only in post-period.
Cassidy, 2017 (Purdue)	Observational, cross-sectional NAVIPPRO® ASI-MV®	Study period: January 2009-December 2015 Pre-period: Sept 2009-June 2010 Post-period 1: Jan 2011-December 2011 Post-period 2: April 2015-December 2015	Used endorsements from ASI-MV® to estimate population-based abuse rate for OxyContin and comparators, stratified by geographic region and treatment modality. Generalized linear models were used to estimate abuse prevalence. Statistical models included drug/compound category variable, time indicator variable and their interaction as the fixed effects. Models included geographic region and treatment setting variables. Models could include treatment setting and region as covariates.	Any OxyContin showed a -41% decrease in post-period 1, and a -52% decrease in post-period 2. Outpatient/methadone treatment modality showed the largest decrease for any OxyContin abuse in post-period 1: -56% and post-period 2: -67%. The largest decrease in abuse for OxyContin was observed in the midwest (-47%) in post-period 1, and the west in post-period 2 (-59%).	(+) Study analyzed treatment setting and geographic regions (+) Definition of OxyContin included a definition with branded and generic oxycodone (-) Abuse prevalence not adjusted for prescription or tablet volume. (-) Shortened post-periods are not necessarily representative of entire post-reformulation period. (-) Post-period 2 is not comparable to the pre-period because changes in screen order occurred in May 2014 and March 2015.

Author, Publication Year (Funding source)	Study Design, Data Source	Study Period, Sites	Methods	Results	Strengths and limitations
		Sites: 874 facilities in 39 states			

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

OxyContin® Postmarketing Requirement (PMR) 3051-2 Final Study Report

Date: August 7th, 2020

Reviewer(s):   Alex Secora, Ph.D., Epidemiology Reviewer
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                                          Office of Surveillance and Epidemiology

Subject   Review of OxyContin PMR 3051-2 final study report – *Changes in Abuse of OxyContin Following its Reformulation with Properties Intended to Deter Abuse as Measured by the RADARS® System Poison Center Program*

Drug Name(s):   OxyContin (oxycodone hydrochloride extended-release)

Application Type/Number: NDA 022272/IND 029038

Applicant/sponsor: Purdue Pharma L.P.

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ABBREVIATIONS:

-1y/3y 1-year period before (3Q2009-2Q2010) compared to the 3-year period after the introduction of reformulated OxyContin (1Q2011-4Q2013), excluding the transition period

-2y/5y 2-year period before (3Q2008-2Q2010) compared to the 5-year period after the introduction of reformulated OxyContin (1Q2011-4Q2015), excluding the transition period

ADF Abuse deterrent formulation

AIC Akaike Information Criteria

CII Schedule II opioids

CI Confidence interval

ER Extended-release

FDA United States Food and Drug Administration

IR Immediate-release

LA Long-acting

N/A Not applicable

NOS Not otherwise specified

PCC Poison control center

PMR Postmarket requirement

PP1 Post Period 1 (2Q2010 to 4Q2012)

PP2 Post Period 2 (1Q2013 to 4Q2016)

Q Yearly quarter (3-month period)

RADARS® System Researched Abuse, Diversion, and Addiction-Related Surveillance System

REMS Risk evaluation and mitigation strategy

ROA Route of abuse

RORR Ratio of rate ratios

SAP Statistical analysis plan

SD Standard deviation

SE Single-entity

US United States

EXECUTIVE SUMMARY

Postmarketing requirement (PMR) study 3051-2 is one of four studies the United States Food and Drug Administration (FDA) required of the sponsor, Purdue Pharma, to evaluate the real-world impact of OxyContin's reformulation on its abuse and associated adverse outcomes. Specifically, PMR study 3051-2 aimed to assess resulting changes in calls to United States poison control centers (PCCs) involving the abuse of OxyContin by any route (overall), and those involving specific routes of abuse (oral, inhalation, injection). This study used data from Researched Abuse, Diversion, and Addiction-Related Surveillance System (RADARS) System Poison Center Program. In conjunction with the other PMR studies (3051-1,3, and 4) and other relevant information, the findings of this study can be used to help inform the overarching question of whether OxyContin's reformulation meaningfully reduced its abuse and associated harms. The reformulation incorporated a high molecular weight polymer (polyethylene oxide) matrix with the intention of making the tablet more difficult to manipulate for the purposes of misuse or abuse, specifically abuse via non-oral routes.

Overview of Study Methods

In brief, the study assessed the change in the rate of exposure calls to PCCs involving the abuse of OxyContin (hereafter, abuse call rate), comparing the two years before (pre-period) to the five years after (post-period) OxyContin's reformulation (-2y/5y study period), excluding a market transition period of two quarters immediately following the marketing of reformulated OxyContin.

Comparator opioids were included in this evaluation to aid causal inference by providing information on background trends in call rates and approximating the "counterfactual" scenario, or what would be expected to have happened to OxyContin abuse call rates had it not been reformulated. The study included three primary opioid comparators with relatively large and stable market share and/or regulatory requirements similar to OxyContin (extended-release [ER] morphine, immediate-release [IR] hydrocodone combination products, and "other schedule II opioids" [composite comparator[i]]); secondary comparators, including heroin, provided additional context.

In addition to descriptive analyses of abuse calls including quarterly counts, demographics, and medical outcomes, investigators calculated rate ratios (RR) by comparing the abuse call rates in the pre- and post-periods for OxyContin and each of the comparator opioid exposure groups (RR = [abuse call rate post-period] / [abuse call rate pre-period]). A ratio of rate ratios (RORR) compared the changes in mean quarterly abuse call rates between the pre- and post-periods comparing OxyContin's change (or RR) to the comparator's change (RORR = [comparator RR] / [OxyContin RR]). In these types of difference in difference models, an RORR >1 reflects a favorable change in abuse call rates for OxyContin relative to that of a comparator; in this context, favorable could mean a greater decline or a smaller increase in abuse call rates for OxyContin comparing periods relative to comparators, or no change for OxyContin but increasing abuse call rates for comparators. An RORR <1 indicates a favorable change for the comparator relative to OxyContin. The study used an analogous approach in comparative interrupted time series (CITS) models, but these measures compared the change in abuse call rate quarterly trends (i.e., slopes) and "immediate shift" (i.e., level change) for OxyContin and comparators; these are referred to as the CITS slope measures and CITS level change measures in this review, and are interpreted like an RORR.

To calculate RRs and RORRs (and CITS measures), investigators utilized several different statistical models (all Poisson regression models); some models estimated the percent change in mean quarterly abuse call rates comparing the time periods, and others used interrupted time series (ITS) methods to estimate the change in the slope of abuse call rates and the level change following market introduction of reformulated OxyContin. We reviewed findings from all models, but the results presented in this review primarily focus on three sets of statistical models based on their interpretability and model performance. The first set of models (Means model 1 and ITS model 5) included general population data[ii] as the rate denominator (i.e., an offset variable), estimating abuse call rates per 100,000 population. These models did not account for changes in utilization over the study period and may overestimate the effect of the reformulation in the face of decreasing OxyContin utilization, if some of the observed decrease in prescribing and availability of OxyContin for abuse was due to factors other than reduced demand for the purpose of abuse or diversion (e.g., changes in formularies/reimbursement, REMS, etc.). The second set of models (Means model 2a and

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[i] Includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone

[ii] 2010 United States census data

ITS model 6a) also included the total number of tablets dispensed as an offset variable, estimating abuse call rates per 100,000 tablets dispensed, and adjusting for the total pharmaceutical exposure calls to PCCs (among individuals >5 years old) as a covariate in the regression model (hereafter, adjusting for call volume). The third set of models (Means model 3a and ITS model 7a) did not use an offset variable, but rather adjusted for the total number of tablets dispensed and call volume as covariates. During the protocol submission and review process, FDA communicated to the sponsor that the third set of models were not preferred due to the expected difficulty in interpreting the findings given they did not use the more intuitive and widely-used offset variable to generate a rate. The models that included tablets dispensed data (Means models 2a and 3a; ITS models 5a and 7a) accounted for changes in utilization, and thus changes in the availability for abuse, but these models may underestimate the effect of the reformulation if the decrease in OxyContin utilization was due, in part, to the reformulation's abuse-deterrent effects (e.g., a decrease in desirability for abuse driving decreased prescribing). Because there is no single, standard scientifically agreed-upon denominator or modeling approach to estimate abuse rates for prescription opioids, we used various models to reflect the potential for varied results based on analytic approach and accompanying assumptions.

Primary models discussed in this review[iii]:

- **Model 1:** mean quarterly abuse call rate per general population (standardized per 100,000 population)
- **Model 2a:** mean quarterly abuse call rate per tablets dispensed (standardized per 100,000 tablets dispensed), adjusted for call volume
- **Model 3a**: mean quarterly abuse call rate, adjusted for the quarterly number of tablets dispensed and call volume
- **Model 5:** ITS model of pre- and post-period quarterly abuse call rate slope and level change per general population
- **Model 6a:** ITS model of pre- and post-period quarterly abuse call rate slope and level change per tablets dispensed, adjusted for call volume
- **Model 7a**: ITS model of pre- and post-period quarterly abuse call rate slope and level change, adjusted for the quarterly number of tablets dispensed and call volume

Due to the inherent uncertainties associated with these data and their interpretation, the study also used multiple sensitivity analyses to assess robustness of the study findings. For example, analyses involved shorter pre- and post-periods (one year pre-period and three year post-period [-1y/3y]) to better understand the near-term, more immediate impact of the reformulation. The study expanded the definition of OxyContin-involved abuse calls to include calls involving "all ER oxycodone" (both brand and generic combined) to explore potential misclassification, particularly in the pre-period when both generic ER oxycodone and brand OxyContin were marketed simultaneously. Additionally, because of the increasing amount of missing formulation data on abuse calls related to both oxycodone and morphine exposures, investigators used multiple imputation methods to impute formulations based on other information provided during the call. The study also included geographical restrictions to assess the impact of other large public health efforts, specifically the 2010-2011 Florida "pill mill" legislation and related law enforcement initiatives that, independent of the reformulation, could have precipitated changes in abuse call rates for some opioids. Finally, to assess larger secular trends in all call types involving OxyContin and comparators, we evaluated exposure call types that were not likely to be directly impacted by OxyContin's reformulation (e.g., unintentional general exposures) after adjusting for changes in utilization.

Key Findings
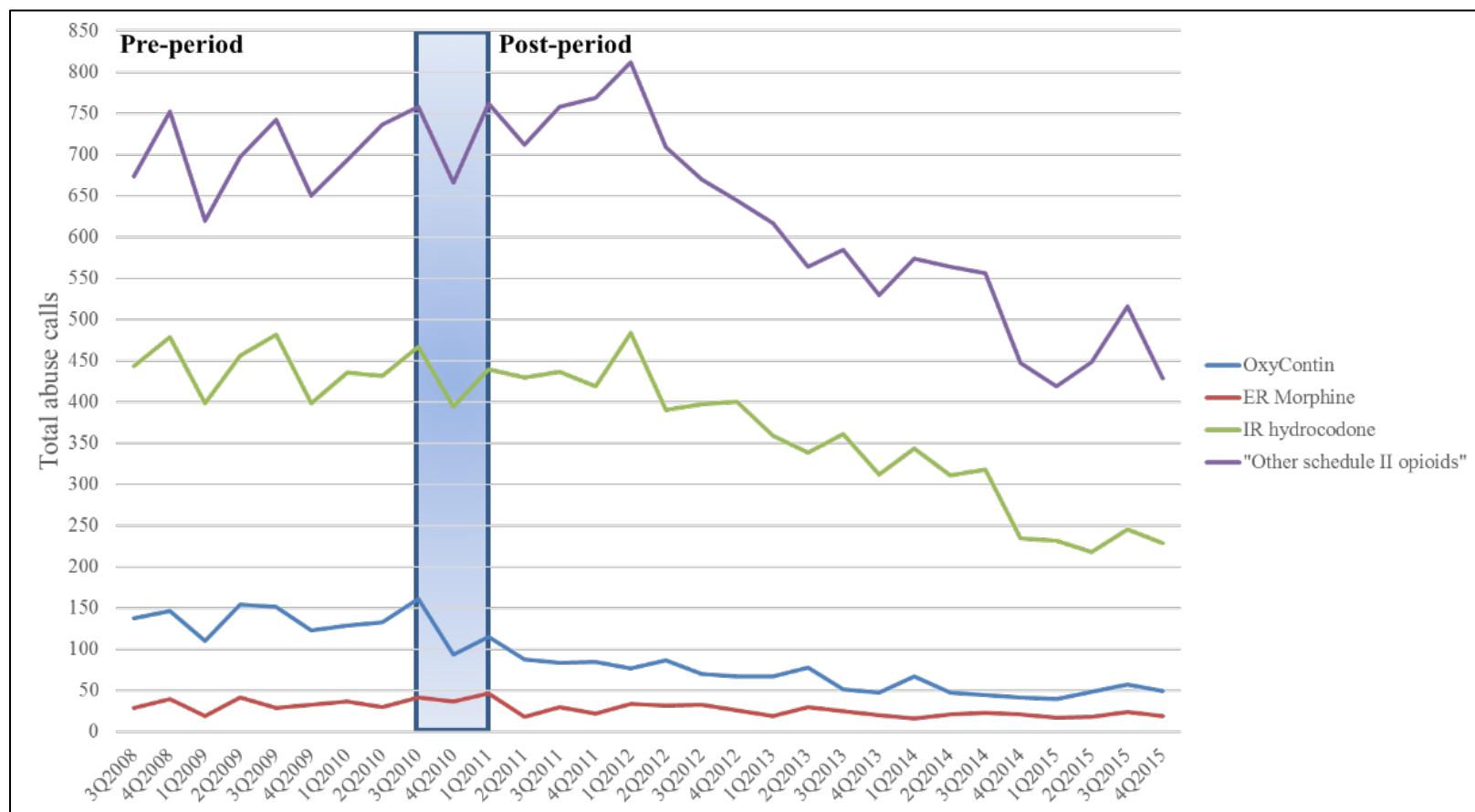
Pre- to post-period changes in quarterly abuse call counts (descriptive data)

Figure 1 shows the quarterly total number of abuse calls made to PCCs in the pre- and post-periods for OxyContin and primary comparator opioids. Immediately following the reformulation, there was an apparent decline in the number of calls involving OxyContin. There was also a decline for the "other schedule II opioids" composite comparator group and for IR hydrocodone, although the downward inflection in trend appeared to occur several quarters later than for OxyContin. There were sustained

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[iii] Models 2b and 3b were the same as models 2a and 3a, respectively, only differing in that they included an additional categorical variable in the regression model that corresponded to the tablet strength involved in the abuse call. Models 2b and 3b were meant as sensitivity analyses but were not implemented due to challenges associated with defining categories of tablet strengths that could be used across opioid groups. Models 4a and 8a were the same as models 3a and 7a, respectively, only differing in that they include dosage units dispensed as a categorical variable rather than a continuous variable. Model 4a and 8a were considered in the protocol, but they were not ultimately implemented due to their worse model performance compared to models 3a and 7a.

declines in the total number of abuse calls for OxyContin, IR hydrocodone, and "all schedule II" opioids in the post-period. ER morphine had the lowest numbers overall, and changes were difficult to discern visually for this comparator.

Figure 1: Total quarterly counts of abuse calls (any route) involving OxyContin and primary comparator opioids (-2y/5y)
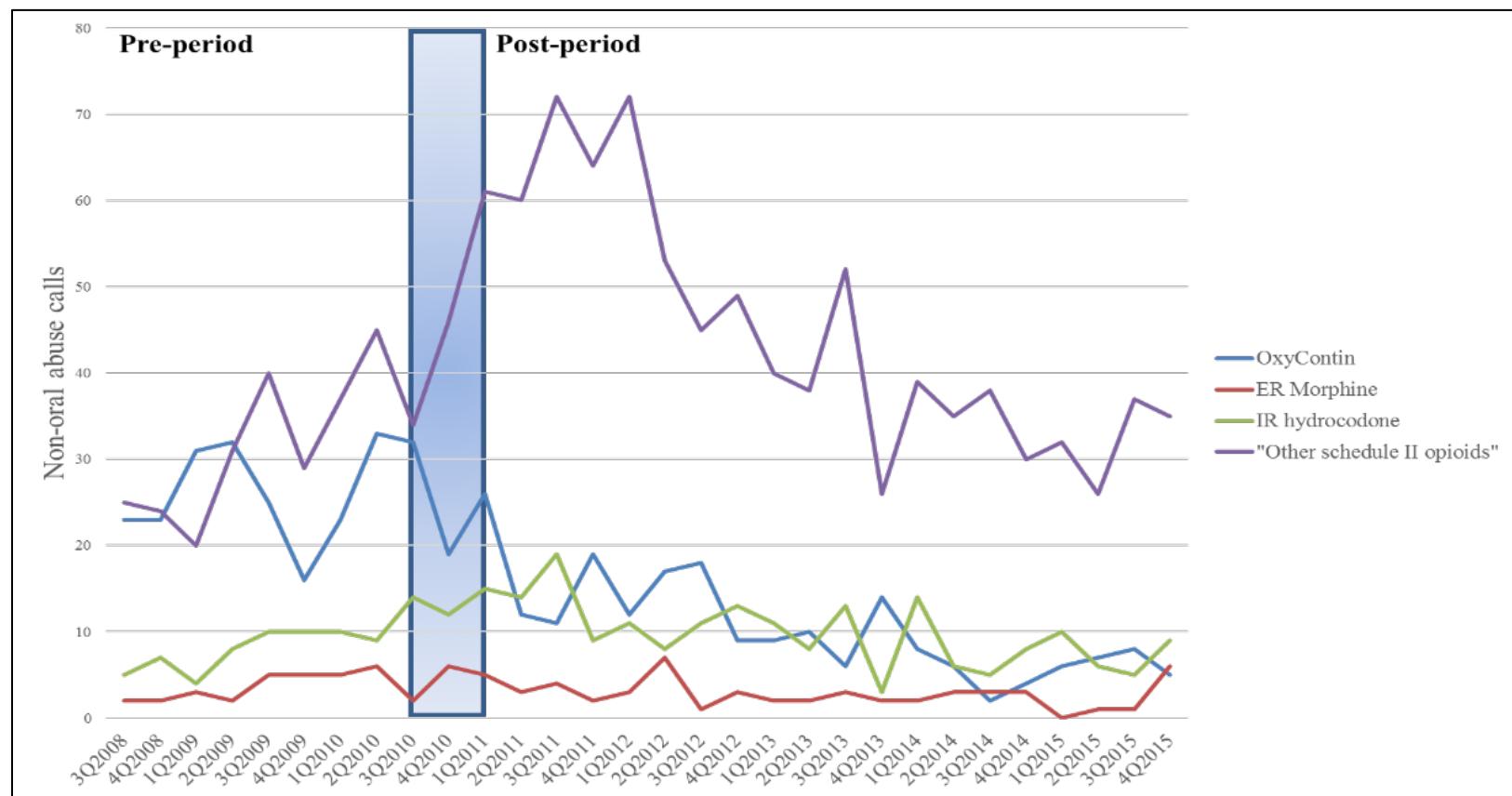
(FDA generated figure using data from the February 21, 2020, sponsor submitted information request response)

Key: extended-release (ER); immediate-release (IR); "other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; the blue box denotes the transition period (excluded from primary analyses)

Figure 2 shows the quarterly number of non-oral (inhalation and injection combined) abuse calls made to PCCs in the pre- and post-periods for OxyContin and primary comparator opioids. Immediately following the reformulation, there was an apparent decline in the number of non-oral abuse calls for OxyContin, and simultaneously an increase for the "other schedule II opioids" composite comparator group, which returned to pre-period levels towards the end of 2012. While the quarterly number of non-oral abuse calls fluctuated throughout the post-period, there was a general declining trend overall for both OxyContin and "other schedule II opioids." The number of non-oral abuse calls for ER morphine and IR hydrocodone were consistently lower than OxyContin in the pre-period but were similar to OxyContin by the end of the post-period.

Figure 2: Total quarterly counts of <u>non-oral</u> abuse calls for OxyContin and primary comparator opioids (-2y/5y)

(FDA generated figure using data from the February 21, 2020, sponsor submitted information request response)

Key: extended-release (ER); immediate-release (IR); "other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; the blue box denotes the transition period (excluded from primary analyses)

Pre- to post-period changes in mean quarterly abuse call rates (via any route)
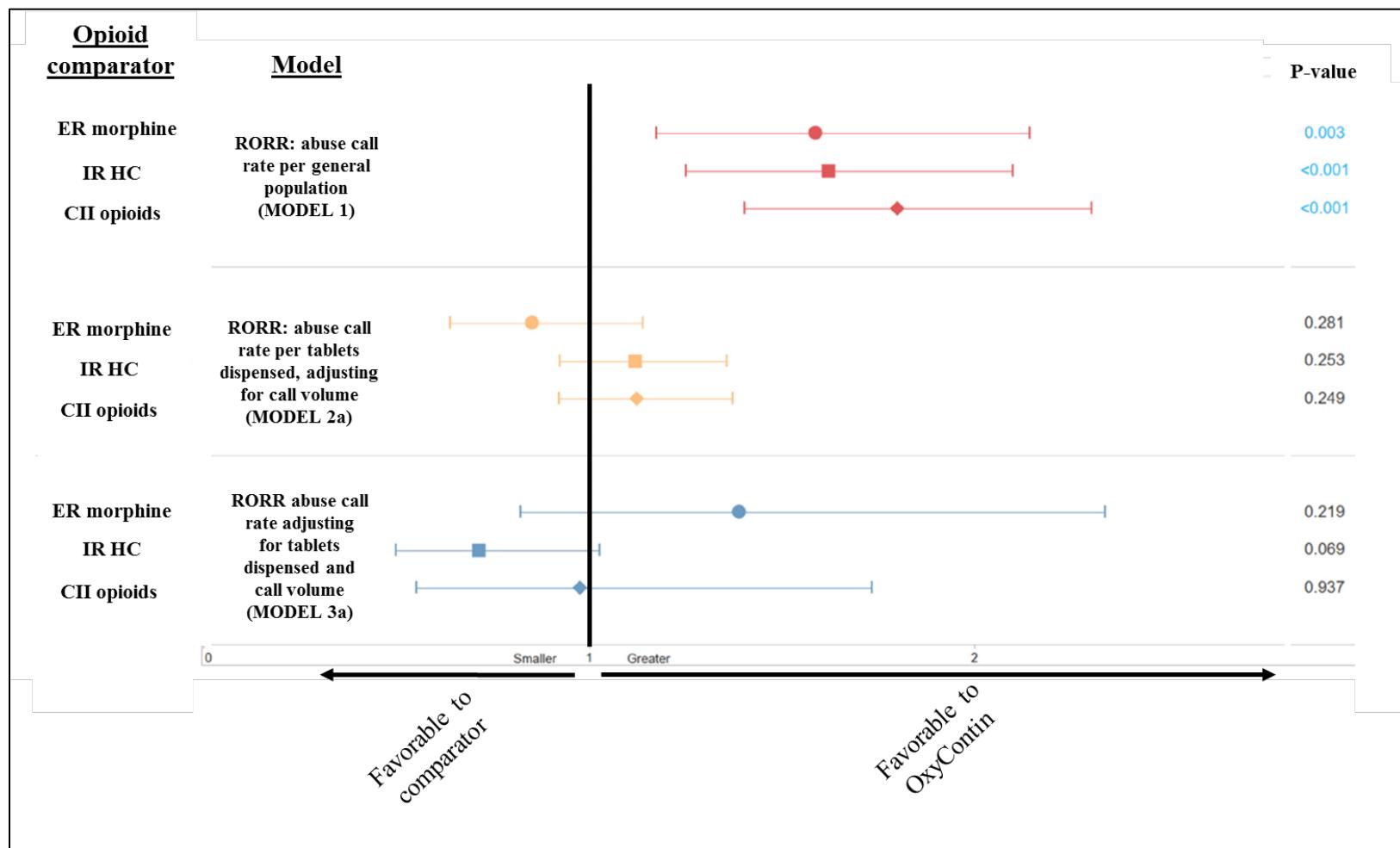
After the introduction of reformulated OxyContin, there was a statistically significant[iv] 55% (95% confidence interval [CI]: -63 to -46%) decrease in the mean quarterly abuse call rate per 100,000 population (Model 1) and a significant 37% (95% CI: -45 to -27%) decrease in the mean quarterly abuse call rate per 100,000 tablets dispensed, adjusting for call volume as a covariate (Model 2a). The model adjusting for tablets dispensed and call volume as covariates (Model 3a) did not show significant declines in the mean OxyContin abuse call rate.

There were also large decreases in mean abuse call rates involving primary comparators, both per general population (Model 1) and per tablets dispensed, adjusting for call volume (Model 2a). Only when modeling abuse call rates per 100,000 population (Model 1) were OxyContin's changes significantly different from that of the primary comparators (See Figure 3), favoring OxyContin (RORRs significantly > 1).

The only comparators with notable increases in mean abuse call rates were the secondary comparators heroin and ER oxymorphone (data not shown).

[iv] Hereafter, "significant" (refers to statistical significance [p<0.05]).

Figure 3: Ratio of Rate Ratios (RORR) comparing change in overall (any route) abuse calls rates for OxyContin to change for primary comparator opioids, by model (-2y/5y)

(Sponsor figure taken from PMR 3051-2 study report; reformatted by FDA)

Key: extended-release (ER); immediate-release (IR); "Other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; confidence intervals (CI); comparing two years before to five years after the reformulation (-2y/5y); RORR > 1 means abuse call rate change comparing periods favors OxyContin, and RORR < 1 means abuse call rate change comparing periods favors the comparator; Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e., total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for the total number of tablets dispensed and call volume as covariates

Sensitivity analyses

Declines in mean abuse call rates per general population (Model 1) were fairly consistent when brand OxyContin and generic oxycodone abuse calls were combined (i.e., "all ER oxycodone"), used shorter pre- and post-periods (i.e., "-1y/3y"), used imputation methods to address calls with missing information on drug formulation (i.e., "with imputation"), and with restricted geographic regions to minimize the potential impact of Florida "pill mill" law enforcement initiatives and legislation occurring around the time of the reformulation (i.e., "excluding Florida"). With the exception of the geographic restriction, the changes in mean OxyContin abuse call rate per 100,000 tablets dispensed were attenuated in these sensitivity analyses.

Interrupted Time Series (ITS) findings: Pre- to post-period changes in overall abuse rate trend and level (via any route)

There was a significant 3.9% decrease in the slope of quarterly OxyContin abuse call rates per general population (Model 5) comparing pre- and post-periods, and a significant 3.6% decrease in the slope of quarterly OxyContin abuse call rates adjusting for tablets dispensed and call volume as covariates (Model 7a); the decline in slope per tablets dispensed was similar to the other models but not significant (Model 6a). OxyContin's decreases in slope were comparable and not significantly different from

those of comparator opioid groups in comparative ITS (CITS) analyses, which may be a function of the more limited power of ITS models when the number of data points is unbalanced across periods and low overall.

With regard to level change, or "immediate shift," OxyContin had a significant 27.5% decline from the model-estimated abuse call rate for the last quarter of the pre-period (2Q2010) to the model-estimated abuse call rate for first quarter of the post-period (1Q2011), per general population (Model 5), and a significant 28.2% decline when adjusting for tablets dispensed and call volume as a covariate (Model 7a). The declines were not significant per tablets dispensed (Model 6a). All CITS level change measures for primary comparators favored OxyContin (i.e., CITS level change measure > 1) across models, but they were only significant for IR hydrocodone and "other schedule II opioids" when modeling abuse call rates per general population (Model 5), and "all schedule II opioids" when modeling abuse call rates adjusting for tablets dispensed and call volume as covariates (Model 7a).

Pre- to post-period changes in mean quarterly abuse call rates, by route

The mean quarterly <u>non-oral</u> abuse call rate per general population (Model 1) for OxyContin decreased more than that of oral abuse (63% compared to 52%, respectively), although these declines were not compared to each other using formal testing of statistical significance. Non-oral abuse call rates for OxyContin per tablets dispensed, adjusting for call volume (Model 2a), also decreased more than oral abuse (47% compared to 32%, respectively), although, again, the differences between oral and non-oral may not have been significantly different from each other. Both per general population (Model 1) and per tablets dispensed, adjusting for call volume (Model 2a), the percent decline in the mean rate of calls involving OxyContin inhalation (Model 1: 66.4%, Model 2a: 49.9%) was slightly larger than the decline in the mean rate of calls involving OxyContin injection (Model 1: 58.9%, Model 2a: 41.8%). The decline in non-oral abuse call rates for OxyContin adjusting for tablets dispensed and call volume as covariates (Model 3a) was not significant.

The changes in non-oral abuse call rate favored OxyContin compared to those of IR hydrocodone and "other schedule II opioids" (RORR >1) across all models, and the changes were significantly different per general population (Model 1) and per tablets dispensed, adjusting for call volume (Model 2a) (See Figure 4). Non-oral abuse call rates increased for both IR hydrocodone and "other schedule II opioids" across models, but the increases were not significant. Comparing OxyContin to ER morphine, the changes in mean quarterly non-oral abuse call rates per population (Model 1) were significantly different from each other (favoring OxyContin; RORR >1); however, the large declines for both OxyContin and ER morphine in mean non-oral abuse call rates per tablets dispensed, adjusting for call volume (Model 2a) and in non-oral abuse call rates adjusting for tablets dispensed and call volume as covariates (Model 3a) were not significantly different from each other. All primary comparators had significant declines in mean oral abuse call rates across nearly all models, and the decline in OxyContin's mean oral abuse call rate was significantly different from those of comparators per general population (Model 1). Of note, the RORRs for the non-oral route were higher than the RORRs for the oral route across comparators and models; for IR hydrocodone and "other schedule II opioids," RORRs for non-oral abuse were roughly double those for oral abuse.

Figure 4: Ratio of Rate Ratios (RORR) comparing change in abuse call rates for OxyContin to change for primary comparator opioids, by model and route (-2y/5y)

ROA	Opioid comparator	RORR: abuse call rate per 100,000 population (MODEL 1)	RORR: abuse call rate per 100,000 tablets dispensed, adjusting for call volume (MODEL 2a)	RORR: abuse call rate adjusting for tablets dispensed and call volume (MODEL 3a)	P-values M1	P-values M2a	P-values M3a
Inhalation	ER morphine				0.149	0.978	0.669
	IR HC				<0.001	<0.001	0.220
	CII opioids				<0.001	<0.001	0.120
Injection	ER morphine				0.094	0.868	0.702
	IR HC				0.041	0.249	0.782
	CII opioids				<0.001	0.004	0.753
Non-oral	ER morphine				0.029	0.985	0.565
	IR HC				<0.001	<0.001	0.189
	CII opioids				<0.001	<0.001	0.208
Oral	ER morphine				0.023	0.113	0.499
	IR HC				0.005	0.965	0.001
	CII opioids				<0.001	0.800	0.333

Favorable to comparator ← 0 … 1 … 2 … 3 … 4 … 5 → Favorable to OxyContin

(Sponsor figure taken from PMR 3051-2 study report; reformatted by FDA)

Key: extended-release (ER); immediate-release (IR); "Other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; confidence intervals (CI); comparing two years before to five years after the reformulation (-2y/5y); Non-oral abuse includes inhalation and injection; RORR > 1 means abuse call rate change comparing periods favors OxyContin, and RORR < 1 means abuse call rate change comparing periods favors the comparator; Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e., total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for the total number of tablets dispensed and call volume as covariates

In descriptive analyses, the proportion of total abuse calls for OxyContin involving non-oral abuse decreased slightly from 18.9% in the pre-period to 15.8% in the post-period, while the percentage reporting oral abuse rose slightly from 66.9% to 71.5%, although these proportions were not compared to each other using formal testing of statistical significance. Approximately 13 to 15% of calls did not contain information on route of abuse for OxyContin over the study period, which was slightly higher than the other comparators which ranged from ~7 to ~11%. The proportion of calls for "other schedule II opioids" involving oral abuse decreased slightly (from 88.0% to 81.5%) and non-oral abuse increased slightly (from 4.5% to 7.5%); ER morphine and IR hydrocodone had very little change in route of abuse profile from the pre- to post-periods.

Changes in abuse rates for secondary (contextual) comparators, including heroin

During the study period, there was a striking increase in quarterly abuse calls involving heroin (Figure 5). Calls involving IR oxycodone remained relatively stable, calls involving methadone declined, and calls involving ER oxymorphone rose rapidly until early 2012, then declined to levels similar to those seen in the late pre-period.

Figure 5: Total quarterly numbers of abuse calls involving OxyContin and secondary comparator opioids (-2y/5y)

(FDA generated figure using data from the February 21, 2020, sponsor submitted information request response)

Key: extended-release (ER); immediate-release (IR)

Changes in mean call rates for other exposure call types

To assess possible secular trends in exposure calls more broadly, the study analyzed calls for exposure reasons other than abuse. OxyContin had significant declines in both intentional misuse and suspected suicide call rates per general population (Model 1), but not per tablets dispensed, adjusted for call volume (Model 2a) or adjusting for tablets dispensed and call volume as covariates (Model 3a). Primary comparators showed consistent declines in both intentional misuse and suspected suicide across models. Also, OxyContin had significant declines in both population- and utilization-based rates of both adverse reactions (which are limited to exposures where the drug was taken as directed) and unintentional exposures (where the drug was taken accidentally) and were similar to the comparator opioids.

Severity of medical outcomes

Comparing the pre- and post-periods, the distribution of medical outcome severity for OxyContin abuse calls was relatively unchanged. In particular, the proportion of abuse-related cases that resulted in a medical outcome designated as major effect (i.e., those where the exposure resulted in signs or symptoms that were life threatening or resulted in significant residual disability or disfigurement), or death, was similar in the pre- and post-periods for both OxyContin and primary comparator opioids. Minor observed shifts may have been, in part, due to changing proportion of cases that were not followed up.

Key Considerations in Interpreting Abuse Call Rate Changes

Accounting for external secular trends and other interventions

Making causal inferences about the effect of OxyContin's reformulation on abuse call rates requires consideration of a number of factors, an important one being alternative explanations for any observed changes. Specific methods and data were used to

explore the impact of secular trends in prescription opioid exposure calls and to evaluate for alternative explanations for any change in abuse call rates including accounting for changing OxyContin availability (i.e., utilization) in various ways, and changing call volume to PCCs. The results of comparative analyses that accounted for utilization were generally attenuated relative to population-based analyses. Broader secular trends in abuse calls are difficult to rule out given that there were large reductions in abuse call rates across most comparators, and also large reductions in OxyContin-related exposure call types that we would not expect to be impacted by the reformulation (i.e., adverse reactions and unintentional general exposures), even after adjusting for changes in utilization. Large and increasing amounts of missing data on product formulation, as well as other data quality issues such as potential misclassification of brand versus generic product exposures, also complicate the interpretation of both the within-drug changes and across-drug comparisons.

The study included comparator opioid drugs to approximate the counterfactual scenario and assist in causal inference. Although each comparator has limitations, ER morphine was particularly limited by low quarterly abuse call rates, especially rates of calls involving non-oral routes, and the large and increasing proportion of morphine exposure calls missing formulation information. From a causal inference perspective, changes in abuse call rates involving OxyContin should be both temporally associated with the marketing of the reformulated product—which they were—but also largely distinct from changes observed in calls involving the primary comparators—which they were not. Although changes in mean population-based abuse call rates were significantly different and favored OxyContin compared to ER morphine and the other comparators, including for non-oral routes, the changes in mean utilization-based abuse call rates for OxyContin were attenuated and not significantly different from that of any comparator for abuse overall (any route), or specifically from ER morphine for abuse by non-oral routes. The comparative results for ER morphine should not be ignored but concerns about its utility as comparator are important to keep in mind when evaluating the impact of the reformulation.

Utilization data (i.e., prescription volume, or amount of drug dispensed) serve as a proxy for availability of a given product for abuse in communities, and thus when estimating pre- versus post-period change in abuse call rates it is important to consider changes in utilization between time periods and differences in utilization when comparing abuse rates or changes in rates for different drugs. Both analyses with and without accounting for utilization are important to consider as part of a range of estimates, as each may either underestimate or overestimate the effect of the reformulation on abuse call rates. However, a meaningful impact of the reformulation should result in robust and reasonably consistent differences between OxyContin and comparators using both approaches, as one would expect that a drug that meaningfully deters abuse would result in a decline in the number of abuse-related calls for a given amount of drug dispensed in the community, and that this decline would be greater than that observed for other opioid analgesics during the same time period. Again, this was not consistently observed in PMR study 3051-2. In addition, comparative RORR estimates were sometimes qualitatively different comparing the two modeling approaches that accounted for utilization, highlighting the uncertainty around these estimates and further complicating their interpretation.

Analyses stratified by route are also important from a causal inference perspective, since the reformulation was designed to impact abuse by non-oral routes. In this study, analyses of changes in oral abuse rates also reinforce the potential for some prevailing secular trends in PCC calls. Comparing periods, there were large declines in mean oral abuse call rates for OxyContin and all comparators, including both population- and utilization-based rates. Both population-based and utilization-based OxyContin oral abuse rate reductions were quite similar to those for the non-oral route, which was not entirely expected given the routes the reformulated product was designed to deter. However, the comparative results (i.e., the RORRs) for the non-oral route more strongly favored OxyContin than did the comparative results for the oral route. This was true across multiple models and comparators, particularly for the IR hydrocodone and "other schedule II opioids" comparators. Route-stratified analyses were limited in that the number of non-oral abuse cases was not sufficient for conducting ITS; however, visual inspection of abuse call counts over time does show an apparent decline in quarterly non-oral abuse calls for OxyContin that roughly coincides with the introduction of the reformulated product and differed in direction from the post-reformulation trend for comparators.

Changes in opioid call trends can also be due to large public policy interventions or changes in illicit drug markets impacting prescription opioid abuse patterns broadly, although perhaps not equally across all products. The results of analyses excluding data from Florida and those restricted to the Western census region were similar to those using data from the entire US, suggesting abuse call rate declines observed for OxyContin were likely not heavily influenced by the Florida "pill mill" legislation and related law enforcement efforts. Of note, OxyContin-specific policies or interventions, like the 2010 OxyContin REMS, could not be controlled for with this type of study design because they occurred around the same time as the market introduction of reformulated OxyContin.

Secondary comparators were helpful for further contextualizing the results observed for OxyContin and primary comparators. Heroin abuse-related calls notably increased after the reformulation, reflecting an emerging dynamic in the opioid abuse landscape around the time of OxyContin's reformulation, whereby opioid analgesic abuse was partially replaced by (or became increasingly mixed with) heroin use. It is important to keep in mind that, although these data were analyzed comparing specific opioid products and product groupings involved in an abuse-related exposure, substance abuse and substance use disorders very commonly involve multiple drugs. Separate FDA analyses of national poison center data showed that from 2014-2018 fewer than half of calls involving oxycodone misuse or abuse were single-substance exposures. While the increase in heroin abuse calls roughly correlates with the timing of the reformulation, it is unclear from these data if and how they are related. If one assumes they are related, it is also not clear whether that would support the causal argument that OxyContin's reformulation drove subsequent declines in abuse call rates involving this product, either overall or route-specific. It is possible that the increases in heroin use during this time acted as one of the larger prevailing trends lowering abuse call rates for nearly all the prescription opioid drugs examined, perhaps impacting some prescription opioids earlier or more than others. At the same time, if OxyContin's reformulation made it less desirable for non-oral abuse, that could have precipitated shifts to heroin in some individuals already abusing or at risk of abusing OxyContin non-orally. Ultimately, the manner in which changes in OxyContin abuse may have influenced or been influenced by increases in heroin use is not entirely clear from this study, as it was not designed to investigate the drivers or effects of increasing heroin use.

Product misclassification and missing data

The declines in OxyContin abuse call rates were generally attenuated in sensitivity analyses addressing product misclassification and missing data—for example, using all ER oxycodone calls rather than restricting to brand-only OxyContin calls, and imputing formulation in calls in which this information was missing. The comparative results (i.e., RORRs), however, were generally consistent with the primary study findings. At the same time, the misclassification of drug product cannot be quantified as there is no way to compare the observed data to "truth" (i.e., complete and accurate call information), and it is unclear how well the imputation methods addressed missing formulation data given the limited variables in the imputation model. Therefore, despite the general consistency across analyses, uncertainty remains with respect to quantifying abuse rates, further complicating the interpretation of the relative changes observed in this study.

Missing data on route was also a potential problem, particularly for OxyContin. Of note, non-oral abuse call rates for unspecified oxycodone increased 37%, and it is unknown what proportion of these calls involved OxyContin versus other oxycodone products, further limiting the ability to quantify any route-specific effect. Nonetheless, the proportion of cases missing those data for OxyContin and comparators was generally stable across periods, so despite some additional uncertainty around the route-specific abuse call rate estimates, the missing route data are unlikely to have had a major effect on the overall interpretation of the non-oral findings.

Synthesis and Overall Interpretation of Study Findings

Effect of OxyContin's reformulation on overall (any route) abuse call rates

The totality of findings from PMR study 3051-2 do not provide robust evidence that the observed decline in <u>overall</u> (i.e., via any route) abuse call rates for OxyContin is attributable to its reformulation rather than to broader secular trends. While the observed declines in the overall abuse call rates for OxyContin were temporally associated with the market introduction of the reformulated product and of a reasonably large magnitude, there were declines in comparator opioids of similar magnitude—particularly when adjusting for changes in the amount of drug dispensed—as well as declines in calls for non-abuse-related exposure calls for both OxyContin and comparators. Taken together, these findings make the prospect of other factors driving down call rates as plausible as the reformulation, although some unknown combination of causes is certainly possible. The change in the mean population-based abuse call rate by any route for OxyContin was significantly different from those for comparators, but this change does not account for the large decrease in prescribed availability of OxyContin (i.e., utilization) relative to comparators. Although fully adjusting for changes in the number of tablets dispensed may underestimate declines in OxyContin abuse call rates attributable to the reformulation, we would still expect a meaningful abuse-deterrent effect to show a change in the number of abuse calls for a given amount of drug dispensed that is larger than the change for comparators; however, this was not the case. The level change ("immediate shift") in OxyContin abuse rate following reformulation was also generally not significantly different from those of comparators after accounting for declines in utilization; nor were any changes in population-based or utilization-based estimates of trends over time (slopes). The causal argument for an attributable decline is further challenged by

commensurate declines in other call types for exposures not expected to be impacted by the reformulation, even after accounting for reduced utilization. Given the challenges associated with PCC data quality, including high levels of missing formulation data for exposures involving oxycodone and morphine, and the potential for misclassification of drug product and exposure reason, it is possible that the overarching limitations of PCC data limit the "assay sensitivity" of this study with respect to accurately measuring and comparing differences in overall abuse call rates between periods. In other words, it is possible that the reformulation did cause some decline in the overall number of exposure calls to poison centers for OxyContin abuse, but there is too much "noise" in these data to clearly differentiate or quantify this effect with a high level of confidence.

Effect of OxyContin's reformulation on non-oral abuse call rates

The totality of evidence from PMR study 3051-2 supports the hypothesis that some decline in non-oral abuse call rates for OxyContin can be reasonably attributed to its reformulation rather than to broader secular trends, but the magnitude of the reformulation's effect on non-oral abuse call rates is uncertain. Stratifying analyses by route and evaluating for a specificity of effect by route can help to establish causal associations that align with the reformulation's design and labeled properties. Calls involving non-oral abuse made up a small proportion of abuse calls overall (<20% for calls involving OxyContin), but unlike for overall abuse call rates (i.e., any route), declines in non-oral abuse call rates were seen for OxyContin but were not seen consistently across the primary comparators. IR hydrocodone and "other schedule II opioids" had no change in mean non-oral abuse call rates and declines in OxyContin's population- and utilization-based non-oral abuse call rates were significantly different from those for both of these comparators. Across all comparators, comparative results for the non-oral route more strongly favored OxyContin than did the comparative results for the oral route. There was also a clear divergence in trend directions for OxyContin and "other schedule II opioids" non-oral abuse calls immediately following the reformulation. Visual inspection of unmodeled trends in quarterly counts shows an apparent *increase* in the number of non-oral abuse calls for "other schedule II opioids" immediately following the introduction of reformulated OxyContin, concurrent with a *decrease* in OxyContin non-oral abuse calls. Only one comparator, ER morphine, had equivocal findings compared to OxyContin, but the interpretation of the ER morphine non-oral abuse call data is complicated by the large amount of missing data on formulation for morphine exposures and the very low quarterly counts of non-oral abuse calls throughout the study period. In this study ER morphine had a relative decrease in utilization-based mean non-oral abuse call rates that was not significantly different from OxyContin's, although the decrease in population-based mean non-oral abuse call rates was significantly greater for OxyContin compared to ER morphine. Taken together, definitively quantifying the contribution of secular trends to the observed declines in OxyContin non-oral abuse rates is not possible, even if it is still reasonable to attribute some of this decline to the reformulation based on the totality of evidence and data from other comparators.

In addition, although the totality of evidence supports some effect of the reformulation on non-oral abuse calls involving OxyContin, the PCC data are limited in that a non-trivial proportion of calls had missing route data, particularly for OxyContin (~13% to ~15%). There was a slight increase in the proportion reporting oral abuse compared to non-oral abuse after the reformulation, but there was no evidence of a shift between non-oral routes (i.e., from snorting to injection), although the data on specific non-oral routes are limited by particularly low quarterly counts. Coupled with the inherent challenges associated with PCC data quality that have been noted, the non-oral abuse results still have a considerable degree of uncertainty, particularly with regard to the magnitude of effect.

Interpretation of other findings

Beyond the specific objectives of PMR study 3051-2, there were other salient findings and data gaps that should be considered in the context of evaluating the reformulation's impact. These data do not suggest that after the reformulation there was much change in the proportion of OxyContin-involved abuse cases resulting in severe medical outcomes or death, although a substantial proportion were missing information on the ultimate medical outcome. Importantly, PCC data are unlikely to capture the most severe overdose cases resulting in unattended, out-of-hospital death. If the reformulation had a disproportionate impact on unattended, out-of-hospital fatal overdose, PMR study 3051-2 would not necessarily have been able to detect this effect.

The post-reformulation abuse call rates for OxyContin do not provide evidence supporting its being a "safer" alternative to other opioid analgesics with respect to abuse. Despite declines in abuse calls following reformulation, calls involving abuse of OxyContin persisted, including calls involving non-oral abuse of this product. Furthermore, abuse call rates remained higher than those for multiple opioid comparators, particularly after accounting for differing levels of prescribed availability (i.e., number of tablets dispensed) for these product groups. Examining the post-period rates can help to contextualize the pre- vs post-

reformulation findings; however, this study was not designed to formally compare abuse call rates across different opioids in the post-reformulation period. Variable levels of missing formulation data complicate the interpretation of post-period abuse call rate comparisons and OxyContin was not compared to all other available opioid analgesic products.

Finally, there was a striking increase in abuse calls involving heroin, with the largest increases occurring after OxyContin's reformulation. Ultimately, the manner in which changes in OxyContin abuse may have influenced, or been influenced by, increases in heroin use is not entirely clear from this study, as it was not designed to investigate the drivers or effects of increasing heroin use.

Conclusions

The totality of findings from PMR study 3051-2 do not provide robust evidence that the observed decline in <u>overall</u> (i.e., via any route) abuse call rates for OxyContin is attributable to its reformulation rather than to broader secular trends. The study findings do support the hypothesis that some decline in <u>non-oral</u> abuse call rates for OxyContin can be reasonably attributed to its reformulation, but the magnitude of the reformulation's impact on non-oral abuse call rates is uncertain. Data from the post-reformulation time period do not provide evidence for reformulated OxyContin being less likely to be abused than other opioid analgesics. Heroin abuse calls increased after reformulated OxyContin was introduced; however, this study was not specifically designed to evaluate substitution effects or causal associations between the reformulation and increases in calls involving other opioids. The findings from this study must be viewed in the context of the other PMR study findings and the entire body of evidence taken into consideration to inform the discussion surrounding the effectiveness of OxyContin's reformulation on reducing abuse in the community.

1 INTRODUCTION

Postmarketing requirement (PMR) study 3051-2 is one of four studies the United States Food and Drug Administration (FDA) required of the sponsor, Purdue Pharma, LP (hereafter, the sponsor), to evaluate the impact of OxyContin's reformulation on its abuse. Specifically, PMR study 3051-2 aimed to assess resulting changes in calls to United States poison control centers (PCCs) involving the abuse of OxyContin by any route (overall), and those involving specific routes of abuse (oral, inhalation, injection). OxyContin (oxycodone hydrochloride, controlled release; New Drug Application [NDA] 022272) was reformulated with physicochemical properties that are intended to deter tablet manipulation for the purposes of abuse primarily via insufflation and injection. The reformulation incorporated a high molecular weight polymer (polyethylene oxide) matrix with the intention of making the tablet more difficult to manipulate for the purposes of misuse or abuse. Based on review of *in vitro* and clinical study data, in 2013 FDA concluded reformulated OxyContin had "abuse-deterrent" characteristics, and the label[v] was updated with its current language:

"The in vitro data demonstrate that OXYCONTIN has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the in vitro data, also indicate that OXYCONTIN has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OXYCONTIN by these routes, as well as by the oral route, is still possible."

Observational studies, including PMR study 3051-2, were required to provide further information on the ability of reformulated OxyContin to deter abuse and reduce abuse-related harms in the postmarket setting. Study 3051-2 used data on exposure calls to United States (US) PCCs from Researched Abuse, Diversion, and Addiction-Related Surveillance System (RADARS) System Poison Center Program to measure changes in the rates of calls involving abuse of the product, comparing the pre-reformulation period of OxyContin marketing to a defined post-reformulation period, relative to comparator opioid analgesic drugs marketed during that time. The three additional required studies evaluate changes from the pre- to post-reformulation in: 1) opioid abuse in a sentinel population of adults who were assessed for substance use disorder and treatment planning, using data from the NAVIPPRO® ASI-MV surveillance system (PMR 3051-1); 2) opioid abuse in a sentinel population of adults entering methadone and non-methadone treatment for opioid use disorder, using data from the RADARS Treatment Center Program (PMR 3051-3); and 3) fatal and non-fatal opioid overdose among a population of patients prescribed OxyContin or comparator opioids (PMR 3051-4).

In 2014, the sponsor submitted studies to support a postmarketing abuse-deterrence labeling claim; these studies were reviewed by the Division of Epidemiology (DEPI) and the Division of Biometrics (DB7), and an Advisory Committee (AC) meeting was scheduled for July 2015 to discuss the studies' findings' in a public forum. In June 2015, the sponsor withdrew their labeling supplement and the AC meeting was cancelled. In 2016, FDA issued formal PMR letters to ensure timely study completion and to allow FDA to provide input on study design and methods. With respect to PMR study 3051-2, the FDA provided the sponsor with several recommendations on ways to improve the study by exploring potential sources of bias and better assessing the robustness of the study's findings, and in 2018, the sponsor submitted a final study report for study 3051-2 incorporating FDA's recommendations.

The objective of this review was to determine whether data from PMR study 3051-2 provide evidence that OxyContin's reformulation reduced exposure calls to US PCCs mentioning abuse of the product (overall and/or via specific routes).

In conjunction with the other PMR studies (3051-1,3, and 4) and other relevant information, the findings of this study can be used to help inform the overarching question of whether OxyContin's reformulation meaningfully reduced its abuse and associated harms. While each study can alone provide important information on the potential impact of the reformulation, it is ultimately necessary to evaluate the totality of evidence from all sources to answer this question.

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[v] OxyContin label (revised 08/2015): https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022272s027lbl.pdf

2   REVIEW METHODS AND MATERIALS

To prepare this document, DEPI reviewed:

- PMR study 3051-2 final study report (EPI8013ORF) - "*Changes in Abuse of OxyContin Following its Reformulation with Properties Intended to Deter Abuse as Measured by the RADARS® System Poison Center Program*" (received July 2018)
  - Study protocol
  - Statistical Analysis Plan (SAP)
  - Study results, including all appendices
- Sponsor submitted responses to Agency information requests:
  - Received November 20, 2019
  - Received January 10, 2020
  - Received February 21, 2020
  - Received February 26, 2020
  - Received March 6, 2020

In brief, this review document provides a summary and interpretation of PMR study 3051-2 methods and main findings, including a discussion of relevant methodological issues and how these impact inferences that can be made based on the study's results. The findings of this review will be used to inform the broader question of whether OxyContin's reformulation was effective in reducing abuse and associated harms. DEPI also conducted a review of the literature to identify other published studies that are closely related to PMR study 3051-2 (i.e., analyses of US poison center call data); search terms and strategy are described in the literature review section of this background document (see background document: OSE Literature Review). Two such studies were identified, and these were reviewed for any additional information that could inform the findings of PMR study 3051-2.

To determine whether OxyContin's reformulation reduced abuse-related exposure calls to US PCCs, PMR study 3051-2 findings were evaluated using FDA's Guidance for Industry, "Abuse-Deterrent Opioids - Evaluation and Labeling,"[vi] and the guiding principles of epidemiology, including principles for making causal inferences from observational data. Interpretation of study findings and conclusions were based on the temporality, strength, consistency, and specificity of observed associations, and alternative explanations for the observed associations, incorporating the results of comparator drugs to approximate the counterfactual scenario (i.e., use of comparators as "negative controls"). Data quality and the utility of specific analytic methods and models were also considered.

3   STUDY METHODS

3.1   STUDY OVERVIEW

PMR study 3051-2 assessed the change in rates of calls to US PCCs involving the abuse of OxyContin overall (any route), and by specific routes (oral, inhalation, injection), comparing the two years before to the five years after OxyContin's reformulation. Comparator opioids were included in this evaluation to provide contextual information on abuse trends unrelated to the reformulation and to aid in causal inference. Due to the inherent uncertainties associated with these data and their interpretation, (e.g., increasing missing formulation information over time, broader changes in PCC call patterns over time or other secular trends, and inability to reliably distinguish between brand and generic products), a number of different analyses were conducted, including imputing missing data, and varying the time period, definition of OxyContin (i.e., brand OxyContin only, or any ER oxycodone including brand and generic), geographical area covered, and models and offsets/covariates used to estimate abuse call rates and account for changes in drug utilization over time. These varied approaches were used to assess robustness of the primary study findings.

[vi] FDA's Guidance for Industry, Abuse-Deterrent Opioids - Evaluation and Labeling (2015): https://www.fda.gov/media/84819/download

3.2   STUDY OBJECTIVES

Note: In this review, ***abuse call rates*** are defined as rates of exposure calls to US PCCs where the reason for exposure was classified as "abuse" and the drugs involved in the exposure included OxyContin (or a comparator drug)

Primary objectives:

1) To measure the changes in mean abuse call rates for OxyContin comparing the two years (pre-period) before its reformulation to the five years (post-period) after its reformulation (-2y/5y)
2) To measure the changes in mean abuse call rates for OxyContin compared to primary comparator opioids (-2y/5y)
3) To measure the changes in mean abuse call rates for OxyContin comparing the year before its reformulation to the three years after its reformulation (-1y/3y)
4) To measure the changes in mean abuse call rates for OxyContin compared to primary comparator opioids (-1y/3y)

Secondary objectives:

1) To assess the abuse call rate trends for OxyContin and comparator opioids (-2y/5y and -1y/3y)
2) To measure the changes in mean non-abuse-related exposure call rates for OxyContin compared to comparator opioids (-2y/5y)
3) To measure the changes in mean abuse call rates for OxyContin compared to comparator opioids by routes of abuse (-2y/5y and -1y/3y)
4) To measure the changes in mean abuse call rates for OxyContin compared to secondary comparator opioids (-2y/5y and -1y/3y)

3.3   OVERARCHING METHODOLOGICAL CONSIDERATIONS FOR PMR STUDY 3051-2

There are several notable aspects of the PMR 3051-2 study design and methods that were intended to address concerns with the data and potential biases, and to assist in the interpretation of study findings.

- To make causal inferences about the impact of OxyContin's reformulation on abuse call rates, one must consider alternative explanations for any observed changes, for example, secular trends in abuse calls that may confound the association. Secular trend bias, or confounding by calendar time, is generally agnostic to directionality, meaning these larger trends could, in theory, make OxyContin's reformulation appear more, or less, favorable relative to its original formulation in terms of reducing abuse call rates. To better isolate the effect of OxyContin's reformulation, the sponsor used comparator opioid drugs to approximate the counterfactual scenario, or what would have been expected to happen to abuse call rates had OxyContin never been reformulated as observed through similar opioid drugs that were not reformulated with abuse deterrent properties. To directly compare the changes in the abuse call rates from the pre- to the post-periods for OxyContin and comparator opioid drugs, quasi-experimental difference in difference methods are implemented to test for statistically significant differences in the pre-post changes in abuse rates, comparing OxyContin and a "negative control" drug. The difference in difference design can to be used to look for causal relationships in settings where a randomized controlled trial is impractical, or potentially even unethical.[vii] Comparators can also be useful in understanding the potential impact of differentially misclassified or missing data, or other issues relevant to the data source specifically. In this study, three primary comparators (extended-release [ER] morphine, immediate-release [IR] hydrocodone combination products, and "other schedule II opioids" [composite comparator[viii]]) were used as "counterfactuals," with which to directly compare to OxyContin. These primary comparators were selected based on their large and relatively stable market history and other characteristics that make them potentially valuable representatives of background abuse call trends.
- Several different statistical models (all Poisson regression models using a difference in difference design) were used to model changes in the abuse call rates for OxyContin and comparator opioids comparing the pre- to post-periods. Some models estimated rate ratios (expressed as percent change) comparing mean quarterly abuse call rates in the pre- and

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[vii] Wing C et al. (2018) Designing Difference in Difference Studies: Best Practices for Public Health Policy Research. Annual Review of Public Health; 39: 453-469.

[viii] Includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, plus IR oxycodone products

post-reformulation time periods, and others used interrupted time series (ITS) methods to estimate the change in the slope of abuse call rates, as well as the "immediate shift" (i.e., level change), comparing the time periods. Because different results are obtained based on which analytic approach is used and its accompanying assumptions, the sponsor ultimately implemented a diverse set of models with differing parametrizations, including those with and without offset variables, and those with and without adjusting for an opioid's utilization rates (i.e., tablets dispensed) and the total pharmaceutical exposure calls to PCCs (i.e., overall call volume to PCCs).
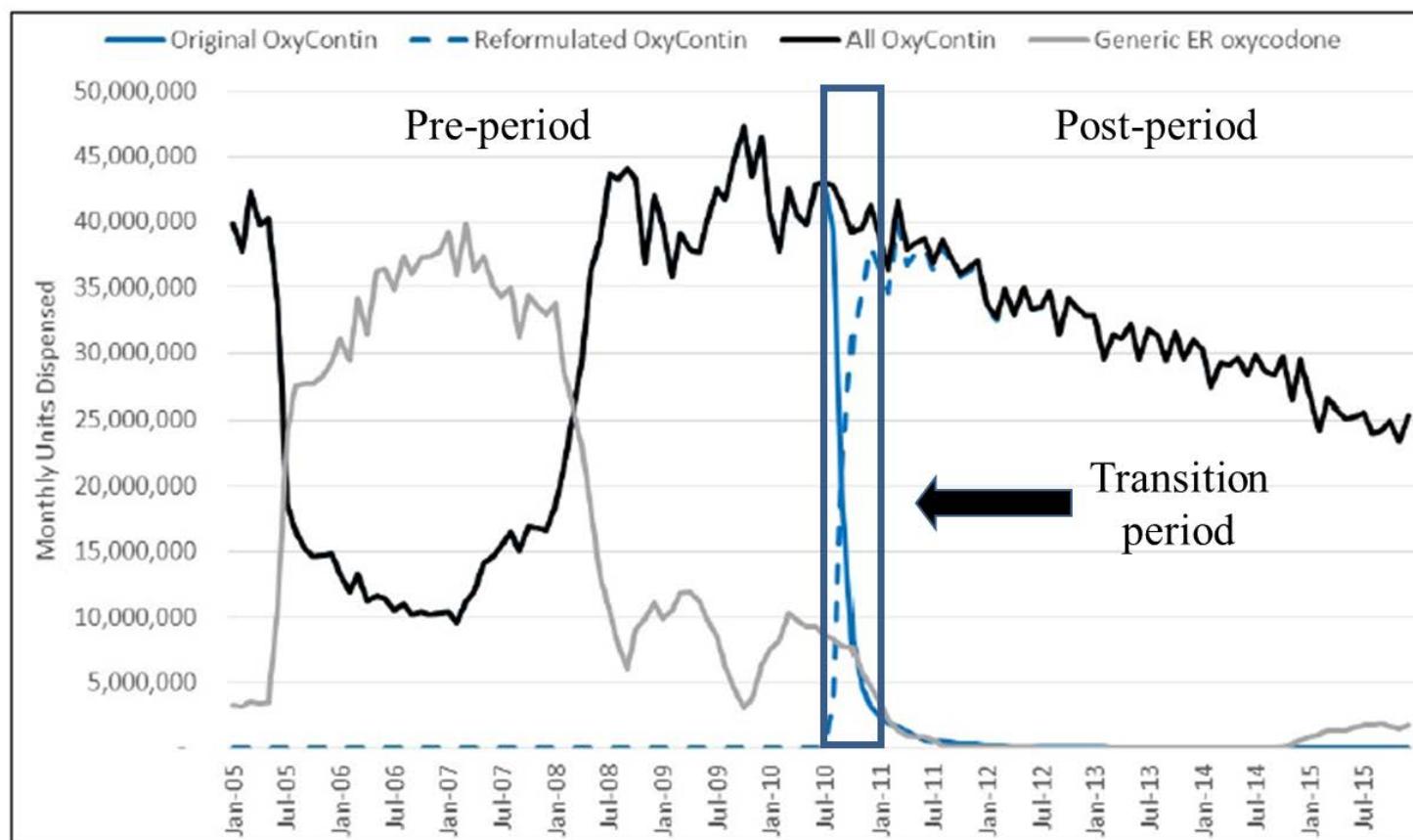
- Abuse of prescription opioid products can only occur when those products are available in the community, generally through retail prescription dispensing. A drug's level of prescription dispensing (e.g., number of tablets dispensed) can be used as a proxy for their community availability for abuse, particularly when comparing between opioid products and/or time periods with different levels of utilization. It makes intuitive sense that the amount of drug prescribed and dispensed is related to the number of abuse cases observed in that a drug must be available to be abused, and prior work has shown that increasing rates of abuse correlate with increasing levels of drug utilization, although the relationship is not entirely straightforward, particularly for drugs with very low or very high prescription volume[ix]. In comparative analyses, not accounting for differing availability can confound comparisons across time and/or across different comparator opioid drugs when attempting to assess the causal relationship between the reformulation and abuse call rates, particularly since OxyContin's utilization rates declined after the reformulation, while the utilization of some other opioid drugs increased. However, some of the decline in OxyContin prescribing may have been due to the reformulation's effect on OxyContin's abuse liability (i.e., reducing demand for purposes of abuse or diversion), and therefore would lie in the causal pathway between the reformulation and changes in abuse call rates. On the other hand, multiple other factors could also have impacted prescribing patterns for OxyContin and other opioids, for example like changes in insurance reimbursement and formularies, the 2010 OxyContin Risk Evaluation and Mitigation Strategy (REMS), law enforcement activity, or patients' or providers' perceived changes in clinical effect.[x] Therefore, models that do not include a measure of utilization may overestimate the effect of the reformulation on abuse call rates in the face of decreasing utilization due to reasons other than the reformulation's impact on abuse liability, whereas models that do include a measure of utilization may underestimate the effect of the reformulation if some of the decrease in OxyContin utilization is, in fact, due to the reformulation's impact on the drug's desirability for abuse and a reduction in demand for this purpose. Therefore, it is important to evaluate abuse call rate changes both with and without incorporating utilization data as each may bias modeled relative rate ratios in different ways.

- Exposure calls made to PCCs are classified under different categories, broadly defined by intentionality. "Intentional exposures" like abuse, misuse, and suspected suicide are differentiated from one another in the data, but there is the potential for misclassification of which type of exposure precipitated the call given the inherent difficulties with accurately determining someone's intent, particularly if they are unconscious. Therefore, looking for changes in call rates for intentional exposures other than abuse around the time of the reformulation is helpful to contextualize changes in abuse call rates for OxyContin, including whether there may be differential misclassification by opioid. Other calls involving OxyContin for exposures not likely to be impacted by OxyContin's reformulation and unrelated to abuse like unintentional general exposures (e.g., accidental pediatric exposures) and adverse reactions were also analyzed to evaluate for secular trends in calls to PCCs involving OxyContin overall.

- Generic ER oxycodone products were concurrently marketed with OxyContin (see Figure 6), albeit to a lesser extent, with their distribution largely phased out by the beginning of the post-reformulation period, after which essentially all dispensed ER oxycodone was the reformulated OxyContin. Because both products were the same opioid moiety and formulation, abuse exposure cases reported to PCCs may have been inadvertently misclassified with respect to the product involved (i.e., brand or generic). The overall extent of misclassification of generic ER oxycodone and OxyContin in these data is unknown, but it would only impact relative comparisons between comparator opioids if it were occurring differentially (i.e., one direction *more* than the other). To better understand the potential impact of misclassification,

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[ix] Secora A, Trinidad JP, Zhang R et al. (2017) Drug availability adjustments in population-based studies of prescription opioid abuse. Pharmacoepidemiology and Drug Safety. 26(2): 180-191; Dasgupta N, Kramer ED, Zalman MA, et al. (2006) Association between non-medical and prescriptive usage of opioids. Drug and alcohol dependence. 82(2): 135-142

[x] Argoff, C.E., S.P. Stanos, and M.S. Wieman, Validity testing of patient objections to acceptance of tamper-resistant opioid formulations. J Pain Res, 2013. 6: p. 367-73

changes in abuse call rates from the pre- to the post-period were evaluated using a less specific definition that included "any ER oxycodone" (i.e., brand OxyContin or generic ER oxycodone reported); these results were compared to results from primary analyses using more narrow definition of OxyContin (i.e., brand only reported). If the observed decline in abuse call rates between periods is robust to a less specific definition of OxyContin (i.e., ER oxycodone), any impacts from the potential misclassification of OxyContin and ER oxycodone may be less important to consider in the context of evaluating the impact of the reformulation.

Figure 6: Monthly dosage units dispensed for ER oxycodone products, 1/2005 – 6/2015

(*Sponsor figure taken from PMR 3051-2 study report; transition period added by FDA*)

- In some abuse call cases, information on drug formulation (i.e., immediate- versus extended-release) involved is unknown or not recorded during the call. The percentage of abuse calls involving oxycodone that were missing formulation information increased over the study period. A similar pattern was seen with ER morphine as well as IR hydrocodone to a lesser extent. One method for mitigating the effects of missing information is using imputed data based on probability distributions derived from the observed data, and assumptions for the mechanism behind the missingness. As sensitivity analyses, multiple imputation methods were used to generate imputed formulation data for calls related to oxycodone, morphine, and hydrocodone, and the results using those data were compared to the results of "complete case" analyses (i.e., excluding cases with missing formulation data). Other methods of imputation were explored, including classifying all cases that were missing formulation information based on the actual proportions of drug dispensed as ER and IR formulations for a given opioid moiety in a given quarter.
- One particular policy intervention around the time of OxyContin's reformulation that could have affected opioid prescribing and/or abuse call rates was the 2010-2012 Florida crackdown on unregulated pain clinics (i.e., "pill mills") to reduce the distribution of opioid analgesics for abuse. These efforts were multifaceted, consisting of targeted efforts by the Drug Enforcement Administration (e.g. "Operation Oxy Alley" [February, 2010] and "Operation Pill Nation" [February, 2011, and August, 2012]), and legislation addressing the rapid proliferation "pill mills" in Florida (October,

2010, and July, 2011). [xi] Because it was believed a substantial percentage of the diverted opioids in some parts of the United States were largely supported through Florida-based "pill mill" activity, their termination shortly after the reformulation could have had an outsized effect on prescription opioid abuse in Florida and other states in the eastern part of the country. The impact may also have differentially affected certain opioids, particularly oxycodone products, which were highly sought after.[xii] As sensitivity analyses, geographically-restricted PCC data (excluding Florida, and including only the Western U.S.) were analyzed to explore whether this effort may have precipitated changes in abuse call rates.

3.4 DESIGN & SETTING

3.4.1 Study Design

Ecological time series (with difference in difference design)

3.4.2 Databases

RADARS Poison Center Program

The Researched Abuse, Diversion, and Addiction-Related Surveillance System (RADARS) Poison Center Program (PCP) provides data on calls made to US PCCs; the PCP coverage areas included ~83% to ~94% of the US general population during the study period. Available data on exposure cases include age, sex, product or substance, call type (informational or exposure-related), reason for exposure, route of administration, date of exposure, medical outcomes (including death), clinical effects, therapies, and a free text field. Intentional exposures are further classified as abuse, misuse, suspected suicide, or other intentional.

IQVIA National Prescription Audit™

The IQVIA National Prescription Audit™ (NPA) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, and long-term care facilities into the hands of consumers via formal prescriptions in the US; data for the NPA audit is a national level estimate of the drug activity from these three channels. The pharmacies in the database account for most retail pharmacies and represent ~92% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data are also collected from approximately 60 – 86% (varies by class and geography) of mail service pharmacies and approximately 75 – 83% of long-term care pharmacies.

3.4.3 Time Period Definitions

Before reformulation (pre-period or baseline period): the time before OxyContin's reformulation (see Figure 7) was used as a reference period with which to compare abuse call rates after the reformulated product was introduced to the market (post-reformulation period).

- **2-year baseline (3Q2008-2Q2010)**: reflects a longer baseline period with a relatively stable market with respect to OxyContin prescription dispensing[xiii]
- **1-year baseline (3Q2009-2Q2010):** reflects the most recent experience prior to OxyContin reformulation

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[xi] Kennedy-Hendricks A. et al (2016) Opioid Overdose Deaths and Florida's Crackdown on Pill Mills. American Journal of Public Health; 106 (2): 291-297

[xii] New York Times, "Florida shutting 'pill mill' clinics", August 31, 2011: https://www.nytimes.com/2011/09/01/us/01drugs.html ; Office of National Drug Control Policy, Fact Sheet, "Prescription Drug Monitoring Programs", April 2011: https://www.ncjrs.gov/pdffiles1/ondcp/pdmp.pdf ; Rigg KK, March SJ, Inciardi JA (2010) Prescription Drug Abuse & Diversion: Role of the Pain Clinic. J Drug Issues; 40(3): 681-702

[xiii] Does not include the large fluctuations in brand versus generic ER oxycodone prescriptions observed in early 2008 after reinstatement of the OxyContin patent
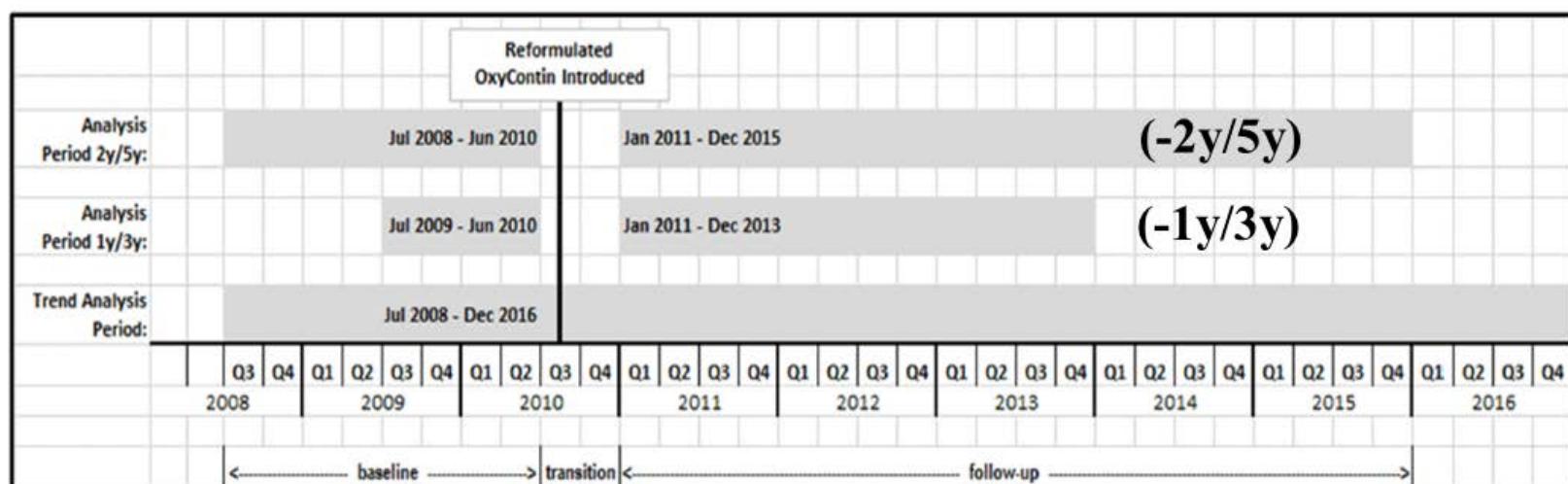
Transition period (excluded): the time between study periods where both the original and reformulated OxyContin may have been available for abuse (see Figure 4)

- **6-month transition (3Q2010-4Q2010):** excluded from analyses as it includes the introduction of reformulated OxyContin to the market, and the decreasing supply and availability of the original OxyContin formulation. In some sensitivity analyses, the transition period was included in the post-reformulation period.

After reformulation (post-period or follow-up period): the time after OxyContin's reformulated product was introduced to the market (see Figure 4) was compared to the pre-period looking for a time period effect on abuse call rates.

- **5-years post-reformulation (1Q2011-4Q2015):** provides an estimate of the sustained effect on abuse calls after the reformulation
    - **Post-period 1 (3Q2010-4Q2013):** used for interrupted time series only (Ad hoc sensitivity analyses conducted by the sponsor)
    - **Post-period 2 (1Q2014-4Q2015):** used for interrupted time series only (Ad hoc sensitivity analyses conducted by the sponsor)
- **3-years post-reformulation (1Q2011-4Q2013):** reflects the more immediate experience following the introduction of reformulated OxyContin

Figure 7: Study periods and analytic windows

(*Sponsor figure taken from PMR 3051-2 study report; years added by FDA*)

Key: Analysis period two years before the reformulation compared to five years after the reformulation, excluding the transition period (-2y/5y); Analysis period one years before the reformulation compared to three years after the reformulation, excluding the transition period (-1y/3y); some trend analyses include data through 2016 (See section 3.4.6.1)

3.4.4 OxyContin Definitions

Two definitions of OxyContin were used in this study to calculate abuse call rates. The main definition (used in all primary analyses) was more specific as rates were calculated based on calls only mentioning OxyContin.

Main definition (more specific)**:** Any OxyContin

- Original OxyContin in the pre-period, and any (original or reformulated) OxyContin in the post-period:
    - Original: The formulation of OxyContin without abuse-deterrent properties that was marketed by the sponsor between January 1996 and August 2010
    - Reformulated: The reformulated version of OxyContin with abuse-deterrent properties that entered the market in August 2010 and substantially replaced the original OxyContin in pharmacies by January 2011

To account for any potential misclassification in the pre-period when both generic ER oxycodone and brand OxyContin were marketed simultaneously, a broader definition of OxyContin was used in sensitivity analyses.

Sensitivity definition (less specific)**:** Any extended-release (ER) oxycodone

- Original OxyContin or generic ER oxycodone in the pre-period, and original OxyContin, reformulated OxyContin, or generic ER oxycodone in the post-period

3.4.5 Outcome Measures[xiv]

Note: All outcomes noted below reflect the circumstances surrounding various types of drug exposures that resulted in calls to PCCs by individuals and/or healthcare providers with the objective of obtaining advice on their clinical management; determinations on intent are generally made by the healthcare professionals who field these calls.

Primary outcome[xv]:

Intentional abuse (hereafter, abuse): An exposure resulting from the intentional improper or incorrect use where the patient was likely attempting to gain a high, euphoric effect or some other psychotropic effect, including recreational use of a substance for any effect.

- Overall (by any route and including multi-substance exposures)
- By specific route of abuse (ROA): cases reporting exposure via one route; multi-substance exposures were excluded unless only one route was reported
    - Oral: swallowing (whole or chewed/dissolved)
    - Inhalation: insufflation and smoking
    - Injection: parenteral
    - Non-oral: unintended route of administration (combined inhalation or injection)
    - *Sensitivity ROA analysis*: All cases were included, regardless of whether multiple routes were reported. If both non-oral and oral routes were both reported in a given case, the case was categorized as non-oral.

Secondary outcomes[xvi]:

Intentional exposures

Intentional misuse: An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect.

Suspected suicide: An exposure resulting from the inappropriate use of a substance for reasons that are suspected to be self-harm.

Unintentional exposures

Therapeutic errors: An unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance. Only exposures to medications or products used as medications are included. Drug interactions resulting from unintentional administration of drugs or foods which are known to interact are also included.

Unintentional general exposures: All unintentional exposures not otherwise defined by therapeutic errors. This category contains mostly accidental exposures.

Adverse reactions

[xiv] In general, FDA has defined "*misuse*" as the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed and "*abuse*" as the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. FDA recognizes that the term abuse has been identified as potentially stigmatizing to individuals with substance use disorders. This is in no way our intent; rather, we are using the term abuse as it has been previously defined specifically by FDA to describe a specific set of behaviors, or as it is used in the studies we are reviewing, when describing the findings of these studies. Note that in this study we are using abuse and misuse definitions from the America Association of Poison Control Centers, which also align with FDA's definitions.

[xv] Definition from America Association of Poison Control Centers (AAPCC)

[xvi] Definition from AAPCC

Unwanted effects due to an allergic, hypersensitivity, or idiosyncratic response to the active ingredient(s), inactive ingredient(s) or excipient of a drug, chemical, or other drug substance when the exposure involves the normal, prescribed, labeled or recommended use of the substance.

3.4.6 Comparators

Primary comparators

Three primary comparators were intended to serve as "negative controls" for OxyContin, reflecting background trends and approximating expected changes in OxyContin abuse call rates in the absence of the reformulation (i.e., the counterfactual scenario). As there is no single ideal comparator, these comparators were chosen to reflect a diverse set of opioid analgesic products with varied characteristics (see Table 1).

- **ER morphine**: an ER opioid analgesic drug used in chronic pain settings, abused via multiple routes, and subject to the same regulatory actions as OxyContin (e.g., the ER/long-acting [ER/LA] opioid Risk Evaluation and Mitigation Strategy [REMS]). ER morphine was not reformulated and had a large market share over the study period
- **Immediate-release (IR) hydrocodone combination products**: an opioid analgesic drug with a large, stable market share over the study period that is commonly abused but with a different route of abuse profile from OxyContin. During the study period, the vast majority of hydrocodone was dispensed as fixed-dose IR combination products, and therefore may have been less subject to misclassification and missing data, compared to oxycodone products.
- **"Other schedule II opioids"** – consisting of ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, morphine, and IR oxycodone (excluding OxyContin and methadone): a composite category of opioid analgesics intended to reflect broad trends affecting the entire class of medications

Table 1: Characteristics of OxyContin and primary comparators

	OxyContin	ER Morphine	IR Hydrocodone	Other Schedule II
Formulation	Extended-release single-entity oxycodone product	Extended-release single-entity morphine product	Immediate-release hydrocodone product most frequently combined with acetaminophen, does not exist as a single-entity product	Composite grouping that includes IR oxycodone, ER and IR hydrocodone, ER and IR oxymorphone, ER and IR hydromorphone, and ER and IR morphine
Abuse Potential	DEA Schedule II product	DEA Schedule II product	DEA Schedule III product during most of the study evaluation period (re-scheduled from CIII to CII in October 2014)	DEA Schedule II (with exception of IR hydrocodone)
Utilization Characteristics[1]	Average number of dosage units dispensed per month during 2011-2015 timeframe ranged from about 25-40 million. Approximate 25% decrease in average number of tablets per month dispensed in 2y/5y period. Original OxyContin approved by the FDA in 1995; reformulated OxyContin approved in 2Q2010 and by 1Q2011 nearly all OxyContin tablets dispensed in US were for reformulated product	Average number of dosage units dispensed per month during 2011-2015 timeframe ranged from about 35-40 million. Approximate 21% increase in average number of tablets dispensed per month in 2y/5y period. Large Increase in number of generic ER morphine products with decline in brand products during study	Average number of dosage units dispensed per month during 2011-2015 timeframe ranged from about 450-660 million. Approximate 3% increase in average number of tablets dispensed per month in 2y/5y period. Decline in tablets dispensed following DEA rescheduling to Schedule II	Average number of dosage units dispensed per month during 2011-2015 timeframe ranged from about 860 million to 1.1 billion. Approximate 10% increase in average number of tablets dispensed per month in 2y/5y period.
Regulation	Subject to ER/LA opioid analgesic regulatory actions such as the ER/LA Opioid Analgesic REMS	Subject to ER/LA opioid analgesic regulatory actions such as the ER/LA Opioid Analgesic REMS	Re-scheduled from Schedule III to Schedule II in October 2014	Subject to ER/LA REMS and rescheduling per individual product

(*Sponsor table taken from PMR 3051-2 study report*)

None of the comparators is likely a perfect approximation of the counterfactual scenario for all questions. For instance, "other schedule II opioids", proposed by the sponsor as a primary comparator, may be useful for assessing secular trends in overall and to some extent non-oral abuse-related calls to PCCs involving prescription opioids more generally. At the same time, its
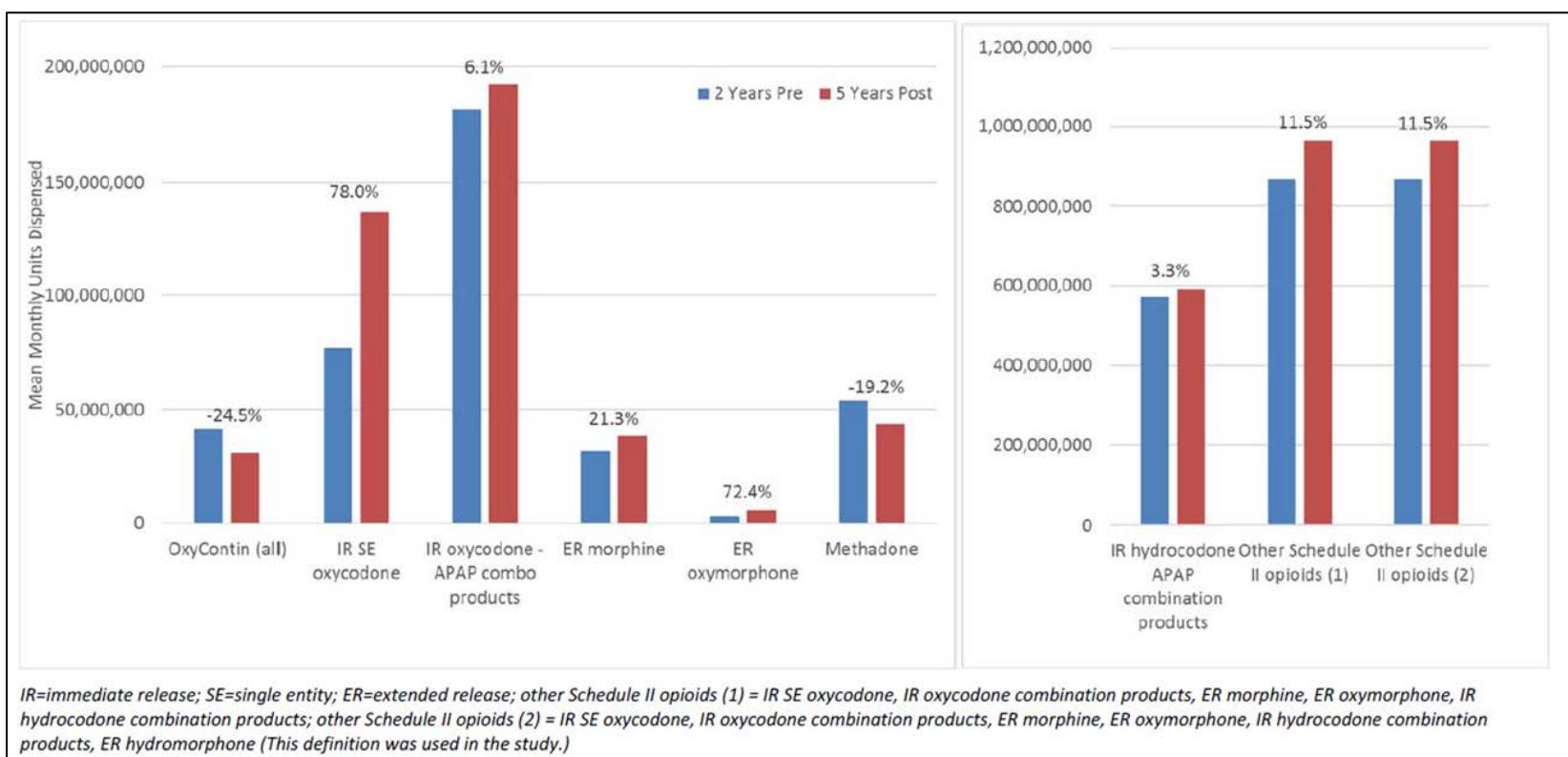
composition changed during the study period, with large increases in the share of dosage units dispensed for IR single-entity (SE) oxycodone (see Figure 8), and the market entry of other opioid analgesics (e.g., ER hydromorphone). Also, despite being a composite comparator, hydrocodone-acetaminophen makes up the bulk of dosage units dispensed for "other schedule II opioids" in this study. ER morphine may be useful for establishing background trends in non-oral abuse or shifting routes of abuse in opioid-related calls; however, while ER morphine had a similar utilization to OxyContin, the mean monthly dosage units dispensed of ER morphine increased by >21% comparing periods, while those of OxyContin decreased by >24%. Large differences in utilization trends creates some added complexity in interpreting change in abuse call rates.

Secondary comparators

Secondary comparators were included to provide further contextual information on opioid-related abuse call rates, and while helpful in interpreting changes in abuse call rates for OxyContin and primary comparators, these comparators had certain limitations that limited their utility as direct primary comparators (i.e. as approximations of the "counterfactual"):

- *ER oxymorphone*: This comparator was reformulated during the post-period and had very low utilization, particularly in the pre-period.
- *IR oxycodone:* Due to the difficulty in reliably distinguishing between SE and combination products in this data source, a composite category of any IR oxycodone was used for context as a comparator of the same active pharmaceutical ingredient; however, this comparator is limited by the changing proportion of IR oxycodone that was SE versus combination during the study period (see Figure 8). In some analyses, results were also stratified by SE and combination products.
- *Methadone*: Due to the difficulty in reliably distinguishing between analgesic and medication-assisted treatment (MAT) formulations, a composite category of any methadone product was used; the utility of this comparator is limited in that utilization-adjusted abuse call rate analyses for methadone are unreliable as not all dispensing of methadone products are captured in retail pharmacy databases (i.e., MAT methadone).
- *Heroin*: This comparator is valuable for understanding broader trends in opioids abuse, but it is not an opioid analgesic, and accounting for availability is not possible.

Figure 8: Pre- to post-period change in mean number of tablets dispensed per month, for OxyContin and comparators

IR=immediate release; SE=single entity; ER=extended release; other Schedule II opioids (1) = IR SE oxycodone, IR oxycodone combination products, ER morphine, ER oxymorphone, IR hydrocodone combination products; other Schedule II opioids (2) = IR SE oxycodone, IR oxycodone combination products, ER morphine, ER oxymorphone, IR hydrocodone combination products, ER hydromorphone (This definition was used in the study.)

(*Sponsor figure taken from PMR 3051-2 study report*)

Other oxycodone exposure categories

- *General oxycodone – category assigned for calls with unknown formulation or product* (oxycodone that was not assigned to a formulation [IR vs. ER, or SE vs. combination product], but was known to be oxycodone): This exposure category was used primarily to understand the extent of missing formulation information.
- *All oxycodone products, excluding OxyContin and general oxycodone*: This composite exposure category was largely ignored due to its similarity to IR oxycodone category.

3.4.7 Denominators (Offsets) and Covariates

- *Population measure: United States Census estimates for the general population*
  For population-based rates, the models included the sum of the population across the three-digit ZIP codes for the residential addresses of all exposure call cases as an offset variable (See Section 3.4.6.1); therefore, all opioid comparators had the same denominator in these analyses. The population denominators used 2010 census population estimates, without adjustment for population growth.
- *Utilization measure: IQVIA National Prescription Audit (NPA) estimates of tablets dispensed*
  For utilization-based rates, the models included the sum of estimates of the total number of tablets dispensed for an individual product or product grouping within a particular quarter and region from primarily retail pharmacies, mail service houses, and long-term care facilities, as an offset variable (See Section 3.4.6.1); quarterly estimates provided by IQVIA were specific to three-digit ZIP codes for the residential addresses of the exposure cases. Some models included the tablets dispensed measure as a covariate in the model. The tablets dispensed measure was chosen as it represents the most granular measure of utilization; one unique recipient can receive a variable number of individual prescriptions, and one individual prescription can contain a variable number of tablets dispensed, each its own opportunity for abuse or diversion. Therefore, the tablets dispensed measure was believed to best reflect a given prescription product's level of community availability for abuse.
- *Total PCC call volume measure: RADARS PCP data on all pharmaceutical exposure calls made to PCCs*
  To adjust for changing exposure call volume to PCCs over the study period, some models included a quarterly measure of the total number of calls made to US PCCs regarding any pharmaceutical exposures involving individuals >5 years old as a covariate in the model. As a sensitivity analyses (part of the March 6, 2020 information request response), the total number of only intentional pharmaceutical exposure calls was adjusted for as a covariate in the model.
  - For reference, the quarterly total number of pharmaceutical exposure calls for individuals >5 years old fluctuated (see Appendix 8.2), but was generally stable across the study period (pre-period range: 160,108 to 176,215; post-period range: 158,527 to 183,322). The quarterly total number of intentional pharmaceutical exposure calls increased consistently (in a linear manner) from the pre-period through the post-period (range over the study period: 57,767 to 77,069).

3.4.8 Analytic Methods

3.4.8.1   Measures and Statistical Models

Primary statistical models:

This study used Poisson regression models to compare mean quarterly abuse call rates in the pre-period to post-period for OxyContin and comparator drugs. In the models (see Table 2), $A_{t,o}$ represents expected number of '**A**'buse calls at a given quarter (denoted by the subscript *t*) for a given opioid drug (denoted by the subscript *o*), P is an indicator for pre-/post-reformulation '**P**'eriod that takes value of 1 if quarter t belongs in the post-period (1Q2011 to 4Q2015) and 0 otherwise, and O is an '**O**'pioid drug indicator with value of O=0 for OxyContin (i.e., reference) and O=1 to n for specific comparator opioids. When included as a variable in ITS analyses T = -7 to n 19, reflects a time (quarter) measure. There are various permutations of models with and with offset variables (either general population or tablets dispensed), and with and without additional covariates (log tablets dispensed and/or log total pharmaceutical calls).

Table 2: Poisson model parameterization**

Model	Offset	Covariate	Model Specification	Objective
Model 1	2010 US Census population	N/A	$\log(A_{t,o}) = \log(2010\,US\,Census_t)$ $+ \alpha_0 + \alpha_1 * P_t + \alpha_2 * O_t + \alpha_3 * P_t * O_t$	Means analyses, Descriptive analyses,
Model 2	Dosage unit dispensed (DUD)	N/A	$\log(A_{t,o}) = \log(DUD_{t,o})$ $+ \alpha_0 + \alpha_1 * P_t + \alpha_2 * O_t + \alpha_3 * P_t * O_t$	Means analyses, Descriptive analyses,
Model 2a	DUD	All pharmaceutical exposure (PE) cases	$\log(A_{t,o}) = \log(DUD_{t,o})$ $+ \alpha_0 + \alpha_1 * P_t + \alpha_2 * O_t + \alpha_3 * P * O_t$ $+ \beta_1 * \log(PE_t)$	Means analyses, Descriptive analyses,
Model 3	N/A	DUD (continuous)	$\log(A_{t,o}) = \alpha_0 + \alpha_1 * P_t + \alpha_2 * O_t + \alpha_3 * P_t * O_t$ $+ \beta_1 * \log(DUD_{t,o})$	Means analyses, Descriptive analyses,
Model 3a	N/A	DUD (continuous), all PE cases	$\log(A_{t,o}) = \alpha_0 + \alpha_1 * P_t + \alpha_2 * O_t + \alpha_3 * P_t * O_t$ $+ \beta_1 * \log(DUD_{t,o}) + \beta_2 * \log(PE_t)$	Means analyses, Descriptive analyses,
Model 5	same as model 1		$\log(A_{t,o}) = \log(2010\,US\,Census_t)$ $+ \alpha_0 + \alpha_1 * P_t + \alpha_2 * O_t + \alpha_3 * P_t * O_t$ $+ (\alpha_4 + \alpha_5 * P_t + \alpha_6 * O_t + \alpha_7 * P_t * O_t) * T$	Interrupted time series (ITS)
Model 6	same as model 2		$\log(A_{t,o}) = \log(DUD_{t,o})$ $+ \alpha_0 + \alpha_1 * P_t + \alpha_2 * O_t + \alpha_3 * P_t * O_t$ $+ (\alpha_4 + \alpha_5 * P_t + \alpha_6 * O_t + \alpha_7 * P_t * O_t) * T$	ITS
Model 6a	same as model 2a		$\log(A_{t,o}) = \log(DUD_{t,o}) + \beta_1 * \log(PE_t)$ $+ \alpha_0 + \alpha_1 * P_t + \alpha_2 * O_t + \alpha_3 * P_t * O_t$ $+ (\alpha_4 + \alpha_5 * P_t + \alpha_6 * O_t + \alpha_7 * P_t * O_t) * T$	ITS
Model 7	same as model 3		$\log(A_{t,o}) = \beta_1 * \log(DUD_{t,o})$ $+ \alpha_0 + \alpha_1 * P_t + \alpha_2 * O_t + \alpha_3 * P_t * O_t$ $+ (\alpha_4 + \alpha_5 * P_t + \alpha_6 * O_t + \alpha_7 * P_t * O_t) * T$	ITS
Model 7a	same as model 3a		$\log(A_{t,o}) = \beta_1 * \log(DUD_{t,o}) + \beta_2 * \log(PE_t)$ $+ \alpha_0 + \alpha_1 * P_t + \alpha_2 * O_t + \alpha_3 * P_t * O_t$ $+ (\alpha_4 + \alpha_5 * P_t + \alpha_6 * O_t + \alpha_7 * P_t * O_t) * T$	ITS

(*FDA generated table based on information in PMR 3051-2 study report*)

**Models 2b and 3b were the same as models 2a and 3a, respectively, only differing in that they included an additional categorical variable in the regression model that corresponded to the tablet strength involved in the abuse call. Models 2b and 3b were meant as sensitivity analyses but were not implemented due to challenges associated with defining categories of tablet strengths that could be used across opioid groups. Models 4a and 8a included dosage units dispensed (DUD) as a categorical variable. Model 4a and 8a were considered in the protocol, but they were not ultimately implemented for the final study report due to their worse model performance compared to models 3a and 7a.

Utilization adjustment:

For Poisson regression models incorporating utilization data with an offset variable (Models 2, 2a, 5, 6, and 6a), the expected number of quarterly abuse calls and tablets dispensed at time *t* are assumed to have a one-to-one, monotone relationship (i.e., with a slope of 1) when the other covariates are fixed at time *t*. In other words, these models assume each unit change in utilization corresponds to a unit change in abuse calls. Using an offset in the model forces a "rate" interpretation that is based on the specific offset used (e.g., mean quarterly number abuse call rate per 100,000 tablets dispensed). For Poisson regression models incorporating utilization data without an offset variable (Models 3, 3a, 7, and 7a), the expected number of quarterly abuse calls are assumed to be linear to the continuous covariate (i.e., [log] tablets dispensed), but the relationship between utilization and the number of abuse calls is more flexible, where the slope can range from -∞ to ∞. With these models, the expected number of abuse calls are modeled as counts per quarter adjusting for tablets dispensed, and therefore, while a "rate per tablets dispensed" interpretation is not appropriate without an offset variable, a standard time-based (quarterly) "rate" interpretation is accurate. We describe the estimates generated by these models as "abuse call rates adjusting for tablets dispensed."

Primary measures to evaluate the reformulation:

1) ***Means analysis:*** *Percent change in mean abuse call rates comparing the pre-period to the post-period*

The Poisson regression models estimated abuse call rate ratios (RRs), or the mean quarterly abuse call rate in the pre-period divided by the mean quarterly abuse call rate in the post period and associated 95% confidence intervals (CIs). For interpretability, the RRs were expressed as a relative percent change in abuse call rates comparing periods for OxyContin and comparators — for example, a hypothetical RR of 0.60 is expressed as a 40% decline in the abuse call rate comparing periods.

A ratio of rate ratios (RORR) was used as the primary measure with which to compare pre- vs. post-period abuse call RRs between OxyContin and comparators (RORR = [comparator RR] / [OxyContin RR]). In these types of difference-in-differences models,[xvii] the RORR is represented by the interaction between time period (binary variable: pre- or post-period) and opioid (with OxyContin as the reference drug); an RORR >1 reflects a more favorable change in abuse call rates for OxyContin relative to that of a comparator (i.e., a greater decline or a smaller increase for OxyContin relative to comparators, or no change for OxyContin but increasing abuse call rates for comparators). An RORR <1 indicates a more favorable change for the comparator (i.e., a smaller decline or a greater increase relative to the comparator, or no change for the comparator but increasing abuse call rates for OxyContin). For the means analysis, some models (see Table 4) calculated population-based (Model 1) or utilization-based (Model 2 and 2a) abuse call rates using an offset variable, while other models calculated utilization adjusted rates (Models 3 and 3a). Models 2a and 3a adjusted for the (log) quarterly total pharmaceutical exposure calls made to PCCs (i.e., PCC call volume).

Null hypothesis: $\alpha_3 = 1$ or RORR = 1 (Means models)

> The change in the mean abuse call rate between periods for OxyContin is not different from the change in the mean abuse call rate between periods for the comparator group

2) **Trend analyses**: *Trends in abuse call rates over time, comparing the pre-period to the post-period*
   a. *Descriptive trend analysis*
   Descriptive plots of observed and model estimated mean abuse call rates by quarter for OxyContin and primary comparator opioids; the model estimated data were from models with and without offsets (Model 1, 2, 2a, 3, and 3a). These analyses were primarily used for visual inspection of abuse call rates by opioid; no comparative descriptive trend analyses were conducted. Similarly, plots of raw counts of abuse calls over time for OxyContin and primary comparators were also reviewed, including separate plots stratified by route of abuse.
   b. *Interrupted Time Series (ITS) Analysis*
   To assess the change in abuse call rates over time in the pre- versus post-periods, an ITS model (Poisson distribution; log link) was used to estimate: 1) change in the slope of quarterly abuse call rates from the pre-period to the post-period, and 2) "immediate shift" or level change from the model-estimated abuse call rate for the last quarter of the pre-reformulation period (2Q2010) to the model-estimated abuse call rate for first quarter of the post-reformulation period (1Q2011); primary ITS analyses excluded the transition period. Like the means analysis, the slopes and level change for OxyContin and comparator opioid groups were expressed as a relative percent change in comparing the pre- and post-periods. Comparative interrupted time-series (CITS) models compared the change in abuse call rate quarterly trends (i.e., slopes and level changes) by period for OxyContin with those for comparator drug groups; CITS is also an extension of the difference in difference model,[xviii] and an analogous measure to the RORR (described above) was used to compare OxyContin to comparators (referred to as CITS measures in this review). For the ITS analyses, some models calculated population-based (Model 5) or utilization-based (Model 6 and 6a) abuse call rate slopes using an offset variable, while other models calculated utilization adjusted abuse call rate slopes (Models 7 and 7a). Models 6a and 7a adjusted for the (log) quarterly total pharmaceutical exposure calls made to PCCs

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[xvii] Wing C et al. (2018) Designing Difference in Difference Studies: Best Practices for Public Health Policy Research. Annual Review of Public Health; 39: 453-469.

[xviii] Bernal JL, et al. (2018) The use of controls in interrupted time series studies of public health interventions. International Journal of Epidemiology; 47 (6): 2082-2093; Bernal JL, et al. (2019) Difference in difference, controlled interrupted time series and synthetic controls. International Journal of Epidemiology; 48 (6): 2062-2063

Null hypotheses:

$\alpha_3 = 1$ (ITS models)

The level change ("immediate shift") in abuse call rate between periods for OxyContin is not different from the level change in abuse call rate between periods for the comparator groups

$\alpha_7 = 1$ (ITS models)

The change in the slope of the abuse call rate between periods for OxyContin is not different from the change in the slope of the abuse call rate between periods for the comparator groups

Model diagnostics:

All models included a multiplicative dispersion parameter to account for over-dispersion. To assess model fit, Akaike Information Criteria statistic (AIC), residual plots, and observed versus predicted plots were evaluated.

Software:

All analyses were performed using the general linear mixed modeling procedure (GLIMMIX) and the generalized linear models (GENMOD) procedure in SAS 9.4.

3.4.8.2 Main Findings Presented in this Review

This summary/synthesis of PMR 3051-2 study findings in this review will primarily show results from Models 1, 2a, and 3a (for the means analysis), and 5, 6a, and 7a (for the ITS analysis). We focused on these six models based on their interpretability and relative model performance (See Appendix 8.1). The results of the models constitute a range of estimates to consider based on the various approaches. Primary results from Models 2 and 3 are included in Appendix 8.4, as well as results from other models used in sensitivity analyses requested by FDA (information request sent September 27, 2019); any discrepant findings with the primary models of interest are noted in the results sections. Of note, models 2b, 3b, 4a, and 8a were considered for use in the protocol, but they were not ultimately implemented for the final study report. Models 2b and 3b were meant as sensitivity analyses since they were the same as models 2a and 3a, respectively, only differing in that they included an additional categorical variable in the regression model that corresponded to the tablet strength involved in the abuse call. Models 2b and 3b were not implemented due to challenges associated with defining categories of tablet strengths that could be used across opioid groups. Also, models 4a and 8a only differed from models 3a and 7a in that the dosage units dispensed variable was included as categorical variable defined by quartiles. The sponsor noted more substantial issues with their model performance compared to models 3a and 7a, and therefore they did not conduct any analyses using these models. From the perspective of FDA, it was acceptable not to run models 2b, 3b, 4a, and 8a given their similarities to the other models.

Primary models discussed in this review**:**

- **Model 1:** mean quarterly abuse call rate per general population (standardized per 100,000 population)
- **Model 2a:** mean quarterly abuse call rate per tablets dispensed (standardized per 100,000 tablets dispensed), adjusted for the quarterly number of pharmaceutical exposures calls made to PCCs involving individuals >5 years old (hereafter, call volume)
- **Model 3a**: mean quarterly abuse call rate, adjusted for the quarterly number of tablets dispensed and call volume
- **Model 5:** interrupted time series (ITS) model of pre- and post-period quarterly abuse call rate slopes and level change per general population
- **Model 6a:** ITS model of pre- and post-period quarterly abuse call rate slopes and level change per tablets dispensed, adjusted for call volume
- **Model 7a**: ITS model of pre- and post-period quarterly abuse call rate slopes and level change, adjusted for the quarterly number of tablets dispensed and call volume

With respect to model performance of the primary models, using AIC, residual analyses, and observed versus predicted plots (See Appendix 8.1), models adjusting for (log) call volume performed better than most of the other models; overall, Model 2a and 3a appeared to perform the best. From the perspective of FDA, modeling a rate with an offset (e.g., abuse call rates per population or tablets dispensed) is an intuitive and interpretable metric with which to compare between opioid drugs. During the protocol submission and review process, Model 3/3a was proposed by the sponsor and was not preferred by FDA due to the expected difficulty in interpreting the findings from that approach. Nevertheless, FDA agreed to review results based on those
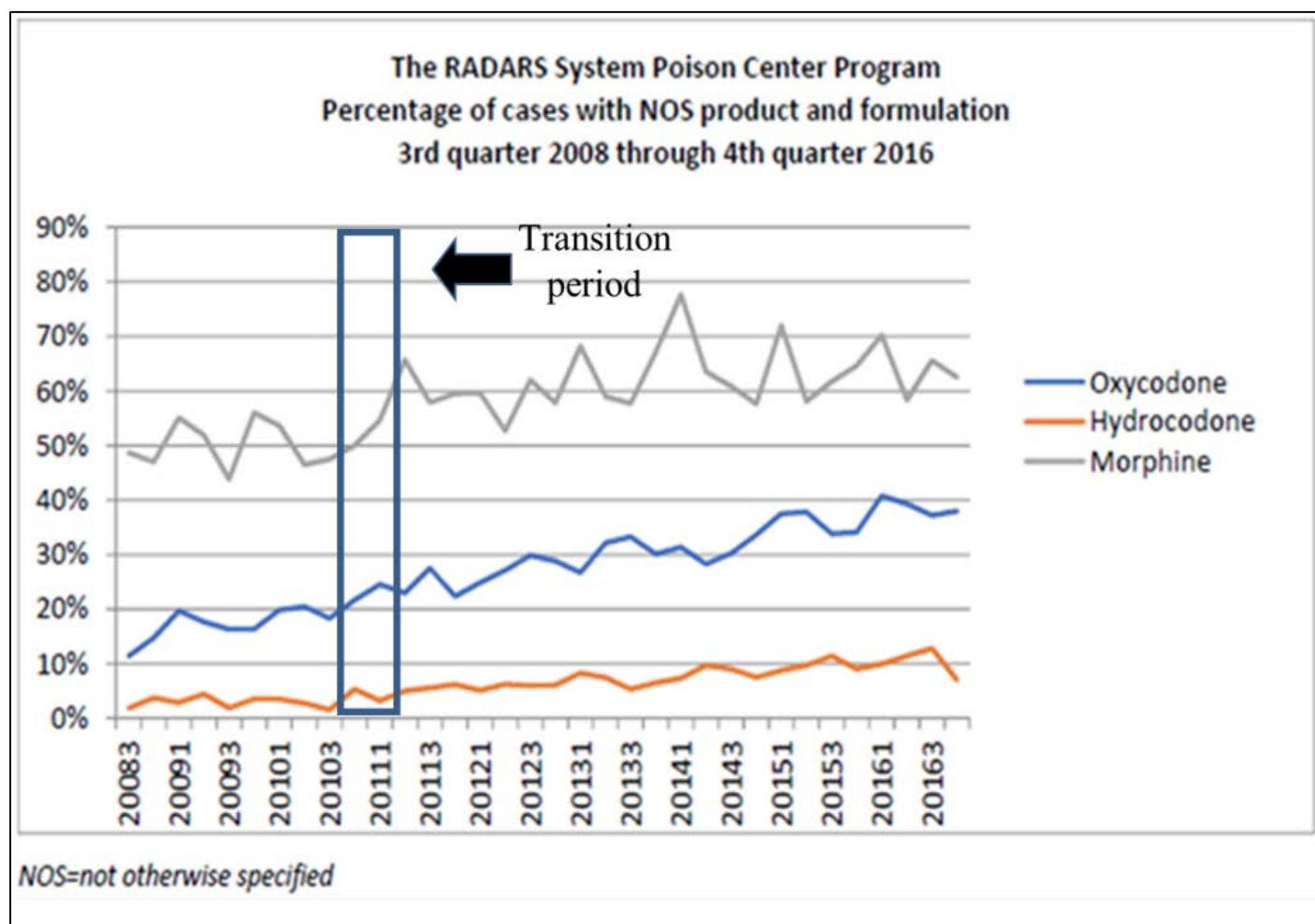
models if the other models were also implemented and the results from the all models were presented together as range of estimates. Model 3a (without an offset) is technically more flexible in terms of the relationship between abuse calls and utilization, and ultimately did have the lowest AIC; however, in the final study report, the sponsor expressed concern about potential collinearity between time (quarter/period) and dosage units dispensed, which created what they describe as "unstable point estimates" that "complicated the interpretation of results." For this review, Model 3a's results were still included in a range of estimates to reflect the variability in findings with different modeling approaches, all of which have distinct strengths and limitations (See background document: OB Statistical Review Memo). Of note, in nearly all analyses, Model 3a had the greatest uncertainty in its estimates (i.e., widest confidence intervals) across opioid drugs; however, results appear to be most disparate from the other models for opioid groups with lower numbers of calls per quarter, such as ER morphine. Therefore, while these results are considered along with results from other models, we ultimately did not weigh them as heavily in our overall interpretation of the study findings.

Our presentation and discussion of the study results focuses mainly on the six models described above, and 1) using the primary study period (-2y/5y); 2) using the specific OxyContin only definition to calculate abuse rates; 3) excluding the transition period (for ITS analyses); 4) using only one 5 year post-period for ITS analyses. The results of analyses using "any ER oxycodone" definition are included in the sensitivity analyses section, while those using a shorter time period (-1y/3y), and those including the transition period and separate, consecutive post-periods (PP1 and PP2) are included in Appendix 8.5. Any discrepant findings with the main analyses are noted in the results section.

3.4.8.3   Missing Data

Due to the increasing proportion of cases in which the specific drug formulation was not available, or not otherwise specified (NOS), which varied differentially across opioid drugs and over time (see Figure 9), imputation methods were used to mitigate the potential for biased analyses. During the study period, the percentage of abuse calls involving oxycodone, but missing data on formulation (i.e., IR vs. ER) increased from ~10% to ~30%. Similarly, the percentage of abuse calls involving morphine, but missing formulation information increased from ~45% to ~75%. With increasing missingness over time, the magnitude of any estimated declines for these opioids could be overestimated if analyses only included cases with data on formulation. Conducting a "complete case" analysis (i.e., excluding cases with missing formulation data) can also bias relative comparisons between opioid groups with differentially missing formulation information, or differential changes in missingness over time.

Figure 9: Proportion of cases missing formulation data, by opioid

The RADARS System Poison Center Program
Percentage of cases with NOS product and formulation
3rd quarter 2008 through 4th quarter 2016

NOS=not otherwise specified

(*Sponsor figure taken from PMR 3051-2 study report; transition period added by FDA*)

In addition to "complete case" analyses, the sponsor conducted a sensitivity analysis using multiple imputation techniques to impute missing/unspecified formulation information across opioid drug groups. These data were assumed to be missing at random (MAR), and imputation models used age category, medical outcome, sex, center code, and year-quarter as predictors to impute formulation data; the imputation model was run at the opioid active pharmaceutical ingredient (API) level, rather than the case level. Missing values for age and medical outcome were assigned to an unknown category for prediction to avoid different imputed values for these variables within each case. Data were imputed for 100 iterations, and analyzed across each of the imputation datasets. Imputations were done using the PROC MI procedure (SAS 9.4).

In a sensitivity analysis conducted in response to an FDA information request (September 2019), and as specified in the final study protocol, the sponsor reallocated cases for unspecified (i.e., general or NOS) oxycodone and morphine based on the proportion of prescriptions dispensed for IR and ER formulations of those respective opioid APIs during a given quarter-year in a given 3-digit zip code.

3.4.8.4   Sensitivity Analyses

1) **Using an "all ER oxycodone" definition of OxyContin**: as described above, a broader definition of OxyContin (i.e., "all ER oxycodone" including both brand and generic ER oxycodone) was used to understand the possible effects of misclassification of the specific drug product involved in the abuse call, particularly since both branded OxyContin and generic ER oxycodone were concurrently marketed during OxyContin's pre-reformulation period.
2) **Multiple imputation methods for missing formulation data**: as described above, imputed formulation data were used to understand the potential impact of differentially missing formulation data over time in comparative analyses for OxyContin and the primary comparators.

3) **Geographical restrictions**: as described above, restricting analyses to specific geographical regions was done to understand the effects of regionally-based opioid-related initiatives, and other possible secular (and/or regional) trends on abuse rates. One prominent regional initiative was the Florida "pill mill" law enforcement crackdown and legislative actions which occurred shortly after the reformulation and may have impacted the abuse call rates differentially across opioids.
   a. Analyses done using all United States, excluding Florida
   b. Analyses done using the West region of United States only
4) **OxyContin abuse calls involving specific tablet strengths**: analyses were restricted to only cases involving higher tablet strength OxyContin as it has been suggested that higher tablet strengths are more desirable for abuse than the lower tablet strengths.
   a. 80 mg tablets reported only
   b. $\geq$40 mg tablets reported only

4   STUDY RESULTS

Note on presentation of results:

- Results (tables and figures) were either abstracted directly from the PMR 3051-2 study report and sponsor-submitted information request responses or re-created by FDA reviewers using data from the final study report or responses to information requests; the origin of the figure/table is noted. While some sponsor-submitted tables and figures have been modified to focus on key findings, the numbers have not been altered.

Notes on terminology:

- In this review, ***abuse call rates*** are defined as rates of exposure calls to US PCCs where the reason for exposure was classified as "abuse" and the drugs involved in the exposure included OxyContin (or a comparator drug). When describing abuse call rate changes from pre- to post-reformulation periods for calls involving OxyContin (or comparators) exposures, we may use the following shorthand terminology for simplicity in text, tables, and figures: "*There was a decline in abuse call rates for OxyContin (or comparator)*" or "*OxyContin's abuse call rate declined*."
- When using the term "*significant*" or "*significance*" we are referring to statistical significance, not necessarily clinical or public health significance.

4.1.1   Descriptive Summary of Abuse Calls in the Pre- and Post-periods

Table 3 shows demographic and summary data on abuse calls involving OxyContin and comparator opioids in the pre- and post-periods. Overall, the sex distribution (predominately male) and mean age of the cases were similar for OxyContin and comparator opioids. Comparing the pre- and post-periods, the mean age increased slightly for all opioid comparators. On average, a case involved the abuse of two substances, and this was also consistent across opioids and study periods. The proportion of abuse-related cases that resulted in a medical outcome designated as major effect [xix] or death was similar in the pre- and post-periods for both OxyContin and all primary comparator opioids; any minor shifts may have been due, in part, to the changing proportion of cases that were not followed up in both periods.

[xix] Major effects are those where the exposure resulted in signs or symptoms that were life threatening or resulted in significant residual disability or disfigurement

Table 3: Abuse-related exposure call summary table for OxyContin and comparators, by opioid and period (-2y/5y)

Variable	Value	OxyContin		ER Morphine		IR Hydrocodone		Other Schedule II Opioids	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post
Gender	Female	324 (29.9%)	429 (32.8%)	86 (33.3%)	180 (36.4%)	1,461 (41.5%)	2,865 (41.6%)	2,212 (39.8%)	4,852 (40.2%)
	Male	758 (69.9%)	880 (67.2%)	172 (66.7%)	314 (63.6%)	2,060 (58.5%)	4,028 (58.4%)	3,347 (60.2%)	7,225 (59.8%)
	Unknown	2 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)	2 (<0.1%)	5 (0.1%)	7 (0.1%)
Age (years)	Mean (SD)	27.9 (11.43)	30.5 (13.37)	29.9 (13.35)	35.3 (15.54)	30.6 (13.55)	32.9 (14.57)	30.3 (13.50)	32.5 (14.09)
Number of Substances	Mean (SD)	2.1 (1.31)	2.1 (1.27)	1.8 (1.30)	2.0 (1.27)	2.2 (1.34)	2.2 (1.29)	2.1 (1.29)	2.1 (1.24)
Medical Outcome	No effect	84 (7.7%)	104 (7.9%)	16 (6.2%)	31 (6.3%)	494 (14.0%)	921 (13.4%)	714 (12.8%)	1,433 (11.9%)
	Minor effect	289 (26.7%)	349 (26.7%)	47 (18.2%)	135 (27.3%)	991 (28.1%)	1,950 (28.3%)	1,474 (26.5%)	3,371 (27.9%)
	Moderate effect	291 (26.8%)	419 (32.0%)	76 (29.5%)	156 (31.6%)	741 (21.0%)	1,774 (25.7%)	1,204 (21.6%)	3,388 (28.0%)
	Major effect	86 (7.9%)	128 (9.8%)	17 (6.6%)	40 (8.1%)	169 (4.8%)	383 (5.6%)	309 (5.6%)	789 (6.5%)
	Death	5 (0.5%)	7 (0.5%)	1 (0.4%)	2 (0.4%)	19 (0.5%)	23 (0.3%)	20 (0.4%)	46 (0.4%)
	Not followed	88 (8.1%)	74 (5.7%)	31 (12.0%)	34 (6.9%)	355 (10.1%)	565 (8.2%)	587 (10.5%)	898 (7.4%)
	Unable to follow-potentially toxic	219 (20.2%)	205 (15.7%)	67 (26.0%)	82 (16.6%)	686 (19.5%)	1,071 (15.5%)	1,139 (20.5%)	1,807 (15.0%)
	Confirmed non-exposure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Unrelated effect	21 (1.9%)	18 (1.4%)	3 (1.2%)	14 (2.8%)	59 (1.7%)	160 (2.3%)	103 (1.9%)	272 (2.3%)
	Death, indirect report	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Missing	1 (0.1%)	5 (0.4%)	0 (0.0%)	0 (0.0%)	9 (0.3%)	48 (0.7%)	14 (0.3%)	80 (0.7%)
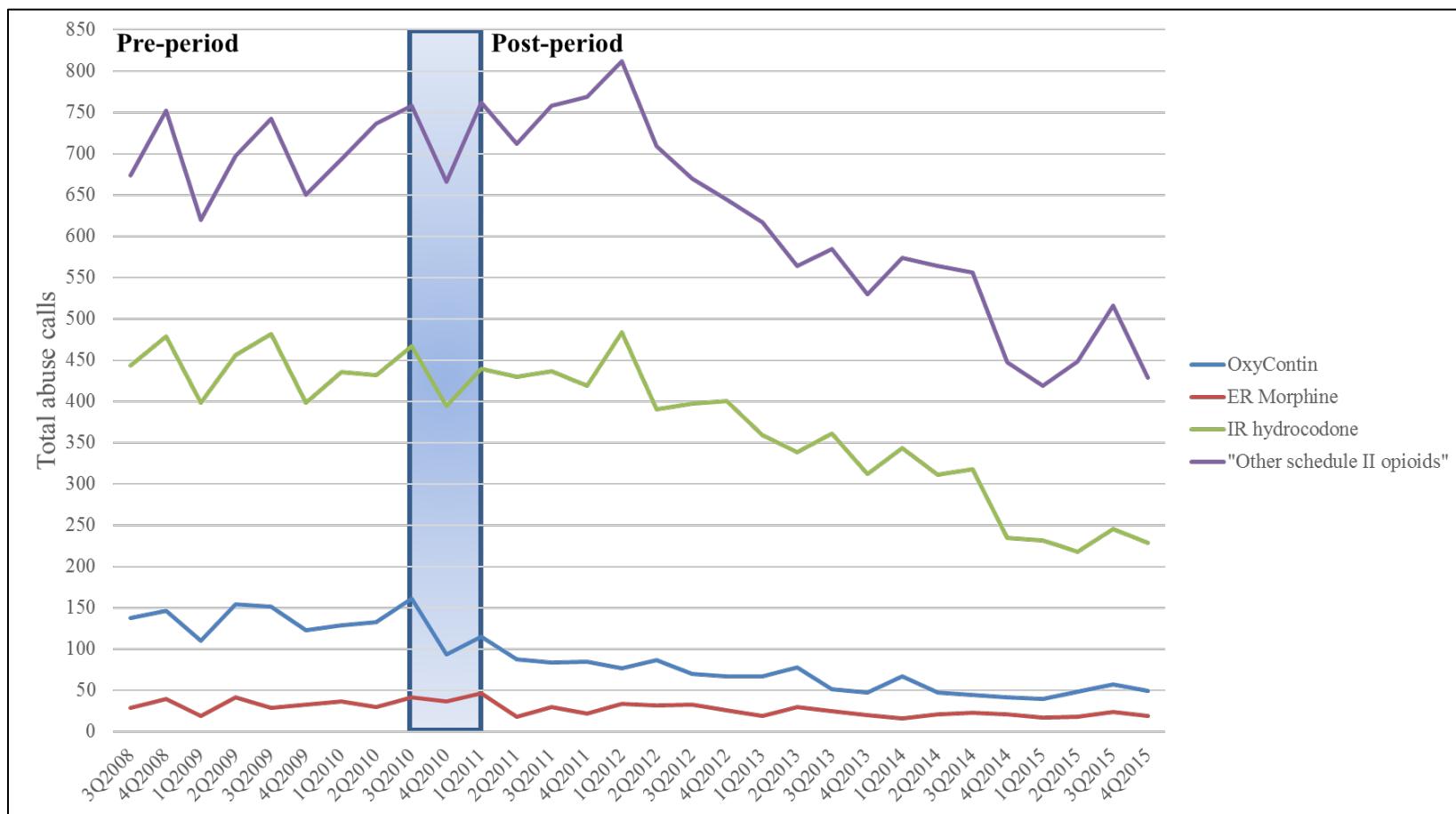
(*Sponsor table taken from PMR 3051-2 study report*)

Key: extended-release (ER); immediate-release (IR); standard deviation (SD); pre-period (pre); post-period (post)

4.1.2 Descriptive Trends in Abuse Calls for OxyContin and Comparator Opioids

Figure 10 shows the quarterly total number of abuse calls made to PCCs in the pre- and post-periods for OxyContin and primary comparator opioids. Immediately following the reformulation, there was an apparent decline in the number for calls involving OxyContin (pre-period range = 110 to 154 calls; post-period range = 40 to 115 calls). A decline was also observed for "other schedule II opioids" composite comparator group (pre-period range = 620 to 752 calls; post-period range = 419 to 662 calls) and for IR hydrocodone (pre-period range = 398 to 479 calls; post-period range = 218 to 483 calls), although the downward inflection in trend appears to occur several quarters later that for OxyContin. Sustained declines in the total number of abuse calls were observed for OxyContin, IR hydrocodone, and "all schedule II" opioids in the post-period. ER morphine had the lowest numbers overall (pre-period range = 19 to 41 calls; post-period range = 16 to 46 calls), and changes were somewhat difficult to discern visually.

Figure 10: Total quarterly numbers of abuse calls (any route) involving OxyContin and primary comparator opioids (-2y/5y)
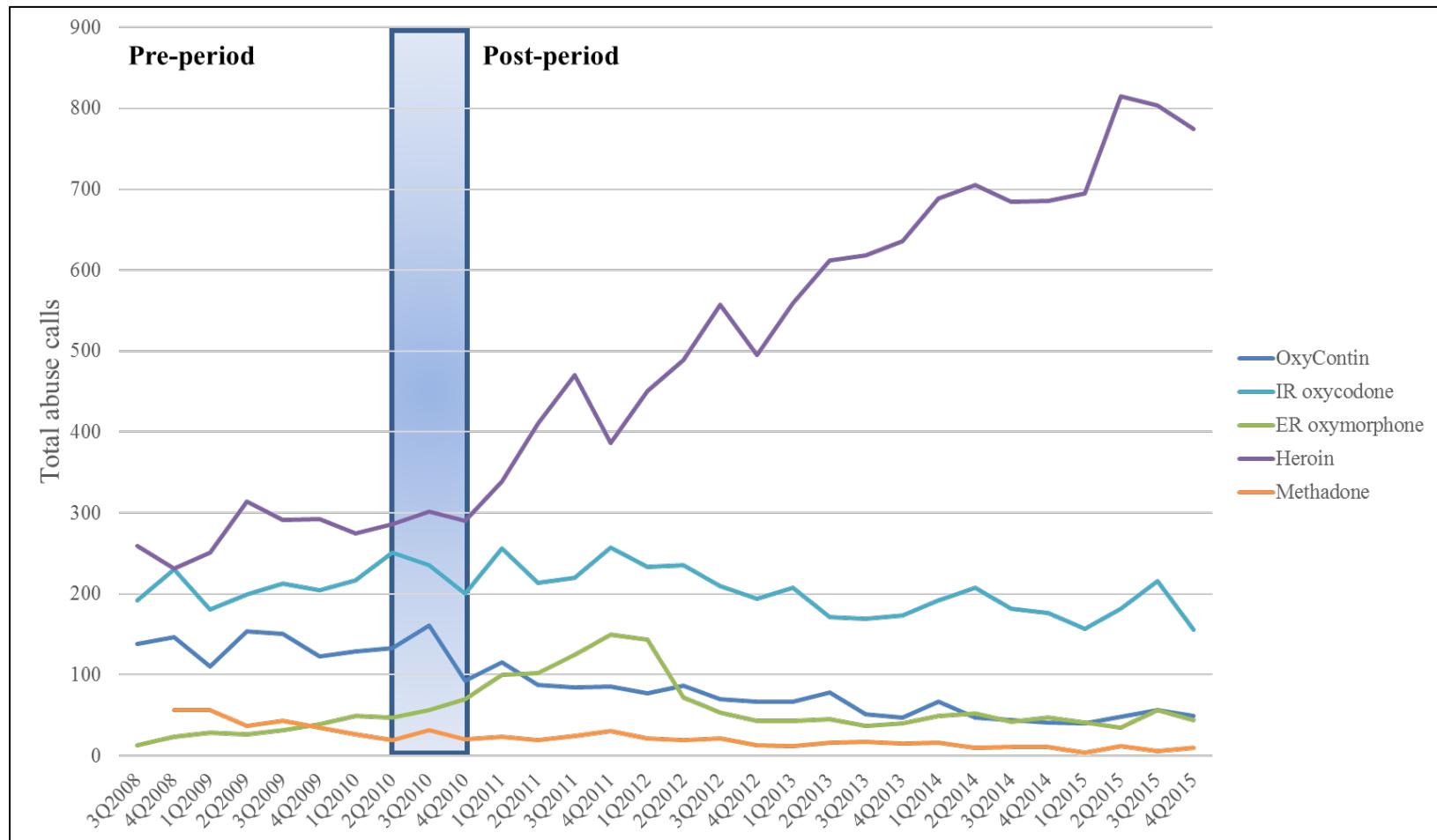
(FDA generated figure using data from the February 21, 2020, sponsor submitted information request response)

Key: extended-release (ER); immediate-release (IR); "other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, plus IR oxycodone; the blue box denotes the transition period (excluded from primary analyses)

Figure 11 shows the total number of abuse calls made to PCCs in the pre- and post-periods for OxyContin and secondary ("contextual") comparator opioids. Most notable in this figure is the rise in heroin abuse calls during the post-period relative to OxyContin.

Figure 11: Total quarterly numbers of abuse calls involving OxyContin and secondary comparator opioids (-2y/5y)

(FDA generated figure using data from the February 21, 2020, sponsor submitted information request response)

Key: extended-release (ER); immediate-release (IR); the blue box denotes the transition period (excluded from primary analyses)

Table 4 shows the mean quarterly abuse call rates per 100,000 population (Model 1) in the pre- and post-periods for OxyContin and select comparators. Mean abuse rates per general population for OxyContin decreased from 0.052 per 100,000 population in the pre-period to 0.023 per 100,000 population in the post-period. Primary comparator groups mean abuse call rates per general population also decreased (IR hydrocodone: 0.168 to 0.122 per 100,000 population; ER morphine: 0.012 to 0.009 per 100,000 population), as did the composite comparator "all schedule II opioids" from 0.266 to 0.214 per 100,000 population. As for secondary ("contextual") comparators, mean abuse call rates per general population for heroin and ER oxymorphone increased, whereas mean abuse call rates per general population for IR oxycodone and methadone decreased. Mean abuse call rates per general population for oxycodone, not otherwise specified (NOS), i.e., without product or formulation information, also increased comparing periods.

Table 4: Mean quarterly abuse call rates for OxyContin and comparator opioids per 100,000 population (Model 1), by period (-2y/5y)

Opioid comparator	Pre-reformulation period Mean quarterly abuse call rate per 100,000 population (Model 1) (95% confidence interval)		Post-reformulation period Mean quarterly abuse call rate per 100,000 population (Model 1) (95% confidence interval)
Primary comparators			
OxyContin	0.052 (0.045 to 0.060)	⬇	0.023 (0.020 to 0.026)
ER morphine	0.012 (0.010 to 0.015)	⬇	0.009 (0.008 to 0.010)
IR hydrocodone	0.168 (0.147 to 0.193)	⬇	0.122 (0.111 to 0.135)
"Other schedule II opioids"	0.266 (0.234 to 0.302)	⬇	0.214 (0.196 to 0.233)
Secondary comparators			
ER oxymorphone	0.004 (0.002 to 0.008)	⬆	0.011 (0.008 to 0.014)
IR oxycodone	0.081 (0.072 to 0.090)	⬇	0.071 (0.066 to 0.076)
Oxycodone (NOS)	0.028 (0.025 to 0.031)	⬆	0.038 (0.035 to 0.040)
Methadone	0.013 (0.010 to 0.017)	⬇	0.006 (0.004 to 0.007)
Heroin	0.105 (0.087 to 0.127)	⬆	0.210 (0.194 to 0.228)
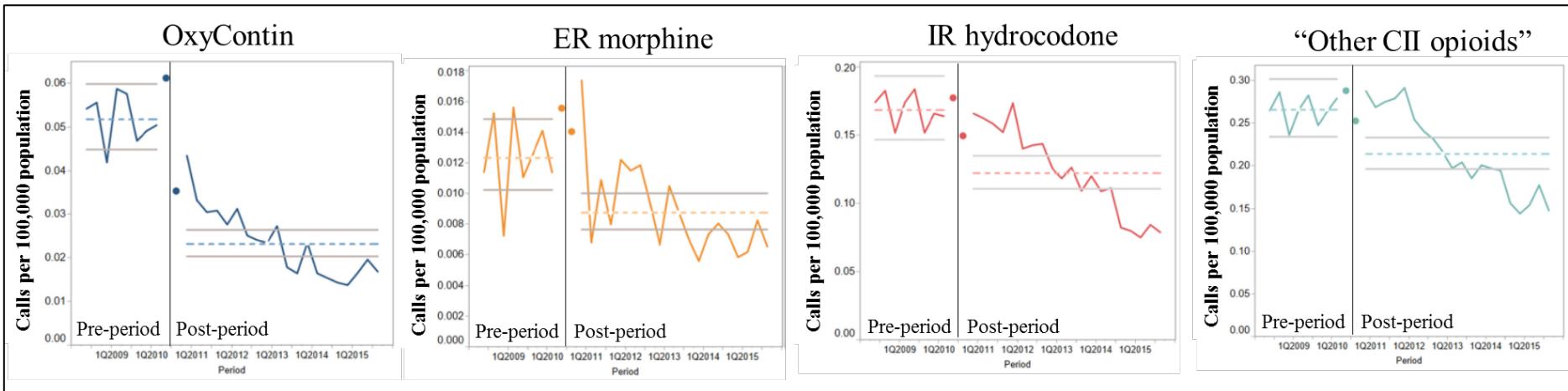
(FDA generated table using data from PMR 3051-2 study report)

Key: extended-release (ER); immediate-release (IR); not otherwise specified (NOS); "other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; parentheses show 95% confidence interval; arrows denote direction of change; Model 1 models an abuse call rate per general population (as an offset)

4.1.3 Descriptive Trends in Observed and Modeled Quarterly Abuse Call Rates for OxyContin and Primary Comparators: Models 1, 2a, and 3a

Figure 12 plots observed quarterly abuse call rates (solid line) and model estimated mean quarterly abuse call rates (dashed line) per 100,000 population in the pre- and post-periods for OxyContin and comparator opioids (Model 1). Across opioid comparators, there is some variation (solid line) in abuse call rates in the pre-period, albeit at different levels of abuse (see y-axis scale); the combined "other schedule II" opioids had the highest pre-period rates, followed by IR hydrocodone, OxyContin, and ER morphine. Declines in abuse call rates per 100,000 population are observed following the transition period for all opioid comparator groups. Declines in model estimated mean quarterly abuse call rates per 100,000 population (dashed line) were observed with OxyContin and lte comparators.

Figure 12: Observed abuse call rates and model estimated mean quarterly abuse call rates per 100,000 population (Model 1), by opioid (-2y/5y) ***Note different y-axis scales***
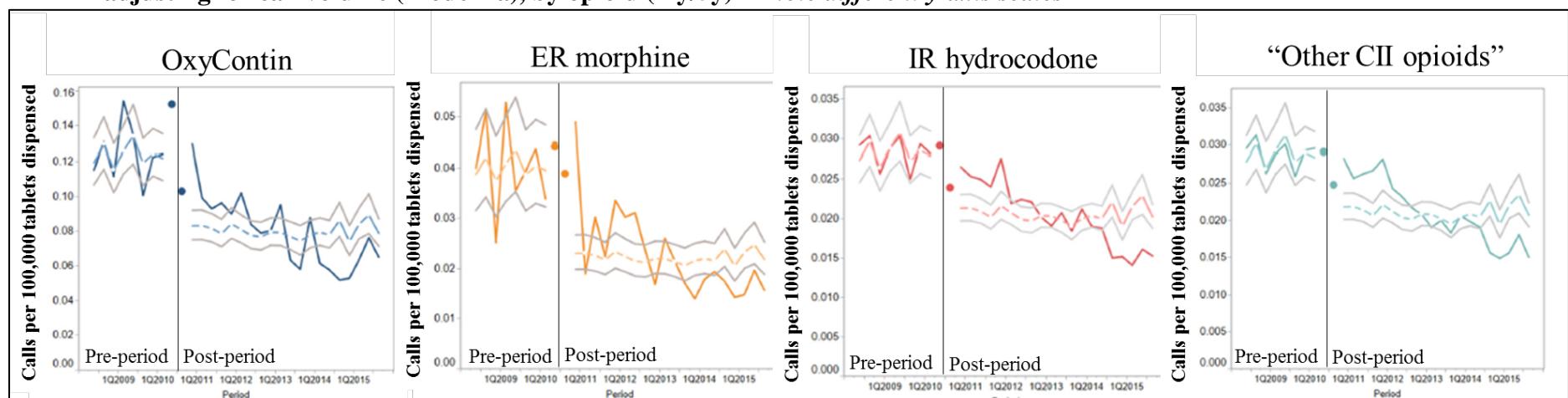
(*Sponsor figure taken from PMR 3051-2 study report; assembled as a panel and formatted by FDA*)

Key: extended-release (ER); immediate-release (IR); schedule II (CII); "other CII opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; Model 1 models an abuse call rate per general population (as an offset); solid line: observed rate; dashed line: model estimated mean abuse call rate; grey solid lines: 95% confidence intervals; vertical line/dots: transition period

Figure 13 plots observed quarterly abuse call rates (solid line) per 100,000 tablets dispensed in the pre- and post-periods and model estimated mean quarterly abuse call rates (dashed line) per 100,000 tablets dispensed, adjusting for call volume (Model 2a), for OxyContin and comparator opioids; because of the quarterly variation in the call volume which is a covariate in the model, the model estimated mean quarterly abuse call rates (and associated 95% confidence interval) vary slightly by quarter. Akin to the abuse call rate per 100,000 population, there is some variation in abuse call rates per 100,000 tablets dispensed (solid line), in the pre-period across opioid comparator groups, again at different scales; however, abuse call rates for OxyContin per 100,000 tablets dispensed were higher than all opioid comparators throughout the study period. Declines in abuse call rates per 100,000 tablets dispensed were observed immediately following the transition period for OxyContin and ER morphine but were more gradual for the other comparators. Model estimated mean quarterly abuse call rates per 100,000 tablets dispensed (dashed lines), adjusting for call volume, were lower in the post-period compared to the pre-period across all opioid comparator groups.

Figure 13: Observed abuse call rates and model estimated mean quarterly abuse call rates per 100,000 tablets dispensed, adjusting for call volume (Model 2a), by opioid (-2y/5y) ***Note different y-axis scales***
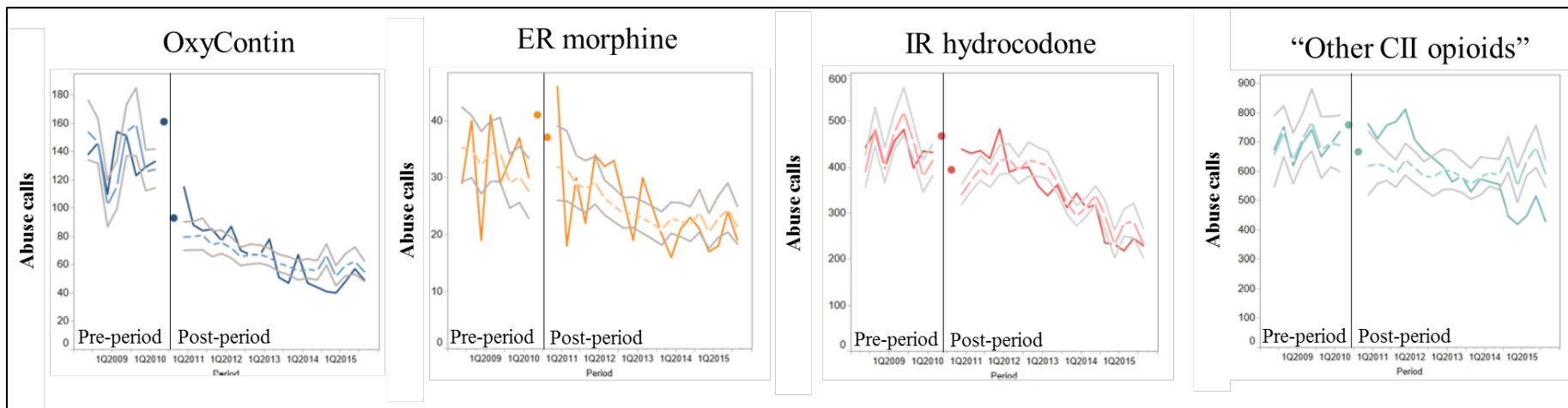
(*Sponsor figure taken from PMR 3051-2 study report; assembled as a panel and formatted by FDA*)

Key: extended-release (ER); immediate-release (IR); schedule II (CII); "other CII opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e., total pharmaceutical exposure calls for persons > 5 years old) as a covariate; solid line: observed rate; dashed line: model estimated mean abuse call rate; grey solid lines: 95% confidence intervals; vertical line/dots: transition period

Figure 14 shows observed quarterly abuse calls (solid line) and model estimated mean quarterly abuse call rates (dashed line) in the pre- and post-periods for OxyContin and comparator opioids, adjusting for tablets dispensed and call volume (Model 3a). In this figure, the solid lines are the same as those depicted in Figure 7 (with different x-axis and y-axis scales). Model estimated mean quarterly abuse call rates adjusting for tablets dispensed and call volume (dashed lines) were generally lower in the post-period compared to the pre-period across the individual opioid drug comparators, particularly for OxyContin, but this was less clear for the "other schedule II opioid" composite comparator.

Figure 14: Observed abuse calls and model estimated mean quarterly abuse call rates adjusting for tablets dispensed and call volume (Model 3a), by opioid (-2y/5y) **Note different y-axis scales**
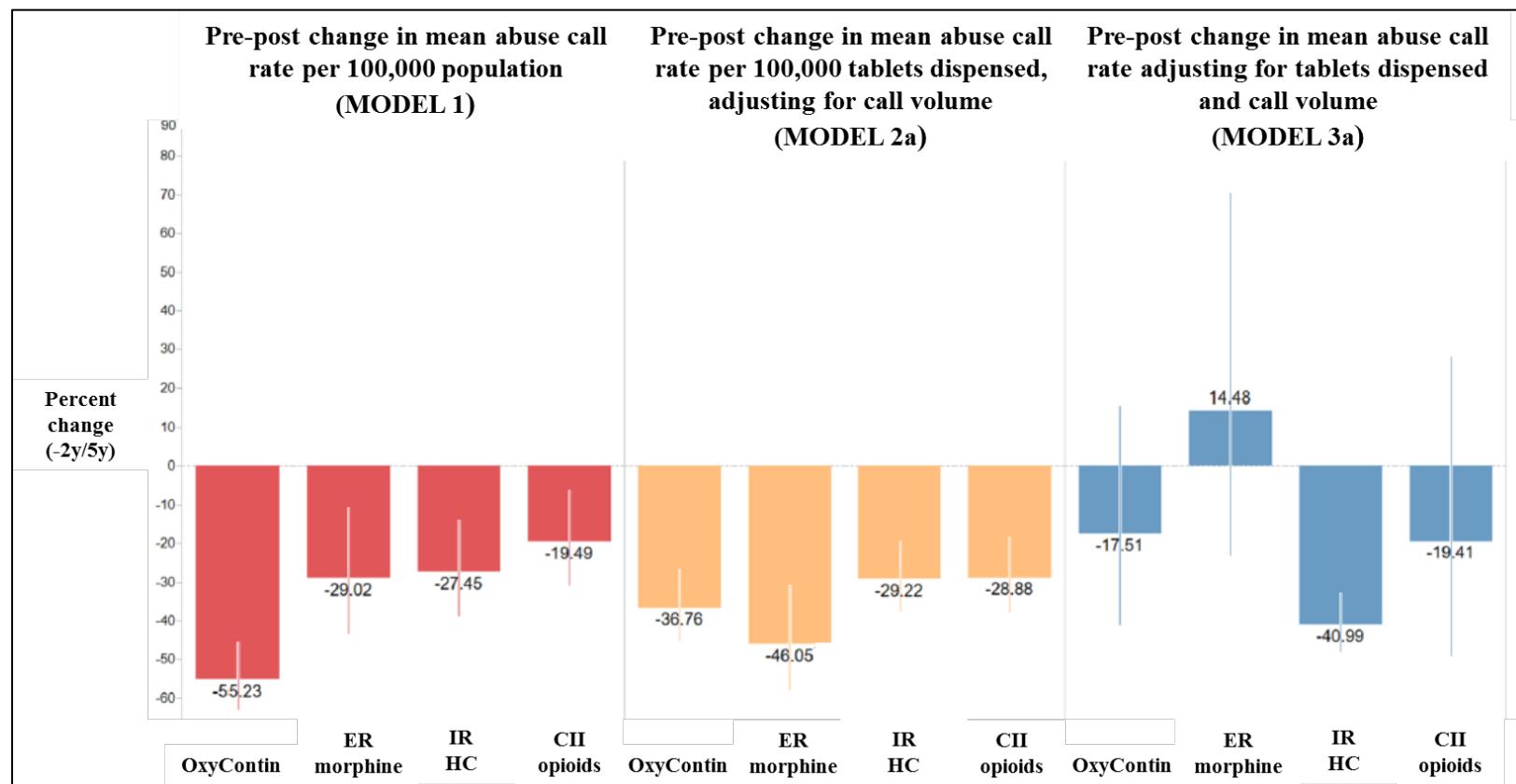
(*Sponsor figure taken from PMR 3051-2 study report; assembled as a panel and formatted by FDA*)

Key: extended-release (ER); immediate-release (IR); schedule II (CII); "other CII opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; Model 3a models an abuse call rate without an offset, adjusting for the total number of tablets dispensed and call volume (i.e., total pharmaceutical exposure calls for persons > 5 years old) as covariates; solid line: observed rate; dashed line: model estimated mean abuse call rate; grey solid lines: 95% confidence intervals; vertical line/dots: transition period

4.1.4 Change in Mean Abuse Call Rates Comparing Pre- to Post-periods for OxyContin and Comparators

Figure 15 shows the percent changes in mean quarterly abuse call rates comparing pre- and post-periods across models. Declines in abuse call rates were observed for OxyContin across models, but they were not significant when modeling abuse call rates adjusting for tablets dispensed and call volume as covariates (Model 3a). OxyContin had the largest significant decline (-55%) in abuse call rates per general population (Model 1), while ER morphine had the largest significant decline (-46%) in abuse call rates per tablet dispensed, adjusting for call volume (Model 2a). IR hydrocodone had the only significant decline (-41%) in abuse call rates adjusting for tablets dispensed and call volume as covariates (Model 3a), and it was the only comparator that had significant declines across all models.

Figure 15: Percent change in mean quarterly abuse call rates for OxyContin and primary comparator opioids, by model (-2y/5y)

(*Sponsor figure taken from PMR 3051-2 study report; reformatted with headers by FDA*)

Key: extended-release (ER); immediate-release hydrocodone (IR HC); schedule II (CII); "CII opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e. total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates; white vertical lines: 95% confidence intervals

When analyses were replicated using truncated pre- and post-periods (-1y/3y), declines were only modestly attenuated for OxyContin and comparator opioids (See Appendix 8.3); ER morphine did not have significant declines in rates per general population (Model 1) using the shorter study period.
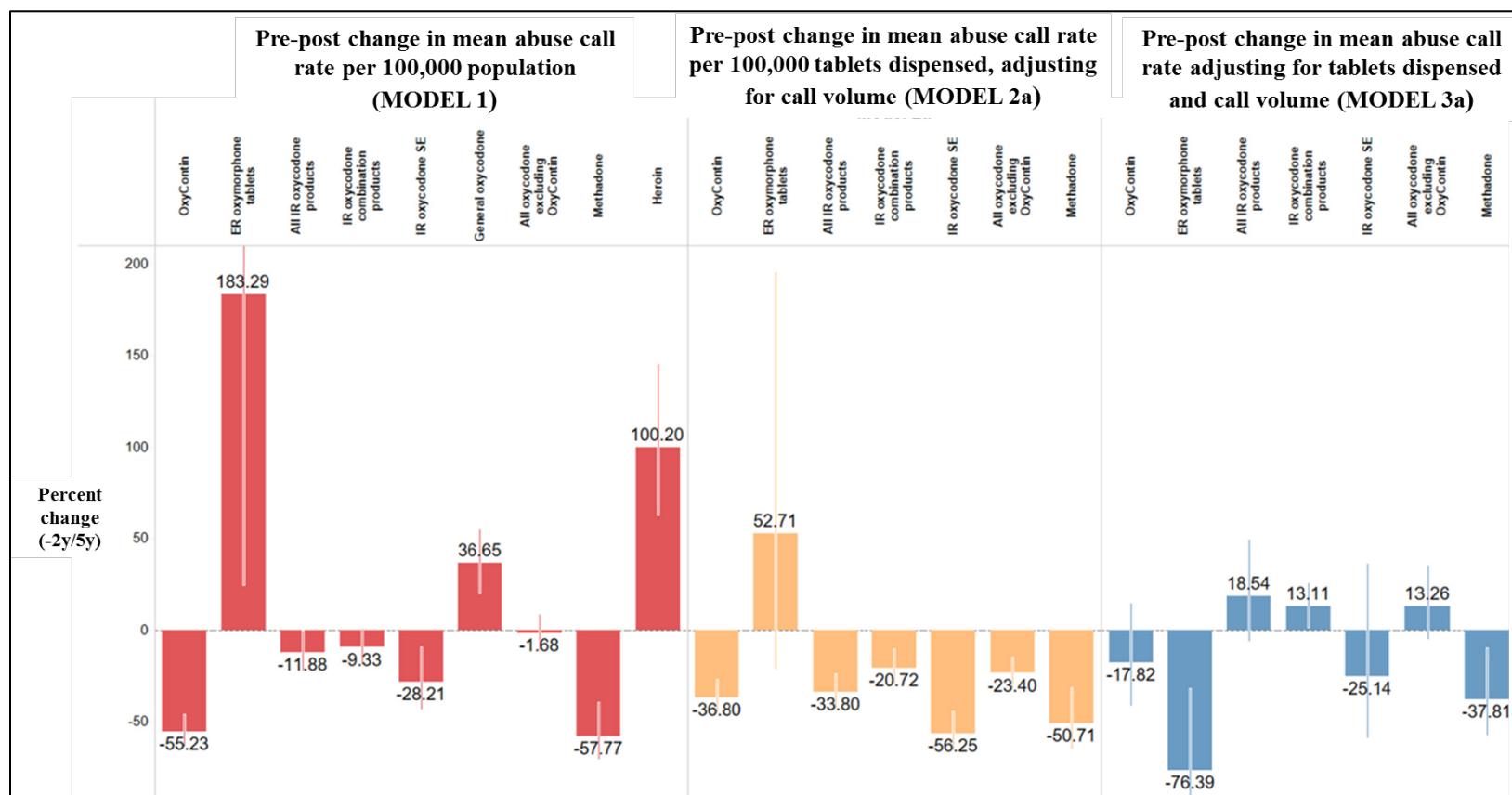
FDA requested that the sponsor re-analyze data adjusting for only total intentional pharmaceutical exposure calls (See Appendix 8.4), rather than total pharmaceutical exposure calls for individuals >5 years old (as a proxy for call volume), and the results were substantially attenuated, most notably for rates per tablets dispensed, adjusting for call volume (Model 2a), and changes were no longer significant for any of the opioids, including OxyContin. The sponsor explained this different result as likely due to collinearity in the model, where intentional exposure calls are highly correlated with time (pearson correlation coefficient [r]= 0.96), as opposed to total pharmaceutical exposure calls (r= 0.31).

Figure 16 shows the percent changes in mean quarterly abuse call rates comparing pre- and post-periods across models for secondary comparators. Methadone had the largest significant decline per general population (Model 1), while ER oxymorphone had the largest increase, followed by heroin (100%). Increases in "general oxycodone" (i.e., oxycodone NOS) (37%) reflect the increase in missing formulation data over time.

ER oxymorphone (53%) was the only comparator that increased when modeling abuse call rates per tablet dispensed, adjusting for call volume (Model 2a), but ER oxymorphone also decreased when modeling abuse call rates adjusting for tablets dispensed and call volume as covariates (Model 3a). All IR oxycodone products (combination and single-entity products) had a borderline significant declines in abuse call rates per general population (p=0.051) (Model 1), and a significant percent decline in abuse call

rates per tablet dispensed, adjusting call volume (Model 2a), but not when adjusting for tablet dispensed and call volume as covariates (Model 3a).

Figure 16: Percent change in mean quarterly abuse call rates for secondary comparator opioids and other contextual opioid groups, by model (-2y/5y)
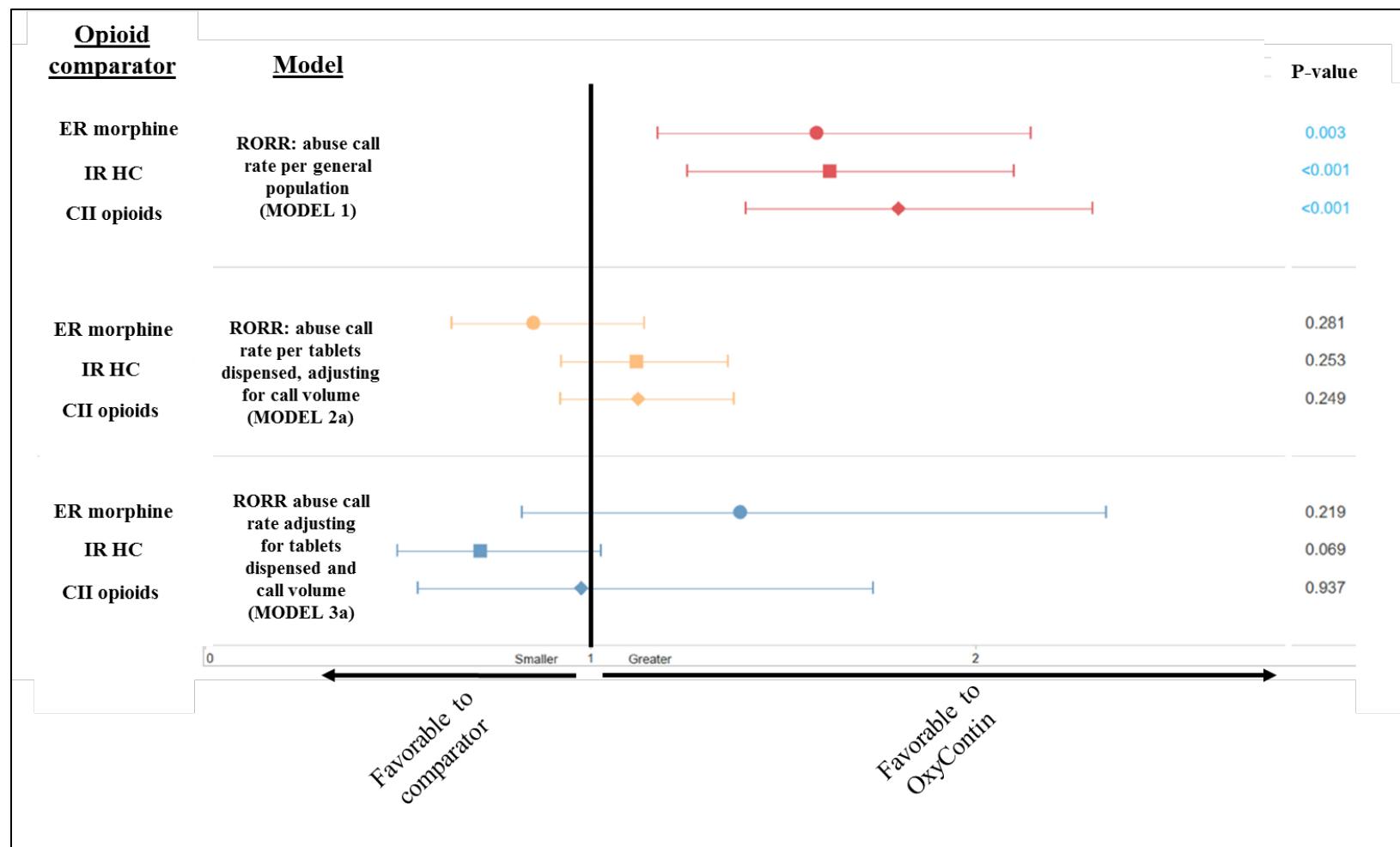
(*Sponsor figure taken from PMR 3051-2 study report; reformatted with headers by FDA*)

Key: extended-release (ER); immediate-release (IR); single-entity (SE); comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e. total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates; white vertical lines: 95% confidence intervals

4.1.4.1 Ratio of Rate Ratios Comparing Primary Comparators to OxyContin

Figure 17 shows the ratio of rate ratios (RORR) across models. RORR is the primary measure used to compare pre- vs. post-period abuse call rate ratios between OxyContin and primary comparators (RORR = [comparator RR] / [OxyContin RR]). The RORRs for all primary comparators were significantly greater than 1 compared to OxyContin (i.e., reflecting a more favorable change for OxyContin relative to the comparator) when modeling abuse call rates per general population (Model 1). Results were more equivocal for OxyContin with other modeling approaches (Model 2a and Model 3a), with RORRs favoring some of the comparator's changes over OxyContin's, but no RORRs were significant using these models. Both when using the shorter time period (-1y/3y) (See Appendix 8.3), and when adjusting for total intentional exposure calls (See Appendix 8.4), RORR results were similar.

Figure 17: Ratio of Rate Ratios (RORR) comparing OxyContin to primary comparator opioids, by model (-2y/5y)

(*Sponsor figure taken from PMR 3051-2 study report; reformatted by FDA*)

Key: extended-release (ER); immediate-release hydrocodone (IR HC); schedule II (CII); "CII opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; Null value = 1 and RORR is relative to OxyContin (reference); a significant RORR > 1 means abuse call rate change comparing periods favors OxyContin and a significant RORR < 1 means abuse call rate change comparing periods favors the comparator; comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e. total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates; horizontal lines: 95% confidence intervals

4.1.5 Descriptive Trends in Abuse Calls for OxyContin and Comparators, by Route of Abuse

Figure 18 shows the quarterly number of <u>oral</u> abuse calls made to PCCs in the pre- and post-periods for OxyContin and primary comparator opioids. When restricting to only oral abuse calls, nearly identical patterns to total calls (see Figure 10) were observed; there was a slight decline in the number for calls for OxyContin (pre-period range = 65 to 105 calls; post-period range = 30 to 75 calls) immediately following the reformulation, which was also observed for IR hydrocodone (pre-period range = 363 to 441 calls; post-period range = 193 to 389 calls) and the "other schedule II opioids" composite comparator group (pre-period range = 652 to 553 calls; post-period range = 663 to 332 calls). The number of oral abuse calls for ER morphine (pre-period range = 16 to 35; post-period range = 12 to 39) was consistently the lowest throughout both the pre- and post-periods. Like with total calls, the declines observed in OxyContin oral abuse calls began shortly after the reformulation and persisted throughout the post-period, whereas for IR hydrocodone and "all schedule II opioids," the decline in oral abuse calls appeared to begin several quarters after the transition period.

Figure 18: Quarterly counts of <u>oral</u> abuse calls involving OxyContin and primary comparator opioids (-2y/5y)
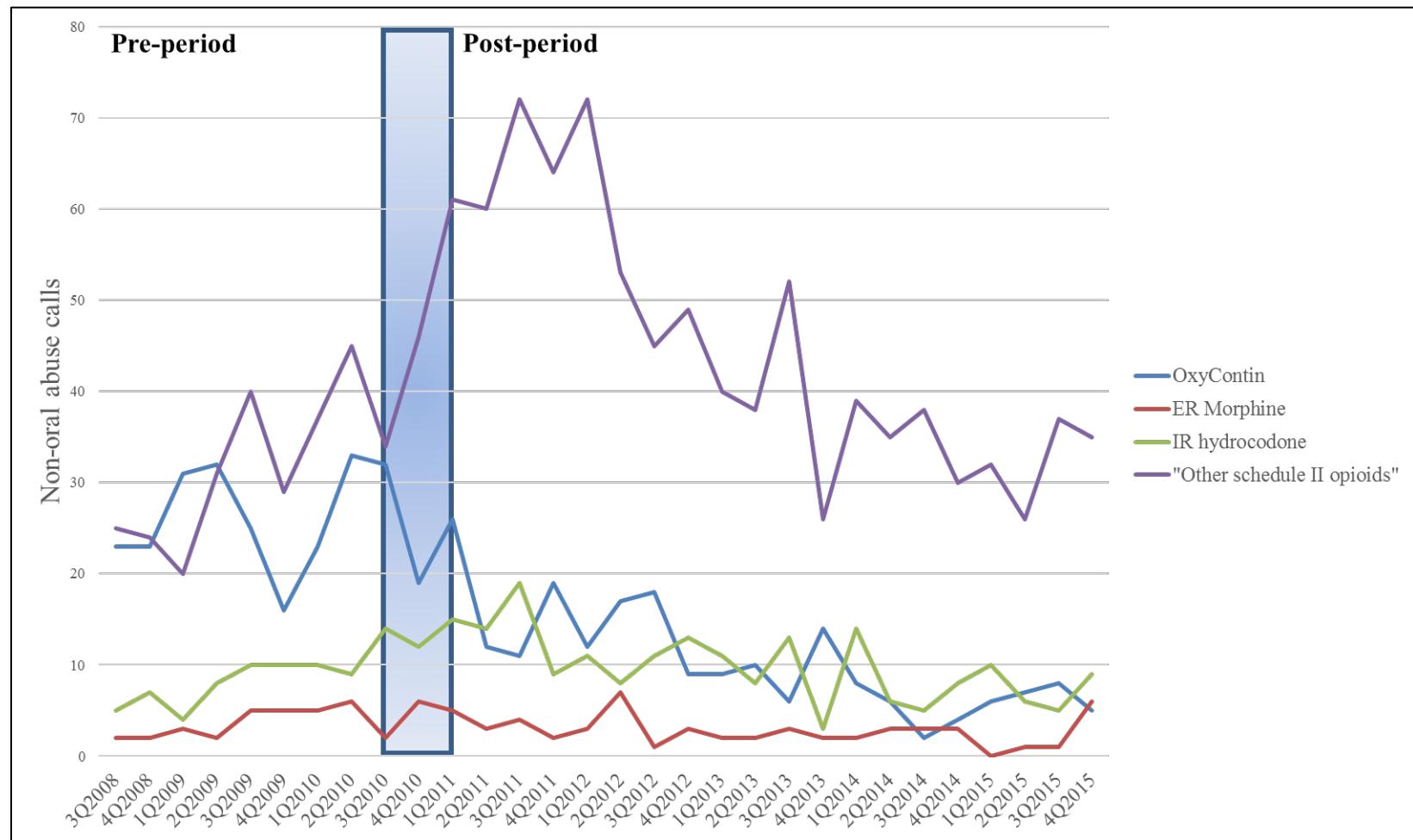
(FDA generated figure using data from the February 21, 2020, sponsor submitted information request response)

Key: extended-release (ER); immediate-release (IR); "other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; the blue box denotes the transition period (excluded from primary analyses)

Figure 19 shows the quarterly number of <u>non-oral (inhalation and injection combined)</u> abuse calls made to PCCs in the pre- and post-periods for OxyContin and primary comparator opioids. Immediately following the reformulation, there was an apparent decline in the number of non-oral abuse calls for OxyContin (pre-period range = 16 to 23 calls; post-period range = 2 to 26 calls), and simultaneously an increase for the "other schedule II opioids" composite comparator group (pre-period range = 24 to 40 calls; post-period range = 26 to 72 calls), which ultimately returned to pre-period levels towards the end of 2012. While the quarterly number of non-oral abuse calls for OxyContin fluctuated throughout the post-period, there was a general declining trend overall. The number of non-oral abuse calls for ER morphine (pre-period range = 2 to 5; post-period range = 0 to 7) and IR hydrocodone (pre-period range = 4 to 10; post-period range = 5 to 19) were consistently lower than OxyContin in the pre-period but were similar to OxyContin by the end of the post-period.

Figure 19: Quarterly counts of <u>non-oral</u> (inhalation and injection) abuse calls for OxyContin and primary comparator opioids (-2y/5y)


(FDA generated figure using data from the February 21, 2020, sponsor submitted information request response)

Key: extended-release (ER); immediate-release (IR); "other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; the blue box denotes the transition period (excluded from primary analyses)

Table 5 shows the mean quarterly oral and non-oral abuse call rates per 100,000 population (Model 1) in the pre- and post-periods for OxyContin and select comparators. Mean oral and non-oral abuse call rates per general population for OxyContin both decreased comparing the pre- and post-periods. Mean oral abuse call rates per general population for primary comparators IR hydrocodone and "all schedule II" opioids also decreased, but their mean non-oral abuse call rates per general population increased from 0.003 to 0.004 per 100,000 population and 0.012 to 0.016 per 100,000 population, respectively. Also, ER morphine had notably lower oral, but particularly non-oral, mean rates per general population in both the pre- and post-periods compared to the other primary comparators. As for secondary ("contextual") comparators, mean oral and non-oral abuse call rates per general population for both heroin[xx] and ER oxymorphone increased, while mean oral abuse call rates per general population decreased for IR oxycodone, but its non-oral abuse call rates per general population increased. Both oral and non-oral abuse call rates per general population also increased for general oxycodone (i.e., oxycodone without formulation information; here, oxycodone NOS); some of these cases may involve OxyContin.

[xx] Oral heroin abuse rates may also involve ingested heroin (bags) for the purposes of smuggling

Table 5: Mean <u>oral</u> and <u>non-oral</u> abuse call rates for OxyContin and comparator opioids per 100,000 population (Model 1), by period (-2y/5y)
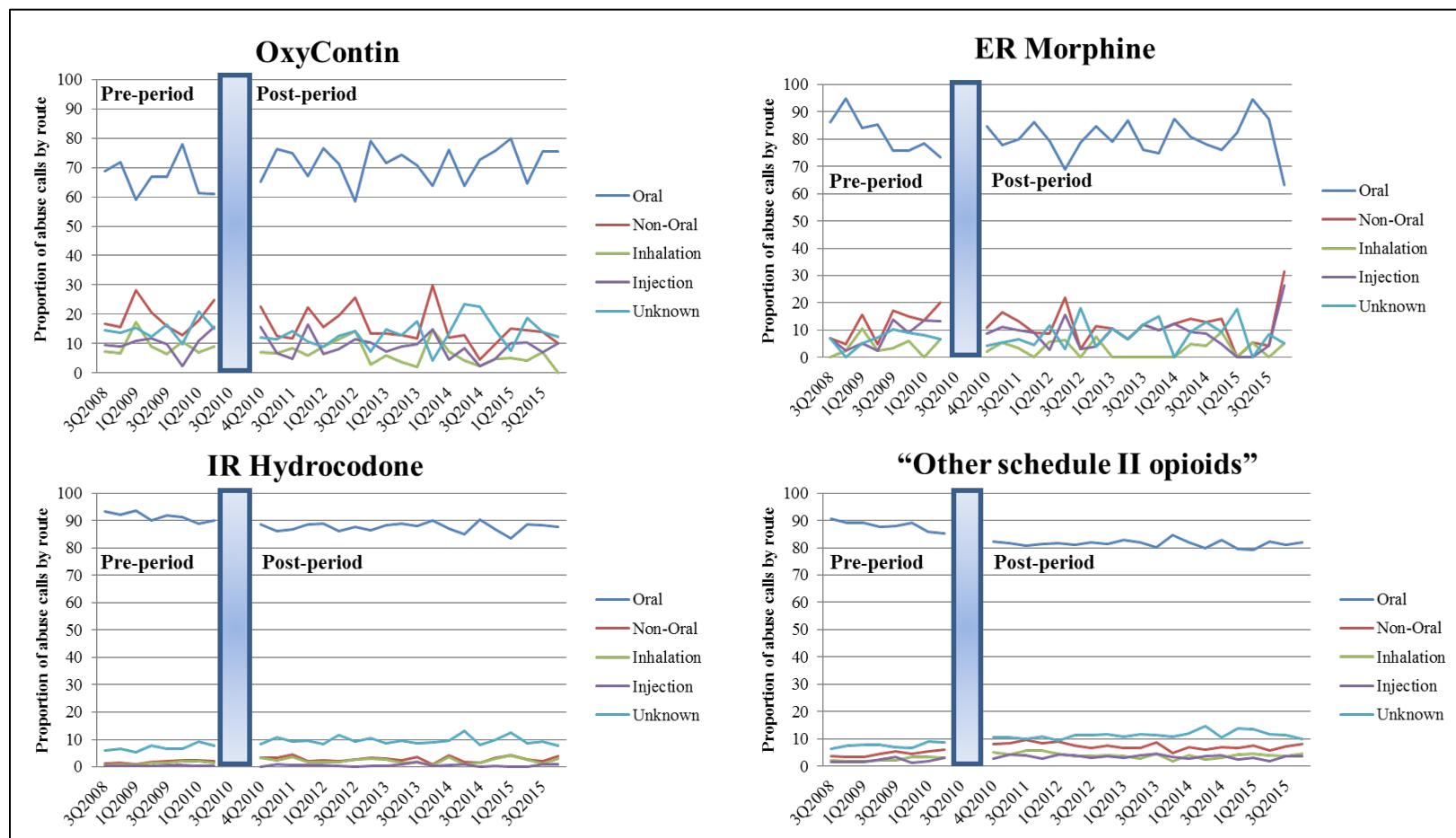
| Opioid comparator	Oral		Non-oral	
	Pre-period Mean quarterly abuse call rate per 100,000 population (Model 1) (95% confidence interval)	**Post-period** Mean quarterly abuse call rate per 100,000 population (Model 1) (95% confidence interval)	**Pre-period** Mean quarterly abuse call rate per 100,000 population (Model 1) (95% confidence interval)	**Post-period** Mean quarterly abuse call rate per 100,000 population (Model 1) (95% confidence interval)
Primary comparators				
OxyContin	0.035 (0.030 to 0.040)	0.017 (0.014 to 0.019)	0.010 (0.008 to 0.012)	0.004 (0.003 to 0.005)
ER morphine	0.010 (0.008 to 0.012)	0.007 (0.006 to 0.008)	0.001 (0.001 to 0.002)	<0.001 (<0.001 to 0.001)
IR hydrocodone	0.154 (0.134 to 0.176)	0.107 (0.097 to 0.118)	0.003 (0.002 to 0.004)	0.004 (0.003 to 0.004)
"Other CII opioids"	0.234 (0.207 to 0.265)	0.174 (0.160 to 0.190)	0.012 (0.009 to 0.016)	0.016 (0.014 to 0.018)
Secondary comparators				
ER oxymorphone	0.002 (0.001 to 0.005)	0.006 (0.004 to 0.008)	0.001 (<0.001 to 0.003)	0.004 (0.003 to 0.005)
IR oxycodone	0.069 (0.062 to 0.076)	0.056 (0.052 to 0.060)	0.005 (0.004 to 0.007)	0.006 (0.005 to 0.007)
Oxycodone (NOS)	0.020 (0.018 to 0.023)	0.026 (0.024 to 0.028)	0.003 (0.003 to 0.004)	0.005 (0.004 to 0.005)
Methadone	0.012 (0.009 to 0.016)	0.005 (0.004 to 0.006)	<0.001 (<0.001 to <0.001)	<0.001 (<0.001 to <0.001)
Heroin	0.027 (0.023 to 0.032)	0.044 (0.041 to 0.048)	0.045 (0.037 to 0.056)	0.102 (0.094 to 0.112)

(FDA generated table using data from PMR 3051-2 study report)

Key: extended-release (ER); immediate-release (IR); not otherwise specified (NOS); Schedule II (CII); "other CII" opioids includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; non-oral includes all calls for inhalation and injection combined; arrow denotes direct of change; Model 1 models an abuse call rate per general population (as an offset)

Figure 20 shows the quarterly proportions of all abuse calls involving OxyContin and primary comparators that mention specific routes of abuse. These proportions remained relatively stable across time periods for all the drug groups, with the vast majority of abuse calls involving oral abuse. For OxyContin and ER morphine there was more quarterly fluctuation than for IR hydrocodone and "all schedule II opioids", likely due to their lower total number of calls, particularly for ER morphine.

Figure 20: Proportion of total abuse calls by route of abuse for OxyContin and primary comparator opioids per quarter (-2y/5y)

(*Sponsor figure taken from February 21, 2020, information request response study; boxes and other formatting added by FDA*)

Key: extended-release (ER); immediate-release (IR); "other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; "unknown" means missing (i.e., not reported or not recorded during the call); the blue boxes represents the transition period between the pre- and post-reformulation periods (data were not available)

Table 6 shows the pre- and post-period proportions of all the abuse calls in that given period involving OxyContin and primary comparators that mention specific routes of abuse. Comparing periods, OxyContin had a slight increase in oral abuse from 67% to 72%, and a slight decrease in non-oral abuse from 19% to 16%; the comparator opioid groups showed relatively consistent proportions in the pre- and post-periods. OxyContin had the greatest proportion of missing route in both the pre- (15%) and post-periods (13%).

Table 6: Pre- and post-period proportions of total abuse calls for OxyContin and comparator opioids, by <u>oral and non-oral</u> route (-2y/5y)

Opioid comparator	Pre-reformulation period			Post-reformulation period		
	Oral	Non-oral	Missing	Oral	Non-oral	Missing
OxyContin	67%	19%	15%	72%	16%	13%
ER morphine	82%	12%	8%	80%	12%	9%
IR hydrocodone	91%	2%	7%	88%	3%	10%
"Other schedule II opioids"	88%	5%	8%	82%	7%	11%
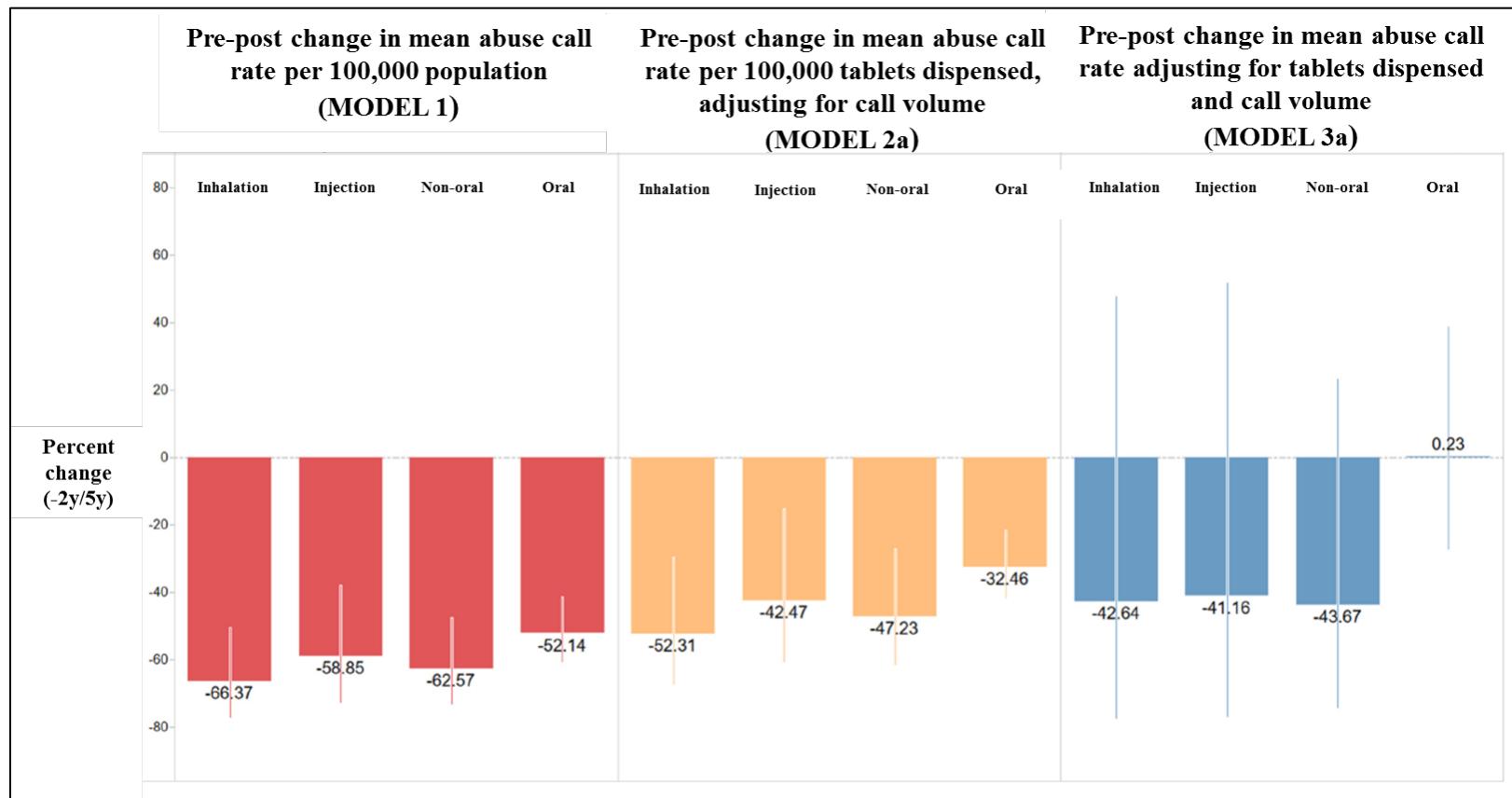
(FDA generated table using data from the February 21, 2020, sponsor submitted information request response)

Key: extended-release (ER); immediate-release (IR); "other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; the percentages reflect the total proportions of all calls in a given period; percentages were rounded to the nearest whole number (may be greater than to 100%)

4.1.6 Change in Mean Abuse Call Rates Comparing Periods for OxyContin and Comparators, by Route of Abuse

Figure 21 shows the percent changes in mean quarterly abuse call rates for OxyContin comparing pre- and post-periods across models stratified by route of abuse (ROA). In general, declines were observed for OxyContin across routes and modeling approaches, but not all were significant. OxyContin had significant declines in non-oral abuse call rates per general population (Model 1: 63%) and per tablets dispensed, adjusting for call volume (Model 2a: 47%), slightly more notably for the inhalation route than the injection route across both models. Declines in non-oral abuse call rates adjusting for tablets dispensed and call volume were not significant. Significant oral abuse call rate declines per general population (Model 1: 52%) and per tablets dispensed, adjusting for call volume (Model 2a: 32%) were also observed.

Figure 21: Percent change in mean quarterly abuse call rates for OxyContin and primary comparator opioids, by model and route (-2y/5y)

(*Sponsor figure taken from PMR 3051-2 study report; reformatted with headers by FDA*)

Key: "Non-oral" includes inhalation and injection; comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e. total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates; white vertical lines: 95% confidence intervals

Table 7 shows the percent changes in mean quarterly abuse call rates comparing pre- and post-periods across models for all primary comparators stratified by ROA. When modeling abuse call rates per general population (Model 1), OxyContin was the only opioid with significant declines for non-oral (combined), inhalation, and injection routes. Significant declines were seen in non-oral abuse call rates per tablets dispensed, adjusting for call volume (Model 2a), for ER morphine (48%) that were similar to those of OxyContin. The decline in OxyContin abuse call rates involving the non-oral route were modestly larger than those involving the oral route, whereas the decline in oral abuse call rates for ER morphine were virtually identical to those involving non-oral abuse, both per general population (Model 1) and per tablets dispensed, adjusted for call volume (Model 2a). Oral abuse call rates for IR hydrocodone and "other schedule II opioids" declined across models, and all were significant except those for "other schedule II opioids" when modeling abuse call rates adjusting for tablets dispensed and call volume (Model 3a). Non-oral abuse call rates for IR hydrocodone and "other schedule II opioids" increased across models, but the increases were not significant.

In summary, only OxyContin showed significant declines in non-oral abuse rates per general population (Model 1). Both OxyContin and ER morphine (but not IR hydrocodone or "all schedule II opioids") showed significant declines in non-oral abuse call rates per tablets dispensed, adjusted for call volume (Model 2a); however, the larger decline in non-oral versus oral abuse call rates was unique to OxyContin among the opioid groups examined.

Table 7: Percent change in mean abuse call rates for OxyContin and primary comparators, by model and route of abuse (-2y/5y)

	Pre-post change in mean abuse call rate per 100,000 population (MODEL 1)	Pre-post change in mean abuse call rate per 100,000 tablets dispensed, adjusting for call volume (MODEL 2a)	Pre-post change in mean abuse call rate adjusting for tablets dispensed and call volume (MODEL 3a)
Inhalation			
OxyContin	-66.37% (-77.23% to -50.32%)	-52.31% (-67.62% to -29.78%)	-42.64% (-77.74% to 47.78%)
ER Morphine	-38.22% (-70.17% to 27.97%)	-52.87% (-77.35% to -1.92%)	-13.39% (-83.12% to 344.54%)
IR Hydrocodone	23.32% (-18.04% to 85.53%)	20.73% (-18.46% to 78.76%)	11.19% (-31.17% to 79.64%)
Other Schedule II	33.02% (-6.76% to 89.76%)	17.92% (-16.24% to 66.01%)	75.57% (-38.73% to 403.07%)
Injection			
OxyContin	-58.85% (-72.74% to -37.89%)	-42.47% (-60.94% to -15.26%)	-41.16% (-77.21% to 51.89%)
ER Morphine	-27.62% (-56.86% to 21.42%)	-45.54% (-67.63% to -8.37%)	-21.30% (-75.17% to 149.45%)
IR Hydrocodone	-7.32% (-52.16% to 79.52%)	-10.47% (-53.13% to 71.02%)	-29.81% (-69.04% to 59.15%)
Other Schedule II	34.10% (-2.74% to 84.89%)	17.26% (-13.01% to 58.07%)	-27.22% (-71.40% to 85.24%)
Non-oral (Inhalation and Injection)			
OxyContin	-62.57% (-73.27% to -47.58%)	-47.23% (-61.72% to -27.27%)	-43.67% (-74.30% to 23.49%)
ER Morphine	-30.80% (-55.38% to 7.32%)	-47.51% (-66.26% to -18.34%)	-18.70% (-69.29% to 115.24%)
IR Hydrocodone	16.51% (-17.45% to 64.44%)	13.44% (-17.80% to 56.54%)	1.28% (-31.59% to 49.96%)
Other Schedule II	33.07% (-1.18% to 79.19%)	17.30% (-10.97% to 54.55%)	19.35% (-50.06% to 185.22%)
Oral			
OxyContin	-52.14% (-60.92% to -41.39%)	-32.46% (-41.86% to -21.54%)	0.23% (-27.63% to 38.81%)
ER Morphine	-30.58% (-45.85% to -11.01%)	-47.29% (-59.70% to -31.06%)	20.28% (-20.84% to 82.75%)
IR Hydrocodone	-30.40% (-41.22% to -17.58%)	-32.16% (-40.33% to -22.88%)	-43.75% (-50.57% to -35.99%)
Other Schedule II	-25.42% (-35.84% to -13.31%)	-34.19% (-42.55% to -24.61%)	-24.17% (-52.23% to 20.38%)

(Sponsor table taken from PMR 3051-2 study report; reformatted with headers by FDA)

Key: extended-release (ER); immediate-release (IR); confidence interval (CI); "other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e. total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates

When analyses were replicated adjusting for total intentional exposure calls (See Appendix 8.4), rather than total pharmaceutical exposure calls (as a proxy for call volume), OxyContin and most comparators showed no significant change in either oral or non-oral abuse call rates, but significant percent increases were observed for IR hydrocodone and "other schedule II opioids" in non-oral abuse call rates.

When the sponsor re-analyzed ROA data including all cases (See Appendix 8.4, rather than excluding cases that reported multiple substances and routes, the results were similar to primary analyses.

Table 8 shows the percent changes in mean quarterly abuse call rates comparing pre- and post-periods across models for secondary ("contextual") comparators stratified by ROA. When modeling abuse call rates per general population (Model 1), or abuse call rates per tablets dispensed, adjusting for call volume (Model 2a), OxyContin was the only opioid with significant declines for non-oral (combined), inhalation, and injection routes. OxyContin and nearly all opioid comparators showed no significant declines in non-oral abuse call rates adjusting for tablets dispensed and call volume as covariates (Model 3a), the exception being ER oxymorphone which showed significant declines in non-oral abuse call rates overall, but specifically in inhalation routes, and a large but not quite significant increase in injection.

Not shown in this table, mean quarterly non-oral abuse call rates for oxycodone NOS (or "general oxycodone") significantly increased (37%, 95% confidence interval [CI]: 20-56%) per general population (Model 1).

Table 8: Percent change in mean quarterly abuse call rates for OxyContin and selected <u>secondary comparators</u>, by model and route of abuse (-2y/5y)

Opioid comparator	Pre-post change in mean abuse call rate per 100,000 population comparing pre- and post-periods (Model 1) (95% confidence interval)	Pre-post change in mean abuse call rate per 100,000 tablets dispensed comparing pre- and post-periods, adjusting for call volume (Model 2a) (95% confidence interval)	Pre-post change in mean abuse call rate comparing pre- and post-periods, adjusting for tablets dispensed and call volume (Model 3a) (95% confidence interval)
Oral			
OxyContin	-52% (-61% to -41%)	-32% (-42% to -22%)	0% (-28 to 39%)
IR oxycodone	-19% (-29% to -9%)	-39% (-44% to -30%)	5% (-17% to 33%)
ER oxymorphone	138% (4% to 444%)	28% (-36% to 156%)	-76% (-94% to -10%)
Methadone	-59% (-71% to -40%)	-52% (-66% to -32%)	-37% (-57% to -8%)
Heroin	66% (37% to 100%)	N/A	N/A
Non-oral			
OxyContin	-63% (-73% to -48%)	-47% (-62% to -27%)	-44% (-74% to 23%)
IR oxycodone	29% (-8% to 81%)	-3% (-32% to 38%)	209% (62% to 489%)
ER oxymorphone	235% (27% to 786%)	81% (18% to 300%)	-85% (-95% to -57%)
Methadone	-68% (-90% to 6%)	-62% (-88% to 18%)	-56% (-89% to 77%)
Heroin	125% (79% to 184%)	N/A	N/A
Inhalation			
OxyContin	-66% (-77% to -50%)	-52% (-68% to -30%)	-43% (-78% to 48%)
IR oxycodone	26% (-6% to 69%)	-5% (-31% to 30%)	156% (48% to 342%)
ER oxymorphone	151% (-28% to 783%)	35% (-53% to 291%)	-97% (-99% to -87%)
Methadone	-63% (-93% to 92%)	-57% (-91% to 119%)	-42% (-92% to 309%)
Heroin	134% (76% to 212%)	N/A	N/A
Injection			
OxyContin	-59% (-73% to -48%)	-42% (-61% to -15%)	-41% (-77% to 52%)
IR oxycodone	34% (-22% to 131%)	1% (-41% to 76%)	299% (20% to 1,228%)
ER oxymorphone	613% (186% to 1,678%)	286% (65% to 805%)	252% (-19% to 1,424%)
Methadone	-70% (-94% to 51%)	-65% (-93% to 66%)	-64% (-95% to 161%)
Heroin	122% (77% to 177%)	N/A	N/A

(FDA generated table using data from PMR 3051-2 study report)

Key: extended-release (ER); immediate-release (IR); confidence interval (CI); comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e. total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates; percentages rounded for display
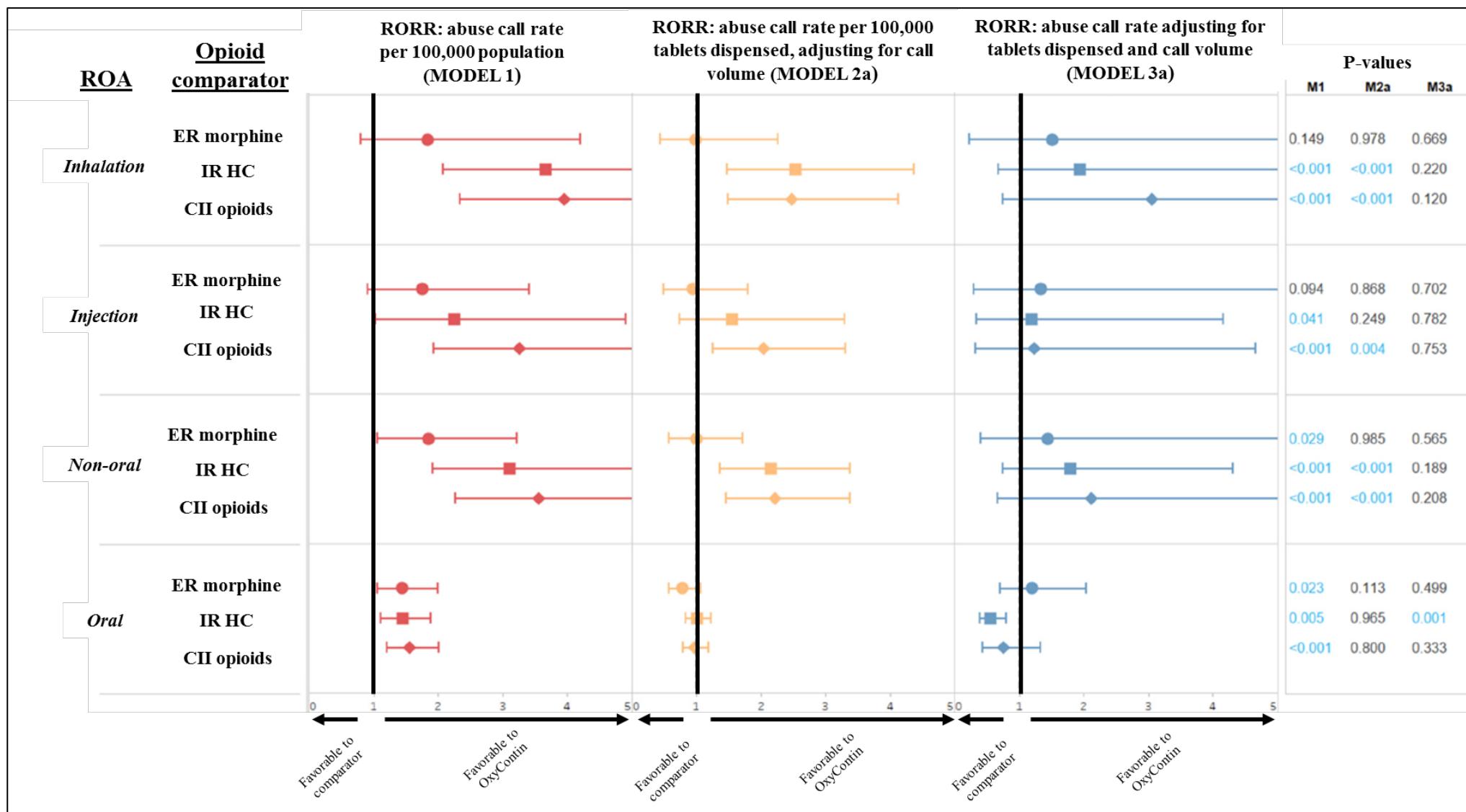
4.1.6.1   Ratio of Rate Ratios Comparing Primary Comparators to OxyContin, by Route

Figure 22 shows the RORRs for primary comparators by ROA across models. The RORRs for IR hydrocodone and "other schedule II opioids" were significantly greater than 1 when modeling non-oral abuse call rates per general population (Model 1) and per tablets dispensed, adjusted for call volume (Model 2a), which favors OxyContin with respect to change in rates between periods. ER morphine had a significant RORR (1.85, 95% CI: 1.06-3.21) for non-oral abuse when modeling non-oral abuse call rates per general population (Model 1), also favoring OxyContin, but not per tablets dispensed, adjusting for call volume (Model 2a). All RORRs favored OxyContin when modeling non-oral abuse call rates adjusting for tablets dispensed and call volume as

covariates (Model 3a) but none were significant. For abuse calls involving the oral route, RORRs were significantly greater than 1 (i.e., favoring OxyContin) only when modeling abuse call rates per general population (Model 1).

Both when using the shorter time period (-1y/3y) (See Appendix 8.3), and when adjusting for only total intentional exposure calls (See Appendix 8.4), RORR results were largely similar to primary analyses, except that the RORR for IR hydrocodone was no longer significant (RORR = 1.41, CI: 0.83-2.41) when using the shorter time period and modeling non-oral abuse call rates per tablets dispensed, adjusting for call volume (Model 2a).

Figure 22: Ratio of Rate Ratios (RORR) comparing OxyContin to primary comparator opioids, by model and ROA (-2y/5y)

(*Sponsor figure taken from PMR 3051-2 study report; reformatted by FDA*)

Key: extended-release (ER); immediate-release hydrocodone (IR HC); schedule II (CII); "CII opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; Null value = 1 and RORR is relative to OxyContin (reference); a significant RORR > 1 means abuse call rate change comparing periods favors OxyContin and a significant RORR < 1 means abuse call rate change comparing periods favors the comparator; comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e. total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates; horizontal lines: 95% confidence intervals

4.1.7 Changes in Total Intentional Exposure Calls, Unintentional Exposure Calls, and Individual Call Types for OxyContin and Comparators

Figure 23 shows the quarterly total number of calls for all intentional exposures (i.e., abuse, misuse, and suspected suicide) for OxyContin and primary comparators. Across opioid groups, the number of calls was generally consistent over time, with more noticeable declines towards the end of the post-period. Compared to IR hydrocodone (and "other schedule II opioids"), the total number of calls for all intentional exposures are much lower for OxyContin and ER morphine.

Figure 23: Total calls involving any intentional exposures for OxyContin and primary comparators (-2y/5y)

(*Sponsor figure taken from March 2020 information request response study; boxes added by FDA*)

Key: extended-release (ER); immediate-release (IR); single-entity (SE); "cases" are equivalent to intentional exposure calls; the transition period and the 2016 data are not included in any primary analyses; "other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; intentional exposures included reports of abuse, misuse, suspected suicide, or unknown

Table 9 shows the percent changes in mean quarterly calls related to pharmaceutical misuse (i.e., improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect) and suspected suicide comparing pre- and post-periods across models. OxyContin had significant declines in both intentional misuse and suspected suicide rates when modeling rates per general population (Model 1), but not rates per tablets dispensed, adjusted for call volume (Model 2a), or rates adjusted for tablets dispensed and call volume as covariates (Model 3a). Primary comparators showed declines in both exposure categories across nearly all models.

Table 9: Percent change in mean intentional misuse and suspected suicide call rates for OxyContin and primary comparators, by model (-2y/5y)
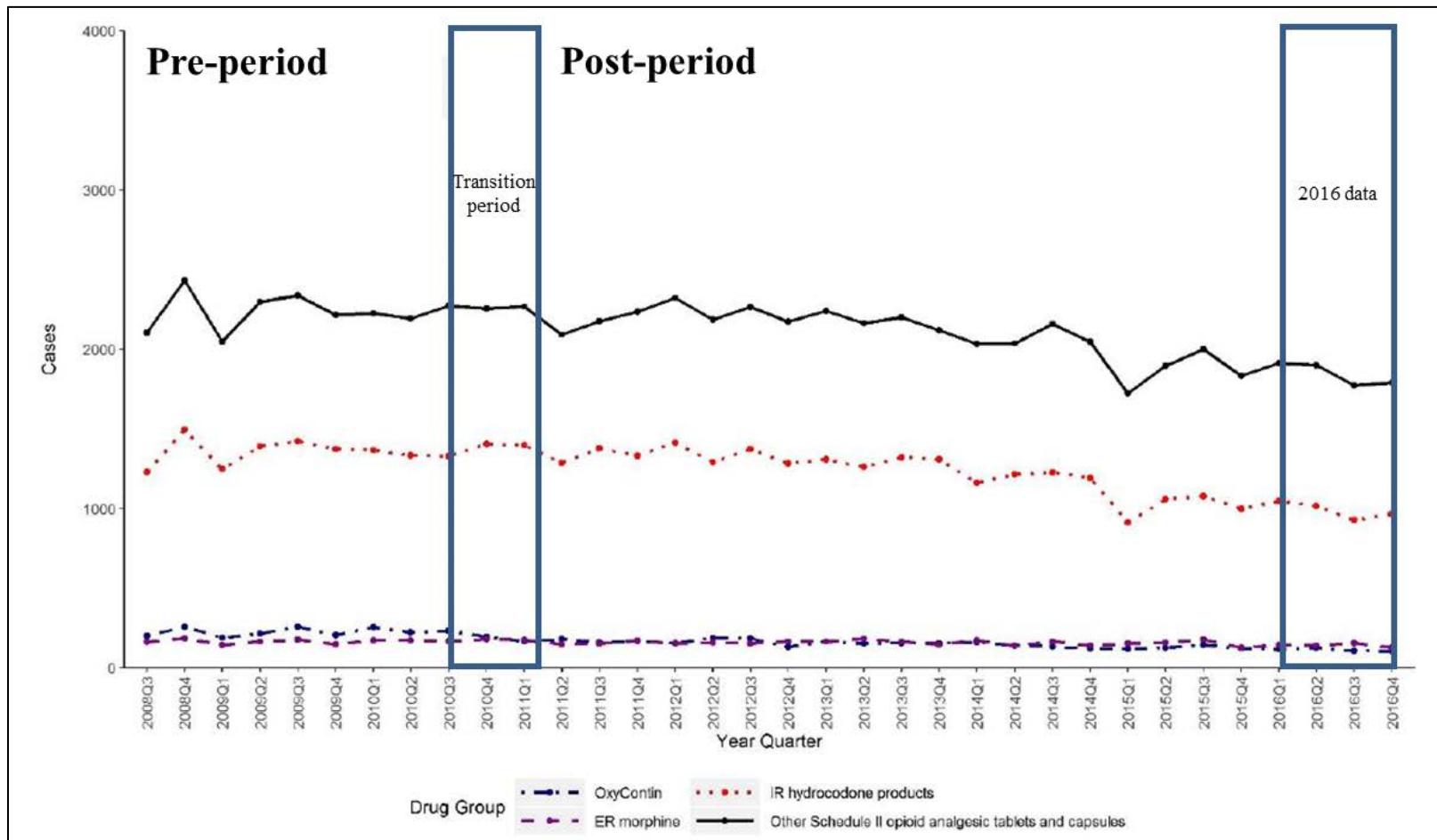
	Pre-post change in mean call rate per 100,000 population (MODEL 1)	Pre-post change in mean call rate per 100,000 tablets dispensed, adjusting for call volume (MODEL 2a)	Pre-post change in mean call rate adjusting for tablets dispensed and call volume (MODEL 3a)
Intentional Misuse			
OxyContin	-34.94% (-45.61% to -22.17%)	-6.93% (-20.45% to 8.88%)	3.96% (-28.81% to 51.81%)
ER Morphine	-12.41% (-29.46% to 8.77%)	-32.62% (-46.81% to -14.63%)	32.23% (-10.85% to 96.11%)
IR Hydrocodone	-18.6% (-28.22% to -7.68%)	-19.64% (-26.25% to -12.44%)	-26.26% (-33.03% to -18.80%)
Other Schedule II	-14.11% (-22.89% to -4.33%)	-23.21% (-30.11% to -15.64%)	-8.71% (-32.80% to 24.01%)
Suspected Suicide			
OxyContin	-31.64% (-39.90% to -22.25%)	-2.73% (-10.85% to 6.13%)	7.97% (-11.92% to 32.36%)
ER Morphine	-8.94% (-18.17% to 1.32%)	-30.31% (-38.71% to -20.76%)	6.00% (-13.46% to 29.84%)
IR Hydrocodone	-6.23% (-13.86% to 2.08%)	-7.89% (-11.52% to -4.11%)	-10.98% (-14.90% to -6.89%)
Other Schedule II	-1.52% (-7.80% to 5.19%)	-12.40% (-16.23% to -8.40%)	-14.51% (-26.32% to -0.81%)

(Sponsor table taken from PMR 3051-2 study report; reformatted with headers by FDA)

Key: extended-release (ER); immediate-release (IR); confidence interval (CI); "other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e. total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates

Figure 24 shows the quarterly total number of calls for all unintentional exposures (i.e., therapeutic errors and unintentional general exposures such as pediatric exposures) for OxyContin and primary comparators. Like intentional exposures, across opioid groups, the number of calls was generally consistent over time, with more noticeable declines towards the end of the post-period. Like intentional exposures, compared to IR hydrocodone (and "other schedule II opioids"), the total number of calls for all unintentional exposures are much lower for OxyContin and ER morphine.

Figure 24: Total calls involving any <u>unintentional exposures </u>for OxyContin and primary comparators (-2y/5y)

(*Sponsor figure taken from March 2020 information request response study; boxes added by FDA*)

Key: extended-release (ER); immediate-release (IR); "cases" are equivalent to unintentional exposure calls; the transition period and the 2016 data are not included in any primary analyses; "other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; unintentional exposures included reports of therapeutic errors, or unintentional general exposures

Table 10 shows the percent changes in mean quarterly calls related to adverse drug reactions and unintentional exposures, including unintentional therapeutic errors and general exposures (i.e., accidental exposures). Like the comparator opioid groups, OxyContin had significant declines in adverse reactions when modeling rates per general population (Model 1), but not rates per tablets dispensed, adjusted for call volume (Model 2a), or rates adjusted for tablets dispensed and call volume as covariates (Model 3a). Unintentional general exposure rates for OxyContin showed significant declines across all models, as did the comparator opioids; unintentional therapeutic errors were not as consistent across comparators and models.

Table 10: Percent change in mean <u>adverse reaction</u> and <u>unintentional exposure</u> call rates for OxyContin and primary comparators, by model (-2y/5y)

	Pre-post change in mean call rate per 100,000 population (MODEL 1)	Pre-post change in mean call rate per 100,000 tablets dispensed, adjusting for call volume (MODEL 2a)	Pre-post change in mean call rate adjusting for tablets dispensed and call volume (MODEL 3a)
Adverse Reactions			
OxyContin	-55.45% (-65.21% to -42.96%)	-37.12% (-49.80% to -21.23%)	-15.92% (-51.51% to 45.81%)
ER Morphine	-47.73% (-56.37% to -37.38%)	-60.3% (-67.21% to -51.93%)	-33.8% (-54.52% to -3.64%)
IR Hydrocodone	-19.34% (-30.48% to -6.42%)	-21.36% (-29.89% to -11.80%)	-25.93% (-35.68% to -14.72%)
Other Schedule II	-21.15% (-30.55% to -10.47%)	-30.4% (-37.90% to -22.01%)	-13.7% (-40.78% to 25.76%)
Unintentional Therapeutic Errors			
OxyContin	-33.03% (-40.30% to -24.87%)	-4.48% (-13.09% to 4.98%)	-9.12% (-27.47% to 13.87%)
ER Morphine	-2.89% (-11.32% to 6.34%)	-25.50% (-33.38% to -16.69%)	7.65% (-9.47% to 27.99%)
IR Hydrocodone	-7.49% (-16.13% to 2.03%)	-8.92% (-14.15% to -3.38%)	-12.98% (-18.68% to -6.87%)
Other Schedule II	-2.76% (-9.06% to 3.98%)	-13.31% (-17.68% to -8.70%)	-15.23% (-28.73% to 0.82%)
Unintentional General Exposures			
OxyContin	-51.71% (-59.62% to -42.25%)	-30.54% (-41.14% to -18.04%)	-35.66% (-57.00% to -3.74%)
ER Morphine	-30.66% (-39.27% to -20.82%)	-46.37% (-53.47% to -38.19%)	-29.5% (-47.76% to -4.85%)
IR Hydrocodone	-27.58% (-34.64% to -19.77%)	-28.13% (-32.79% to -23.14%)	-32.59% (-37.57% to -27.22%)
Other Schedule II	-27.40% (-33.18% to -21.13%)	-34.74% (-39.27% to -29.88%)	-28.49% (-43.94% to -8.77%)

(Sponsor table taken from PMR 3051-2 study report; reformatted with headers by FDA)

Key: extended-release (ER); immediate-release (IR); confidence interval (CI); "other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e. total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates

4.1.8   Interrupted Time Series Analyses

Figure 25 shows an interrupted time series (ITS) plot of the pre- and post-period abuse call rate slopes and level change (or "immediate shift") per general population (Model 5) for OxyContin. OxyContin had a significant decrease in level change (comparing the modeled rate estimates in the quarters before and after the transition period, excluding the transition period), and an observable downward inflection in the slope.

Figure 25: ITS plot of the slopes and level change in the abuse call rate comparing the pre- and post-periods for OxyContin per general population (Model 5)
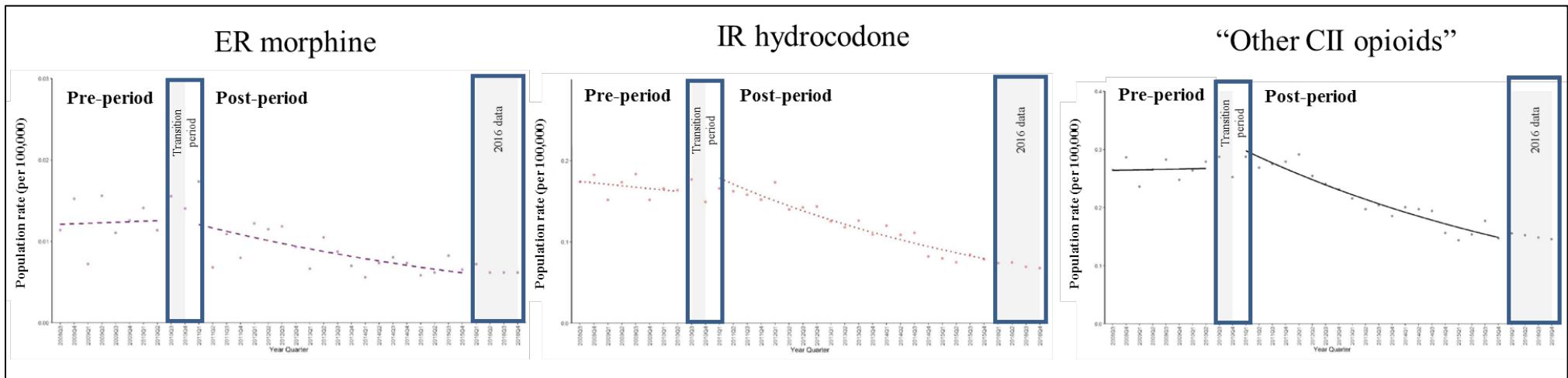
(*Sponsor figure taken from March 2020 information request response study; numbers and boxes added by FDA*)

Key: * statistically significant (p<0.05); Interrupted time series (ITS) model 5 models an abuse call rate slope and level change per general population (as an offset); the transition period and the 2016 data are not included in any primary analyses

Figure 26 shows an ITS panel plot of the pre- and post-period abuse call rate slopes and level changes (or "immediate shift") per general population (Model 5) for primary comparators. The only significant level change of any comparator was for "other schedule II opioids", which had a level change increase (11.4%, CI: 0.47% to 23.5%). Like OxyContin, all comparators had observable downward inflections in their slopes comparing the pre and post-periods.

Figure 26: ITS plot of the slopes and level change in the abuse call rate comparing the pre- and post-periods for primary comparators per general population (Model 5)
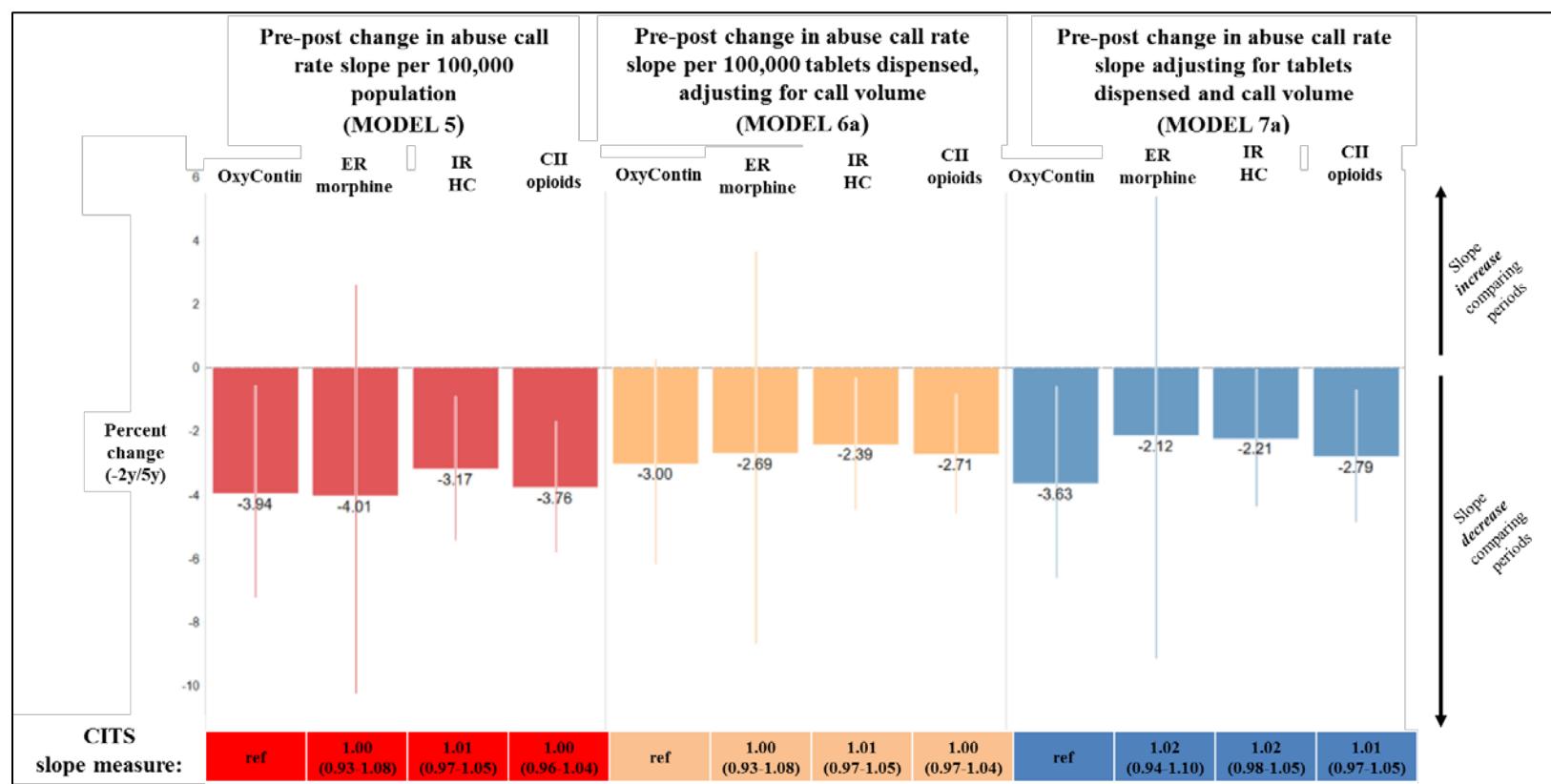
(*Sponsor figure taken from March 2020 information request response study; boxes and panel formatting added by FDA*)

Key: * statistically significant (p<0.05); Interrupted time series (ITS) model 5 models an abuse call rate slope and level change per general population (as an offset); the transition period and the 2016 data are not included in any primary analyses

In response to an FDA information request (September 2019), the sponsor plotted the pre- and post-period abuse call rate slopes and level change (or "immediate shift") per tablets dispensed adjusting for total calls related to intentional pharmaceutical exposures (Model 6a*), rather than total pharmaceutical exposures as was done in primary analyses; they also plotted abuse call rate slopes and level change adjusting for tablets dispensed and total calls related to intentional exposures as covariates (Model 7a*). In both sets of figures, the ITS plots were very similar to those per general population for OxyContin and nearly all comparators shown above (see Appendix 8.6).

Figure 27 shows the percent changes in quarterly abuse call rate <u>slopes</u> comparing pre- and post-periods for OxyContin and primary comparators. Across opioids and models, the percent declines in slopes were overall similar. Comparative interrupted time-series (CITS) models were used to directly compare OxyContin's change in slope to those of the comparator drug groups; an analogous measure to the RORR (shown below as "CITS slope measure") was estimated whereby a CITS slope measure > 1 means the abuse call rate slope change comparing periods favors OxyContin and a CITS slope measure < 1 means the abuse call rate slope change comparing periods favors the comparator. CITS analyses showed no significant difference between the change in slope for OxyContin and the change in slope for any of the comparators (i.e., there was no significant CITS slope measure). Notably, the confidence intervals around ER morphine's abuse call rate slope change estimates across models were particularly large, distinct form the other comparator opioid drugs.

Figure 27: Percent change in quarterly abuse call rate slopes for OxyContin and primary comparators, by model (-2y/5y)
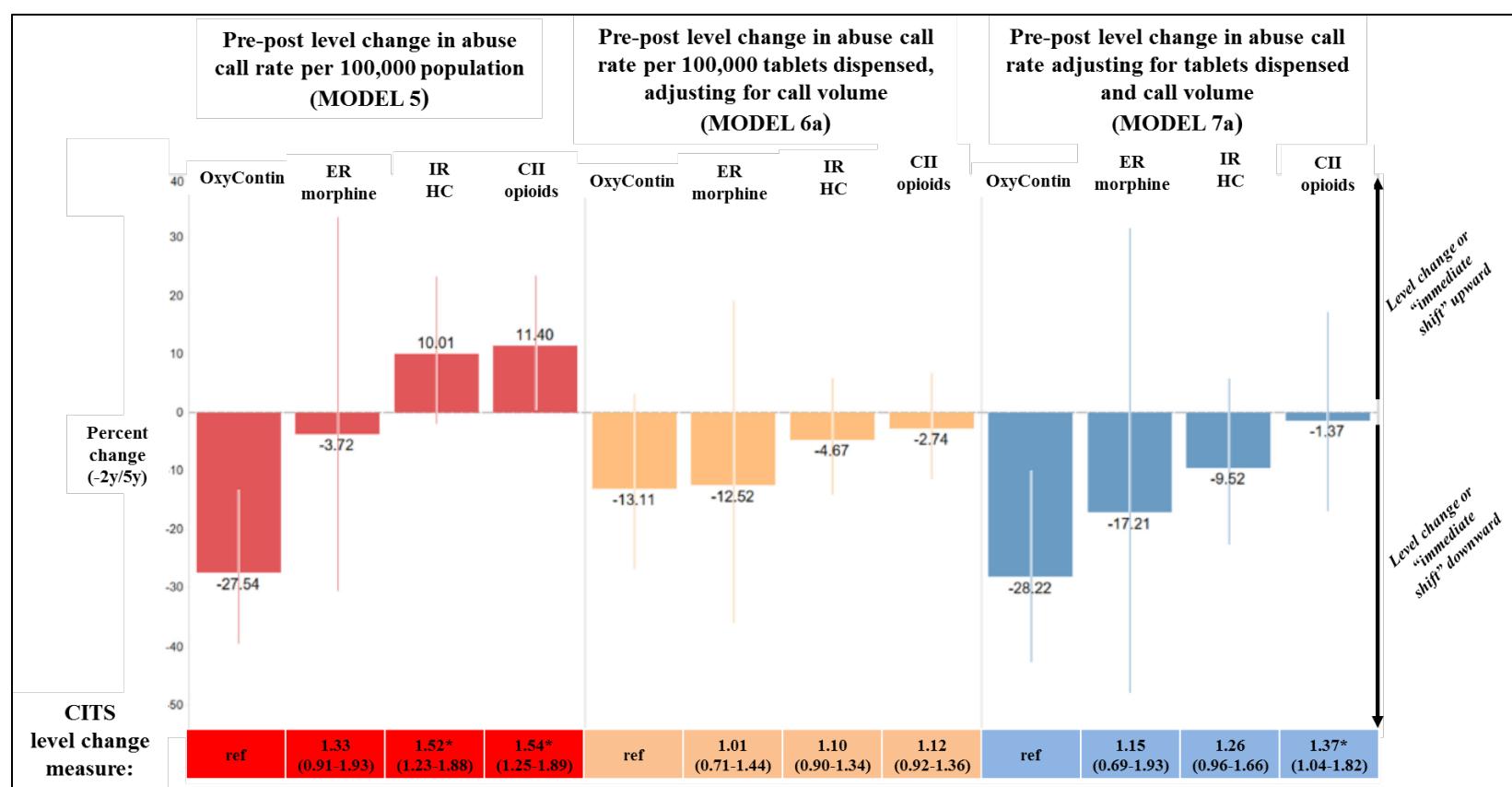
(*Sponsor figure taken from PMR 3051-2 study report; reformatted by FDA, including adding CITS slope measure*)

Key: *= statistically significant (p<0.05); extended-release (ER); immediate-release hydrocodone (IR HC); comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); schedule II (CII); "CII opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; comparative interrupted time series (CITS); For CITS, null value = 1 and OxyContin is the reference; CITS is a type of difference-in difference model that uses an equivalent measure (here, "CITS slope measure") to that of the ratio of rate ratios (RORR) in means analyses, with an equivalent interpretation (i.e., a CITS measure > 1 means the change in abuse call rate slope comparing periods favors OxyContin and a CITS measure < 1 means the change in abuse call rate slope comparing periods favors the comparator; ITS model 5 models an abuse call rate slope per general population (as an offset); ITS model 6a models an abuse call rate slope per tablets dispensed (as an offset), adjusting call volume (i.e., all pharmaceutical exposure cases of persons >5 years old) as a covariate; ITS model 7a models an abuse call rate slope, adjusting for tablets dispensed and call volume as covariates; vertical lines: 95% confidence intervals

Both when analyses were replicated with the transition period included in the post-period (see Appendix 8.5), and when analyses were replicated adjusting for total intentional exposure calls, rather than total pharmaceutical exposure calls (as a proxy for call volume), the results were largely the same (see Appendix 8.6). In another analysis using two separate, consecutive post-periods (PP1 and PP2, see section 3.4.1.3), the percent change in slope comparing the pre-period to the PP1 was more pronounced for both OxyContin and ER morphine across the three ITS models, but estimates were still not significantly different from the other comparators in CITS analyses.

Figure 28 shows the percent changes in model-estimated abuse call rate for the last quarter of the pre-period (2Q2010) compared to the model-estimated abuse call rate for first quarter of the post-period period (1Q2011); this is also described as the level change (or "immediate shift"). Downward level changes were observed for OxyContin across models, but only when modeling abuse call rates per general population (Model 5) and abuse call rates adjusting for tablets dispensed and call volume as covariates (Model 7a) were the changes significant. CITS models were also used to directly compare OxyContin's level change to those of the comparator drug groups; an analogous measure to the RORR and CITS slope measure was estimated, shown below as "CITS level change measure". In CITS analyses, all CITS level change measures for primary comparators favored OxyContin (i.e., CITS level change measure > 1) across models, but they were only significantly for some specifc comparisons. CITS level change measures for IR hydrocodone and "other schedule II opioids" favored OxyContin when modeling abuse call rates per general population (Model 5), and only "all schedule II opioids" when modeling abuse call rates adjusting for tablets dispensed and call volume as covariates (Model 7a).

Figure 28: Percent change in the abuse call rates immediately following the reformulation (<u>level change</u> or "<u>immediate shift</u>") for OxyContin and primary comparators, by model (-2y/5y)

(*Sponsor figure taken from PMR 3051-2 study report; reformatted by FDA, including adding CITS level change measure*)

Key: *= statistically significant (p<0.05); extended-release (ER); immediate-release hydrocodone (IR HC); level change or "immediate shift" means comparing the model-estimated abuse call rate for the last quarter of the pre-period (2Q2010) to the model-estimated abuse call rate for first quarter of the post-period period (1Q2011); two years before to five years after the reformulation, excluding the transition period (-2y/5y); schedule II (CII); "CII opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; comparative interrupted time series (CITS); For CITS, null value = 1 and OxyContin is the reference; CITS is a type of difference in difference model that uses an equivalent measure (here, "CITS level change measure") to that of the ratio of rate ratios (RORR) in means analyses, with an equivalent interpretation (i.e., a CITS measure > 1 means the level change in model-estimated abuse call rates comparing periods favors OxyContin and a CITS measure < 1 means the level

change in model-estimated abuse call rates comparing periods favors the comparator; ITS model 5 models an abuse call rate slope per general population (as an offset); ITS model 6a models an abuse call rate slope per tablets dispensed (as an offset), adjusting call volume (i.e., all pharmaceutical exposure cases of persons >5 years old) as a covariate; ITS model 7a models an abuse call rate slope, adjusting for tablets dispensed and call volume as covariates; vertical lines: 95% confidence intervals

4.1.9   Sensitivity Analyses

4.1.9.1   Using an Expanded OxyContin Definition (Brand and Generic ER Oxycodone)

Table 11 shows the percent changes in mean quarterly abuse call rates comparing pre- and post-periods using different definitions of OxyContin: 1) OxyContin only, and 2) any ER oxycodone (including both brand and generic ER oxycodone). When comparing the definitions, percent changes were similar for abuse call rates per general population (Model 1), somewhat attenuated for abuse call rates per tablets dispensed, adjusting for call volume (Model 2a), when using the ER oxycodone definition, and qualitatively different for abuse call rates adjusted for tablets dispensed and call volume as covariates (Model 3a).

Table 11: Percent change in mean abuse call rates for OxyContin and ER oxycodone, by model (-2y/5y)

OxyContin definition	Pre-post change in mean abuse call rate per 100,000 population (MODEL 1)	Pre-post change in mean abuse call rate per 100,000 tablets dispensed, adjusting for call volume (MODEL 2a)	Pre-post change in mean abuse call rate adjusting for tablets dispensed and call volume (MODEL 3a)
2y/5y			
OxyContin	-55.23% (-63.14% to -45.63%)	-37.76% (-46.47% to -27.63%)	-18.55% (-42.19% to 14.76%)
ER oxycodone	-56.21% (-64.02% to -46.71%)	-27.28% (-36.90% to -16.20%)	99.05% (30.48% to 203.67%)

(*Sponsor table taken from PMR 3051-2 study report; reformatted with headers by FDA*)

Key: extended-release (ER); confidence intervals (CI); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for total pharmaceutical exposure calls for persons > 5 years old as a covariate; Model 3a models an abuse call rate without an offset, adjusting for the total number of tablets dispensed and total pharmaceutical exposure calls for persons > 5 years old as covariates

Table 12 shows the RORR (for any route of abuse) and CITS measures (slope and level change separately) when the ER oxycodone (including both brand and generic ER oxycodone) definition is used. The results are largely the same as those using the OxyContin only definition (Table 14, highlighted cells represent discrepancies), and most of the discrepancies occur when modeling abuse call rates adjusting for tablets dispensed and call volume as covariates (Models 3a and 7a). Of note, ER morphine had an RORR of 0.73 (CI: 0.55-0.97) in abuse call rates relative to the ER oxycodone's when modeling abuse call rates per general population (Model 2a), which was a qualitatively different result than when using OxyContin only as the definition.

Table 12: Ratio of Rate Ratios (RORR) and comparative interrupted time series results for ER oxycodone, by model (-2y/5y)

Opioid comparator relative to any ER oxycodone, including brand and generic products	Pre-post change in mean abuse call rate per 100,000 population (Model 1 and 5) (95% confidence interval)	Pre-post change in mean abuse call rate per 100,000 tablets dispensed, adjusting for call volume (Model 2a and 6a) (95% confidence interval)	Pre-post change in mean abuse call rate comparing pre- and post-periods, adjusting for tablets dispensed and call volume (Model 3a and 7a) (95% confidence interval)
Ratio of Rate Ratios (RORR) for means analysis (Models 1, 2a, and 3a)			
ER morphine	1.62 (1.20-2.19)*	0.73 (0.55-0.97)*	0.58 (0.33-1.02)
IR hydrocodone	1.66 (1.28-2.15)*	0.96 (0.80-1.16)	0.30 (0.19-0.45)*
"Other schedule II opioids"	1.84 (1.43-2.36)*	0.97 (0.80-1.17)	0.41 (0.22-0.75)*
CITS slope measure (RORR equivalent) for ITS analysis (Models 5, 6a, and 7a)			
ER morphine	0.99 (0.92-1.07)	1.00 (0.94-1.08)	1.01 (0.93-1.09)
IR hydrocodone	1.00 (0.96-1.04)	1.01 (0.97-1.04)	1.01 (0.97-1.05)
"Other schedule II opioids"	1.00 (0.96-1.04)	1.00 (0.97-1.04)	1.00 (0.97-1.04)
CITS level change measure (RORR equivalent) for ITS analysis (Models 5, 6a, and 7a)			
ER morphine	1.31 (0.90-1.91)	0.87 (0.62-1.23)	0.95 (0.41-2.18)
IR hydrocodone	1.50 (1.22-1.85)*	0.95 (0.79-1.14)	1.04 (0.51-2.11)
"Other schedule II opioids"	1.52 (1.24-1.86)*	0.97 (0.81-1.16)	1.13 (0.56-2.31)

(FDA generated table using data from PMR 3051-2 study report)

Key: *= statistically significant (p<0.05); yellow highlight = different from "OxyContin only" analyses; extended-release (ER); immediate-release (IR); level change or "immediate shift" means comparing the model-estimated abuse call rate for the last quarter of the pre-period (2Q2010) to the model-estimated abuse call rate for first quarter of the post-period period (1Q2011); two years before to five years after the reformulation, excluding the transition period (-2y/5y); "other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; ratio of rate ratios (RORR); comparative interrupted time series (CITS); Null value = 1 and RORR/CITS measures are relative to ER oxycodone (reference); an RORR > 1 means abuse call rate change comparing periods favors ER oxycodone and an RORR < 1 means abuse call rate change comparing periods favors the comparator; CITS is a type of difference-in difference model that uses an equivalent measure (here, "CITS measure") to that of the ratio of rate ratios (RORR) in means analyses, with an equivalent interpretation (i.e., a CITS measure > 1 means the slope or level change in model-estimated abuse call rates comparing periods favors ER oxycodone and a CITS measure < 1 means the slope or level change in model-estimated abuse call rates comparing periods favors the comparator; Model 1/5 models an abuse call rate per general population (as an offset); Model 2a/6a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e. total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a/7a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates

When looking at only non-oral abuse call rates (inhalation and injection), the comparative results (i.e., RORRs) using ER oxycodone were very similar to those when using OxyContin only (See Appendix 8.4).

4.1.9.2 Using Imputation for Missing Formulation Data

Table 13 shows the percent changes in mean quarterly abuse call rates comparing pre- and post-periods using different methods for handling missing formulation data: 1) "complete case" analyses whereby only cases without missing formulation data are included, and 2) multiple imputation whereby missing formulation data is imputed based on other case-level variables. Across

all opioid comparators and models, declines in observed abuse call rates from analyses using imputed formulation data are slightly attenuated relative to the "complete case" analyses. The most impacted estimates were for ER morphine, as formulation data were more often missing among morphine exposures as compared to the other comparator opioids; IR hydrocodone results were the least impacted.

Table 13: Percent change in mean abuse call rates for OxyContin and ER morphine with and without imputation, by model (-2y/5y)

Missing data methodology	Pre-post change in mean abuse call rate per 100,000 population (Model 1) (95% confidence interval)	Pre-post change in mean abuse call rate per 100,000 tablets dispensed, adjusting for call volume (Model 2a) (95% confidence interval)	Pre-post change in mean abuse call rate, adjusting for tablets dispensed and call volume (Model 3a) (95% confidence interval)
OxyContin			
Complete case	-55% (-63% to -46%)	-37% (-45% to -27%)	-18% (-41% to 16%)
Imputation	-47% (-56% to -37%)	-25% (-34% to -14%)	-13% (-36% to 19%)
ER Morphine			
Complete case	-29% (-44% to -11%)	-46% (-58% to -31%)	14% (-23% to 71%)
Imputation	-10% (-25% to 8%)	-31% (-44% to -16%)	24% (-11% to 73%)
IR Hydrocodone			
Complete case	-27% (-39% to -14%)	-29% (-38% to -20%)	-41% (-48% to -33%)
Imputation	-25% (-36% to -12%)	-26% (-35% to -17%)	-38% (-45% to -30%)

(FDA generated table using data from PMR 3051-2 study report)

Key: extended-release (ER); immediate-release (IR); confidence interval (CI); comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); "Complete case" means excluding oxycodone cases without formulation information (i.e. oxycodone, not otherwise specified), whereas "imputation" means imputing formulation for cases missing those data; Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e. total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates; percentages rounded for display

Table 14 shows the RORR (for any route of abuse) when using multiple imputation for cases missing product formulation information. The RORR results from analyses using multiple imputation are largely the same as analyses using only cases with complete formulation information ("complete case" analyses). While each opioid group had different amounts of missingness, the trends increased at a similar rate over time (see Figure 6) for all opioid comparators, and therefore, resulted in RORRs with imputation that were similar to those from the primary (complete case) analyses.

Table 14: Ratio of Rate Ratios (RORR) for analyses using imputed formulation information when data are missing, by model (-2y/5y)

Opioid comparator relative to OxyContin (With imputation)	Pre-post change in mean abuse call rate per 100,000 population (Model 1) (95% confidence interval)	Pre-post change in mean abuse call rate per 100,000 tablets dispensed, adjusting for call volume (Model 2a) (95% confidence interval)	Pre-post change in mean abuse call rate, adjusting for tablets dispensed and call volume (Model 3a) (95% confidence interval)
ER morphine	1.70 (1.33-2.19)*	0.92 (0.72-1.17)	1.42 (0.90-2.24)
IR hydrocodone	1.42 (1.12-1.80)*	0.98 (0.82-1.17)	0.72 (0.71-1.00)
"Other schedule II opioids"	1.66 (1.33-2.06)*	1.04 (0.87-1.23)	1.01 (0.62-1.64)

(FDA generated table using data from PMR 3051-2 study report)

Key: *= statistically significant (p<0.05); yellow highlight = different from "complete case" analyses; extended-release (ER); immediate-release (IR); two years before to five years after the reformulation, excluding the transition period (-2y/5y); "other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; missing formulation data were imputed for cases involving oxycodone, morphine, and hydrocodone; ratio of rate ratios (RORR); Null value = 1 and RORR are relative to OxyContin (reference); a RORR > 1 means abuse call rate change comparing periods favors OxyContin and a RORR < 1 means abuse call rate change comparing periods favors the comparator; Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e. total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates

The Agency additionally requested two additional sensitivity analyses (September, 2019): 1) whereby oxycodone (and morphine) cases without a specified formulation were allocated into ER and IR oxycodone (or morphine) groups based on the proportion of ER and IR oxycodone (or morphine) dispensed (using IQVIA utilization data) in a given covered quarter (See Appendix 8.4), and 2) whereby all oxycodone cases without a specified formulation were assumed to be ER oxycodone (or ER morphine). In both of these analyses, significant percent declines and RORRs were preserved, but attenuated, for OxyContin per general population (Model 1). Percent declines for ER morphine were not significant per general population (Model 1) when allocating cases based on dispensing data.

4.1.9.3   Imposing geographical restrictions on which exposure calls are included

Table 15 shows the percent changes in mean quarterly abuse call rates comparing pre- and post-periods using regional restrictions to account for regional policy initiatives, specifically the Florida "pill mill" legislation and related law enforcement activities implemented from late 2010 through 2011: 1) analyses confined to exposures from the western US census region, and 2) analyses that excludes Florida exposure calls. The percent declines in abuse call rates in both geographically-restricted analyses are generally consistent with the results using the entire coverage area (i.e., all of the US) across models (see Table 15), including RORR data (Data not shown).

Table 15: Percent change in mean abuse call rates for OxyContin and primary comparators with and without geographical restrictions, by model (-2y/5y)

PCC data coverage	Pre-post change in mean abuse call rate per 100,000 population (MODEL 1)	Pre-post change in mean abuse call rate per 100,000 tablets dispensed, adjusting for call volume (MODEL 2a)	Pre-post change in mean abuse call rate adjusting for tablets dispensed and call volume (MODEL 3a)
OxyContin			
Entire Coverage	-55.23% (-63.14% to -45.63%)	-37.76% (-46.47% to -27.63%)	-18.55% (-42.19% to 14.76%)
Western Census	-56.63% (-66.70% to -43.52%)	-43.22% (-54.38% to -29.34%)	-13.26% (-44.94% to 36.65%)
Excluding Florida	-54.38% (-62.60% to -44.34%)	-38.74% (-47.60% to -28.38%)	-22.98% (-44.09% to 6.11%)
ER Morphine			
Entire Coverage	-29.02% (-43.59% to -10.69%)	-46.05% (-57.98% to -30.72%)	14.48% (-23.15% to 70.55%)
Western Census	-36.72% (-53.49% to -13.90%)	-53.66% (-66.22% to -36.45%)	-24.71% (-59.60% to 40.33%)
Excluding Florida	-26.90% (-43.26% to -5.82%)	-43.83% (-57.15% to -26.36%)	21.16% (-22.07% to 88.37%)
IR Hydrocodone			
Entire Coverage	-27.45% (-38.77% to -14.03%)	-29.22% (-37.72% to -19.54%)	-40.99% (-48.15% to -32.85%)
Western Census	-21.83% (-33.30% to -8.39%)	-35.62% (-43.08% to -27.19%)	-38.66% (-48.13% to -27.46%)
Excluding Florida	-25.86% (-37.73% to -11.72%)	-28.27% (-37.04% to -18.28%)	-41.31% (-48.96% to -32.52%)
Other Schedule II			
Entire Coverage	-19.49% (-30.93% to -6.15%)	-28.88% (-38.01% to -18.41%)	-19.41% (-49.34% to 28.22%)
Western Census	-20.64% (-31.87% to -7.55%)	-40.36% (-47.95% to -31.66%)	-40.82% (-55.49% to -21.31%)
Excluding Florida	-16.37% (-28.93% to -1.60%)	-28.32% (-38.17% to -16.90%)	-6.25% (-43.60% to 55.83%)

(Sponsor table taken from PMR 3051-2 study report; reformatted with headers by FDA)

Key: extended-release (ER); immediate-release (IR); confidence interval (CI); two years before to five years after the reformulation, excluding the transition period (-2y/5y); "other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e. total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates

4.1.9.4 Stratifying by OxyContin Dosage Strength

Table 16 shows the percent changes in mean quarterly abuse call rates comparing pre- and post-periods stratified by tablet strength. Some published reports[xxi] indicate that higher milligram strength tablets were more sought after for diversion and abuse than lower milligram strength tablets. When compared to all OxyContin dose strengths combined, significant percent declines in abuse call rates for cases involving 80 mg and ≥40 mg OxyContin tablets were larger when modeling abuse call rates per general population (Model 1) and per tablets dispensed, adjusting call volume (Model 2a). Abuse call rate changes adjusting for tablets dispensed and call volume as covariates (Model 3a) were not significant for any OxyContin dose strength. The findings of all dose stratified analyses are likely limited by missing dose strength data.

[xxi] Rigg KK, Kurtz SP, Surratt HL (2012) Patterns of prescription medication diversion among drug dealers. Drugs (Abingdon Engl); 19(2): 144–155.

Table 16: Percent change in mean abuse call rates for OxyContin, by model and tablet strength (-2y/5y)

Dosage strength	Pre-post change in mean abuse call rate per 100,000 population (MODEL 1)	Pre-post change in mean abuse call rate per 100,000 tablets dispensed, adjusting for call volume (MODEL 2a)	Pre-post change in mean abuse call rate adjusting for tablets dispensed and call volume (MODEL 3a)
2y/5y			
OxyContin all doses	-55.23% (-63.14% to -45.63%)	-37.76% (-46.47% to -27.63%)	-18.55% (-42.19% to 14.76%)
OxyContin 80 mg	-76.33% (-82.47% to -68.05%)	-48.99% (-60.03% to -34.90%)	8.14% (-41.96% to 101.50%)
OxyContin ≥ 40 mg	-73.16% (-79.36% to -65.08%)	-53.58% (-61.91% to -43.42%)	-8.89% (-41.98% to 43.06%)
ER oxycodone all doses	-56.21% (-64.02% to -46.71%)	-27.28% (-36.90% to -16.20%)	99.05% (30.48% to 203.67%)
ER oxycodone 80 mg	-76.27% (-82.28% to -68.23%)	-40.41% (-52.32% to -25.52%)	109.91% (10.24% to 299.70%)

(Sponsor table taken from PMR 3051-2 study report; reformatted with headers by FDA)

Key: extended-release (ER); immediate-release (IR); milligram (mg); confidence interval (CI); "ER oxycodone" includes brand and generic ER oxycodone; two years before to five years after the reformulation, excluding the transition period (2y/5y); "other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e. total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates

4.2 SPONSOR'S INTERPRETATION OF PMR STUDY 3051-2 RESULTS

"Results of this study are consistent with the hypothesis that the introduction of reformulated OxyContin resulted in a meaningful and sustained decline in intentional abuse of OxyContin during the study period in this poison center population. The observed decline in OxyContin abuse, however, varies by measure of abuse and was not always statistically differentiated from the primary comparator opioids. Similarly, when assessing the non-oral routes of abuse (inhalation [including snorting], injecting and non-oral), the decline in OxyContin intentional abuse was more pronounced than for IR hydrocodone combination products and other Schedule II opioids, while statistical significance varied.

The model with dosage units dispensed as an offset and adjusting for all pharmaceutical exposures (Model 2a) was the most appropriate for assessing changes in abuse in this population. Among models assessed, for OxyContin, IR hydrocodone combination products and other Schedule II opioids, Model 2a produced the most reliable estimates. Model 2a met the model assumptions, had the best model performance and was not impaired by collinearity issues, however, due to methodologic limitations, Model 2a was unable to estimate relative changes in abuse for ER morphine."

5 DISCUSSION

5.1 SUMMARY OF PMR STUDY 3051-2 RESULTS

5.1.1 Descriptive Changes in Quarterly Abuse Call Counts (Via any Route and Non-oral)

Visual inspection of quarterly trends finds a decline in the number of abuse calls involving OxyContin immediately following the reformulation; declines in calls involving "other schedule II opioids" and for IR hydrocodone appear several quarters later. ER morphine had the lowest numbers overall throughout both periods.

There was also apparent decline in the number of non-oral abuse calls for OxyContin immediately following the reformulation, and simultaneously an increase for the "other schedule II opioids" comparator group. The number of non-oral abuse calls for ER morphine and IR hydrocodone were consistently lower than OxyContin in the pre-period, but were similar to OxyContin by the end of the post-period.

5.1.2 Changes in Mean Abuse Call Rates (Via any Route)

After the introduction of reformulated OxyContin, there was a significant 55% (95% CI: -63 to -46%) decrease in the mean quarterly abuse call rate per 100,000 population (Model 1) and a significant 37% (95% CI: -45 to -27%) decrease in the mean quarterly abuse call rate per 100,000 tablets dispensed, adjusting for call volume as a covariate (Model 2a) (See Table 17). The model adjusting for tablets dispensed and call volume as covariates (Model 3a) did not show significant declines in the mean OxyContin abuse call rate.

There were also large decreases in mean abuse call rates involving primary comparators, both per general population (Model 1) and per tablets dispensed, adjusting for call volume (Model 2a). Only when modeling abuse call rates per 100,000 population (Model 1) were OxyContin's changes significantly different from that of the primary comparators (See Table 17), favoring OxyContin (RORRs significantly > 1).

The only comparators with notable increases in mean abuse call rates were the secondary comparators heroin and ER oxymorphone.

Sensitivity analyses

Declines in mean abuse call rates per general population (Model 1) were fairly consistent when brand OxyContin and generic oxycodone abuse calls were combined (i.e., "all ER oxycodone"), used shorter pre- and post-periods (i.e., "-1y/3y"), used imputation methods to address calls with missing information on drug formulation (i.e., "with imputation"), and with restricted geographic regions to minimize the potential impact of Florida "pill mill" law enforcement initiatives and legislation occurring around the time of the reformulation (i.e., "excluding Florida"). With the exception of the geographic restriction, the changes in mean OxyContin abuse call rate per 100,000 tablets dispensed were attenuated in these sensitivity analyses.

It is unclear why the results from Model 3a using the "all ER oxycodone" definition for OxyContin are so inconsistent with the other models. With an already limited number of data points and variables, it is not unexpected that changing any one variable in the model could impact the results to some degree, but the qualitative change was rather unusual and further validates FDA's concerns with Model 3a's interpretability.

Table 17: Summary of key study findings from mean quarterly rate analyses (any route)

Opioid comparator	Model 1: Pre-post change in mean abuse call rate per 100,000 population (95% CI)	Model 1: Ratio of rate ratios (RORR) (95% CI)	Model 2a: Pre-post change in mean abuse call rate per 100,000 tablets dispensed, adjusting for call volume (95% CI)	Model 2a: Ratio of rate ratios (RORR) (95% CI)	Model 3a: Pre-post change in mean abuse call rate, adjusting for tablets dispensed and call volume (95% CI)	Model 3a: Ratio of rate ratios (RORR) (95% CI)
Key study findings						
OxyContin (-2y/5y)	-55% (-63 to -46)*	ref	-37% (-45 to -27)*	ref	-19% (-42 to 15)	ref
ER morphine	-29% (-44 to -11)*	1.60 (1.16-2.21)*	-46% (-58 to -31)*	0.90 (0.72-1.20)	-7% (-43 to 50)	1.56 (0.91-2.68)
IR hydrocodone	-27% (-39 to -14)*	1.63 (1.25-2.12)*	-29% (-38 to -20)*	1.16 (0.95-1.41)	-10% (-25 to 8)	0.75 (0.54-1.06)
"Other schedule II opioids"	-19% (-31 to -6)*	1.83 (1.42-2.37)*	-29% (-38 to -18)*	1.15 (0.94-1.42)	2% (-25 to 37)	1.20 (0.66-2.19)
Sensitivity analyses						
OxyContin (-1y/3y)	-46% (-57 to -33)*		-28% (-37 to -17)*		-16% (-45 to 28)	
"all ER oxycodone"	-56% (-64 to -47)*		-27% (-37 to -16)*		99% (30 to 204)*	
OxyContin (with imputation)	-47% (-56 to -37)*		-25% (-34 to -14)*		-13% (-36 to 19)	
OxyContin (excluding Florida)	-54% (-63 to -44)*		-39% (-48 to -28)*		-23% (-44 to 6)	

(FDA generated table using data from PMR 3051-2 study report)

Key: * = statistically significant (p<0.05); extended-release (ER); immediate-release (IR); "Other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; confidence intervals (CI); comparing two years before to five years after the reformulation (-2y/5y); comparing one year before to three years after the reformulation (-1y/3y); RORR > 1 means abuse call rate change comparing periods favors OxyContin, and RORR < 1 means abuse call rate change comparing periods favors the comparator; "all ER oxycodone" sensitivity analyses combined brand OxyContin and generic ER oxycodone; OxyContin (with imputation) sensitivity analyses used imputation methods to address calls with missing information on drug formulation; OxyContin (excluding Florida) sensitivity analyses restricted the geographic region to minimize the potential impact of Florida "pill mill" law enforcement initiatives and legislation occurring around the time of the reformulation; Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e., total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for the total number of tablets dispensed and call volume as covariates

5.1.3 Interrupted Time Series (ITS) Findings: Pre- to Post-period Changes in Trend and Level

There was a significant 3.9% decrease in the slope of quarterly OxyContin abuse call rates per general population (Model 5) comparing pre- and post-periods, and a significant 3.6% decrease in the slope of quarterly OxyContin abuse call rates adjusting for tablets dispensed and call volume as covariates (Model 7a); the decline in slope per tablets dispensed was similar to the other models but not significant (Model 6a). OxyContin's decreases in slope were comparable and not significantly different from those of comparator opioid groups in comparative ITS (CITS) analyses, which may be a function of the more limited power of ITS models when the number of data points is unbalanced across periods and low overall.

With regard to level change, or "immediate shift," OxyContin had a significant 27.5% decline from the model-estimated abuse call rate for the last quarter of the pre-period (2Q2010) to the model-estimated abuse call rate for first quarter of the post-period (1Q2011), per general population (Model 5), and a significant 28.2% decline when adjusting for tablets dispensed and call volume as a covariate (Model 7a). The declines were not significant per tablets dispensed (Model 6a). All CITS level change measures for primary comparators favored OxyContin (i.e., CITS level change measure > 1) across models, but they were only significant for IR hydrocodone and "other schedule II opioids" when modeling abuse call rates per general population (Model

5), and "all schedule II opioids" when modeling abuse call rates adjusting for tablets dispensed and call volume as covariates (Model 7a).

5.1.4 Changes in Mean Abuse Call Rates by Route of Abuse

The mean quarterly <u>non-oral</u> abuse call rate per general population (Model 1) for OxyContin decreased more than that of oral abuse (63% compared to 52%, respectively), although these declines were not compared to each other using formal testing of statistical significance (See Table 18). Non-oral abuse call rates for OxyContin per tablets dispensed, adjusting for call volume (Model 2a), also decreased more than oral abuse (47% compared to 32%, respectively), although, again, the differences between oral and non-oral may not have been significantly different from each other. Both per general population (Model 1) and per tablets dispensed, adjusting for call volume (Model 2a), the percent decline in the mean rate of calls involving OxyContin inhalation (Model 1: 66.4%, Model 2a: 49.9%) was slightly larger than the decline in the mean rate of calls involving OxyContin injection (Model 1: 58.9%, Model 2a: 41.8%). The decline in non-oral abuse call rates for OxyContin adjusting for tablets dispensed and call volume as covariates (Model 3a) was not significant.

The changes in non-oral abuse call rate favored OxyContin compared to those of IR hydrocodone and "other schedule II opioids" (RORR >1) across all models, and the changes were significantly different per general population (Model 1) and per tablets dispensed, adjusting for call volume (Model 2a) (See Table 18). Non-oral abuse call rates increased for both IR hydrocodone and "other schedule II opioids" across models, but the increases were not significant. Comparing OxyContin to ER morphine, the changes in mean quarterly non-oral abuse call rates per population (Model 1) were significantly different from each other (favoring OxyContin; RORR >1); however, the large declines for both OxyContin and ER morphine in mean non-oral abuse call rates per tablets dispensed, adjusting for call volume (Model 2a) and in non-oral abuse call rates adjusting for tablets dispensed and call volume as covariates (Model 3a) were not significantly different from each other. All primary comparators had significant declines in mean oral abuse call rates across nearly all models, and the decline in OxyContin's mean oral abuse call rate was significantly different from those of comparators per general population (Model 1). Of note, the RORRs for the non-oral route were higher than the RORRs for the oral route across comparators and models; for IR hydrocodone and "other schedule II opioids," RORRs for non-oral abuse were roughly double those for oral abuse.

Table 18: Summary of primary findings from means analysis, by route

Opioid comparator (-2y/5y)	Route of abuse	Model 1: Pre-post change in mean abuse call rate per 100,000 population (95% CI)	Model 1: Ratio of rate ratios (RORR) (95% CI)	Model 2a: Pre-post change in mean abuse call rate per 100,000 tablets dispensed, adjusting for call volume (95% CI)	Model 2a: Ratio of rate ratios (RORR) (95% CI)	Model 3a: Pre-post change in mean abuse call rate, adjusting for tablets dispensed and call volume (95% CI)	Model 3a: Ratio of rate ratios (RORR) (95% CI)
OxyContin	Oral	-52% (-61 to -41)*	ref	-32% (-42 to -22)*	ref	0% (-38 to 39)	ref
	Non-oral	-63% (-73 to -48)*		-47% (-62 to -27)*		-44% (-74 to 23)	
ER Morphine	Oral	-31% (-46 to -11)*	1.45 (1.05-2.00)*	-47% (-60 to -31)*	0.78 (0.58-1.06)	20% (-21 to 83)	1.20 (0.71-2.04)
	Non-oral	-31% (-55 to 7)	1.85 (1.06-3.21)*	-48% (-66 to -18)*	0.96 (0.58-1.71)	-19% (-69 to 115)	1.44 (0.41-5.03)
IR hydrocodone	Oral	-30% (-41 to -18)*	1.45 (1.12-1.89)*	-32% (-40 to -23)	1.00 (0.83-1.22)	-44 (-51 to -36)*	0.56 (0.40-0.80)*
	Non-oral	17% (-17 to 64)	3.11 (1.92-5.04)*	13% (-18 to 57)	2.15 (1.37-3.38)*	1% (-32 to 50)	1.80 (0.75-4.31)
"Other schedule II opioids"	Oral	-25% (-36 to 13)*	1.56 (1.21-2.01)*	-34% (-43 to -25)*	0.97 (0.80-1.19)	-24% (-52 to 20)	0.76 (0.43-1.33)
	Non-oral	33% (-1 to 79)	3.56 (2.27-5.57)*	17% (-11 to 55)	2.22 (1.46-3.38)*	19% (-50 to 185)	2.12 (0.66-6.82)

(FDA generated table using data from PMR 3051-2 study report)

Key: * = statistically significant (p<0.05); extended-release (ER); immediate-release (IR); "Other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; confidence intervals (CI); comparing two years before to five years

after the reformulation (-2y/5y); Non-oral abuse includes inhalation and injection; RORR > 1 means abuse call rate change comparing periods favors OxyContin, and RORR < 1 means abuse call rate change comparing periods favors the comparator; Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (i.e., total pharmaceutical exposure calls for persons > 5 years old) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for the total number of tablets dispensed and call volume as covariates

In descriptive analyses, the proportion of total abuse calls for OxyContin involving non-oral abuse decreased slightly from 18.9% in the pre-period to 15.8% in the post-period, while the percentage reporting oral abuse rose slightly from 66.9% to 71.5%, although these proportions were not compared to each other using formal testing of statistical significance. Approximately 13 to 15% of calls did not contain information on route of abuse for OxyContin over the study period, which was slightly higher than the other comparators which ranged from ~7 to ~11%. The proportion of calls for "other schedule II opioids" involving oral abuse decreased slightly (from 88.0% to 81.5%) and non-oral abuse increased slightly (from 4.5% to 7.5%); ER morphine and IR hydrocodone had very little change in route of abuse profile from the pre- to post-periods.

5.1.5 Pre- to post-period changes in quarterly abuse call counts for secondary (contextual) comparators

During the study period, there was a striking increase in quarter abuse calls involving heroin. Calls involving IR oxycodone remained relatively stable, calls involving methadone declined, and calls involving ER oxymorphone rose rapidly until early 2012, then declined to levels similar to those seen in the late pre-period.

5.1.6 Changes in Mean Call Rates for Other Exposure Call Types

To assess possible secular trends in exposure calls more broadly, the study analyzed calls for exposure reasons other than abuse. OxyContin had significant declines in both intentional misuse and suspected suicide call rates per general population (Model 1), but not per tablets dispensed, adjusted for call volume (Model 2a) or adjusting for tablets dispensed and call volume as covariates (Model 3a). Primary comparators showed consistent declines in both intentional misuse and suspected suicide across models. Also, OxyContin had significant declines in both population- and utilization-based rates of both adverse reactions (which are limited to exposures where the drug was taken as directed) and unintentional exposures (where the drug was taken accidentally) and were similar to the comparator opioids.

5.1.7 Severity of Medical Outcome

Comparing the pre- and post-periods, the distribution of medical outcome severity for OxyContin abuse calls was relatively unchanged. In particular, the proportion of abuse-related cases that resulted in a medical outcome designated as major effect (i.e., those where the exposure resulted in signs or symptoms that were life threatening or resulted in significant residual disability or disfigurement), or death, was similar in the pre- and post-periods for both OxyContin and primary comparator opioids. Minor observed shifts may have been, in part, due to changing proportion of cases that were not followed up.

5.2 REVIEW OF RELATED PUBLISHED LITERATURE

Published studies using PCC call data concluded that the overall reductions in abuse calls (any route) were likely driven by the reformulation but compared to PMR study 3051-2 these studies used a limited set of comparators and more limited methods of analysis which is likely why DEPI interpreted similar data differently. DEPI identified three published studies using US PCC call data to look at change in OxyContin-related abuse calls (see Appendix 8.7 for summary literature table) before and after the reformulation, only one (Dart et al., 2015) not indicating authorship by and funding from the sponsor. One study used National Poison Data System (NPDS) data (Coplan et al., 2013), the repository for all data collected from poison centers in the US, and the other two studies used RADARS poison center program data (Severtson et al., 2013 and Dart et al., 2015), the subset of NPDS data used in PMR study 3051-2. Only Severtson et al., 2013 and Coplan et al., 2013 formally compared abuse call rates for OxyContin, while the other study (Dart et al., 2015) described visual trends in abuse calls rates from 2002-2013.

Although both Severtson et al., 2013 and Coplan et al., 2013 used slightly shorter time periods (-1y/2y and -2y/2y) than PMR study 3051-2, with a different set of comparators, and adjusted for different utilization measures (prescriptions dispensed, and unique recipients of drug dispensed), the primary results with respect to OxyContin (or "ER oxycodone" in the NPDS study) were largely similar to those from PMR study 3051-2. There were significant declines in OxyContin abuse call rates in both studies, as well as in calls related to other exposures like adverse reactions, unintentional general exposures, and unintentional

therapeutic errors, both with and without adjusting for different measures of utilization. Severtson et al., 2013 also showed declines in both abuse and unintentional therapeutic error exposure calls for the composite comparator (all other prescription opioids) after adjusting for unique recipients of drug dispensed (URDD), consistent with what was observed with the "other schedule II opioids" category in PMR study 3051-2. Also, over a longer time scale (from 2002Q4 to 2013Q4), Dart et al. showed decreasing trends in abuse call rates for "ER oxycodone" coinciding with the introduction of the reformulation, along with increasing trends in heroin calls. In Coplan et al., 2013, large increases in heroin abuse calls were also observed; however, discordant with PMR study 3051-2, quarterly population-based rates of calls involving single-entity (SE) oxycodone abuse, adverse reactions, and unintentional exposure increased from the pre- to post-period. After adjusting for utilization, a decreasing trend for SE oxycodone was observed across all exposure call categories, more in line with what was observed in PMR study 3051-2. The discordant finding may be due to the shorter pre- and post-periods compared to what was used in PMR study 3051-2.

Different from PMR study 3051-2, Severtson et al. and Coplan et al. were limited by shorter study periods and a limited number of comparators, yet they ultimately concluded that there were significant declines in abuse call rates for OxyContin after the reformulation and that these declines were larger than for the assessed comparator opioid groups. Both authors inferred a favorable impact of the reformulation based on these more limited analyses despite no assessment of ROA specific rates, as did Dart et al. which used multiple data streams in addition to PCC data. From the perspective of FDA, it is not scientifically rigorous to attribute changes in abuse call rates directly to OxyContin's reformulation based on analyses using only a limited number of comparators and limited measures to account for changes in prescribed availability. Given the noted challenges with PCC data overall, inferences should be made using multiple comparators since some have greater levels of missing information than others. Also, changes between periods in the amount of drug available for abuse for OxyContin and comparators may not be reflected in less granular measures of utilization (i.e., prescriptions dispensed or URDD) making utilization-adjusted analyses more difficult to interpret. Therefore, while the results of these published analyses were relatively similar to some from PMR study 3051-2, the analyses from PMR study 3051-2 were much more rigorous and comprehensive, involving multiple comparators and multiple methods, including sensitivity analyses, to compare changes between comparators and OxyContin. This allowed for a more informed assessment of the relative changes in abuse call rates for OxyContin and may be why our interpretation of similar data are somewhat different from theirs.

We also reviewed Coplan et al., 2016, which presented selected results from the sponsor's 2014 labeling supplement submission (see Appendix 8.7). With respect to the PCC call analyses, the selected results focused on the shorter time period (-1y/3y) and one opioid comparator ("other schedule II opioids"). The population-based abuse call rate changes for OxyContin from PMR study 3051-2 were all similar, but generally smaller, compared to the analogous RADARS PCC results presented in Coplan et al., 2016, perhaps a function of the slightly different approaches for modeling the data. The changes in utilization-based rates were also smaller in PMR 2, perhaps due to the use of different measures of utilization (Coplan et al., 2016 used prescriptions dispensed). PMR study 3051-2 comparative results were similar to as the analogous RADARS PCC results presented in Coplan et al. (2016) for overall (any route) and non-oral abuse call rates, but not oral abuse call rates. Coplan et al. (2016) also showed selected results from the sponsor's NPDS analysis which were largely the same as those from the RADARS PCC analysis given the already substantial coverage of the RADARS PCC data.

5.3   KEY CONSIDERATIONS IN INTERPRETING ABUSE CALL RATE CHANGES

Making causal inferences about the effect of OxyContin's reformulation on abuse call rates requires consideration of a number of factors, an important one being alternative explanations for any observed changes. These alternative explanations may be related to a changing opioid abuse landscape—for example, larger secular trends in prescribing and abuse of prescription opioids, availability and use of heroin, or law enforcement activities to reduce rogue prescribing and diversion of OxyContin and other drugs—or they may be internal to the data source—for example, changes in patterns of PCC use by the public or healthcare providers, or changes in levels of missing data on drug product, formulation, or ROA. Specific methods and other available PCC data were used to explore the impact of secular trends in prescription opioid exposure calls and to evaluate for alternative explanations for any change in abuse call rates, including accounting for changing OxyContin availability (i.e., utilization) in various ways, and changing call volume to PCCs. The results of comparative analyses that accounted for utilization were generally attenuated relative to population-based analyses. Broader secular trends in abuse calls are also difficult to rule out given that there were large reductions in abuse call rates across most comparators, and large reductions in OxyContin-related

exposure call types that we would not expect to be impacted by the reformulation, even after adjusting for changes in utilization. Large and increasing amounts of missing data on product formulation, as well as other data quality issues such as potential misclassification of brand versus generic product exposures, also complicate the interpretation of both the within-drug changes and across-drug comparisons.

5.3.1 Accounting for External Secular Trends and Other Interventions

5.3.1.1 Comparators as Approximations of the Counterfactual

The study included comparator opioid drugs to approximate the counterfactual scenario and assist in causal inference, although each has limitations with respect to its ability to accurately represent what would have been expected to happen to abuse call rates had OxyContin never been reformulated. Comparators do not help with differentiating between the impact of other OxyContin-specific interventions around the time of the reformulation, for example, the 2010 OxyContin Risk Evaluation and Mitigation Strategy (REMS), but they may represent a reasonable "negative control" with respect to approximating the effects of broader changes in drug abuse patterns and public policy and regulatory interventions. ER morphine is, in theory, particularly useful as a comparator because of its large and relatively stable market share, its abuse via non-oral routes, and its being subject to the same ER/LA opioid class REMS as OxyContin. However, ER morphine was also limited by low quarterly abuse call rates, especially rates of calls involving non-oral routes, and the large and increasing proportion of morphine exposure calls missing formulation information. While we agree with the sponsor that ER morphine's utility as a comparator is somewhat limited, we do not believe that the estimates are invalid, and thus they should be considered along with the other primary comparators.

From a causal inference perspective, changes in abuse call rates involving OxyContin should be both temporally associated with the marketing of the reformulated product—which they were—but also largely distinct from that of the primary comparators, despite their limitations—which they were not. Although changes in mean population-based abuse call rates were significantly different and favored OxyContin compared to ER morphine and the other comparators, including for non-oral routes, the changes in mean utilization-based abuse call rates for OxyContin were attenuated and not significantly different from that of any comparator for abuse overall (any route), or specifically from ER morphine for abuse by non-oral routes. The comparative results for ER morphine should not be ignored but concerns about its utility as comparator are important to keep in mind when evaluating the impact of the reformulation.

5.3.1.2 Accounting for Changes in Opioid Utilization and Call Volume

Utilization data serve as a proxy for availability of a given product in communities, and thus when estimating pre- versus post-period change in abuse call rates it is important to consider changes in utilization between time periods and when comparing abuse rates or changes in rates for different drugs. During the study period, OxyContin was the only primary comparator opioid to have a decline in the number of tablets dispensed (see Figure 5), whereas ER morphine, IR hydrocodone, and "other schedule II opioids" all increased. Both analyses with and without accounting for utilization are important to consider as part of a range of estimates since they may either underestimate or overestimate the effect of the reformulation on abuse call rates. That said, a meaningful impact of the reformulation should result in robust and reasonably consistent differences between OxyContin and comparators using both approaches, as one would expect that a drug that meaningfully deters abuse would result in a decline in the number of abuse-related calls for a given amount of drug dispensed in the community, and that this decline would be greater than that observed for other opioid analgesics during the same time period. Again, this was not consistently observed in PMR study 3051-2. For overall (i.e., any route) and non-oral analyses, the changes in mean abuse call rates observed for OxyContin were significantly different from all the comparators per general population (favoring OxyContin), but per tablets dispensed, only non-oral abuse call rates for IR hydrocodone and "other schedule II opioids" were different from OxyContin (again, favoring OxyContin). Comparative results of analyses adjusting for tablets dispensed as a covariate were not significant for any comparator. In ITS analyses, the level change observed for OxyContin was larger than for IR hydrocodone and "other schedule II opioids" per general population, but only larger than that of "other schedule II opioids" when adjusting for tablets dispensed as a covariate. Also, because the exact nature of the relationship between opioid utilization and calls to PCCs involving abuse is unclear, two different modeling approaches were implemented to incorporate utilization data. In this study comparative RORR estimates were sometimes qualitatively different comparing the two modeling approaches that accounted for utilization, highlighting the uncertainty around these estimates and further complicating their interpretation.

Poisson regression models fit better when adjusting for all pharmaceutical exposure calls of individuals >5 years old as proxy for changing call volume, as the total number of pharmaceutical exposure calls showed some variability over time (See Appendix 8.2). When adjusting for intentional pharmaceutical exposure calls, percent changes comparing periods were attenuated for multiple opioids, but the results of comparative analyses were generally unchanged. Given the limited number of data points and variables, it is not unexpected that changing any one variable in the model could impact the results to some extent, which is part of the reason why considering a range of estimates based on various models is useful.

5.3.1.3   Stratification by Route of Abuse

Analyses stratified by route are also important to consider from a causal inference perspective, since the reformulation was designed to impact abuse by non-oral routes. In this study, these analyses also reinforce the potential for some prevailing secular trends in PCC calls. Comparing periods, there were large declines in mean oral abuse call rates for OxyContin and all comparators, including both population- and utilization-based rates. Both population-based and utilization-based OxyContin oral abuse rate reductions were quite similar to those for the non-oral route, which was not entirely expected given the routes the reformulated product was designed to deter. However, the comparative results (RORRs) for the non-oral route more strongly favored OxyContin than did the comparative results for the oral route. This was true across multiple models and comparators, particularly for the IR hydrocodone and "other schedule II opioids" comparators. At the same time, there was also a slight shift upward in the proportion of abuse calls reporting oral route of OxyContin abuse. Route-stratified analyses were limited in that the number of non-oral abuse cases was not sufficient for conducting ITS analyses to determine whether there was a significant level change in route-specific abuse calls immediately following introduction of reformulated OxyContin; visual inspection of abuse call counts over time does show an apparent decline in quarterly non-oral abuse calls for OxyContin that roughly coincides with the introduction of the reformulated product and differed in direction from the post-reformulation trend for comparators.

5.3.1.4   Accounting for the Florida Legislation in Abuse Call Rates

Changes in opioid call trends can also be due to large public policy interventions or changes in illicit drug markets impacting prescription opioid abuse patterns broadly, although perhaps not equally across all products. The results of analyses excluding data from Florida and those restricted to the Western census region were similar to those using data from the entire US, suggesting abuse call rate declines observed for OxyContin were likely not heavily influenced by the Florida "pill mill" legislation and related law enforcement efforts. In a study by Kennedy-Hendricks et al.[xxii] looking at changes in opioid overdose death after several Florida initiatives[xxiii] surrounding pain clinics, investigators found large declines in mortality from prescription opioid overdose. These declines were larger than what would have been expected had the changes in trends in Florida been the same as changes in trends in North Carolina (the "control" state). These published data suggest that the multiple initiatives in Florida around the time of OxyContin's reformulation likely impacted prescription opioid abuse and overdose rates in that state, and possibly in other states where diverted product from Florida was distributed. The effects of other smaller, regional interventions were not explored in this PMR study 3051-2, but it is unlikely they had a meaningful impact on national abuse call rates. Of note, OxyContin-specific policies or interventions, like the 2010 OxyContin REMS, could not be controlled for with this type of study design if they occurred around the same time as the market introduction of reformulated OxyContin.

5.3.1.5   Contextual Trends in Abuse of Other Opioids (Secondary Comparators)

Secondary comparators were helpful for further contextualizing the results observed for OxyContin and primary comparators. Heroin abuse-related calls notably increased after the reformulation, reflecting an emerging dynamic in the opioid abuse landscape around the time of OxyContin's reformulation, whereby prescription opioid analgesic abuse was partially replaced by (or became increasingly mixed with) heroin use. It is important to keep in mind that, although these data were analyzed

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[xxii] Kennedy-Hendricks A. et al (2016) Opioid Overdose Deaths and Florida's Crackdown on Pill Mills. American Journal of Public Health; 106 (2): 291-297

[xxiii] The first initiative called "Operation Oxy Alley" was led by the US Drug Enforcement Agency (DEA) in February 2010. This was followed by DEA's "Operation Pill Nation" in February 2011 and August 2012. Two laws were also put into place – October 2010 and July 2011 – limiting opioid prescribing/dispensing, pain clinic advertising, and prohibiting physicians from dispensing most narcotic medications on-site.

comparing specific opioid products and product groupings involved in an abuse-related exposure, substance abuse and substance use disorders very commonly involve multiple drugs. While the increase observed in heroin abuse calls correlates with the timing of the reformulation, this may or may not support the causal argument that OxyContin's reformulation drove subsequent declines in abuse call rates, overall or route-specific. There is some evidence[xxiv] suggesting that heroin became a cheaper and more available alternative to prescription opioid drugs for abuse in some parts of the US, with changes to illicit drug supply chains around the time of OxyContin's reformulation; price and availability also coupled with its greater potency make population-level shifts from prescription opioid abuse to heroin abuse not unreasonable to expect, irrespective of other interventions. In fact, evidence for some shift is undeniable when looking at the decreasing proportion of overdose deaths associated with prescription opioids relative to those associated with illicit opioids (heroin, and later, illicit fentanyl analogs).[xxv] It is possible that the increases in heroin use during this time[xxvi] acted as one of the larger prevailing trends lowering abuse call rates for nearly all the prescription opioid drugs examined, perhaps impacting some specific drugs more than others. At the same time, if OxyContin's reformulation made it less desirable for non-oral abuse, that could precipitate shifts to heroin in some individuals already abusing or at risk of abusing OxyContin non-orally. Therefore, while street price and availability may be important factors influencing the shifts from prescription opioids to illicit opioids, it is also possible that some proportion of the shift to heroin was directly due to OxyContin's reformulation. Regardless, it certainly seems difficult to attribute the whole, or even the majority, of the increase in heroin to OxyContin's reformulation (see Figures 7 and 8), even if there were a 1:1 substitution of heroin for OxyContin after reformulation. Ultimately, the manner in which changes in OxyContin abuse may have influenced or been influenced by increases in heroin use is not entirely clear from this study, as it was not designed to investigate the drivers of increasing heroin use or motivations for shifts to heroin. Therefore, inferences based on these shifts are merely correlational, and are not scientifically rigorous enough for causal inferences with respect to the reformulation.

It is also noteworthy that ER oxymorphone abuse call rates increased comparing pre- and post-periods. Like heroin, the availability of ER oxymorphone increased throughout the study period, with the tablets dispensed increasing >72% comparing periods, albeit remaining at a very low level relative to other comparators (see Figure 5). As a single-ingredient ER product with higher tablet strengths, this product may too have been a convenient substitute for some around the time of OxyContin's reformulation. In 2012, Opana ER (oxymorphone hydrochloride) was reformulated with abuse-deterrent properties that had unintended consequences leading to it being withdrawn from the market, specifically, changes in its ROA-profile from predominantly snorting to predominantly injecting and adverse health effects associated with injection of the reformulated product.[xxvii] The observed increases in non-oral ER oxymorphone abuse calls, as well as heroin abuse calls, following OxyContin's reformulation illustrate the dynamic and interdependent nature of opioid abuse patterns and the challenges in fully characterizing the impacts of OxyContin's reformulation within this changing landscape.

5.3.1.6   Trends in Other Exposure Call Types

Large declines were observed in utilization-adjusted rates of calls involving OxyContin exposures not directly related to abuse (and therefore, at least in theory, independent of the abuse-deterrent effects of the reformulation), such as for adverse reactions (a category used when the drug was taken as directed) and unintentional general exposures (e.g., pediatric exposures). This suggests broader trends with respect to PCC calls for OxyContin, and prescription opioids more generally since declines in these types of exposure calls were also observed across comparators. Declines were not observed in utilization-adjusted misuse or suspected suicide calls involving OxyContin, as was seen for some comparators. It may sometimes be difficult to determine what the actual intent of an exposure was, but it is notable that the declines in utilization-adjusted misuse and suspected suicide call rates involving OxyContin were smaller than those observed for abuse calls. The possibility of misclassification of exposure

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[xxiv] U.S. Department of Justice, Drug Enforcement Administration; 2018 National Drug Threat Assessment (DEA-DCT-DIR-032-18) October, 2018; https://www.dea.gov/sites/default/files/2018-11/DIR-032-18%202018%20NDTA%20final%20low%20resolution.pdf

[xxv] Hedegaard H, Miniño AM, Warner M. Drug overdose deaths in the United States, 1999–2018. NCHS Data Brief, no 356. Hyattsville, MD: National Center for Health Statistics. 2020.

[xxvi] Substance Abuse and Mental Health Services Administration. (2019). Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health (HHS Publication No. PEP19-5068, NSDUH Series H-54). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/

[xxvii] FDA press announcement: https://www.fda.gov/news-events/press-announcements/fda-requests-removal-opana-er-risks-related-abuse

type also cannot be ruled out as an explanation for some of these observations, and misclassification, in general, is a prevailing issue with PCC data. Nonetheless, the declines in non-abuse-related call types—particularly in OxyContin adverse reaction and unintentional exposure call rates even after accounting for declines in OxyContin dispensing—further contribute to uncertainty about how much of the decline in abuse call rates for OxyContin, if any, can be reasonably attributed to the reformation rather than broader changes in PCC use for medical advice for prescription opioid exposures.

5.3.2   Exploring the Impact of Misclassification and Missing Data

The declines in OxyContin abuse call rates were generally attenuated in sensitivity analyses addressing product misclassification and missing data—for example, using all ER oxycodone calls rather than restricting to brand-only OxyContin calls, and imputing formulation in calls in which this information was missing. The comparative results (i.e., RORRs), however, were generally consistent with the primary study findings. At the same time, the misclassification of drug product cannot be quantified as there is no way to compare the observed data to "truth" (i.e., complete and accurate call information), and it is unclear how well the imputation methods addressed missing formulation data given the limited variables in the imputation model. Missing data on route was also prevalent, and not addressed. Therefore, despite the general consistency across analyses, uncertainty remains with respect to quantifying abuse rates, further complicating the interpretation of the relative changes observed in this study.

While the extent of misclassification is unknown, the sensitivity analysis using "any ER oxycodone" (i.e., brand OxyContin or generic ER oxycodone) suggests that likely some misclassification between brand and generic products occurred, but this misclassification was not enough to substantively alter the study's main findings. The observed percent changes and RORRs were both generally robust to a less specific definition of OxyContin (or "any ER oxycodone"), with the exception of some notable and difficult to interpret discrepancies when modeling abuse call rates adjusting for tablets dispensed and call volume as covariates.

As noted, in some instances information on drug formulation (i.e., IR versus ER) was not recorded, and these data are differentially missing across opioid moiety and time (see Figure 6). The multiple imputation model the sponsor used only included age, sex, medical outcome, center code, and year-quarter as predictors to impute formulation data, where some of those variables also had missing data; given the large amounts of missingness for oxycodone and morphine exposures, it is unclear how accurate the imputation model was and whether the sponsor's assumptions on missingness were demonstrated. Nevertheless, the trends in missing formulation information appeared to increase at a similar rate over time for all opioid comparators, and even though percent declines were attenuated, particularly for ER morphine, the RORRs were largely consistent when comparing the "complete case" analysis results (i.e., only including those cases that specified formulation) to those from imputed analyses. While these multiple imputation analyses, however limited, suggested that those missing data did not meaningfully impact comparative analyses in this study, FDA additionally requested analyses using different methods to impute missing formulation data, and again, percent declines were also attenuated (relative to the "complete case" analyses), but RORRs were mostly unaffected.

In the main analyses, ROA data were not included for abuse calls that involved more than one drug and route. It is also important to keep in mind that, although these data were analyzed comparing specific opioid products and product groupings, substance abuse and substance use disorders very commonly involve multiple drugs. Separate FDA analyses of national poison center data found that from 2014-2018 fewer than half of calls involving oxycodone misuse or abuse were single-substance exposures.[xxviii] Because polysubstance abuse is relatively common, ROA analyses could underestimate abuse call rates by route and could bias comparisons between drugs if a specific comparator is disproportionately associated with polysubstance abuse that involves multiple routes. However, the results of a sensitivity analysis using data from all calls (including those reporting multiple drugs and multiple routes) also showed similar comparative results, likely due to the limited number of multi-substance/multi-route abuse cases involving OxyContin. Missing data on route was also a problem, particularly for OxyContin. Of note, non-oral abuse call rates for unspecified oxycodone increased 37%, and it is unknown what proportion of these calls involved OxyContin versus other oxycodone products, further limiting the ability to quantify any route-specific effect. Nonetheless, the proportion of cases missing those data for OxyContin and comparators was generally stable across periods, so despite some additional uncertainty

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[xxviii] January 15, 2020, Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting: https://www.fda.gov/media/134128/download

around the route-specific abuse call rate estimates, the missing route data are unlikely to have had a major effect on the overall interpretation of the non-oral findings.

5.4 ASSUMPTIONS TO ENABLE CAUSAL INFERENCE REGARDING THE REFORMULATION'S EFFECT ON ABUSE IN THE COMMUNITY

Ecological analyses like PMR study 3051-2 measure outcomes at the aggregate-, or group-, level, and compare group-level rates across time periods to evaluate a public health intervention. However meticulously ecological analyses are designed and conducted, making causal inferences based on their findings is often challenging due to the noted difficulty with adequately controlling for prevailing secular trends and other confounding factors even with rigorous methods and sensitivity analyses. While potentially valuable for understanding the impact of community-level interventions, PMR study 3051-2 and other such group-level analyses should not be conflated with individual-level study designs, such as cohort studies, which are capable of estimating the risk, or probability, of an individual experiencing a particular outcome (e.g., abuse, overdose, etc).

To enable causal assessments in PMR study 3051-2 with respect to evaluating the reformulation's effect on abuse in the community, several overarching assumptions are necessary. One must assume that abuse-related calls to PCCs capture some large, consistent, and representative proportion (i.e., sampling fraction) of abuse overall in the population, and specifically, the types of abuse that would be impacted by the reformulation (i.e., non-oral abuse). There are no available data supporting this assumption, but it is still foundational, and must be true if the study findings support any causal interpretation about changes in abuse rates in the population. Also, because this study relies on data collected in only some cases, it shares some of the limitations of spontaneous reporting systems, for example assumed under-ascertainment, and missing information. Notably, PCC data do not typically capture unattended, out-of-hospital deaths,[xxix] so an opioid product that is more likely to be involved in such cases may be differentially under-ascertained in these data overall. Only differential under-ascertainment by study period would bias relative change comparisons between opioids, so one must assume that there were no opioid-product-specific changes in the likelihood of making a call for an exposure (i.e., case ascertainment) over the study period; there are no available data supporting this assumption either.

5.5 OVERALL INTERPRETATION OF PMR STUDY 3051-2 FINDINGS

Our primary goal in interpreting PMR study 3051-2 results is to determine whether the data support the hypothesis that changes in abuse call rates for OxyContin can be reasonably attributed to its reformulation and the effectiveness of the abuse-deterrent properties. The use of comparators can help to determine whether the data support such causal inference, and specific sensitivity analyses can help to better understand the uncertainty surrounding the study findings.

Effect of OxyContin's reformulation on <u>overall</u> (any route) abuse call rates:

The totality of findings from PMR study 3051-2 do not provide robust evidence that the observed decline in <u>overall</u> (i.e., via any route) abuse call rates for OxyContin is attributable to its reformulation rather than to broader secular trends. While the observed declines in the overall abuse call rates for OxyContin were temporally associated with the market introduction of the reformulated product and of a reasonably large magnitude, there were declines in comparator opioids of similar magnitude—particularly when adjusting for changes in the amount of drug dispensed—as well as declines in calls for non-abuse-related exposures for both OxyContin and comparators. Taken together, these findings make the prospect of other factors driving down call rates as plausible as the reformulation, although some, unknown combination of causes is certainly possible. The change in the mean population-based abuse call rate by any route for OxyContin was significantly different from those for comparators, but this change does not account for the large decrease in prescribed availability of OxyContin (i.e., utilization) relative to comparators. Although fully adjusting for changes in the number of tablets dispensed may underestimate declines in OxyContin abuse call rates attributable to the reformulation if the reformulation drove some declines in dispensing for abuse purposes (i.e., the reduced prescribing was in one branch of the causal pathway), we would still expect a meaningful abuse-deterrent effect to show a change in the number of abuse calls for a given amount of drug dispensed that is larger than the change for comparators; however, this was not the case. The level change ("immediate shift") in OxyContin abuse rate following

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[xxix] Mallama CA, et al. (2019) A comparison of opioid-involved fatalities captured in the National Poison Data System to data derived from US death certificate literal text. Pharmacoepidemiology and Drug Safety; 28 (10): 1377-1385

reformulation was also generally not significantly different from those of comparators after accounting for declines in utilization; nor were any changes in population-based or utilization-based estimates of trends over time (slopes). The causal argument for an attributable decline is also challenged by commensurate declines in other call types for exposures not expected to be impacted by the reformulation, even after accounting for reduced utilization. However, given the challenges associated with PCC data quality, including high levels of missing formulation data for exposures involving oxycodone and morphine, and the potential for misclassification of drug product and exposure reason, it is possible that the overarching limitations of these PCC data limit the "assay sensitivity" of this study with respect to accurately measuring and comparing differences in overall abuse call rates between periods. In other words, it is possible that the reformulation did cause some decline in the overall number of exposure calls to poison centers for OxyContin abuse, but there is too much "noise" in these data to clearly differentiate or quantify this effect with a high level of confidence.

There are several possible explanations for the observed declines in overall abuse call rates for both OxyContin and comparators. The first is that these declines were caused by a common set of other factors—some of these factors might be internal to the data, like increasingly missing formulation information, and some external, like law enforcement efforts or increased availability and lower prices for heroin. A second explanation, which is more favorable to an abuse-deterrent effect of OxyContin's reformulation, is that the reformulation caused decreases in abuse of OxyContin, both through decreased OxyContin dispensing and decreased abuse of what was dispensed into communities, whereas declines in comparator opioids were caused by other factors. And finally, it is possible that some individuals who had been abusing multiple prescription opioids, including OxyContin as well as primary comparator opioids, shifted to heroin or other alternative drugs after the reformulation, driving down the rates for comparators simultaneously with those of OxyContin. If this occurred, the comparators were not truly unaffected by the intervention (i.e., OxyContin's reformulation), making their use as negative controls problematic. The "true" reason for the observed declines in abuse calls rates for OxyContin as well as comparators is perhaps some mixture of all of these explanations, but the totality of evidence is equivocal on the reformulated OxyContin having a distinct, robust effect on abuse independent of the other potential explanations. It is not unreasonable to expect that some proportion of those who abused OxyContin by mostly non-oral routes, or who would have transitioned to those routes, migrated to heroin or other drugs around the time OxyContin was reformulated; however, this study was not designed to assess this causal relationship (i.e., to determine the effect of OxyContin's reformulation on abuse of heroin or other drugs or the effect of increased availability of these alternative drugs on abuse of OxyContin). Nevertheless, the increase in abuse-related calls involving heroin is notable, and it is consistent with data from other sources suggesting at least a temporal association between the reformulation and increases in heroin abuse and overdoses (see background document: OSE Literature Review).

Considering that the vast majority of abuse exposure calls overall involve oral routes of exposure, it is not entirely unexpected to see similar results for overall (i.e., any route) and oral abuse analyses. The reformulation was not expected to substantially affect oral OxyContin abuse call rates, given that its properties were primarily designed to impede abuse via non-oral (intravenous or intranasal) routes, but large decreases in oral abuse call rates were observed for OxyContin, as well as for all of the primary comparators, including IR hydrocodone, for which abuse exposure calls overwhelmingly involve oral routes. Decreases in specifically oral abuse for all comparators somewhat reinforces that there are likely larger trends at play across prescription opioids during this time. Of note in this analysis, the data could not differentiate between oral routes (i.e., swallowing whole versus chewing or dissolving), and therefore, some of the decline observed in OxyContin oral abuse call rates could be a result of less chewing, but this is speculative and does not explain the decreases in oral abuse calls for comparators.

Effect of OxyContin's reformulation on <u>non-oral</u> abuse call rates:

The totality of evidence from PMR study 3051-2 does support the hypothesis that some decline in non-oral abuse call rates for OxyContin can be reasonably attributed to its reformulation rather than to broader secular trends, but the magnitude of the reformulation's effect on non-oral abuse call rates is uncertain. Stratifying analyses by route and evaluating for a specificity of effect by route can help to establish causal associations that align with the reformulation's design and labeled properties. Calls involving non-oral abuse made up a small proportion of abuse calls overall (<20% for OxyContin), but unlike for overall abuse call rates (i.e., any route), declines in non-oral abuse call rates were seen for OxyContin but not seen consistently across the primary comparators. IR hydrocodone and "other schedule II opioids" had no change in mean non-oral abuse call rates and declines in OxyContin's population- and utilization-based non-oral abuse call rates were significantly different from those for both of these comparators. Across all comparators, comparative results for the non-oral route more strongly favored OxyContin than did the comparative results for the oral route. There was also a clear divergence in trend

directions for OxyContin and "other schedule II opioids" non-oral abuse calls immediately following the reformulation. Visual inspection of unmodeled trends in quarterly counts shows an apparent *increase* in the number of non-oral abuse calls for "other schedule II opioids" immediately following the introduction of reformulated OxyContin, concurrent with a *decrease* in OxyContin non-oral abuse calls. Only one comparator, ER morphine, had equivocal findings compared to OxyContin, but the interpretation of the ER morphine non-oral abuse call data is complicated by the large amount of missing data on formulation for morphine exposures and the very low quarterly counts of non-oral abuse calls throughout the study period. In this study ER morphine had a relative decrease in utilization-based mean non-oral abuse call rates that was not significantly different from OxyContin's, although the decrease in population-based mean non-oral abuse call rates was significantly greater for OxyContin compared to ER morphine. Taken together, definitively quantifying the contribution of secular trends to the observed declines in OxyContin non-oral abuse rates is not possible, even if it is still reasonable to attribute some of this decline to the reformulation based on the totality of evidence and data from other comparators.

While the totality of evidence supports some effect of the reformulation on non-oral abuse calls involving OxyContin, the PCC data are limited in that a non-trivial proportion of calls had missing route data, particularly for OxyContin (~13% to ~15%). There was a slight increase in the proportion reporting oral abuse compared to non-oral abuse after the reformulation, but there was no evidence of a shift between non-oral routes (i.e., from snorting to injection), although the data on specific non-oral routes are limited by particularly low quarterly counts. Coupled with the inherent challenges associated with PCC data quality that have been noted, the non-oral abuse call rate data continue to generate considerable uncertainty, particularly with regard to the magnitude of effect.

Interpretation of other findings:

Beyond the specific objectives of PMR study 3051-2, there were other salient findings and data gaps that should be considered in the context of evaluating the reformulation's impact. These data do not suggest that after the reformulation there was much change in the proportion of OxyContin-involved abuse cases resulting in severe medical outcomes or death, although a substantial proportion were missing information on the ultimate medical outcome. Importantly, PCC data are unlikely to capture the most severe overdose cases resulting in unattended, out-of-hospital death If the reformulation had a disproportionate impact on unattended, out-of-hospital fatal overdose, PMR study 3051-2 would not necessarily have been able to detect this effect.

The post-reformulation abuse call rates for OxyContin do not provide evidence supporting its being a "safer" alternative to other opioid analgesics with respect to abuse. Despite declines in abuse calls following reformulation, calls involving abuse of OxyContin persisted, including calls involving non-oral abuse of this product. Furthermore, abuse call rates remained higher than those for multiple opioid comparators, particularly after accounting for differing levels of prescribed availability (i.e., number of tablets dispensed) for these product groups. Examining the post-period rates can help to contextualize the pre- vs post-reformulation findings; however, this study was not designed to formally compare abuse call rates across different opioids in the post-reformulation period. Variable levels of missing formulation data complicate the interpretation of post-period abuse call rate comparisons and OxyContin was not compared to all other available opioid analgesic products.

Finally, there was a striking increase in abuse calls involving heroin, with the largest increases occurring after OxyContin's reformulation. Ultimately, the manner in which changes in OxyContin abuse may have influenced, or been influenced by, increases in heroin use is not entirely clear from this study, as it was not designed to investigate the drivers or effects of increasing heroin use.

6   CONCLUSION

The totality of findings from PMR study 3051-2 do not provide robust evidence that the observed decline in <u>overall</u> (i.e., via any route) abuse call rates for OxyContin is attributable to its reformulation rather than to broader secular trends. The study findings do support the hypothesis that some decline in <u>non-oral</u> abuse call rates for OxyContin can be reasonably attributed to its reformulation, but the magnitude of the reformulation's impact on non-oral abuse call rates is uncertain. Data from the post-reformulation time period do not provide evidence for reformulated OxyContin being less likely to be abused than other opioid analgesics. Heroin abuse calls increased after reformulated OxyContin was introduced; however, this study was not specifically designed to evaluate substitution effects or causal associations between the reformulation and increases in calls involving other opioids. The findings from this study must be viewed in the context of the other PMR study findings and the entire body of

evidence taken into consideration to inform the discussion surrounding the effectiveness of OxyContin's reformulation on reducing abuse in the community.

7 REFERENCES

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Dart RC, Surratt HL, Cicero TJ, et al. (2015) Trends in Opioid Analgesic Abuse and Mortality in the United States. The New England Journal of Medicine; 37 (2): 241-248

Severtson GS, Bartelson BB, Davis JM et al. (2013) Reduced Abuse, Therapeutic Errors, and Diversion Following Reformulation of Extended-Release Oxycodone in 2010. Journal of Pain; 14 (10): 1122-1130

8 APPENDICES

8.1 SPONSOR DESCRIPTION OF MODEL DIAGNOSTICS FROM PMR STUDY 3051-2

Akaike Information criteria (AIC):

Table 1: AIC model fit statistic values for changes in intentional abuse of OxyContin (-2y/5y)

Model for OxyContin Abuse	AIC
Model 1	323.26
Model 2	272.93
Model 2a	261.25
Model 3	265.78
Model 3a	254.43

AIC=Akaike Information Criteria; Model 1: Rate of abuse/Census population. Model 2: Rate of abuse/Dosage units dispensed. Model 2a: Rate of abuse/Dosage units dispensed adjusting for pharmaceutical exposures. Model 3: Abuse count adjusting for dosage units dispensed (continuous). Model 3a: Abuse count adjusting for dosage units dispensed (continuous) and pharmaceutical exposures.

Table 2: AIC model fit statistic values for changes in intentional abuse for OxyContin relative to primary comparators (-2y/5y)
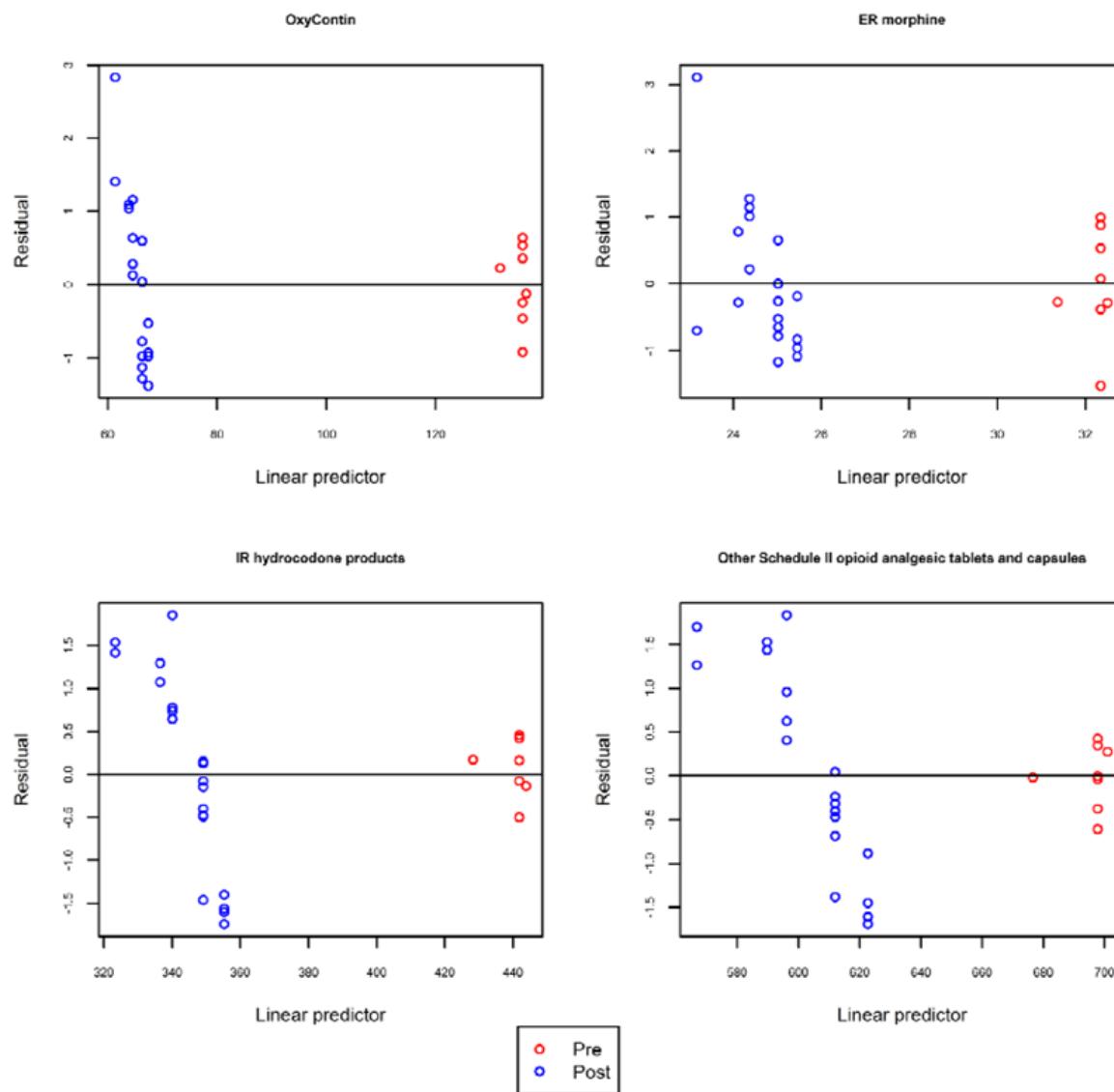
Model for OxyContin and Primary Comparator Opioids	AIC
Model 1	2054.46
Model 2	1708.19
Model 2a	1666.89
Model 3	1569.45
Model 3a	1517.49

AIC=Akaike Information Criteria; Model 1: Rate of abuse/Census population. Model 2: Rate of abuse/Dosage units dispensed. Model 2a: Rate of abuse/Dosage units dispensed adjusting for pharmaceutical exposures. Model 3: Abuse count adjusting for dosage units dispensed (continuous). Model 3a: Abuse count adjusting for dosage units dispensed (continuous) and pharmaceutical exposures.

Residual plots:

The residual plots by opioid for Model 1 reveal that the residuals were not randomly scattered for OxyContin and all primary comparator opioids. The residuals for the pre-reformulation period were smaller than those for the post-reformulation period.
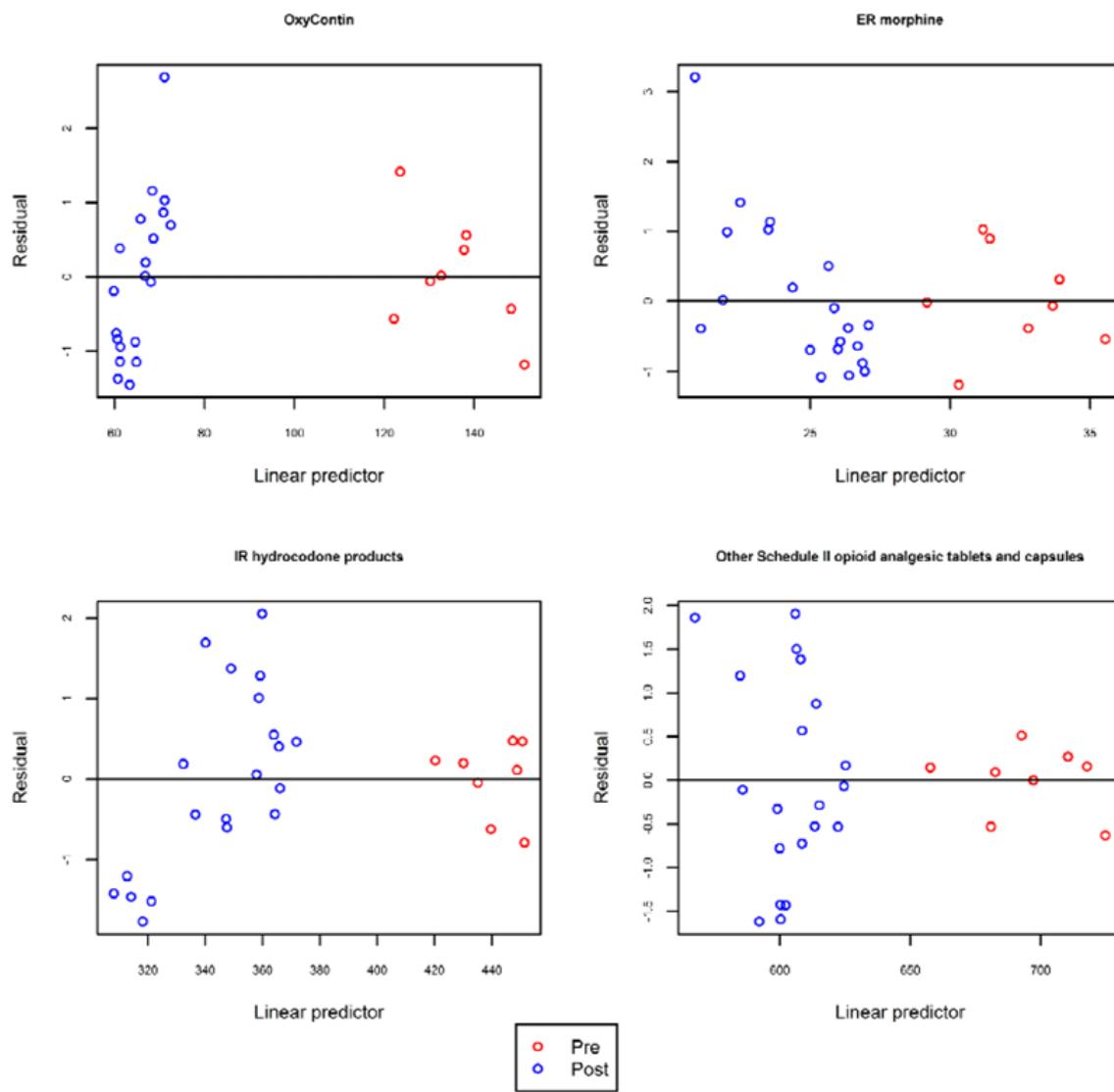
Figure 1: Model 1 standardized Pearson residual versus linear predictor

IR=immediate release; ER=extended release; Pre: pre-reformulation data points; Post: post-reformulation data points.
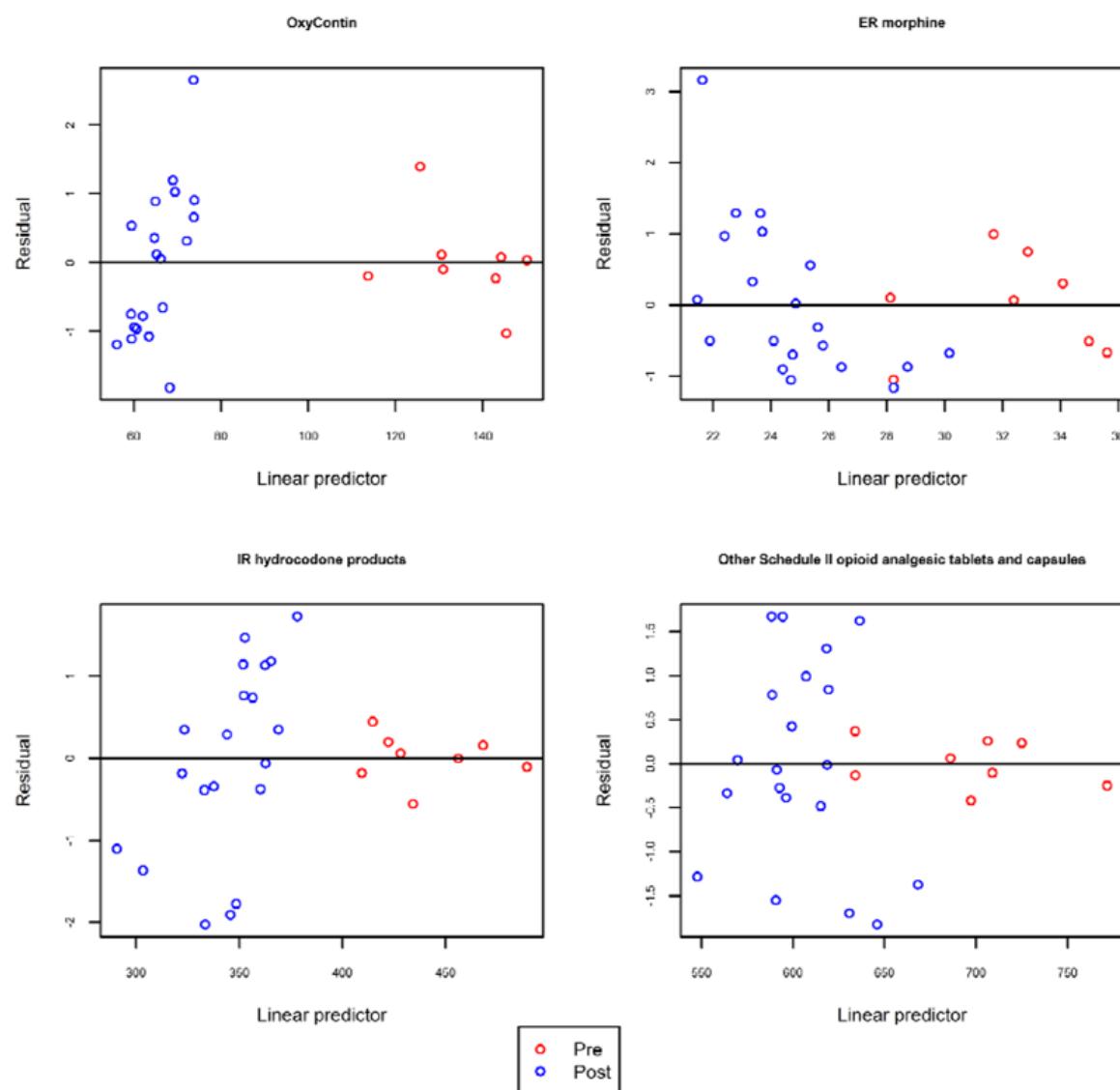
The residuals plots by opioid for Model 2 reveal that there were no apparent residual patterns for OxyContin and all primary comparator opioids. Similarly, for Model 2a, there were no apparent residual patterns either.

Figure 2: Model 2 standardized Pearson residual versus linear predictor

IR=immediate release; ER=extended release; Pre: pre-reformulation data points; Post: post-reformulation data points.
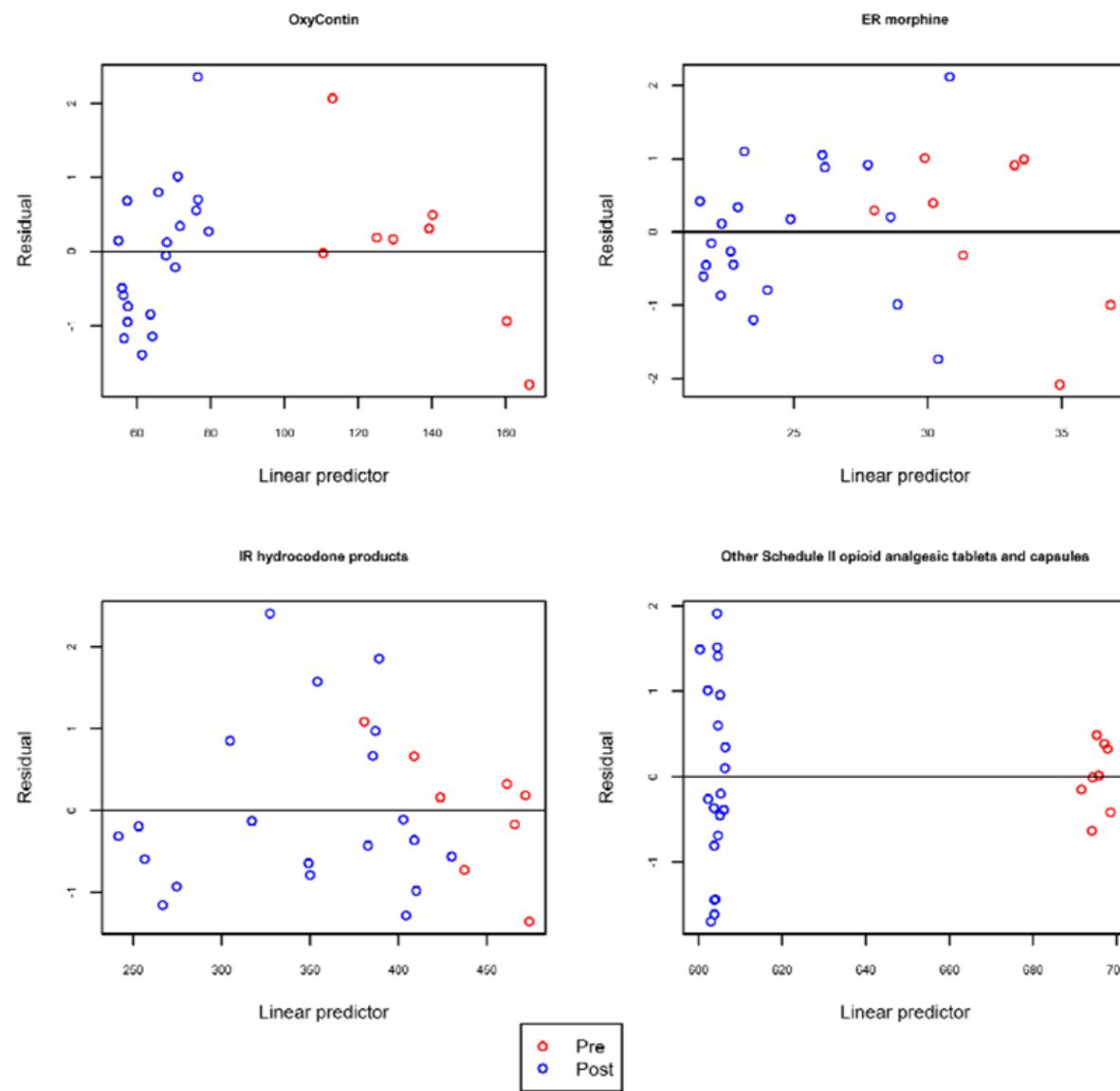
Figure 3: Model 2a standardized Pearson residual versus linear predictor

IR=immediate release; ER=extended release; Pre: pre-reformulation data points; Post: post-reformulation data points.

For Model 3, there were no apparent patterns for OxyContin, ER Morphine, or IR hydrocodone combination products in the residual plots. However, the residuals were not randomly scattered along the linear predictor in the residual plot for the "other schedule II opioids" comparator.
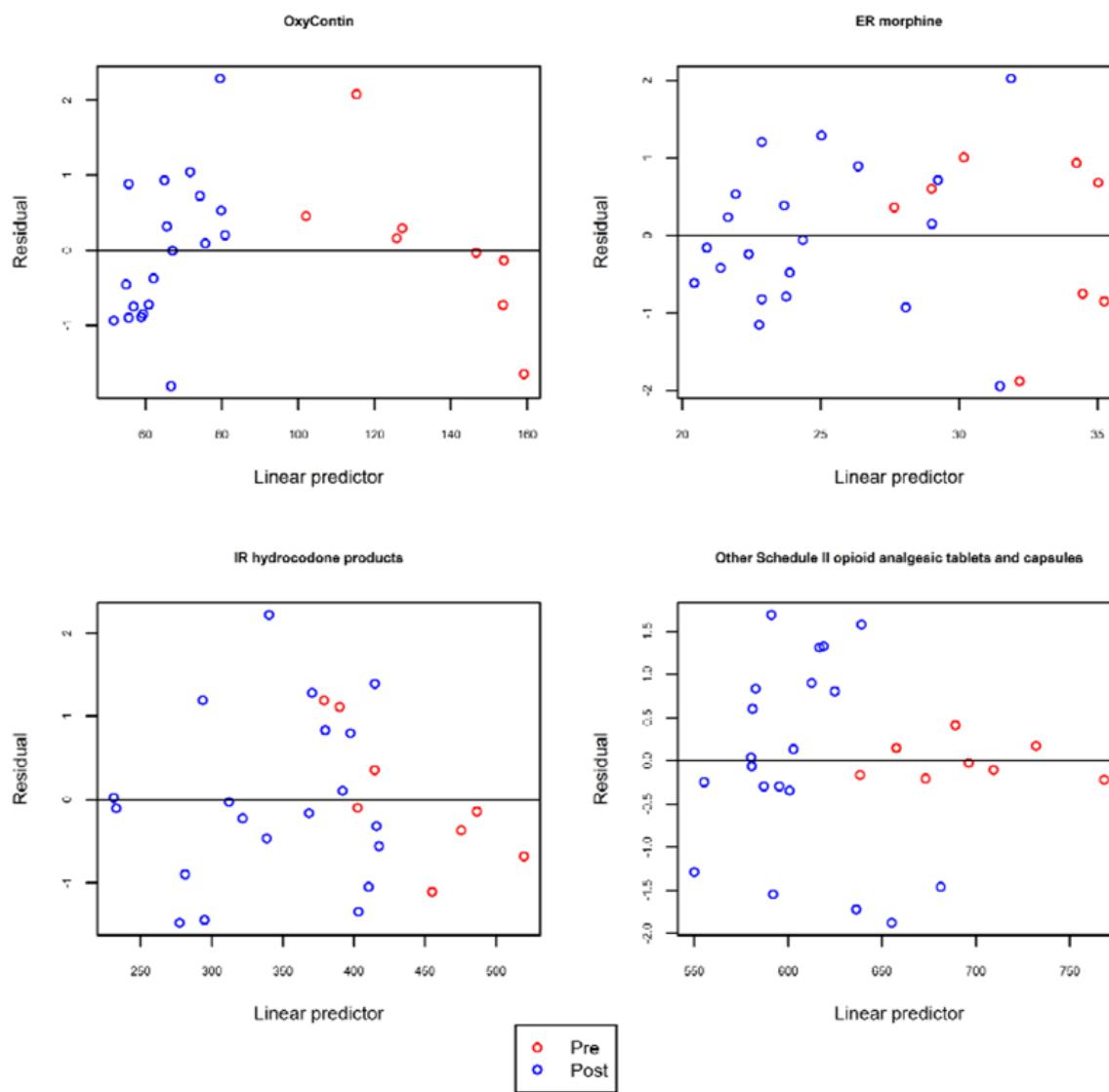
Figure 4: Model 3 standardized Pearson residual versus linear predictor

IR=immediate release; ER=extended release; Pre: pre-reformulation data points; Post: post-reformulation data points.

For Model 3a, there were no apparent residual patterns for OxyContin and all primary comparator opioids.

Figure 5: Model 3a standardized Pearson residual versus linear predictor
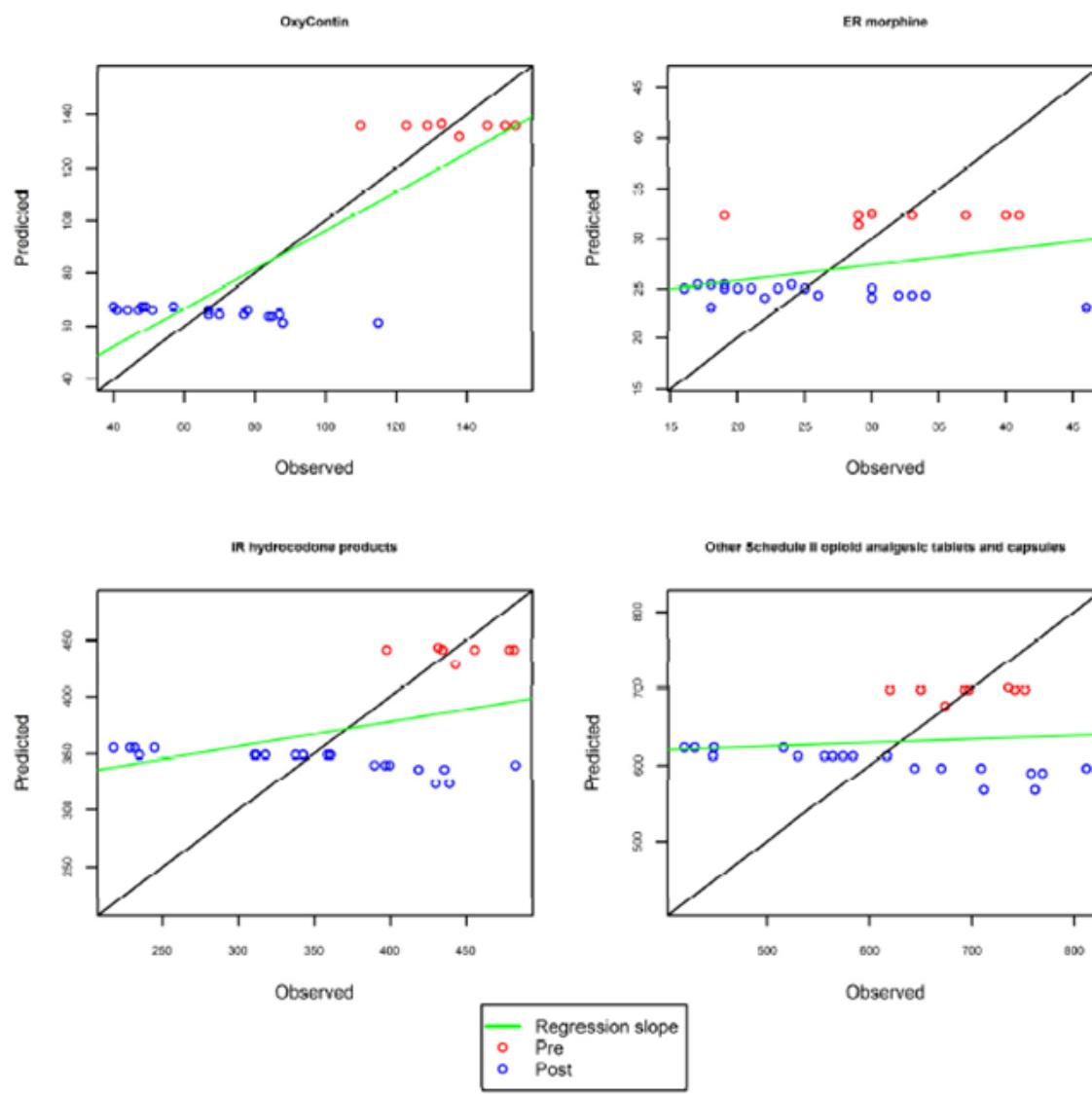
IR=immediate release; ER=extended release; Pre: pre-reformulation data points; Post: post-reformulation data points.

Observed versus Predicted Plots

The observed versus predicted plots include a line of unity and are overlaid with a regression slope line (green). The line of unity is the line where the model-estimated values would equal the observed values if the model fit the data perfectly. The regression line is the model-predicted values regressed on the observed values. When the regression line and the line of unity are close, it indicates that the model was potentially a good fit.
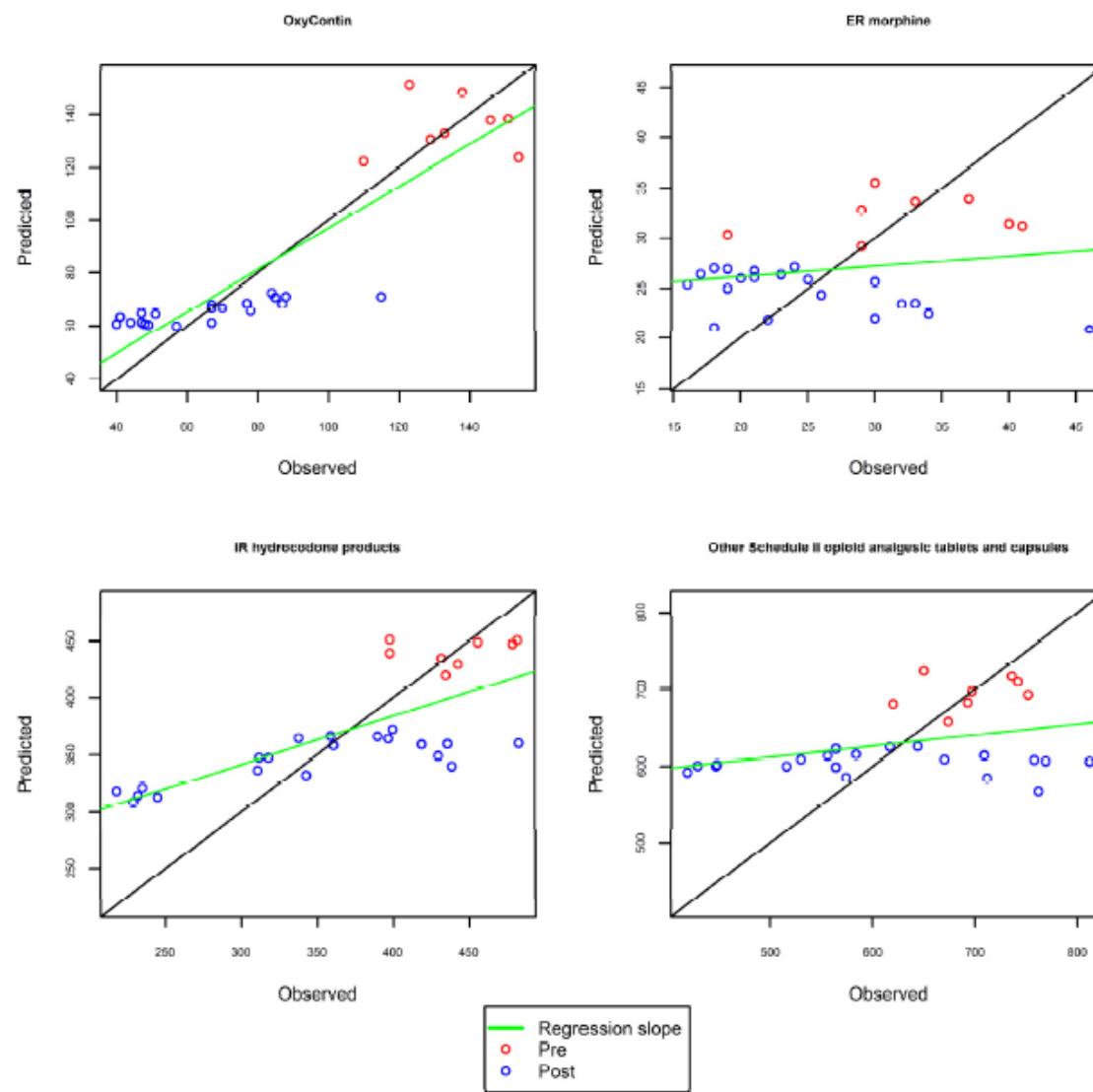
Across models, the fit appears to be better when modeling abuse call rates related to calls for OxyContin and IR hydrocodone combination products than when modeling abuse call rates related to calls for ER morphine and "other schedule II opioids"

Figure 6: Model 1 observed versus predicted
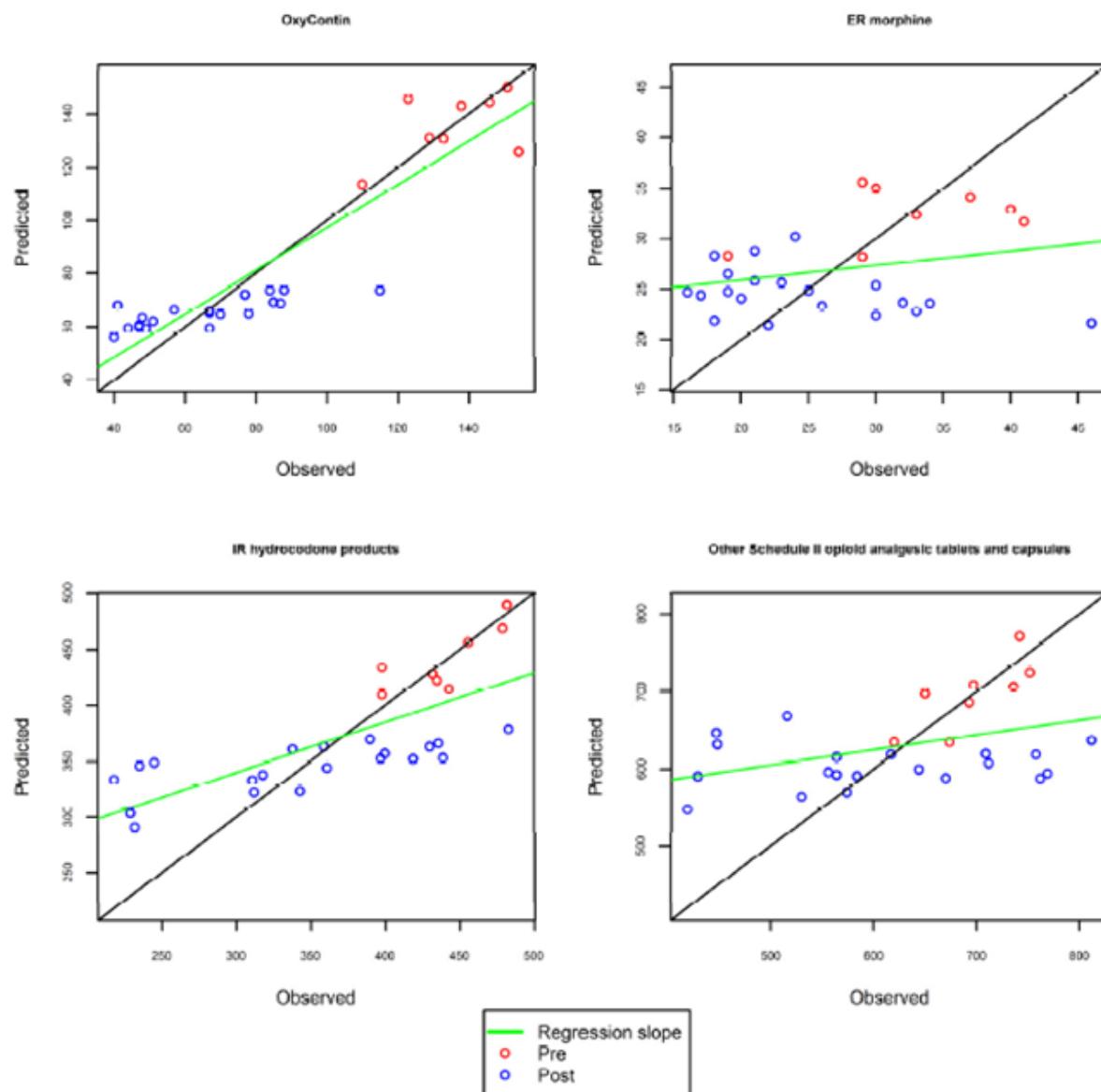
IR=immediate release; ER=extended release; Pre: pre-reformulation data points; Post: post-reformulation data points. Regression slope (green): linear regression of predicted regressed on observed data; Line of unity (black): diagonal line where observed=predicted.

Figure 7: Model 2 observed versus predicted
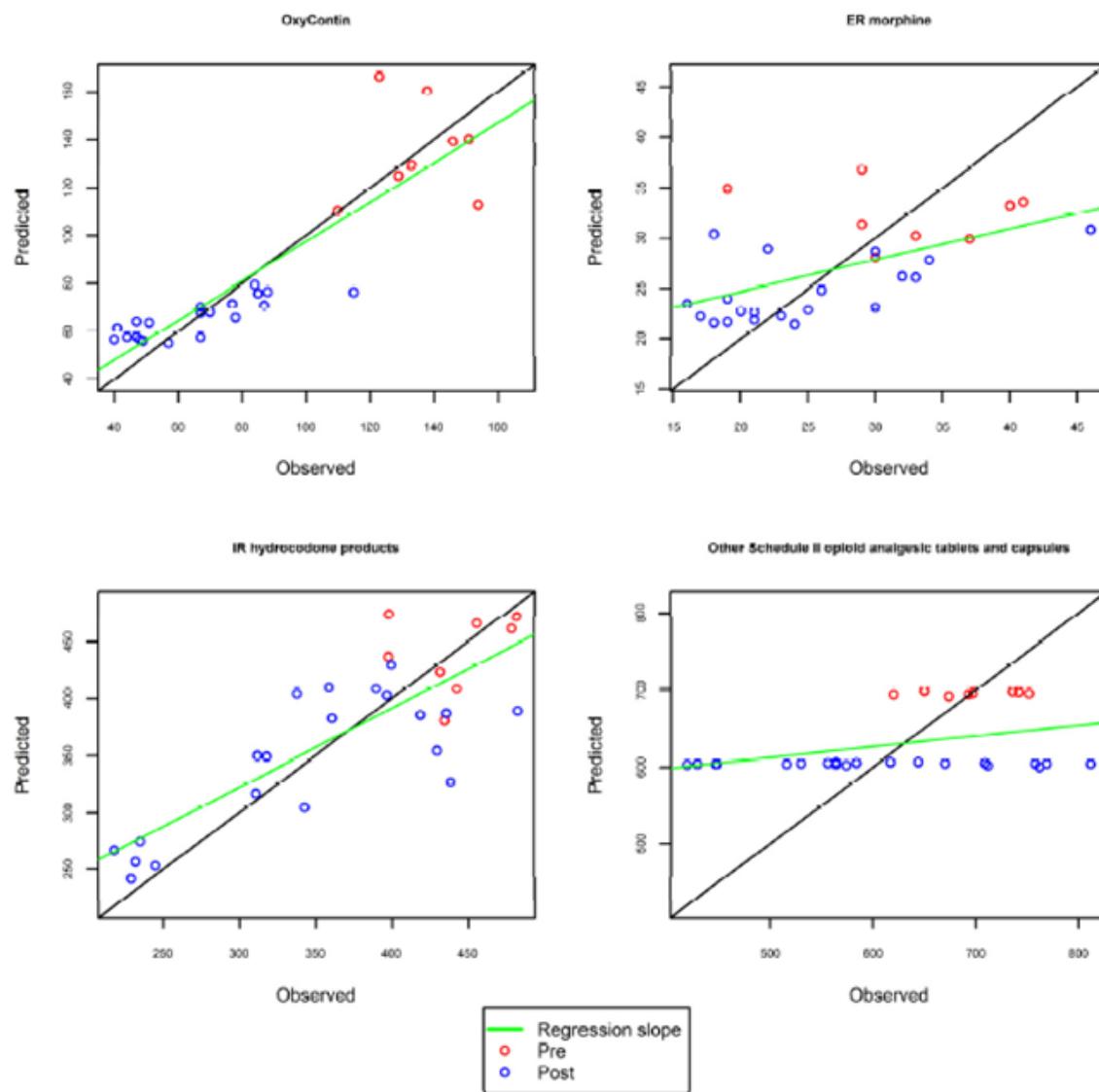
IR=immediate release; ER=extended release; Pre: pre-reformulation data points; Post: post-reformulation data points. Regression slope (green): linear regression of predicted regressed on observed data; Line of unity (black): diagonal line where observed=predicted.

Figure 8: Model 2a observed versus predicted
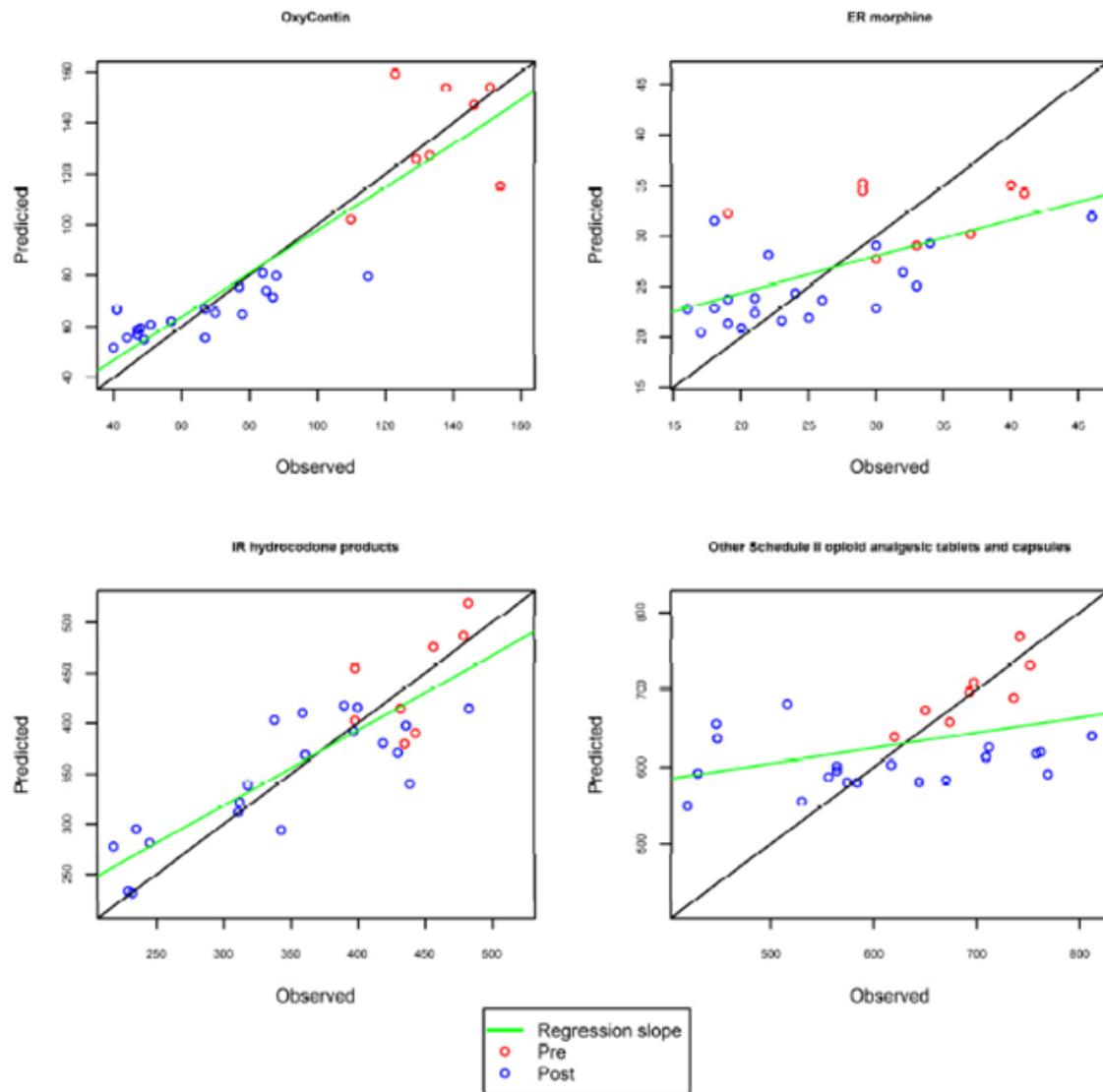
IR=immediate release; ER=extended release; Pre: pre-reformulation data points; Post: post-reformulation data points. Regression slope (green): linear regression of predicted regressed on observed data; Line of unity (black): diagonal line where observed=predicted.

Figure 9: Model 3 observed versus predicted

IR=immediate release; ER=extended release; Pre: pre-reformulation data points; Post: post-reformulation data points. Regression slope (green): linear regression of predicted regressed on observed data; Line of unity (black): diagonal line where observed=predicted.
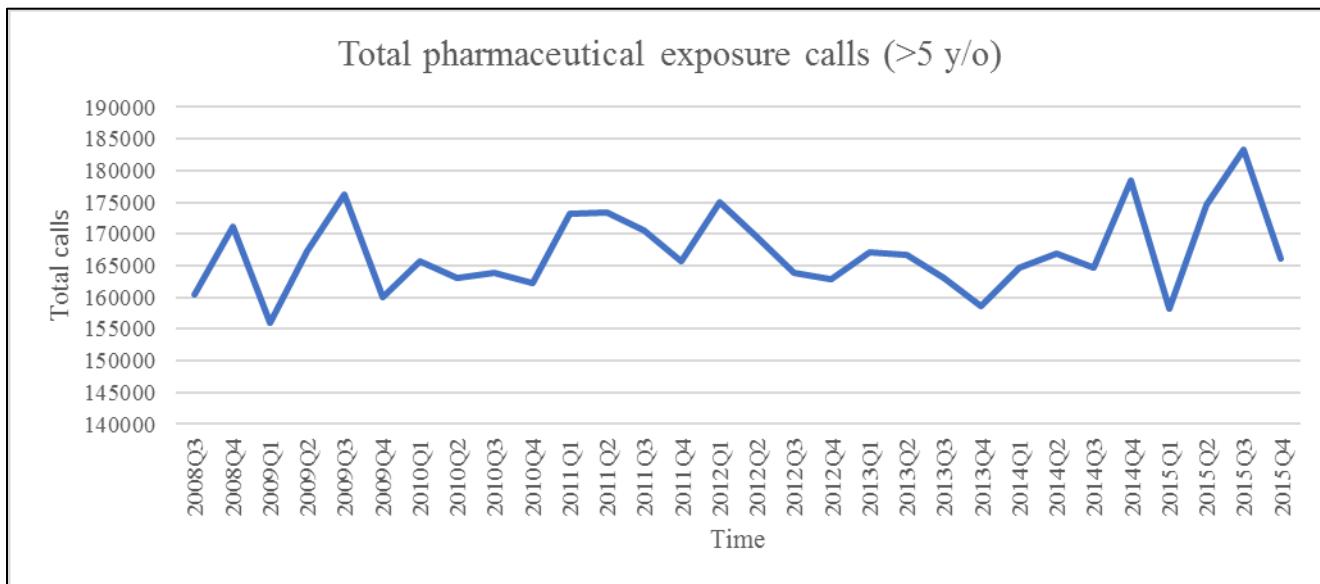
Figure 10: Model 3a observed versus predicted

IR=immediate release; ER=extended release; Pre: pre-reformulation data points; Post: post-reformulation data points. Regression slope (green): linear regression of predicted regressed on observed data; Line of unity (black): diagonal line where observed=predicted.
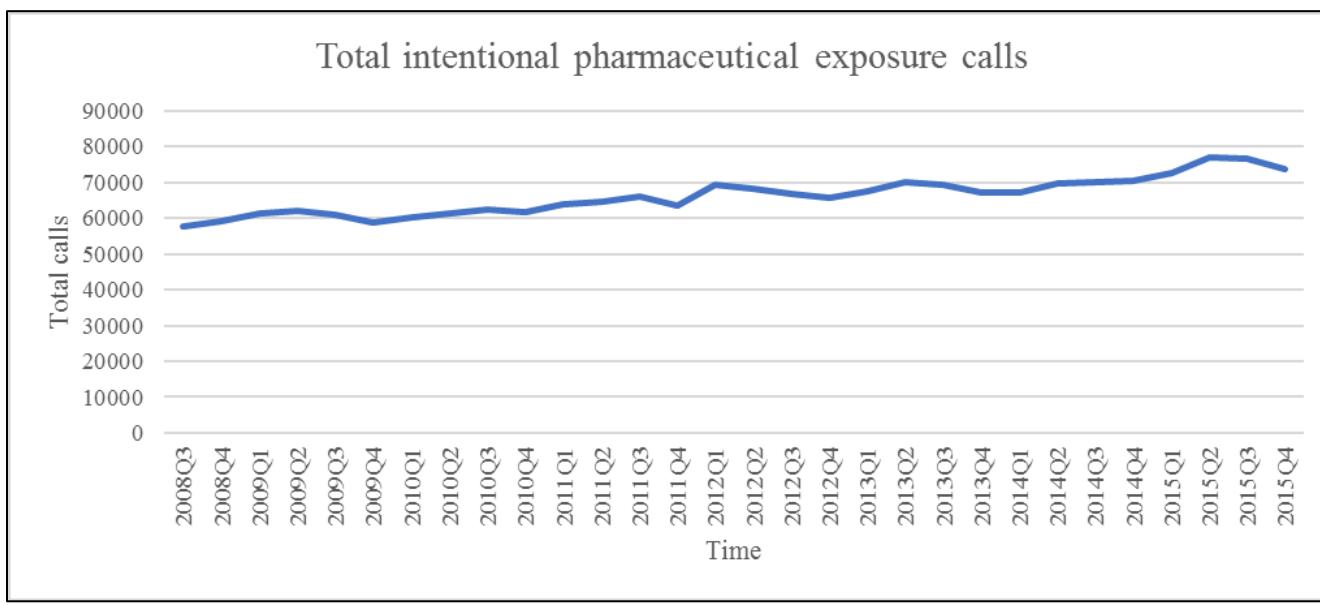
8.2   TOTAL NUMBER CALLS MADE POISON CENTERS INVOLVING PHARMACEUTICALS FROM 2008 - 2015

Figure 11: Total pharmaceutical exposure calls for individuals >5 years old, by quarter (2008Q3-2015Q4)

FDA figure: These data were taken from the PMR 3051-2 study report

Figure 12: Total intentional pharmaceutical exposure calls, by quarter (2008Q3-2015Q4)

FDA figure: These data were taken from the sponsor information request response from February 11, 2020

8.3 RESULTS COMPARING 1 YEAR BEFORE VERSUS 3 YEARS AFTER THE REFORMULATION (MEANS ANALYSIS)

Table 3: Percent change (95% CI) in intentional abuse of OxyContin and primary comparators after the introduction of reformulated OxyContin using different modeling approaches (-1y/3y)

	Model 1 % change (95% CI)	Model 2 % change (95% CI)	Model 2a % change (95% CI)	Model 3 % change (95% CI)	Model 3a % change (95% CI)
OxyContin	-46.20% (-56.88% to -32.87%)	-25.33% (-38.00% to -10.07%)	-27.14% (-36.28% to-16.68%)	-8.30% (-48.00% to 61.69%)	-16.24% (-45.30% to 28.24%)
ER Morphine	-18.24% (-38.94% to 9.48%)	-30.85% (-49.88% to -4.59%)	-32.06% (-49.04% to -9.42%)	13.83% (-28.40% to 80.95%)	-7.19% (-42.55% to 49.94%)
IR Hydrocodone	-14.15% (-25.64% to -0.88%)	-19.26% (-29.23% to -7.88%)	-20.79% (-27.31% to -13.68%)	-5.15% (-29.26% to 27.16%)	-9.93% (-25.13% to 8.35%)
Other Schedule II	-9.26% (-22.27% to 5.94%)	-18.28% (-29.84% to -4.82%)	-19.88% (-28.10% to-10.72%)	30.74% (-8.87% to 87.57%)	1.5% (-24.96% to 37.30%)

CI=confidence interval; ER=extended release; IR hydrocodone=immediate release hydrocodone combination products; Model 1: Rate of abuse/Census population. Model 2: Rate of abuse/Dosage units dispensed. Model 2a: Rate of abuse/Dosage units dispensed adjusting for pharmaceutical exposures. Model 3: Abuse count adjusting for dosage units dispensed (continuous). Model 3a: Abuse count adjusting for dosage units dispensed (continuous) and pharmaceutical exposures.

Table 4: Ratio of rate ratios (95% CI) for intentional abuse of primary compactors versus OxyContin after the introduction of reformulated OxyContin using different modeling approaches (-1y/3y)

	Model 1 RORR (95% CI)	Model 2 RORR (95% CI)	Model 2a RORR (95% CI)	Model 3 RORR (95% CI)	Model 3a RORR (95% CI)
ER Morphine	1.520 (1.053 to 2.192)	0.926 (0.639 to 1.343)	0.932 (0.679 to 1.281)	1.241 (0.597 to 2.582)	1.108 (0.585 to 2.099)
IR Hydrocodone	1.596 (1.226 to 2.077)	1.081 (0.861 to 1.358)	1.087 (0.927 to 1.275)	1.034 (0.546 to 1.959)	1.075 (0.677 to 1.709)
Other Schedule II	1.687 (1.287 to 2.210)	1.094 (0.861 to 1.392)	1.100 (0.926 to 1.306)	1.426 (0.728 to 2.793)	1.212 (0.722 to 2.034)

Ratio of risk ratios (RORR)=(comparator risk ratio)/(OxyContin risk ratio). CI=confidence interval; ER=extended release; IR hydrocodone=immediate release hydrocodone combination products; Model 1: Rate of abuse/Census population. Model 2: Rate of abuse/Dosage units dispensed. Model 2a: Rate of abuse/Dosage units dispensed adjusting for pharmaceutical exposures. Model 3: Abuse count adjusting for dosage units dispensed (continuous). Model 3a: Abuse count adjusting for dosage units dispensed (continuous) and pharmaceutical exposures.

Table 5: Percent change (95% CI) in intentional abuse of OxyContin and primary comparators after the introduction of reformulated OxyContin using different modeling approaches, by route of abuse (-1y/3y)

	Model 1 % change (95% CI)	Model 2 % change (95% CI)	Model 2a % change (95% CI)	Model 3 % change (95% CI)	Model 3a % change (95% CI)
Inhalation					
OxyContin	-49.91% (-67.16% to -23.60%)	-30.49% (-53.64% to 4.22%)	-32.68% (-56.37% to 3.86%)	12.75% (-67.99% to 297.16%)	4.32% (-72.59% to 297.10%)
ER Morphine	-43.33% (-80.49% to 64.63%)	-52.07% (-83.68% to 40.76%)	-53.15% (-83.82% to 35.65%)	56.97% (-80.26% to 1147.94%)	25.01% (-84.88% to 933.92%)
IR Hydrocodone	11.71% (-31.66% to 82.62%)	5.06% (-35.06% to 69.96%)	2.49% (-35.01% to 61.62%)	38.13% (-51.44% to 292.90%)	28.75% (-52.76% to 250.94%)
Other Schedule II	29.35% (-17.72% to 103.33%)	16.48% (-25.80% to 82.87%)	13.53% (-24.75% to 71.29%)	225.44% (20.18% to 781.24%)	145.86% (-12.52% to 591.00%)
Injection					
OxyContin	-44.76% (-68.49% to -3.16%)	-23.33% (-55.73% to 32.76%)	-26.26% (-57.49% to 27.94%)	-68.48% (-94.70% to 87.29%)	-77.54% (-96.38% to 39.29%)
ER Morphine	-44.90% (-65.24% to -12.67%)	-53.40% (-71.02% to -25.08%)	-54.66% (-70.83% to -29.52%)	-26.16% (-69.78% to 80.44%)	-53.40% (-81.61% to 18.09%)
IR Hydrocodone	-1.62% (-59.70% to 140.19%)	-7.47% (-62.28% to 126.94%)	-10.18% (-63.79% to 122.81%)	-25.36% (-90.93% to 513.87%)	-32.99% (-91.82% to 448.94%)
Other Schedule II	34.73% (-5.47% to 92.02%)	21.33% (-14.47% to 72.12%)	17.64% (-9.57% to 53.05%)	59.00% (-37.57% to 304.89%)	-8.98% (-57.16% to 93.37%)
Non-oral (Inhalation and Injection)					
OxyContin	-47.20% (-64.48% to -21.52%)	-26.72% (-50.11% to 7.62%)	-29.33% (-52.54% to 5.25%)	-46.65% (-84.00% to 77.92%)	-55.23% (-87.05% to 54.72%)
ER Morphine	-44.53% (-64.66% to -12.93%)	-53.08% (-70.65% to -25.00%)	-54.27% (-70.19% to -29.83%)	-11.14% (-61.44% to 104.77%)	-35.68% (-72.66% to 51.32%)
IR Hydrocodone	8.98% (-26.94% to 62.57%)	2.49% (-30.59% to 51.34%)	-0.31% (-30.37% to 42.73%)	23.01% (-48.08% to 191.47%)	12.05% (-49.35% to 147.85%)
Other Schedule II	31.35% (-6.12% to 83.78%)	18.29% (-15.18% to 64.97%)	14.93% (-10.84% to 48.15%)	139.91% (10.38% to 421.45%)	62.14% (-19.08% to 224.86%)
Oral					
OxyContin	-42.77% (-54.71% to -27.67%)	-20.57% (-34.19% to -4.13%)	-22.47% (-32.30% to -11.21%)	32.51% (-20.79% to 121.66%)	21.43% (-15.27% to 74.03%)
ER Morphine	-13.90% (-37.72% to 19.02%)	-27.18% (-48.95% to 3.87%)	-28.44% (-48.00% to -1.52%)	25.39% (-23.92% to 106.68%)	2.36% (-38.88% to 71.41%)
IR Hydrocodone	-16.63% (-27.55% to -4.07%)	-21.59% (-31.08% to -10.80%)	-23.07% (-29.16% to -16.45%)	-8.32% (-31.33% to 22.40%)	-12.83% (-27.01% to 4.11%)
Other Schedule II	-14.70% (-26.36% to -1.20%)	-23.18% (-33.53% to -11.23%)	-24.67% (-31.97% to -16.59%)	21.46% (-13.97% to 71.49%)	-5.62% (-29.18% to 25.76%)

CI=confidence interval; ER=extended release; IR hydrocodone=immediate release hydrocodone combination products; Model 1: Rate of abuse/Census population. Model 2: Rate of abuse/Dosage units dispensed. Model 2a: Rate of abuse/Dosage units dispensed adjusting for pharmaceutical exposures. Model 3: Abuse count adjusting for dosage units dispensed (continuous). Model 3a: Abuse count adjusting for dosage units dispensed (continuous) and pharmaceutical exposures.

Table 6: Ratio of rate ratios (95% CI) for intentional abuse of primary compactors versus OxyContin after the introduction of reformulated OxyContin using different modeling approaches, by route of abuse (-1y/3y)

	Model 1 RORR (95% CI)	Model 2 RORR (95% CI)	Model 2a RORR (95% CI)	Model 3 RORR (95% CI)	Model 3a RORR (95% CI)
Inhalation					
ER Morphine	1.131 (0.359 to 3.563)	0.69 (0.218 to 2.180)	0.696 (0.221 to 2.193)	1.392 (0.123 to 15.744)	1.198 (0.099 to 14.449)
IR Hydrocodone	2.23 (1.167 to 4.264)	1.511 (0.806 to 2.835)	1.522 (0.812 to 2.854)	1.225 (0.238 to 6.293)	1.234 (0.233 to 6.532)
Other Schedule II	2.582 (1.391 to 4.795)	1.676 (0.914 to 3.072)	1.686 (0.928 to 3.064)	2.886 (0.580 to 14.375)	2.357 (0.443 to 12.530)
Injection					
ER Morphine	0.997 (0.482 to 2.062)	0.608 (0.294 to 1.256)	0.615 (0.304 to 1.245)	2.343 (0.319 to 17.201)	2.075 (0.275 to 15.678)
IR Hydrocodone	1.781 (0.620 to 5.111)	1.207 (0.422 to 3.455)	1.218 (0.421 to 3.524)	2.368 (0.150 to 37.407)	2.984 (0.185 to 48.124)
Other Schedule II	2.439 (1.256 to 4.736)	1.583 (0.825 to 3.034)	1.595 (0.867 to 2.937)	5.045 (0.674 to 37.742)	4.053 (0.581 to 28.275)
Non-oral (Inhalation and Injection)					
ER Morphine	1.051 (0.576 to 1.915)	0.64 (0.349 to 1.174)	0.647 (0.361 to 1.161)	1.666 (0.385 to 7.210)	1.437 (0.324 to 6.379)
IR Hydrocodone	2.064 (1.175 to 3.625)	1.399 (0.809 to 2.418)	1.411 (0.825 to 2.411)	2.306 (0.524 to 10.143)	2.503 (0.577 to 10.863)
Other Schedule II	2.488 (1.480 to 4.182)	1.614 (0.971 to 2.684)	1.626 (1.014 to 2.607)	4.497 (1.073 to 18.844)	3.622 (0.892 to 14.707)
Oral					
ER Morphine	1.504 (1.009 to 2.243)	0.917 (0.613 to 1.370)	0.923 (0.653 to 1.306)	0.946 (0.462 to 1.939)	0.843 (0.451 to 1.577)
IR Hydrocodone	1.457 (1.109 to 1.914)	0.987 (0.786 to 1.240)	0.992 (0.847 to 1.163)	0.692 (0.383 to 1.248)	0.718 (0.481 to 1.071)
Other Schedule II	1.49 (1.130 to 1.965)	0.967 (0.763 to 1.226)	0.972 (0.820 to 1.151)	0.917 (0.493 to 1.703)	0.777 (0.493 to 1.226)

CI=confidence interval; ER=extended release; IR hydrocodone=immediate release hydrocodone combination products; Model 1: Rate of abuse/Census population. Model 2: Rate of abuse/Dosage units dispensed. Model 2a: Rate of abuse/Dosage units dispensed adjusting for pharmaceutical exposures. Model 3: Abuse count adjusting for dosage units dispensed (continuous). Model 3a: Abuse count adjusting for dosage units dispensed (continuous) and pharmaceutical exposures.

Table 7: Percent change (95% CI) in other exposure calls for OxyContin and primary comparators after the introduction of reformulated OxyContin using different modeling approaches (-1y/3y)

	Model 1 % change (95% CI)	Model 2 % change (95% CI)	Model 2a % change (95% CI)	Model 3 % change (95% CI)	Model 3a % change (95% CI)
Intentional Misuse					
OxyContin	-31.04% (-46.00% to -11.94%)	-4.30% (-22.73% to 18.53%)	-5.77% (-24.42% to 17.49%)	28.22% (-32.77% to 144.57%)	21.13% (-37.55% to 134.95%)
ER Morphine	-4.54% (-29.14% to 28.61%)	-19.26% (-41.97% to 12.34%)	-20.16% (-41.43% to 8.85%)	39.58% (-11.96% to 121.31%)	26.73% (-20.69% to 102.50%)
IR Hydrocodone	-9.96% (-19.52% to 0.72%)	-15.32% (-23.87% to -5.82%)	-16.35% (-23.29% to -8.79%)	5.87% (-13.70% to 29.87%)	3.09% (-12.14% to 20.95%)
Other Schedule II	-7.26% (-17.03% to 3.65%)	-16.48% (-25.47% to -6.41%)	-17.53% (-24.40% to -10.04%)	32.60% (8.64% to 61.84%)	17.37% (-2.15% to 40.78%)
Suspected Suicide					
OxyContin	-26.51% (-37.52% to -13.58%)	1.98% (-10.40% to 16.08%)	0.91% (-9.43% to 12.42%)	18.01% (-20.01% to 74.10%)	11.91% (-19.94% to 56.43%)
ER Morphine	-1.66% (-14.88% to 13.61%)	-16.83% (-29.63% to -1.69%)	-17.47% (-29.20% to -3.79%)	10.16% (-13.15% to 39.72%)	1.52% (-20.52% to 29.67%)
IR Hydrocodone	-1.81% (-8.42% to 5.28%)	-7.66% (-12.87% to -2.14%)	-8.44% (-12.52% to -4.16%)	-0.97% (-12.82% to 12.48%)	-3.21% (-12.29% to 6.80%)
Other Schedule II	0.35% (-5.86% to 6.96%)	-9.63% (-15.06% to -3.86%)	-10.41% (-14.21% to -6.45%)	5.96% (-9.60% to 24.21%)	-4.48% (-16.13% to 8.78%)
Adverse Reactions					
OxyContin	-42.78% (-53.95% to -28.91%)	-20.59% (-34.61% to -3.58%)	-22.48% (-34.18% to -8.70%)	3.56% (-42.84% to 87.61%)	-5.07% (-43.17% to 58.57%)
ER Morphine	-44.90% (-57.53% to -28.52%)	-53.40% (-64.94% to -38.06%)	-54.20% (-64.20% to -41.41%)	-23.69% (-51.94% to 21.18%)	-37.00% (-60.27% to -0.12%)
IR Hydrocodone	-11.38% (-25.67% to 5.64%)	-16.66% (-30.33% to -0.31%)	-18.21% (-29.66% to -4.90%)	19.85% (-15.38% to 69.75%)	13.89% (-14.10% to 50.98%)
Other Schedule II	-11.67% (-24.35% to 3.13%)	-20.45% (-32.27% to -6.57%)	-21.99% (-31.00% to -11.79%)	26.38% (-14.97% to 87.84%)	0.49% (-29.30% to 42.83%)
Unintentional Therapeutic Errors					
OxyContin	-29.85% (-37.10% to -21.76%)	-2.64% (-13.70% to 9.84%)	-3.44% (-14.53% to 9.08%)	-33.05% (-50.71% to -9.08%)	-35.79% (-52.12% to -13.91%)
ER Morphine	0.97% (-10.59% to 14.01%)	-14.61% (-26.66% to -0.57%)	-15.12% (-25.00% to -3.94%)	11.10% (-9.72% to 36.71%)	4.74% (-13.03% to 26.15%)
IR Hydrocodone	-3.07% (-9.41% to 3.72%)	-8.84% (-15.00% to -2.22%)	-9.44% (-15.20% to -3.28%)	6.25% (-6.85% to 21.19%)	4.49% (-7.60% to 18.15%)
Other Schedule II	0.36% (-4.76% to 5.76%)	-9.62% (-14.60% to -4.35%)	-10.23% (-14.62% to -5.61%)	3.70% (-10.52% to 20.18%)	-3.79% (-17.07% to 11.61%)
Unintentional General Exposures					
OxyContin	-47.62% (-58.92% to -33.20%)	-27.30% (-42.88% to -7.48%)	-27.73% (-42.48% to -9.18%)	-44.00% (-73.44% to 18.06%)	-44.77% (-73.19% to 13.77%)
ER Morphine	-29.88% (-39.80% to -18.32%)	-40.69% (-48.77% to -31.34%)	-40.95% (-49.55% to -30.88%)	-38.13% (-53.52% to -17.65%)	-39.89% (-55.57% to -18.66%)
IR Hydrocodone	-17.78% (-24.35% to -10.64%)	-22.68% (-28.48% to -16.40%)	-23.04% (-28.81% to -16.80%)	-12.98% (-26.70% to 3.31%)	-13.59% (-27.15% to 2.49%)
Other Schedule II	-19.48% (-24.27% to -14.39%)	-27.49% (-31.94% to -22.75%)	-27.84% (-31.76% to -23.69%)	-7.21% (-18.88% to 6.14%)	-10.39% (-22.22% to 3.23%)

CI=confidence interval; ER=extended release; IR hydrocodone=immediate release hydrocodone combination products; Model 1: Rate of abuse/Census population. Model 2: Rate of abuse/Dosage units dispensed. Model 2a: Rate of abuse/Dosage units dispensed adjusting for pharmaceutical exposures. Model 3: Abuse count adjusting for dosage units dispensed (continuous). Model 3a: Abuse count adjusting for dosage units dispensed (continuous) and pharmaceutical exposures.

Table 8: Percent change (95% CI) in intentional abuse of OxyContin and primary comparators after the introduction of reformulated OxyContin using different modeling approaches (-1y/3y)

	Model 1 % Change (95% CI)	Model 2 % Change (95% CI)	Model 2a % Change (95% CI)	Model 3 % Change (95% CI)	Model 3a % Change (95% CI)
OxyContin	-46.20% (-56.88% to -32.87%)	-25.33% (-38.00% to -10.07%)	-26.98% (-36.31% to -16.29%)	-8.30% (-48.00% to 61.69%)	-13.94% (-45.44% to 35.75%)
ER oxymorphone tablets	191.99% (3.55% to 723.35%)	82.95% (-17.32% to 304.79%)	77.86% (-13.14% to 264.18%)	-63.09% (-82.95% to -20.11%)	-62.42% (-80.65% to -26.99%)
All IR oxycodone products	-9.61% (-23.71% to 7.11%)	-23.81% (-35.90% to -9.45%)	-25.30% (-35.41% to -13.62%)	34.56 (-13.46% to 109.21%)	1.94% (-35.43% to 60.93%)
IR oxycodone combination products	-6.32% (-17.76% to 6.72%)	-12.22% (-23.91% to 1.28%)	-13.69% (-24.11% to -1.84%)	21.73% (3.87% to 42.68%)	7.33% (-11.75% to 30.54%)
IR oxycodone SE	-29.12% (-49.45% to -0.60%)	-47.92% (-62.63% to -27.44%)	-49.15% (-62.65% to -30.77%)	-18.55% (-73.15% to 147.05%)	-37.25% (-78.29% to 81.35%)
General oxycodone	22.76% (6.16% to 41.97%)	NA	NA	NA	NA
All oxycodone excluding OxyContin	-1.99% (-15.11% to 13.17%)	-15.34% (-26.83% to -2.06%)	-16.96% (-26.80% to -5.79%)	29.97% (-8.77% to 85.15%)	1.39% (-30.13% to 47.13%)
Methadone	-41.35% (-56.94% to -20.11%)	-35.10% (-51.22% to -13.66%)	-36.47% (-51.08% to -17.49%)	-25.49% (-46.90% to 4.57%)	-29.95% (-49.36% to -3.10%)
Heroin	65.75% (34.06% to 104.94%)	NA	NA	NA	NA

CI=confidence interval; ER=extended release; IR=immediate release; SE=single entity; NA=Not applicable; Model 1: Rate of abuse/Census population. Model 2: Rate of abuse/Dosage units dispensed. Model 2a: Rate of abuse/Dosage units dispensed adjusting for pharmaceutical exposures. Model 3: Abuse count adjusting for dosage units dispensed (continuous). Model 3a: Abuse count adjusting for dosage units dispensed (continuous) and pharmaceutical exposures.

8.4 RESULTS OF ALL OTHER STATISTICAL MODELS THAT WERE IMPLEMENTED FOR MEANS ANALYSIS

These data were taken from the sponsor information request response from February 11, 2020

For reference:

^ = quarterly total intentional pharmaceutical exposure calls as an offset variable

* = (log) quarterly total intentional pharmaceutical exposure calls as a covariate (rather than quarterly total pharmaceutical exposures) to adjust for call volume

Table 9: Percent change in mean quarterly abuse call rates and ratio of rate ratios (RORR), by model (-2y/5y)

Opioid	Model	Percent Change (95% CI)	RORR (95% CI)
OxyContin	model 1	-55.23% (-63.14% to -45.63%)	Reference
	model 1^	-57.85% (-65.55% to -48.43%)	
	model 2	-35.12% (-44.46% to -24.21%)	
	model 2a*	-7.66% (-21.59% to 8.74%)	
	model 3	-14.82% (-40.72% to 22.40%)	
	model 3a*	-15.90% (-40.13% to 18.12%)	
ER morphine	model 1	-29.02% (-43.59% to -10.69%)	1.586 (1.174 to 2.142)
	model 1^	-33.17% (-47.12% to -15.54%)	1.586 (1.164 to 2.160)
	model 2	-44.71% (-57.28% to -28.43%)	0.852 (0.631 to 1.152)
	model 2a*	-20.42% (-37.46% to 1.26%)	0.862 (0.661 to 1.124)
	model 3	19.54% (-21.40% to 81.81%)	1.403 (0.806 to 2.443)
	model 3a*	20.29% (-22.07% to 85.66%)	1.430 (0.824 to 2.482)
IR hydrocodone	model 1	-27.45% (-38.77% to -14.03%)	1.621 (1.252 to 2.098)
	model 1^	-31.69% (-43.08% to -18.03%)	1.621 (1.235 to 2.127)
	model 2	-27.48% (-36.22% to -17.54%)	1.118 (0.914 to 1.368)
	model 2a*	2.97% (-8.78% to 16.23%)	1.115 (0.944 to 1.318)
	model 3	-38.63% (-46.43% to -29.70%)	0.720 (0.489 to 1.061)
	model 3a*	-9.00% (-23.00% to 7.53%)	1.082 (0.740 to 1.582)
Other Schedule II opioids	model 1	-19.49% (-30.93% to -6.15%)	1.799 (1.404 to 2.304)
	model 1^	-24.20% (-35.77% to -10.54%)	1.799 (1.385 to 2.335)
	model 2	-27.10% (-36.59% to -16.18%)	1.124 (0.912 to 1.385)
	model 2a*	4.05% (-8.53% to 18.35%)	1.127 (0.949 to 1.338)
	model 3	-14.69% (-46.78% to 36.74%)	1.002 (0.552 to 1.816)
	model 3a*	4.75% (-25.21% to 46.71%)	1.246 (0.772 to 2.011)

Key: extended-release (ER); immediate-release (IR); schedule II (CII); "Other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; RORR is relative to OxyContin (reference) where null equals 1; an RORR > 1 means abuse call rate change comparing periods favors OxyContin and an RORR < 1 means abuse call rate change comparing periods favors the comparator; comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (here, total intentional pharmaceutical exposure calls) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates

Table 10: Percent change in mean quarterly abuse call rates and ratio of rate ratios (RORR) for OxyContin and primary comparator opioids, by route of abuse and model (-2y/5y)

ROA	Opioid	Model	Percent Change (95% CI)	RORR (95% CI)	ROA	Opioid	Model	Percent Change (95% CI)	RORR (95% CI)
Oral	OxyContin	model 1	-52.14% (-60.92% to -41.39%)	Reference	Non-oral that combines inhalation, injection and other routes	OxyContin	model 1	-62.57% (-73.27% to -47.58%)	Reference
		model 1^	-54.94% (-63.50% to -44.38%)				model 1^	-64.76% (-74.98% to -50.35%)	
		model 2	-30.64% (-40.89% to -18.60%)				model 2	-45.75% (-60.37% to -25.73%)	
		model 2a*	-0.69% (-16.03% to 17.45%)				model 2a*	-14.89% (-39.94% to 20.61%)	
		model 3	3.61% (-27.50% to 48.08%)				model 3	-41.71% (-72.93% to 25.53%)	
		model 3a*	1.75% (-28.34% to 44.47%)				model 3a*	-41.52% (-70.41% to 15.58%)	
	ER morphine	model 1	-30.58% (-45.85% to -11.01%)	1.450 (1.053 to 1.999)		ER morphine	model 1	-30.80% (-55.38% to 7.32%)	1.849 (1.063 to 3.214)
		model 1^	-34.64% (-49.23% to -15.86%)	1.450 (1.044 to 2.015)			model 1^	-34.85% (-58.00% to 1.07%)	1.849 (1.059 to 3.226)
		model 2	-45.92% (-59.06% to -28.57%)	0.780 (0.566 to 1.075)			model 2	-46.10% (-65.39% to -16.05%)	0.994 (0.577 to 1.710)
		model 2a*	-21.69% (-39.70% to 1.69%)	0.789 (0.592 to 1.050)			model 2a*	-14.22% (-46.80% to 38.30%)	1.008 (0.596 to 1.705)
		model 3	25.99% (-19.40% to 96.94%)	1.216 (0.686 to 2.154)			model 3	-15.46% (-68.35% to 125.78%)	1.450 (0.417 to 5.043)
		model 3a*	26.83% (-20.60% to 102.58%)	1.247 (0.694 to 2.238)			model 3a*	-13.87% (-67.71% to 129.74%)	1.473 (0.446 to 4.862)
	IR hydrocodone	model 1	-30.40% (-41.22% to -17.58%)	1.454 (1.117 to 1.894)		IR hydrocodone	model 1	16.51% (-17.45% to 64.44%)	3.112 (1.922 to 5.039)
		model 1^	-34.47% (-45.34% to -21.43%)	1.454 (1.101 to 1.920)			model 1^	9.70% (-23.16% to 56.60%)	3.112 (1.899 to 5.101)
		model 2	-30.43% (-38.79% to -20.91%)	1.003 (0.817 to 1.231)			model 2	16.46% (-15.47% to 60.45%)	2.147 (1.371 to 3.362)
		model 2a*	-0.63% (-12.05% to 12.27%)	1.001 (0.843 to 1.187)			model 2a*	82.16% (29.29% to 156.65%)	2.140 (1.420 to 3.226)
		model 3	-41.39% (-48.81% to -32.90%)	0.566 (0.386 to 0.829)			model 3	5.85% (-28.38% to 56.44%)	1.816 (0.768 to 4.295)
		model 3a*	-14.04% (-27.28% to 1.61%)	0.845 (0.572 to 1.248)			model 3a*	111.15% (32.65% to 236.13%)	3.610 (1.584 to 8.229)
	Other schedule II opioids	model 1	-25.42% (-35.84% to -13.31%)	1.558 (1.211 to 2.006)		Other schedule II opioids	model 1	33.07% (-1.18% to 79.19%)	3.555 (2.268 to 5.572)
		model 1^	-29.78% (-40.33% to -17.36%)	1.558 (1.194 to 2.034)			model 1^	25.29% (-7.85% to 70.34%)	3.555 (2.244 to 5.633)
		model 2	-32.47% (-41.13% to -22.53%)	0.974 (0.789 to 1.202)			model 2	20.49% (-9.04% to 59.61%)	2.221 (1.457 to 3.386)
		model 2a*	-3.04% (-14.59% to 10.07%)	0.976 (0.821 to 1.162)			model 2a*	89.70% (40.06% to 156.94%)	2.229 (1.529 to 3.248)
		model 3	-19.80% (-49.69% to 27.85%)	0.774 (0.430 to 1.393)			model 3	29.70% (-46.65% to 215.31%)	2.225 (0.688 to 7.195)
		model 3a*	-2.11% (-29.65% to 36.20%)	0.962 (0.594 to 1.558)			model 3a*	83.46% (-11.50% to 280.32%)	3.137 (1.157 to 8.505)
Inhalation	OxyContin	model 1	-66.37% (-77.23% to -50.32%)	Reference	Injection	OxyContin	model 1	-58.85% (-72.74% to -37.89%)	Reference
		model 1^	-68.34% (-78.65% to -53.04%)				model 1^	-61.25% (-74.51% to -41.11%)	
		model 2	-51.26% (-66.50% to -29.08%)				model 2	-40.36% (-59.40% to -12.39%)	
		model 2a*	-18.21% (-47.02% to 26.26%)				model 2a*	-13.76% (-44.63% to 34.32%)	
		model 3	-41.24% (-76.53% to 47.13%)				model 3	-38.32% (-75.92% to 58.00%)	
		model 3a*	-40.40% (-74.71% to 40.48%)				model 3a*	-38.68% (-74.16% to 45.51%)	
	ER morphine	model 1	-38.22% (-70.17% to 27.97%)	1.837 (0.804 to 4.197)		ER morphine	model 1	-27.62% (-56.86% to 21.42%)	1.759 (0.908 to 3.407)
		model 1^	-41.83% (-71.88% to 20.33%)	1.837 (0.804 to 4.200)			model 1^	-31.86% (-59.43% to 14.47%)	1.759 (0.903 to 3.425)
		model 2	-51.87% (-76.90% to 0.29%)	0.987 (0.433 to 2.252)			model 2	-43.62% (-66.44% to -5.29%)	0.945 (0.496 to 1.803)
		model 2a*	-17.92% (-62.27% to 78.60%)	1.004 (0.439 to 2.295)			model 2a*	-17.52% (-53.69% to 46.90%)	0.956 (0.512 to 1.786)
		model 3	-10.74% (-82.85% to 364.69%)	1.519 (0.230 to 10.035)			model 3	-17.12% (-74.05% to 164.66%)	1.344 (0.302 to 5.988)
		model 3a*	-7.94% (-82.72% to 390.40%)	1.544 (0.236 to 10.118)			model 3a*	-16.20% (-73.32% to 163.21%)	1.367 (0.326 to 5.734)
	IR hydrocodone	model 1	23.32% (-18.04% to 85.53%)	3.667 (2.084 to 6.450)		IR hydrocodone	model 1	-7.32% (-52.16% to 79.52%)	2.252 (1.034 to 4.907)
		model 1^	16.11% (-23.69% to 76.65%)	3.667 (2.062 to 6.521)			model 1^	-12.74% (-55.11% to 69.62%)	2.252 (1.027 to 4.940)
		model 2	23.27% (-16.37% to 81.69%)	2.529 (1.474 to 4.338)			model 2	-7.36% (-51.40% to 76.59%)	1.553 (0.733 to 3.292)
		model 2a*	106.12% (35.50% to 213.57%)	2.520 (1.514 to 4.195)			model 2a*	33.62% (-33.59% to 168.84%)	1.549 (0.738 to 3.255)
		model 3	14.93% (-28.36% to 84.38%)	1.956 (0.697 to 5.492)			model 3	-25.70% (-67.41% to 69.40%)	1.205 (0.345 to 4.207)
		model 3a*	148.16% (42.54% to 332.03%)	4.163 (1.504 to 11.526)			model 3a*	28.79% (-50.14% to 232.63%)	2.100 (0.582 to 7.585)
	Other schedule II opioids	model 1	33.02% (-6.76% to 89.76%)	3.955 (2.333 to 6.704)		Other schedule II opioids	model 1	34.10% (-2.74% to 84.89%)	3.259 (1.933 to 5.493)
		model 1^	25.24% (-13.35% to 81.01%)	3.955 (2.306 to 6.783)			model 1^	26.26% (-8.78% to 74.76%)	3.259 (1.918 to 5.536)
		model 2	20.45% (-14.42% to 69.51%)	2.471 (1.488 to 4.104)			model 2	21.42% (-10.49% to 64.72%)	2.036 (1.246 to 3.326)
		model 2a*	102.91% (41.92% to 190.13%)	2.481 (1.569 to 3.923)			model 2a*	76.08% (18.69% to 161.23%)	2.042 (1.283 to 3.249)
		model 3	86.43% (-34.65% to 431.89%)	3.173 (0.788 to 12.781)			model 3	-17.95% (-68.66% to 114.82%)	1.330 (0.346 to 5.110)
		model 3a*	162.22% (15.87% to 493.41%)	4.399 (1.348 to 14.363)			model 3a*	13.68% (-54.33% to 182.98%)	1.854 (0.528 to 6.514)

Key: extended-release (ER); immediate-release (IR); schedule II (CII); "Other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; RORR is relative to OxyContin (reference) where null equals 1; an RORR > 1 means abuse call rate change comparing periods favors OxyContin and an RORR < 1 means abuse call rate change comparing periods favors the comparator; comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (here, total intentional pharmaceutical exposure calls) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates

Table 11: Percent change in mean quarterly abuse call rates and ratio of rate ratios (RORR) for ER oxycodone (with imputed formulation) and primary comparator opioids, by model (-2y/5y)

Opioid	Model	Percent Change (95% CI)	RORR (95% CI)
OxyContin + generic ER Oxycodone + unspecified oxycodone (based on proportion dispensed that was ER)	model 1	-52.79% (-60.54% to -43.53%)	Reference
	model 1^	-55.55% (-63.11% to -46.45%)	
	model 2	-31.58% (-40.71% to -21.05%)	
	model 2a*	-7.60% (-20.83% to 7.83%)	
	model 3	-16.85% (-40.84% to 16.86%)	
	model 3a*	-17.93% (-40.51% to 13.24%)	
ER morphine + unspecified morphine (based on proportion dispensed that was ER)	model 1	-10.05% (-23.85% to 6.26%)	1.905 (1.492 to 2.434)
	model 1^	-15.31% (-28.79% to 0.74%)	1.905 (1.477 to 2.458)
	model 2	-29.93% (-42.28% to -14.94%)	1.024 (0.805 to 1.303)
	model 2a*	-4.47% (-20.62% to 14.98%)	1.034 (0.834 to 1.282)
	model 3	23.91% (-9.32% to 69.31%)	1.490 (0.939 to 2.365)
	model 3a*	23.53% (-10.70% to 70.88%)	1.505 (0.953 to 2.377)
IR hydrocodone	model 1	-27.45% (-38.77% to -14.03%)	1.537 (1.201 to 1.967)
	model 1^	-31.69% (-43.08% to -18.03%)	1.537 (1.184 to 1.995)
	model 2	-27.48% (-36.22% to -17.54%)	1.060 (0.874 to 1.285)
	model 2a*	-2.26% (-13.12% to 9.95%)	1.058 (0.900 to 1.243)
	model 3	-38.63% (-46.43% to -29.70%)	0.738 (0.512 to 1.065)
	model 3a*	-14.90% (-27.40% to -0.25%)	1.037 (0.723 to 1.487)
Other schedule II opioids	model 1	-13.08% (-23.77% to -0.89%)	1.841 (1.475 to 2.299)
	model 1^	-18.16% (-29.08% to -5.55%)	1.841 (1.456 to 2.329)
	model 2	-21.29% (-30.03% to -11.46%)	1.150 (0.956 to 1.385)
	model 2a*	6.54% (-5.33% to 19.91%)	1.153 (0.981 to 1.355)
	model 3	-8.41% (-38.19% to 35.72%)	1.102 (0.655 to 1.853)
	model 3a*	8.83% (-19.49% to 47.11%)	1.326 (0.853 to 2.062)

Key: extended-release (ER); immediate-release (IR); schedule II (CII); "Other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; RORR is relative to OxyContin (reference) where null equals 1; an RORR > 1 means abuse call rate change comparing periods favors OxyContin and an RORR < 1 means abuse call rate change comparing periods favors the comparator; comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (here, total intentional pharmaceutical exposure calls) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates

Table 12: Percent change in mean quarterly abuse call rates and ratio of rate ratios (RORR) for OxyContin and primary comparator opioids, by route of abuse (all exposures including multi-substance and multi-route exposures) and model (-2y/5y)

ROA	Opioid	Model	Percent Change (95% CI)	RORR (95% CI)	ROA	Opioid	Model	Percent Change (95% CI)	RORR (95% CI)
Oral	OxyContin	model 1	-53.88% (-62.04% to -43.96%)	Reference	Non-oral that combines inhalation, injection and other routes	OxyContin	model 1	-62.27% (-71.09% to -50.77%)	Reference
		model 1^	-56.57% (-64.52% to -46.85%)				model 1^	-64.48% (-72.93% to -53.39%)	
		model 2	-33.15% (-42.76% to -21.93%)				model 2	-45.32% (-57.16% to -30.22%)	
		model 2a*	-5.09% (-19.56% to 11.97%)				model 2a*	-20.50% (-38.73% to 3.15%)	
		model 3	-8.58% (-36.07% to 30.73%)				model 3	-44.99% (-69.71% to -0.07%)	
		model 3a*	-9.94% (-36.28% to 27.28%)				model 3a*	-44.86% (-67.70% to -5.88%)	
	ER morphine	model 1	-28.35% (-44.18% to -8.03%)	1.553 (1.132 to 2.132)		ER morphine	model 1	-25.00% (-47.52% to 7.20%)	1.988 (1.274 to 3.103)
		model 1^	-32.54% (-47.67% to -13.04%)	1.553 (1.123 to 2.149)			model 1^	-29.38% (-50.68% to 1.10%)	1.988 (1.268 to 3.118)
		model 2	-44.19% (-57.73% to -26.31%)	0.835 (0.607 to 1.148)			model 2	-41.57% (-59.23% to -16.27%)	1.069 (0.692 to 1.650)
		model 2a*	-19.88% (-38.31% to 4.06%)	0.844 (0.634 to 1.124)			model 2a*	-14.04% (-40.64% to 24.48%)	1.081 (0.713 to 1.640)
		model 3	25.02% (-21.07% to 98.04%)	1.368 (0.764 to 2.449)			model 3	-20.16% (-63.95% to 76.84%)	1.451 (0.537 to 3.923)
		model 3a*	25.72% (-22.03% to 102.70%)	1.396 (0.774 to 2.518)			model 3a*	-19.52% (-63.08% to 75.42%)	1.460 (0.567 to 3.755)
	IR hydrocodone	model 1	-28.26% (-39.44% to -15.02%)	1.555 (1.202 to 2.013)		IR hydrocodone	model 1	8.55% (-13.90% to 36.87%)	2.877 (2.022 to 4.095)
		model 1^	-32.45% (-43.69% to -18.98%)	1.555 (1.185 to 2.041)			model 1^	2.21% (-19.99% to 30.56%)	2.877 (1.996 to 4.148)
		model 2	-28.29% (-36.92% to -18.48%)	1.073 (0.877 to 1.312)			model 2	8.51% (-10.82% to 32.04%)	1.985 (1.451 to 2.714)
		model 2a*	1.56% (-10.00% to 14.61%)	1.070 (0.904 to 1.267)			model 2a*	57.37% (28.68% to 92.45%)	1.979 (1.496 to 2.618)
		model 3	-39.44% (-47.10% to -30.66%)	0.662 (0.452 to 0.971)			model 3	-5.99% (-25.28% to 18.27%)	1.709 (0.901 to 3.239)
		model 3a*	-10.77% (-24.37% to 5.27%)	0.991 (0.674 to 1.456)			model 3a*	58.33% (19.83% to 109.21%)	2.872 (1.572 to 5.246)
	Other schedule II opioids	model 1	-22.14% (-32.85% to -9.73%)	1.688 (1.322 to 2.156)		Other schedule II opioids	model 1	28.49% (3.95% to 58.83%)	3.406 (2.424 to 4.786)
		model 1^	-26.70% (-37.58% to -13.91%)	1.688 (1.304 to 2.185)			model 1^	20.98% (-3.37% to 51.47%)	3.406 (2.394 to 4.845)
		model 2	-29.50% (-38.38% to -19.34%)	1.055 (0.859 to 1.295)			model 2	16.35% (-4.41% to 41.61%)	2.128 (1.556 to 2.911)
		model 2a*	0.36% (-11.33% to 13.60%)	1.057 (0.891 to 1.254)			model 2a*	69.66% (39.20% to 106.79%)	2.134 (1.618 to 2.814)
		model 3	-16.55% (-47.08% to 31.60%)	0.913 (0.512 to 1.629)			model 3	30.99% (-29.67% to 143.97%)	2.381 (1.006 to 5.638)
		model 3a*	2.09% (-25.80% to 40.45%)	1.134 (0.708 to 1.816)			model 3a*	71.11% (5.48% to 177.57%)	3.103 (1.509 to 6.382)
Inhalation	OxyContin	model 1	-65.78% (-73.29% to -56.16%)	Reference	Injection	OxyContin	model 1	-58.89% (-70.56% to -42.58%)	Reference
		model 1^	-67.78% (-74.93% to -58.59%)				model 1^	-61.29% (-72.48% to -45.55%)	
		model 2	-50.41% (-60.67% to -37.46%)				model 2	-40.41% (-56.17% to -18.98%)	
		model 2a*	-18.58% (-37.95% to 6.83%)				model 2a*	-32.91% (-52.85% to -4.54%)	
		model 3	-52.43% (-72.96% to -16.31%)				model 3	-34.98% (-69.22% to 37.35%)	
		model 3a*	-51.71% (-71.02% to -19.53%)				model 3a*	-35.15% (-68.56% to 33.76%)	
	ER morphine	model 1	-18.91% (-50.34% to 32.42%)	2.370 (1.368 to 4.105)		ER morphine	model 1	-27.18% (-55.01% to 17.85%)	1.771 (0.986 to 3.182)
		model 1^	-23.65% (-53.30% to 24.84%)	2.370 (1.364 to 4.116)			model 1^	-31.44% (-57.75% to 11.24%)	1.771 (0.980 to 3.202)
		model 2	-36.83% (-61.78% to 4.40%)	1.274 (0.732 to 2.215)			model 2	-43.28% (-65.05% to -7.95%)	0.952 (0.536 to 1.689)
		model 2a*	5.33% (-37.08% to 76.34%)	1.294 (0.747 to 2.241)			model 2a*	-35.89% (-61.71% to 7.33%)	0.956 (0.545 to 1.676)
		model 3	10.66% (-61.25% to 216.06%)	2.326 (0.706 to 7.661)			model 3	-22.34% (-73.65% to 128.91%)	1.194 (0.321 to 4.446)
		model 3a*	11.34% (-61.88% to 225.19%)	2.306 (0.703 to 7.559)			model 3a*	-22.18% (-73.27% to 126.55%)	1.200 (0.330 to 4.363)
	IR hydrocodone	model 1	8.56% (-18.88% to 45.30%)	3.173 (2.164 to 4.651)		IR hydrocodone	model 1	2.49% (-22.95% to 36.33%)	2.493 (1.607 to 3.868)
		model 1^	2.22% (-24.70% to 38.75%)	3.173 (2.136 to 4.712)			model 1^	-3.50% (-27.44% to 28.32%)	2.493 (1.598 to 3.888)
		model 2	8.52% (-15.81% to 39.88%)	2.188 (1.552 to 3.086)			model 2	2.45% (-22.86% to 36.06%)	1.719 (1.132 to 2.612)
		model 2a*	77.56% (41.11% to 123.44%)	2.181 (1.614 to 2.947)			model 2a*	15.25% (-18.85% to 63.67%)	1.718 (1.129 to 2.613)
		model 3	-11.66% (-34.42% to 19.01%)	1.857 (0.981 to 3.517)			model 3	0.87% (-28.90% to 43.11%)	1.551 (0.680 to 3.542)
		model 3a*	72.36% (25.97% to 135.82%)	3.569 (1.964 to 6.488)			model 3a*	21.18% (-23.89% to 92.93%)	1.869 (0.789 to 4.423)
	Other schedule II opioids	model 1	27.33% (-0.54% to 63.01%)	3.721 (2.622 to 5.280)		Other schedule II opioids	model 1	31.92% (3.91% to 67.47%)	3.209 (2.128 to 4.837)
		model 1^	19.88% (-7.79% to 55.86%)	3.721 (2.588 to 5.350)			model 1^	24.20% (-2.55% to 58.31%)	3.209 (2.111 to 4.877)
		model 2	15.29% (-8.72% to 45.62%)	2.325 (1.673 to 3.231)			model 2	19.45% (-4.65% to 49.64%)	2.005 (1.369 to 2.934)
		model 2a*	90.00% (54.25% to 134.04%)	2.334 (1.756 to 3.101)			model 2a*	34.62% (0.20% to 80.86%)	2.007 (1.382 to 2.913)
		model 3	78.19% (-12.30% to 262.02%)	3.746 (1.513 to 9.272)			model 3	-30.50% (-65.36% to 39.43%)	1.069 (0.385 to 2.970)
		model 3a*	142.13% (50.33% to 289.99%)	5.014 (2.495 to 10.078)			model 3a*	-21.91% (-61.39% to 57.94%)	1.204 (0.438 to 3.309)

Key: extended-release (ER); immediate-release (IR); schedule II (CII); "Other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; RORR is relative to OxyContin (reference) where null equals 1; an RORR > 1 means abuse call rate change comparing periods favors OxyContin and an RORR < 1 means abuse call rate change comparing periods favors the comparator; comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (here, total intentional pharmaceutical exposure calls) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates

Table 13: Percent change in mean quarterly abuse call rates and ratio of rate ratios (RORR) for ER oxycodone (including oxycodone not otherwise specified [NOS]) and primary comparator opioids, by model (-2y/5y)

Opioid	Model	Percent Change (95% CI)	RORR (95% CI)
Any ER Oxycodone + NOS	model 1	-25.58% (-33.40% to -16.83%)	Reference
	model 1^	-29.93% (-37.45% to -21.50%)	
	model 2	28.35% (17.70% to 39.97%)	
	model 2a*	68.93% (44.76% to 97.14%)	
	model 3	29.69% (-6.98% to 80.81%)	
	model 3a*	4.79% (-31.80% to 61.01%)	
ER morphine	model 1	-29.02% (-43.59% to -10.69%)	0.954 (0.739 to 1.231)
	model 1^	-33.17% (-47.12% to -15.54%)	0.954 (0.735 to 1.237)
	model 2	-44.71% (-57.28% to -28.43%)	0.431 (0.328 to 0.566)
	model 2a*	-26.33% (-42.29% to -5.95%)	0.436 (0.335 to 0.568)
	model 3	19.54% (-21.40% to 81.81%)	0.922 (0.540 to 1.574)
	model 3a*	20.01% (-21.69% to 83.91%)	1.145 (0.625 to 2.099)
IR hydrocodone	model 1	-27.45% (-38.77% to -14.03%)	0.975 (0.796 to 1.194)
	model 1^	-31.69% (-43.08% to -18.03%)	0.975 (0.786 to 1.209)
	model 2	-27.48% (-36.22% to -17.54%)	0.565 (0.484 to 0.660)
	model 2a*	-4.40% (-15.41% to 8.03%)	0.566 (0.482 to 0.664)
	model 3	-38.63% (-46.43% to -29.70%)	0.473 (0.330 to 0.678)
	model 3a*	-17.71% (-30.24% to -2.93%)	0.785 (0.485 to 1.272)
Other schedule II opioids	model 1	-19.49% (-30.93% to -6.15%)	1.082 (0.895 to 1.307)
	model 1^	-24.20% (-35.77% to -10.54%)	1.082 (0.885 to 1.322)
	model 2	-27.10% (-36.59% to -16.18%)	0.568 (0.482 to 0.669)
	model 2a*	-3.51% (-15.29% to 9.91%)	0.571 (0.484 to 0.674)
	model 3	-14.69% (-46.78% to 36.74%)	0.658 (0.369 to 1.171)
	model 3a*	-0.38% (-30.22% to 42.22%)	0.951 (0.539 to 1.676)

Key: extended-release (ER); immediate-release (IR); schedule II (CII); "Other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; RORR is relative to OxyContin (reference) where null equals 1; an RORR > 1 means abuse call rate change comparing periods favors OxyContin and an RORR < 1 means abuse call rate change comparing periods favors the comparator; comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (here, total intentional pharmaceutical exposure calls) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates

Table 14: Percent change in mean quarterly abuse call rates and ratio of rate ratios (RORR) for ER oxycodone and primary comparator opioids, by route of abuse and model (-2y/5y)

ROA	Opioid	Model	Percent Change (95% CI)	RORR (95% CI)
Oral	Any ER oxycodone	model 1	-53.69% (-62.17% to -43.30%)	Reference
		model 1^	-56.39% (-64.66% to -46.20%)	
		model 2	-20.13% (-31.50% to -6.87%)	
		model 2a*	14.28% (-2.30% to 33.67%)	
		model 3	140.92% (51.11% to 284.10%)	
		model 3a*	91.79% (15.39% to 218.79%)	
	ER morphine	model 1	-30.58% (-45.85% to -11.01%)	1.499 (1.088 to 2.065)
		model 1^	-34.64% (-49.23% to -15.86%)	1.499 (1.079 to 2.082)
		model 2	-45.92% (-59.06% to -28.57%)	0.677 (0.493 to 0.930)
		model 2a*	-21.38% (-39.44% to 2.05%)	0.688 (0.520 to 0.911)
		model 3	25.99% (-19.40% to 96.94%)	0.523 (0.274 to 0.998)
		model 3a*	26.73% (-20.43% to 101.85%)	0.661 (0.332 to 1.317)
	IR hydrocodone	model 1	-30.40% (-41.22% to -17.58%)	1.503 (1.155 to 1.956)
		model 1^	-34.47% (-45.34% to -21.43%)	1.503 (1.139 to 1.984)
		model 2	-30.43% (-38.79% to -20.91%)	0.871 (0.713 to 1.064)
		model 2a*	-0.26% (-11.66% to 12.62%)	0.873 (0.743 to 1.025)
		model 3	-41.39% (-48.81% to -32.90%)	0.243 (0.150 to 0.395)
		model 3a*	-16.57% (-29.31% to -1.53%)	0.435 (0.251 to 0.755)
	Other schedule II opioids	model 1	-25.42% (-35.84% to -13.31%)	1.610 (1.251 to 2.072)
		model 1^	-29.78% (-40.33% to -17.36%)	1.610 (1.234 to 2.101)
		model 2	-32.47% (-41.13% to -22.53%)	0.845 (0.688 to 1.039)
		model 2a*	-2.67% (-14.20% to 10.42%)	0.852 (0.723 to 1.003)
		model 3	-19.80% (-49.69% to 27.85%)	0.333 (0.172 to 0.644)
		model 3a*	-3.55% (-31.01% to 34.85%)	0.503 (0.272 to 0.931)
Inhalation	Any ER oxycodone	model 1	-65.90% (-76.40% to -50.70%)	Reference
		model 1^	-67.89% (-77.86% to -53.43%)	
		model 2	-41.18% (-58.07% to -17.50%)	
		model 2a*	-2.64% (-34.66% to 45.07%)	
		model 3	201.22% (-20.26% to 1037.82%)	
		model 3a*	108.86% (-48.84% to 752.64%)	
	ER morphine	model 1	-38.22% (-70.17% to 27.97%)	1.812 (0.801 to 4.097)
		model 1^	-41.83% (-71.88% to 20.33%)	1.812 (0.801 to 4.099)
		model 2	-51.87% (-76.90% to 0.29%)	0.818 (0.365 to 1.837)
		model 2a*	-18.52% (-62.50% to 77.00%)	0.837 (0.372 to 1.882)
		model 3	-10.74% (-82.85% to 364.69%)	0.296 (0.036 to 2.465)
		model 3a*	-8.54% (-82.69% to 383.15%)	0.438 (0.049 to 3.877)
	IR hydrocodone	model 1	23.32% (-18.04% to 85.53%)	3.616 (2.086 to 6.267)
		model 1^	16.11% (-23.69% to 76.65%)	3.616 (2.064 to 6.335)
		model 2	23.27% (-16.37% to 81.69%)	2.096 (1.252 to 3.507)
		model 2a*	104.65% (34.82% to 210.66%)	2.102 (1.297 to 3.407)
		model 3	14.93% (-28.36% to 84.38%)	0.382 (0.093 to 1.564)
		model 3a*	119.82% (26.47% to 282.06%)	1.052 (0.223 to 4.978)
	Other schedule II opioids	model 1	33.02% (-6.76% to 89.76%)	3.900 (2.338 to 6.507)
		model 1^	25.24% (-13.35% to 81.01%)	3.900 (2.311 to 6.583)
		model 2	20.45% (-14.42% to 69.51%)	2.048 (1.266 to 3.312)
		model 2a*	101.44% (41.22% to 187.35%)	2.069 (1.348 to 3.177)
		model 3	86.43% (-34.65% to 431.89%)	0.619 (0.114 to 3.364)
		model 3a*	149.82% (9.02% to 472.45%)	1.196 (0.230 to 6.222)

ROA	Opioid	Model	Percent Change (95% CI)	RORR (95% CI)
Non-oral that combines inhalation, injection and other routes	Any ER oxycodone	model 1	-61.87% (-72.46% to -47.20%)	Reference
		model 1^	-64.09% (-74.21% to -50.00%)	
		model 2	-34.23% (-50.47% to -12.67%)	
		model 2a*	2.97% (-25.01% to 41.39%)	
		model 3	209.46% (12.53% to 751.04%)	
		model 3a*	123.00% (-22.95% to 545.41%)	
	ER morphine	model 1	-30.80% (-55.38% to 7.32%)	1.815 (1.051 to 3.133)
		model 1^	-34.85% (-58.00% to 1.07%)	1.815 (1.047 to 3.145)
		model 2	-46.10% (-65.39% to -16.05%)	0.820 (0.484 to 1.387)
		model 2a*	-13.90% (-46.51% to 38.59%)	0.836 (0.503 to 1.389)
		model 3	-15.46% (-68.35% to 125.78%)	0.273 (0.067 to 1.119)
		model 3a*	-14.32% (-67.75% to 127.64%)	0.384 (0.091 to 1.630)
	IR hydrocodone	model 1	16.51% (-17.45% to 64.44%)	3.055 (1.902 to 4.907)
		model 1^	9.70% (-23.16% to 56.60%)	3.055 (1.879 to 4.968)
		model 2	16.46% (-15.47% to 60.45%)	1.771 (1.154 to 2.716)
		model 2a*	82.81% (30.05% to 156.99%)	1.775 (1.206 to 2.614)
		model 3	5.85% (-28.38% to 56.44%)	0.342 (0.116 to 1.012)
		model 3a*	84.44% (16.32% to 192.43%)	0.827 (0.249 to 2.742)
	Other schedule II opioids	model 1	33.07% (-1.18% to 79.19%)	3.489 (2.245 to 5.423)
		model 1^	25.29% (-7.85% to 70.34%)	3.489 (2.221 to 5.481)
		model 2	20.49% (-9.04% to 59.61%)	1.832 (1.229 to 2.731)
		model 2a*	90.39% (40.94% to 157.20%)	1.849 (1.302 to 2.627)
		model 3	29.70% (-46.65% to 215.31%)	0.419 (0.109 to 1.611)
		model 3a*	72.44% (-17.34% to 259.72%)	0.773 (0.209 to 2.864)
Injection	Any ER oxycodone	model 1	-57.87% (-71.83% to -37.01%)	Reference
		model 1^	-60.34% (-73.66% to -40.28%)	
		model 2	-27.35% (-49.30% to 4.10%)	
		model 2a*	6.38% (-29.78% to 61.17%)	
		model 3	255.95% (-3.89% to 1218.32%)	
		model 3a*	175.96% (-27.09% to 944.50%)	
	ER morphine	model 1	-27.62% (-56.86% to 21.42%)	1.718 (0.892 to 3.309)
		model 1^	-31.86% (-59.43% to 14.47%)	1.718 (0.887 to 3.326)
		model 2	-43.62% (-66.44% to -5.29%)	0.776 (0.413 to 1.459)
		model 2a*	-16.03% (-52.76% to 49.25%)	0.789 (0.429 to 1.451)
		model 3	-17.12% (-74.05% to 164.66%)	0.233 (0.040 to 1.340)
		model 3a*	-16.55% (-73.47% to 162.51%)	0.302 (0.052 to 1.754)
	IR hydrocodone	model 1	-7.32% (-52.16% to 79.52%)	2.200 (1.015 to 4.770)
		model 1^	-12.74% (-55.11% to 69.62%)	2.200 (1.008 to 4.802)
		model 2	-7.36% (-51.40% to 76.59%)	1.275 (0.609 to 2.669)
		model 2a*	35.94% (-32.37% to 173.25%)	1.278 (0.616 to 2.650)
		model 3	-25.70% (-67.41% to 69.40%)	0.209 (0.044 to 0.981)
		model 3a*	11.71% (-55.98% to 183.50%)	0.405 (0.076 to 2.165)
	Other schedule II opioids	model 1	34.10% (-2.74% to 84.89%)	3.183 (1.902 to 5.327)
		model 1^	26.26% (-8.78% to 74.76%)	3.183 (1.888 to 5.369)
		model 2	21.42% (-10.49% to 64.72%)	1.671 (1.043 to 2.678)
		model 2a*	79.19% (21.12% to 165.12%)	1.684 (1.081 to 2.624)
		model 3	-17.95% (-68.66% to 114.82%)	0.231 (0.045 to 1.171)
		model 3a*	5.08% (-57.91% to 162.36%)	0.381 (0.073 to 1.973)

Key: extended-release (ER); immediate-release (IR); schedule II (CII); "Other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; RORR is relative to OxyContin (reference) where null equals 1; an RORR > 1 means abuse call rate change comparing periods favors OxyContin and an RORR < 1 means abuse call rate change comparing periods favors the comparator; comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (here, total intentional pharmaceutical exposure calls) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates

8.5 RESULTS OF ALL OTHER STATISTICAL MODELS THAT WERE IMPLEMENTED FOR INTERRUPTED TIME SERIES ANALYSIS

For reference:

^ = quarterly total intentional pharmaceutical exposure calls as an offset variable

* = (log) quarterly total intentional pharmaceutical exposure calls as a covariate (rather than quarterly total pharmaceutical exposures) to adjust for call volume

Table 15: Percent change in quarterly abuse call rate slopes and comparative interrupted time series (CITS) slope measure, by model (-2y/5y)

Opioid	Model	Slope in pre (3Q2008 To 2Q2010)	Slope in post (1Q2011 To 4Q2015)	Change in slope (95%)	CITS slope measure (95% CI)
OxyContin	model 5 (corresponds to model 1 for % change and RORR)	0.990 (0.958 to 1.022)	0.951 (0.939 to 0.962)	-3.94% (-7.21% to -0.55%)	Reference
	model 5^ (model 1^)	0.989 (0.958 to 1.020)	0.948 (0.937 to 0.959)	-4.11% (-7.24% to -0.87%)	
	model 6 (model 2)	0.997 (0.963 to 1.032)	0.965 (0.953 to 0.978)	-3.14% (-6.64% to 0.49%)	
	model 6a* (model 2a*)	0.994 (0.962 to 1.028)	0.961 (0.948 to 0.974)	-3.32% (-6.70% to 0.18%)	
	model 7 (model 3)	0.993 (0.960 to 1.026)	0.955 (0.940 to 0.971)	-3.78% (-7.14% to -0.30%)	
	model 7a* (model 3a*)	0.991 (0.959 to 1.024)	0.953 (0.937 to 0.968)	-3.86% (-7.16% to -0.44%)	
ER morphine	model 5 (model 1)	1.005 (0.943 to 1.072)	0.965 (0.947 to 0.983)	-4.01% (-10.23% to 2.65%)	0.999 (0.927 to 1.078)
	model 5^ (model 1^)	1.004 (0.943 to 1.069)	0.962 (0.945 to 0.979)	-4.20% (-10.25% to 2.25%)	0.999 (0.928 to 1.075)
	model 6 (model 2)	0.983 (0.922 to 1.048)	0.955 (0.938 to 0.973)	-2.80% (-9.05% to 3.88%)	1.003 (0.930 to 1.083)
	model 6a* (model 2a*)	0.981 (0.921 to 1.044)	0.951 (0.933 to 0.970)	-3.00% (-9.15% to 3.56%)	1.003 (0.931 to 1.081)
	model 7 (model 3)	0.975 (0.871 to 1.092)	0.951 (0.899 to 1.006)	-2.49% (-9.84% to 5.46%)	1.013 (0.930 to 1.104)
	model 7a* (model 3a*)	0.972 (0.869 to 1.086)	0.947 (0.895 to 1.001)	-2.58% (-9.82% to 5.26%)	1.013 (0.931 to 1.103)
IR hydrocodone	model 5 (model 1)	0.990 (0.968 to 1.012)	0.958 (0.952 to 0.965)	-3.17% (-5.41% to -0.88%)	1.008 (0.967 to 1.051)
	model 5^ (model 1^)	0.989 (0.965 to 1.013)	0.956 (0.949 to 0.962)	-3.35% (-5.80% to -0.85%)	1.008 (0.967 to 1.051)
	model 6 (model 2)	0.994 (0.974 to 1.015)	0.969 (0.963 to 0.975)	-2.53% (-4.60% to -0.42%)	1.006 (0.964 to 1.050)
	model 6a* (model 2a*)	0.992 (0.971 to 1.014)	0.965 (0.957 to 0.973)	-2.73% (-4.86% to -0.54%)	1.006 (0.965 to 1.049)
	model 7 (model 3)	0.994 (0.974 to 1.016)	0.970 (0.962 to 0.978)	-2.49% (-4.63% to -0.29%)	1.013 (0.972 to 1.057)
	model 7a* (model 3a*)	0.993 (0.971 to 1.014)	0.966 (0.957 to 0.976)	-2.65% (-4.86% to -0.39%)	1.013 (0.971 to 1.056)
Other schedule II opioids	model 5 (model 1)	1.002 (0.981 to 1.023)	0.964 (0.959 to 0.970)	-3.76% (-5.80% to -1.68%)	1.002 (0.962 to 1.043)
	model 5^ (model 1^)	1.001 (0.980 to 1.022)	0.961 (0.956 to 0.967)	-3.96% (-6.06% to -1.82%)	1.002 (0.962 to 1.042)
	model 6 (model 2)	0.996 (0.975 to 1.017)	0.968 (0.962 to 0.973)	-2.82% (-4.90% to -0.70%)	1.003 (0.961 to 1.047)
	model 6a* (model 2a*)	0.994 (0.973 to 1.015)	0.964 (0.956 to 0.971)	-3.03% (-5.11% to -0.89%)	1.003 (0.962 to 1.046)
	model 7 (model 3)	0.999 (0.975 to 1.022)	0.968 (0.962 to 0.974)	-3.06% (-5.35% to -0.72%)	1.007 (0.965 to 1.052)
	model 7a* (model 3a*)	0.997 (0.974 to 1.021)	0.964 (0.957 to 0.972)	-3.26% (-5.55% to -0.91%)	1.006 (0.965 to 1.050)

Note: These data were taken from the sponsor information request response from February 11, 2010

Key: extended-release (ER); immediate-release (IR); schedule II (CII); "Other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; CITS slope measure is relative to OxyContin (reference) where null equals 1; a CITS slope measure > 1 means abuse call rate slope comparing periods favors OxyContin and a CITS slope measure < 1 means abuse call rate slope comparing periods favors the comparator; comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (here, total intentional pharmaceutical exposure calls) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates

Table 16: Percent change in quarterly abuse call rate slopes and level change (here, "intercept") and comparative interrupted time series (CITS) slope and level change measures for OxyContin and primary comparators, by model (-2y/5y)

Case Definition	Offset	Covariates	Region	Drug Group	Period	Imputation	Comparison period	Parameter	Transition included	% Change (95% CI)	% Change p-value	CITS measure	P-value
Model 2	Intentional Abuse Exposure	Dosage Units Dispensed		Entire Coverage Area	OxyContin®	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Excluded	-3.14% (-6.64% to 0.49%)	0.089		
								Intercept	Transition Excluded	-11.14% (-26.69% to 7.70%)	0.229		
				ER morphine	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Excluded	-2.80% (-9.05% to 3.88%)	0.402	1.003 (0.930 to 1.083)	0.928
								Intercept	Transition Excluded	-10.70% (-35.55% to 23.74%)	0.497	1.005 (0.688 to 1.468)	0.979
				IR hydrocodone products	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Excluded	-2.53% (-4.60% to -0.42%)	0.019	1.006 (0.964 to 1.050)	0.772
								Intercept	Transition Excluded	-2.69% (-12.40% to 8.10%)	0.611	1.095 (0.880 to 1.364)	0.416
				Other Schedule II opioid analgesic tablets and capsules	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Excluded	-2.82% (-4.90% to -0.70%)	0.009	1.003 (0.961 to 1.047)	0.880
								Intercept	Transition Excluded	-0.73% (-10.57% to 10.19%)	0.890	1.117 (0.898 to 1.391)	0.321
Model 3	Intentional Abuse Exposure	Dosage Units Dispensed		Entire Coverage Area	OxyContin®	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Excluded	-3.78% (-7.14% to -0.30%)	0.034		
								Intercept	Transition Excluded	-26.06% (-42.85% to -4.33%)	0.022		
				ER morphine	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Excluded	-2.49% (-9.84% to 5.46%)	0.528	1.013 (0.930 to 1.104)	0.762
								Intercept	Transition Excluded	-13.29% (-46.83% to 41.41%)	0.568	1.173 (0.675 to 2.038)	0.572
				IR hydrocodone products	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Excluded	-2.49% (-4.63% to -0.29%)	0.026	1.013 (0.972 to 1.057)	0.534
								Intercept	Transition Excluded	-3.91% (-17.92% to 12.48%)	0.619	1.299 (0.961 to 1.758)	0.089
				Other Schedule II opioid analgesic tablets and capsules	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Excluded	-3.06% (-5.35% to -0.72%)	0.011	1.007 (0.965 to 1.052)	0.734
								Intercept	Transition Excluded	3.51% (-14.53% to 25.35%)	0.724	1.400 (1.016 to 1.930)	0.040

Key: extended-release (ER); immediate-release (IR); schedule II (CII); "Other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; CITS measure is relative to OxyContin (reference) where null equals 1; a CITS measure > 1 favors OxyContin (in slope change or level change [here, intercept]) and a CITS measure < 1 favors the comparator; comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (here, total intentional pharmaceutical exposure calls) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates

Table 17: Percent change in quarterly abuse call rate slopes and level change (here, "intercept") and comparative interrupted time series (CITS) slope and level change measures for OxyContin and primary comparators, by model (-2y/5y) **transition period included in post-period**

	Case Definition	Offset	Covariates	Region	Drug Group	Period	Imputation	Comparison period	Parameter	Transition included	% Change (95% CI)	% Change p-value	CITS measure	P-value
Model 1	Intentional Abuse Exposure	2010 Census Population		Entire Coverage Area	OxyContin®	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Included	-4.63% (-8.51% to -0.58%)	0.025		
									Intercept	Transition Included	-12.01% (-28.74% to 8.64%)	0.234		
					ER morphine	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Included	-4.42% (-10.36% to 1.92%)	0.167	1.002 (0.928 to 1.082)	0.955
									Intercept	Transition Included	9.63% (-19.50% to 49.30%)	0.559	1.246 (0.857 to 1.811)	0.249
					IR hydrocodone products	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Included	-2.78% (-5.21% to -0.29%)	0.029	1.019 (0.971 to 1.070)	0.440
									Intercept	Transition Included	13.43% (0.26% to 28.34%)	0.045	1.289 (1.010 to 1.646)	0.042
					Other Schedule II opioid analgesic tablets and capsules	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Included	-3.39% (-5.64% to -1.09%)	0.004	1.013 (0.966 to 1.062)	0.597
									Intercept	Transition Included	13.64% (1.50% to 27.23%)	0.027	1.292 (1.017 to 1.641)	0.036
Model 2a	Intentional Abuse Exposure	Dosage Units Dispensed	All Pharmaceutical Exposures >5	Entire Coverage Area	OxyContin®	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Included	-3.51% (-6.92% to 0.03%)	0.052		
									Intercept	Transition Included	-0.25% (-16.92% to 19.75%)	0.978		
					ER morphine	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Included	-3.17% (-8.89% to 2.91%)	0.300	1.004 (0.935 to 1.077)	0.923
									Intercept	Transition Included	2.36% (-23.66% to 37.24%)	0.876	1.026 (0.726 to 1.450)	0.883
					IR hydrocodone products	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Included	-2.32% (-4.40% to -0.19%)	0.033	1.012 (0.971 to 1.056)	0.566
									Intercept	Transition Included	0.31% (-9.67% to 11.39%)	0.954	1.006 (0.815 to 1.241)	0.959
					Other Schedule II opioid analgesic tablets and capsules	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Included	-2.56% (-4.46% to -0.62%)	0.010	1.010 (0.969 to 1.052)	0.640
									Intercept	Transition Included	1.58% (-7.58% to 11.65%)	0.745	1.018 (0.829 to 1.251)	0.862
Model 3a	Intentional Abuse Exposure		Dosage Units Dispensed, All Pharmaceutical Exposures >5	Entire Coverage Area	OxyContin®	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Included	-3.65% (-7.21% to 0.04%)	0.053		
									Intercept	Transition Included	-2.46% (-22.02% to 22.00%)	0.827		
					ER morphine	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Included	-2.78% (-9.44% to 4.37%)	0.436	1.009 (0.931 to 1.093)	0.826
									Intercept	Transition Included	-0.24% (-31.18% to 44.61%)	0.990	1.023 (0.663 to 1.578)	0.919
					IR hydrocodone products	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Included	-2.26% (-4.37% to -0.11%)	0.040	1.014 (0.971 to 1.060)	0.518
									Intercept	Transition Included	-2.95% (-14.95% to 10.75%)	0.657	0.995 (0.767 to 1.290)	0.970
					Other Schedule II opioid analgesic tablets and capsules	2 vs. 5 yrs	Excluding NOS	Post Period to Pre Period	Slope	Transition Included	-2.48% (-4.49% to -0.44%)	0.018	1.012 (0.970 to 1.057)	0.582
									Intercept	Transition Included	0.12% (-12.46% to 14.50%)	0.986	1.026 (0.791 to 1.333)	0.845

Key: extended-release (ER); immediate-release (IR); schedule II (CII); "Other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; CITS measure is relative to OxyContin (reference) where null equals 1; a CITS measure > 1 favors OxyContin (in slope change or level change [here, intercept]) and a CITS measure < 1 favors the comparator; comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (here, total intentional pharmaceutical exposure calls) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates

Table 18: Percent change in quarterly abuse call rate slopes and level change (here, "intercept") and comparative interrupted time series (CITS) slope and level change measures for OxyContin and primary comparators, by model (-2y/5y) **two consecutive post-periods**

Case Definition	Offset	Covariates	Region	Drug Group	Period	Imputation	Comparison period	Parameter	Transition included	% Change (95% CI)	% Change p-value	CITS measure	P-value
Intentional Abuse Exposure	2010 Census Population		Entire Coverage Area	OxyContin*	2 vs. 5 yrs	Excluding NOS	Post Period 1 to Pre Period	Slope	Transition Included	-6.29% (-10.19% to -2.22%)	0.003		
								Intercept	Transition Included	-4.71% (-22.67% to 17.43%)	0.651		
							Post Period 2 to Post Period 1	Slope	Transition Included	5.79% (-0.85% to 12.88%)	0.089		
								Intercept	Transition Included	1.78% (-25.25% to 38.60%)	0.911		
Model 1				ER morphine	2 vs. 5 yrs	Excluding NOS	Post Period 1 to Pre Period	Slope	Transition Included	-5.09% (-11.41% to 1.67%)	0.137	1.013 (0.934 to 1.098)	0.759
								Intercept	Transition Included	14.15% (-17.83% to 58.57%)	0.430	1.198 (0.811 to 1.768)	0.364
							Post Period 2 to Post Period 1	Slope	Transition Included	5.55% (-3.02% to 14.87%)	0.211	0.998 (0.897 to 1.110)	0.966
								Intercept	Transition Included	-13.45% (-42.52% to 30.34%)	0.489	0.850 (0.509 to 1.420)	0.536
				IR hydrocodone products	2 vs. 5 yrs	Excluding NOS	Post Period 1 to Pre Period	Slope	Transition Included	-1.93% (-4.33% to 0.52%)	0.121	1.046 (0.996 to 1.099)	0.070
								Intercept	Transition Included	8.40% (-3.91% to 22.28%)	0.190	1.138 (0.894 to 1.448)	0.295
							Post Period 2 to Post Period 1	Slope	Transition Included	-3.70% (-6.62% to -0.69%)	0.016	0.910 (0.847 to 0.978)	0.010
								Intercept	Transition Included	-3.08% (-15.67% to 11.38%)	0.659	0.952 (0.679 to 1.336)	0.777
				Other Schedule II opioid analgesic tablets and capsules	2 vs. 5 yrs	Excluding NOS	Post Period 1 to Pre Period	Slope	Transition Included	-3.20% (-5.66% to -0.68%)	0.013	1.033 (0.983 to 1.086)	0.200
								Intercept	Transition Included	12.38% (-0.69% to 27.17%)	0.064	1.179 (0.925 to 1.503)	0.183
							Post Period 2 to Post Period 1	Slope	Transition Included	-1.13% (-4.03% to 1.87%)	0.457	0.935 (0.870 to 1.004)	0.063
								Intercept	Transition Included	-1.91% (-14.63% to 12.71%)	0.786	0.964 (0.687 to 1.352)	0.831
Intentional Abuse Exposure	Dosage Units Dispensed	All Pharmaceutical Exposures >5	Entire Coverage Area	OxyContin*	2 vs. 5 yrs	Excluding NOS	Post Period 1 to Pre Period	Slope	Transition Included	-4.52% (-8.19% to -0.71%)	0.021		
								Intercept	Transition Included	4.45% (-13.90% to 26.71%)	0.659		
							Post Period 2 to Post Period 1	Slope	Transition Included	3.08% (-2.97% to 9.52%)	0.326		
								Intercept	Transition Included	1.81% (-23.56% to 35.61%)	0.902		
Model 2a				ER morphine	2 vs. 5 yrs	Excluding NOS	Post Period 1 to Pre Period	Slope	Transition Included	-3.84% (-9.91% to 2.63%)	0.238	1.007 (0.933 to 1.087)	0.855
								Intercept	Transition Included	6.38% (-22.07% to 45.23%)	0.697	1.019 (0.706 to 1.469)	0.922
							Post Period 2 to Post Period 1	Slope	Transition Included	5.34% (-2.81% to 14.17%)	0.206	1.022 (0.924 to 1.130)	0.673
								Intercept	Transition Included	-13.79% (-41.53% to 27.11%)	0.454	0.847 (0.523 to 1.372)	0.499
				IR hydrocodone products	2 vs. 5 yrs	Excluding NOS	Post Period 1 to Pre Period	Slope	Transition Included	-1.91% (-4.02% to 0.25%)	0.082	1.027 (0.982 to 1.074)	0.237
								Intercept	Transition Included	-2.21% (-12.06% to 8.74%)	0.680	0.936 (0.751 to 1.167)	0.557
							Post Period 2 to Post Period 1	Slope	Transition Included	-3.21% (-5.81% to -0.52%)	0.019	0.939 (0.879 to 1.003)	0.062
								Intercept	Transition Included	3.11% (-8.68% to 16.43%)	0.621	1.013 (0.742 to 1.383)	0.936
				Other Schedule II opioid analgesic tablets and capsules	2 vs. 5 yrs	Excluding NOS	Post Period 1 to Pre Period	Slope	Transition Included	-2.42% (-4.43% to -0.37%)	0.021	1.022 (0.978 to 1.068)	0.336
								Intercept	Transition Included	0.48% (-9.11% to 11.08%)	0.926	0.962 (0.774 to 1.195)	0.726
							Post Period 2 to Post Period 1	Slope	Transition Included	-1.86% (-4.23% to 0.57%)	0.133	0.952 (0.892 to 1.016)	0.138
								Intercept	Transition Included	2.22% (-8.59% to 14.32%)	0.700	1.004 (0.738 to 1.366)	0.980
Intentional Abuse Exposure	Dosage Units Dispensed, All Pharmaceutical Exposures >5		Entire Coverage Area	OxyContin*	2 vs. 5 yrs	Excluding NOS	Post Period 1 to Pre Period	Slope	Transition Included	-4.85% (-8.70% to -0.84%)	0.018		
								Intercept	Transition Included	0.78% (-19.63% to 26.37%)	0.947		
							Post Period 2 to Post Period 1	Slope	Transition Included	3.46% (-2.81% to 10.14%)	0.286		
								Intercept	Transition Included	1.27% (-24.33% to 35.52%)	0.932		
Model 3a				ER morphine	2 vs. 5 yrs	Excluding NOS	Post Period 1 to Pre Period	Slope	Transition Included	-2.02% (-8.57% to 5.01%)	0.564	1.030 (0.950 to 1.116)	0.476
								Intercept	Transition Included	-8.85% (-37.41% to 32.76%)	0.629	0.905 (0.583 to 1.403)	0.654
							Post Period 2 to Post Period 1	Slope	Transition Included	10.08% (-0.50% to 21.79%)	0.063	1.064 (0.945 to 1.198)	0.305
								Intercept	Transition Included	-8.24% (-38.36% to 36.60%)	0.672	0.906 (0.553 to 1.484)	0.695
				IR hydrocodone products	2 vs. 5 yrs	Excluding NOS	Post Period 1 to Pre Period	Slope	Transition Included	-1.72% (-4.02% to 0.64%)	0.151	1.033 (0.985 to 1.083)	0.182
								Intercept	Transition Included	-0.43% (-12.76% to 13.65%)	0.949	0.988 (0.760 to 1.284)	0.928
							Post Period 2 to Post Period 1	Slope	Transition Included	-3.68% (-7.06% to -0.17%)	0.040	0.931 (0.867 to 1.000)	0.049
								Intercept	Transition Included	1.01% (-13.34% to 17.73%)	0.898	0.997 (0.718 to 1.386)	0.988
				Other Schedule II opioid analgesic tablets and capsules	2 vs. 5 yrs	Excluding NOS	Post Period 1 to Pre Period	Slope	Transition Included	-2.42% (-4.47% to -0.32%)	0.024	1.026 (0.979 to 1.074)	0.287
								Intercept	Transition Included	-0.17% (-13.32% to 14.97%)	0.981	0.991 (0.758 to 1.294)	0.945
								Slope	Transition Included	-1.81% (-4.41% to 0.88%)	0.185	0.949 (0.887 to 1.015)	0.129
							Post Period 2 to Post Period 1	Intercept	Transition Included	2.73% (-10.53% to 17.96%)	0.702	1.014 (0.735 to 1.400)	0.930

Key: extended-release (ER); immediate-release (IR); schedule II (CII); "Other schedule II opioids" includes ER and IR formulations of hydrocodone, oxymorphone, hydromorphone, and morphine, and IR oxycodone; CITS measure is relative to OxyContin (reference) where null equals 1; a CITS measure > 1 favors OxyContin (in slope change or level change [here, intercept]) and a CITS measure < 1 favors the comparator; comparing two years before to five years after the reformulation, excluding the transition period (-2y/5y); Model 1 models an abuse call rate per general population (as an offset); Model 2a models an abuse call rate per tablets dispensed (as an offset), adjusting for call volume (here, total intentional pharmaceutical exposure calls) as a covariate; Model 3a models an abuse call rate without an offset, adjusting for tablets dispensed and call volume as covariates

8.6 INTERRUPTED TIME SERIES PLOTS FOR OTHER MODELS 2A AND 3A
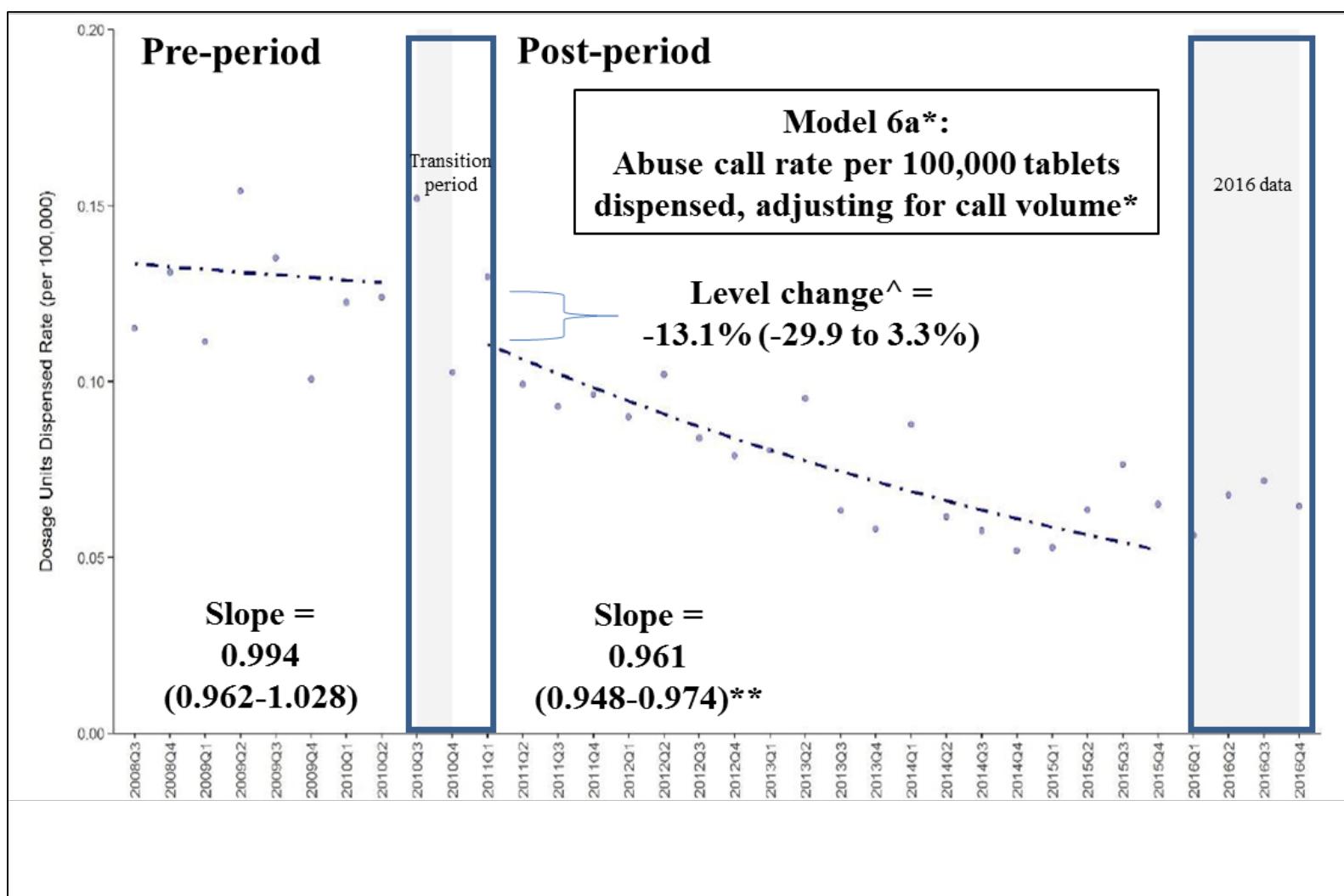
These data were taken from the sponsor information request response from March 6, 2020

For reference:

^ = quarterly total intentional pharmaceutical exposure calls as an offset variable

* = (log) quarterly total intentional pharmaceutical exposure calls as a covariate (rather than quarterly total pharmaceutical exposures) to adjust for call volume
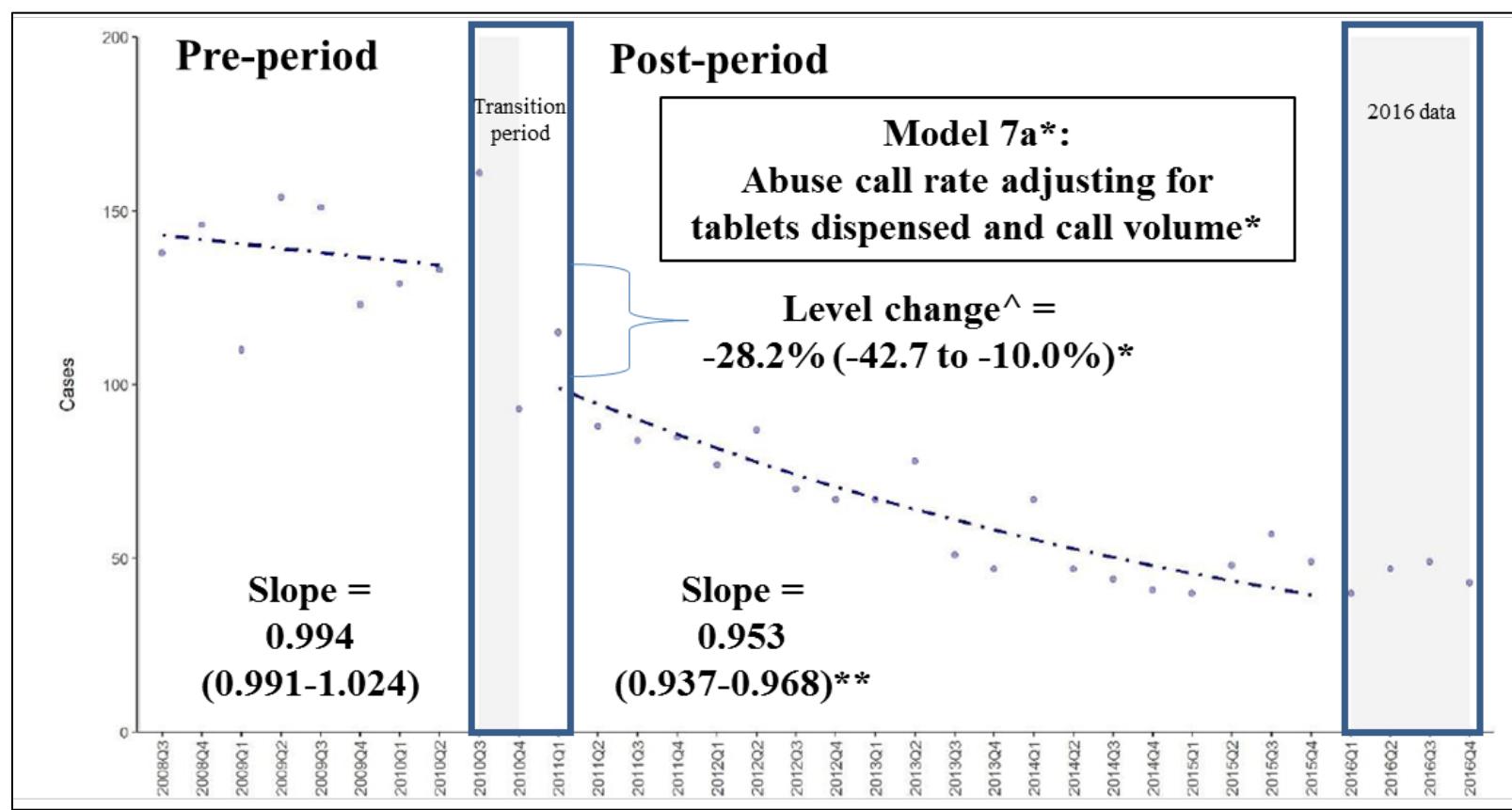
Figure 13: ITS plot of the slopes and level change in the abuse call rate comparing the pre- and post-periods for OxyContin per tablets dispensed, adjusting for total intentional exposure calls only (Model 6a*)

(*Sponsor figure taken from March 2020 information request response; reformatted with numbers and boxes by FDA*)

Key: ** = statistically significant (p<0.05); * = the model used to create this figure adjusted for "call volume" using total intentional pharmaceutical exposure calls, rather than total pharmaceutical exposures calls; ^the model used to calculate this level change adjusted for "call volume" using total pharmaceutical exposures calls, rather than total intentional pharmaceutical exposure calls (data are shown in Figure 26); Interrupted time series (ITS) model 6a* models an abuse call rate slope per tablets dispensed (as an offset), adjusting for all intentional exposure calls (i.e., "call volume") as a covariate; the solid black line denotes the end of the pre-reformulation period and the beginning of the post-reformulation period (shaded region is transition period); the shaded region in the post-period was not included in analyses (outside of study window)

Figure 14: ITS plot of the slopes and level change in the abuse call rate comparing the pre- and post-periods for OxyContin adjusting for tablets dispensed and total intentional exposure calls only (Model 7a*)

(*Sponsor figure taken from March 2020 information request response; reformatted with numbers and boxes by FDA*)

Key: ** = statistically significant (p<0.05); * = the model used to create this figure adjusted for "call volume" using total intentional pharmaceutical exposure calls, rather than total pharmaceutical exposures calls; ^the model used to calculate this level change adjusted for "call volume" using total pharmaceutical exposures calls, rather than total intentional pharmaceutical exposure calls (data are shown in Figure 26); Interrupted time series (ITS) model 7a* models an abuse call rate slope adjusting tablets dispensed and all intentional exposure calls (i.e., "call volume") as covariates; the solid black line denotes the end of the pre-reformulation period and the beginning of the post-reformulation period (shaded region is transition period); the shaded region in the post-period was not included in analyses (outside of study window)

Figure 15: ITS plot of the slopes and level change in the abuse call rate comparing the pre- and post-periods for ER morphine per tablets dispensed, adjusting for total intentional exposure calls only (Model 6a*)
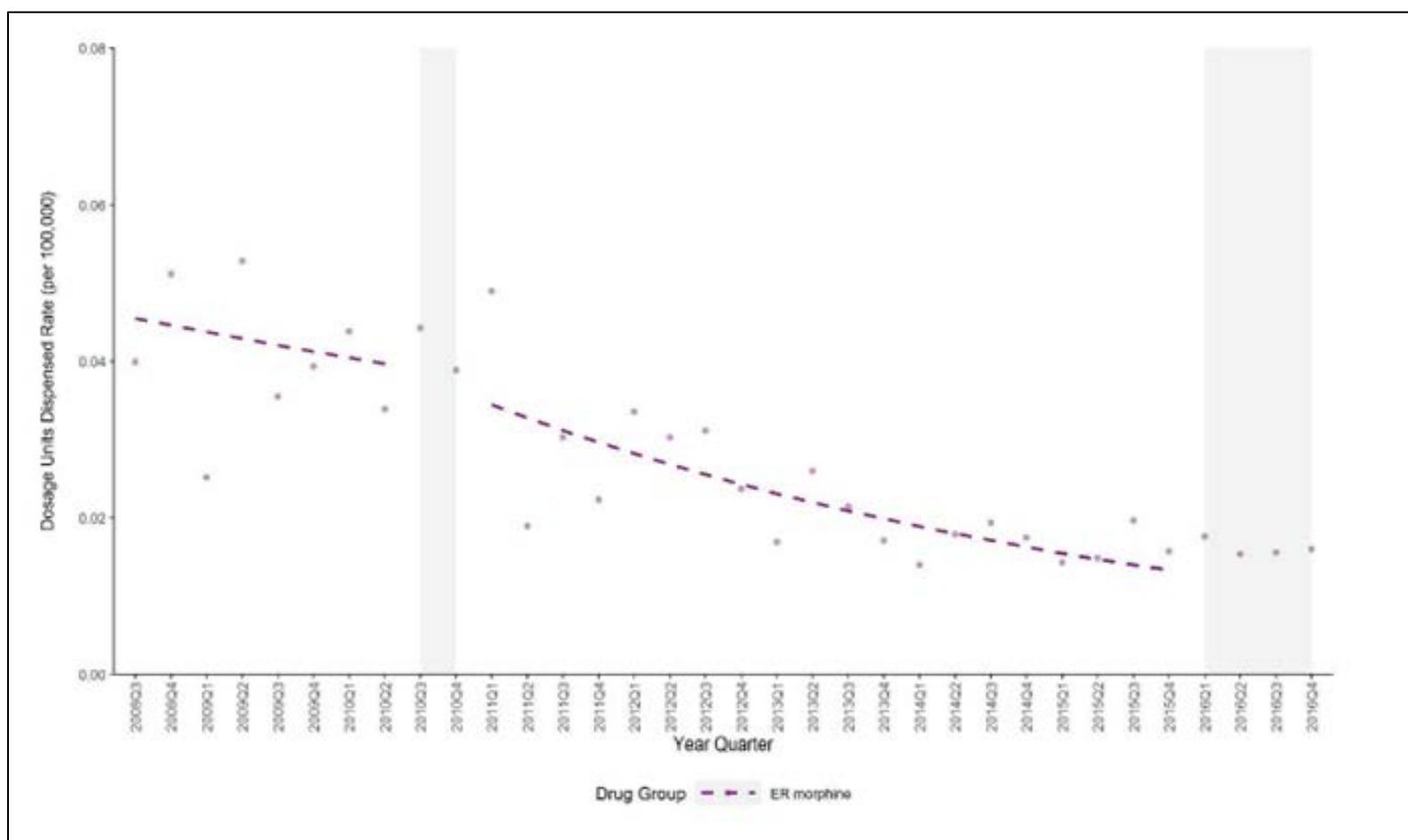
Figure 16: ITS plot of the slopes and level change in the abuse call rate comparing the pre- and post-periods for IR hydrocodone per tablets dispensed, adjusting for total intentional exposure calls only (Model 6a*)
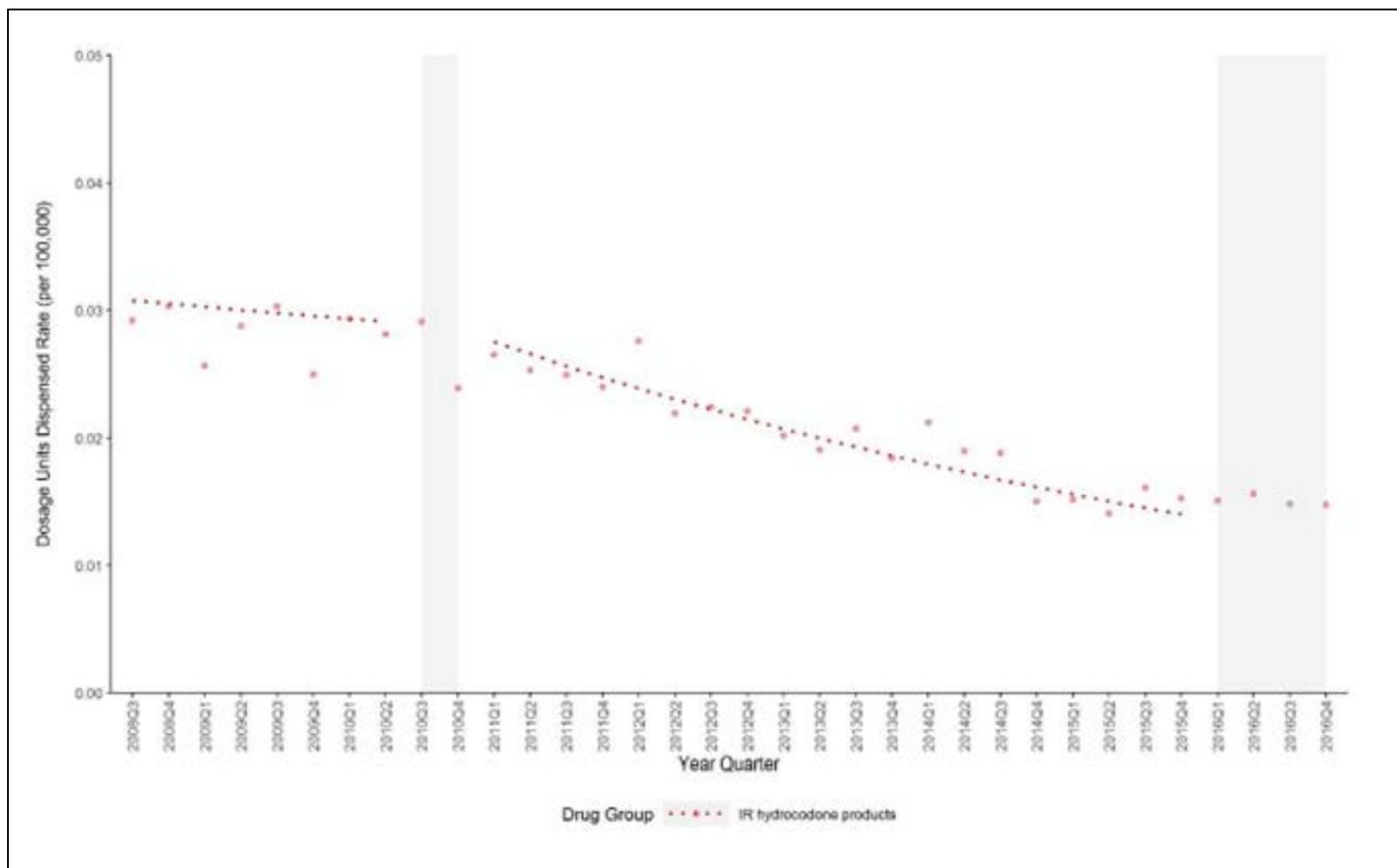
Figure 17: ITS plot of the slopes and level change in the abuse call rate comparing the pre- and post-periods for "other schedule II opioids" per tablets dispensed, adjusting for total intentional exposure calls only (Model 6a*)
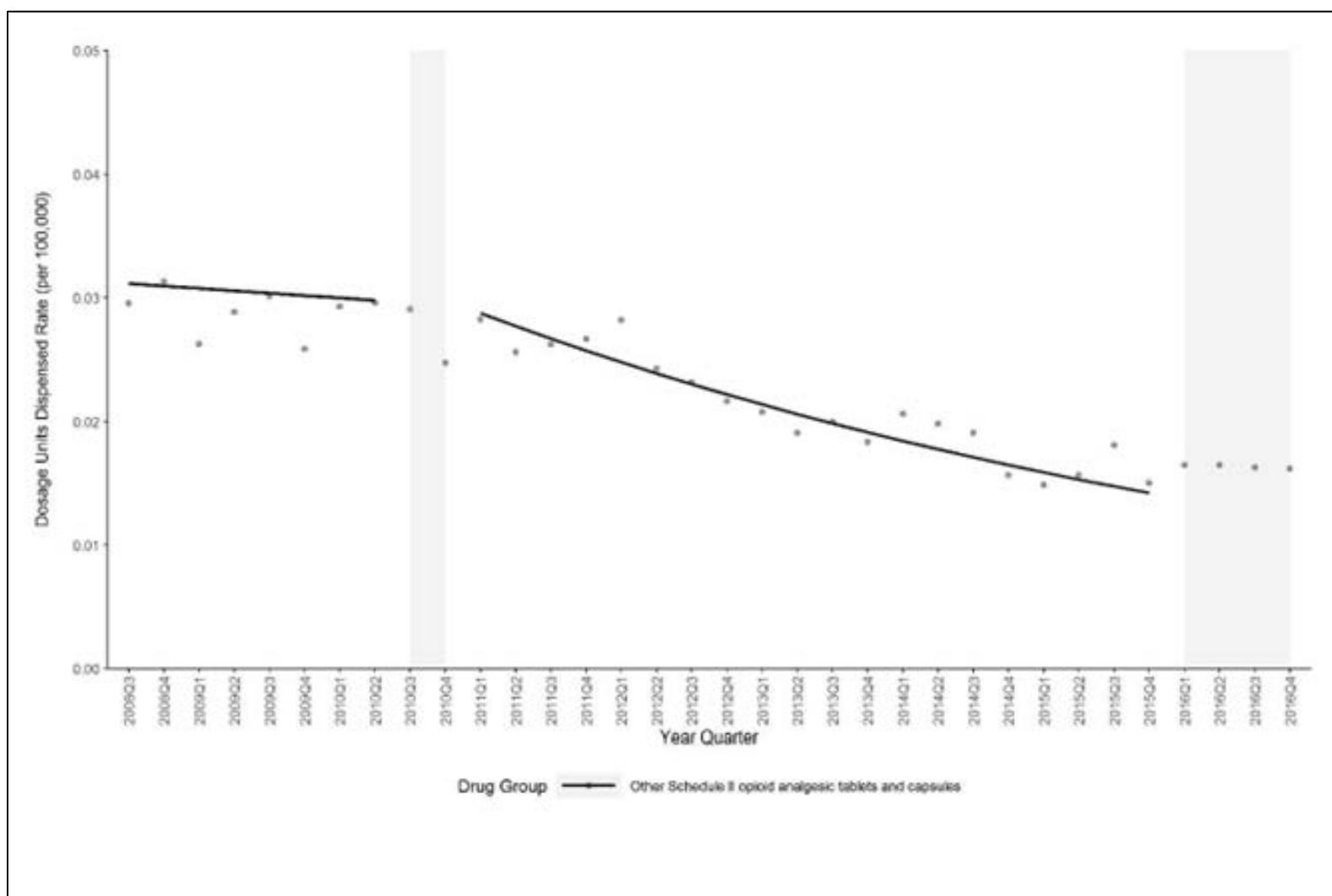
Figure 18: ITS plot of the slopes and level change in the abuse call rate comparing the pre- and post-periods for ER morphine per tablets dispensed, adjusting for total intentional exposure calls only (Model 7a*)
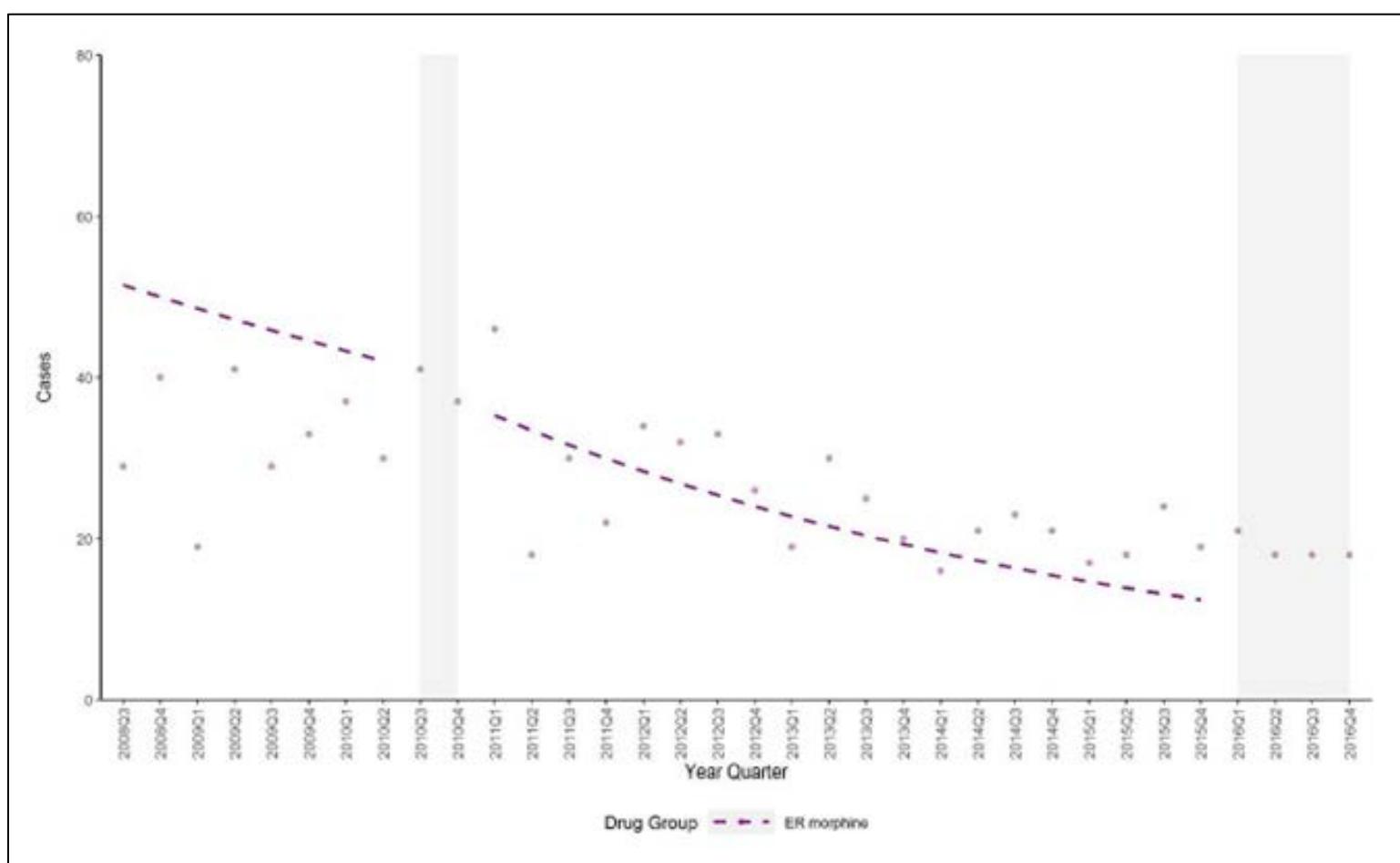
Figure 19: ITS plot of the slopes and level change in the abuse call rate comparing the pre- and post-periods for IR hydrocodone per tablets dispensed, adjusting for total intentional exposure calls only (Model 7a*)
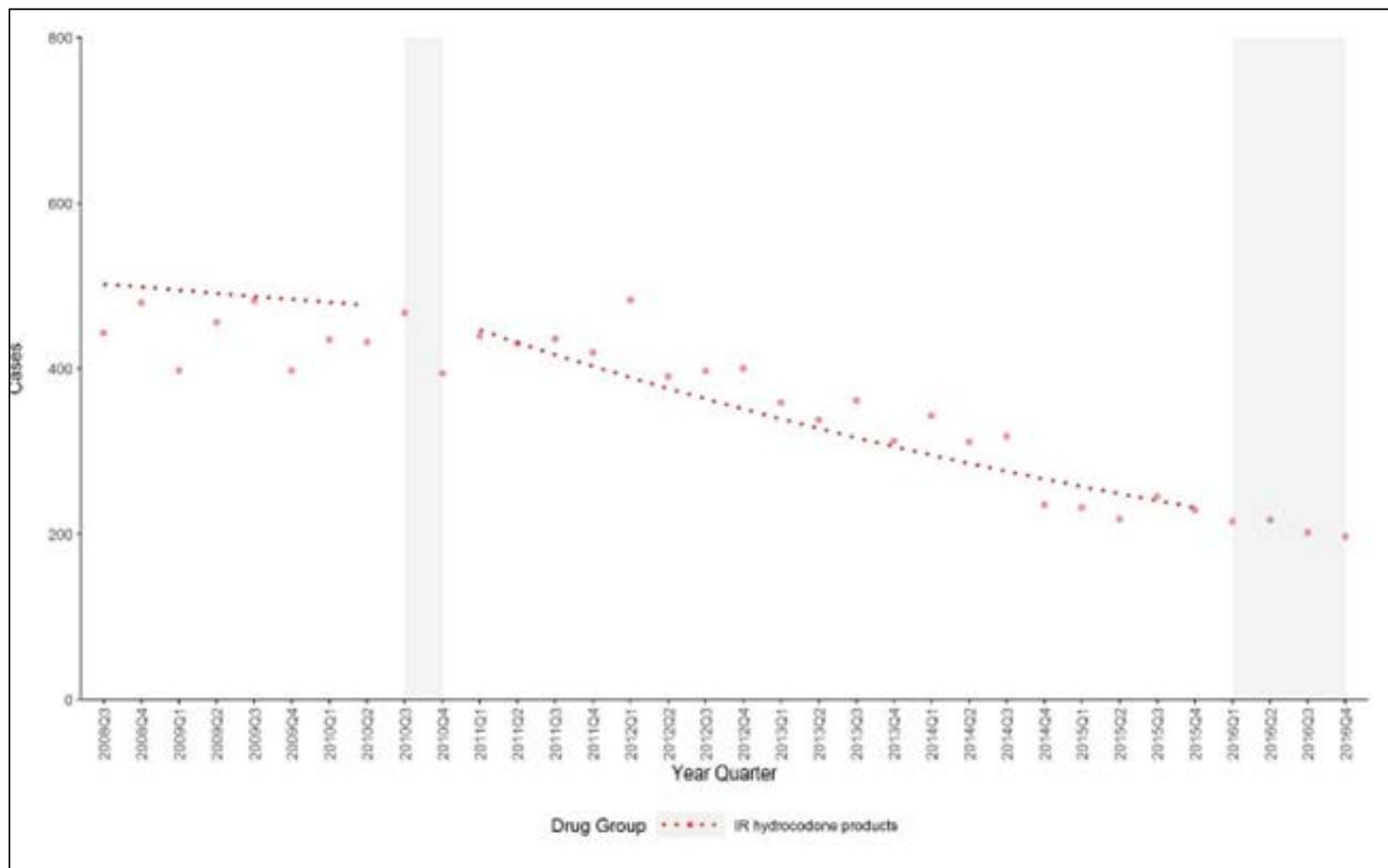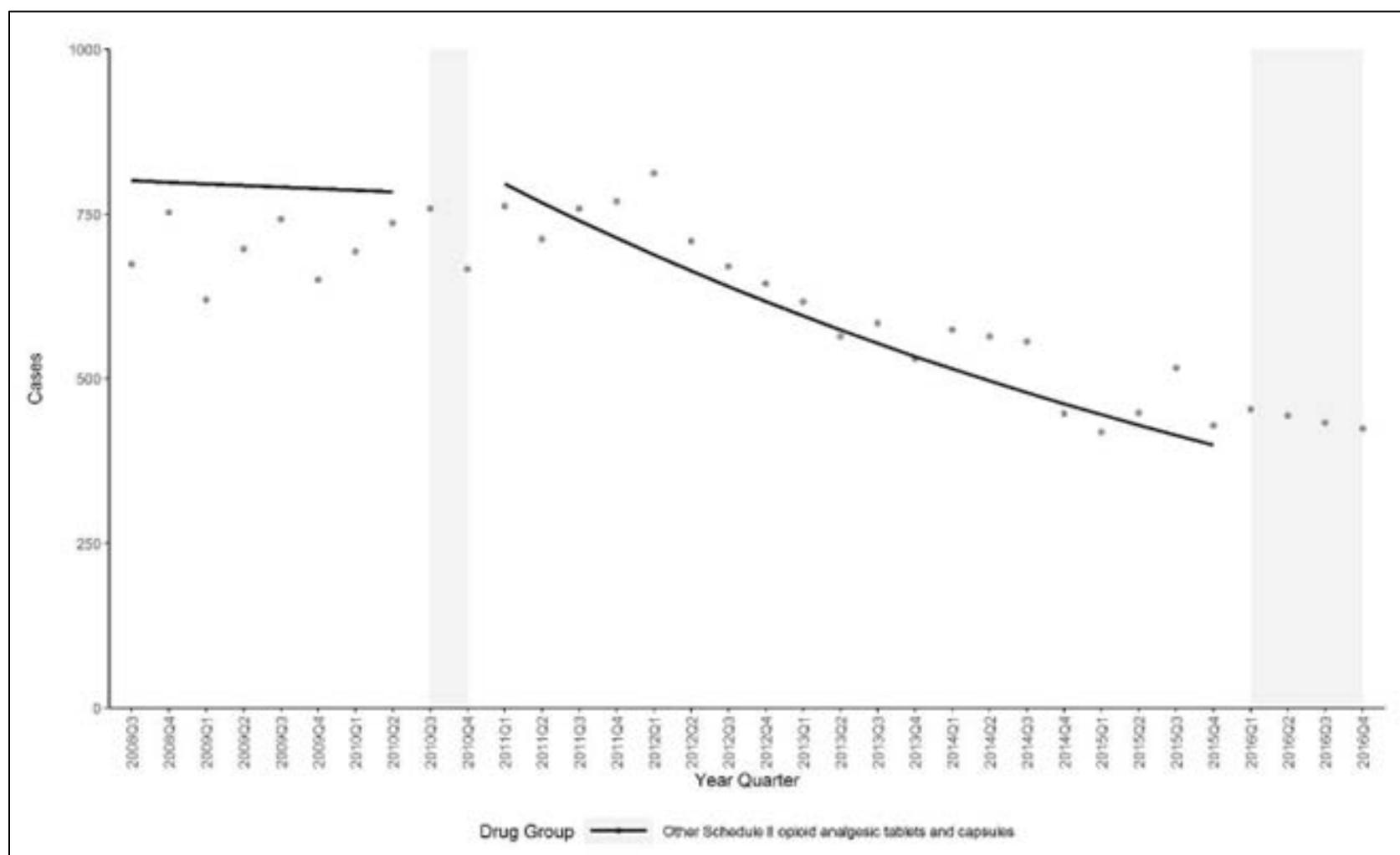
Figure 20: ITS plot of the slopes and level change in the abuse call rate comparing the pre- and post-periods for "other schedule II opioids" per tablets dispensed, adjusting for total intentional exposure calls only (Model 7a*)

8.7 LITERATURE REVIEW SUMMARY TABLE

Author, date	Data sources	Time period	Findings	Authors' Conclusions	Limitations
Coplan et al, 2013	National Poison Data System (NPDS) covering all US poison centers IMS health (now IQVIA) utilization data	One year before versus two years after introduction of reformulated OxyContin (7/2009–6/2010 vs 9/2010–9/2012)	Comparing pre- to post-reformulation, mean abuse exposure calls per quarter declined 36% (95% confidence interval [CI]: 23-40) for OxyContin, increased 20% (95% CI: 13-33) for other single-entity (SE) oxycodone, and increased 42% (95% CI: 24-41) for heroin. OxyContin had statistically significant decline per 1,000 prescriptions dispensed (-31% [CI:-39% to -23%]); this was not assessed for other SE oxycodone. Unintentional therapeutic error calls per quarter declined 20% (95% CI: 9-26) for OxyContin and increased 19% (95% CI: 7-26) for other SE oxycodone. Similar to abuse, there were statistically significant declines for OxyContin per prescriptions dispensed. Unintentional general exposures exposure calls per quarter declined 39% (95% CI: 29-49) for OxyContin and remained unchanged for other SE oxycodone and heroin. When looking at abuse by milligram strength for OxyContin exposures, percent declines were greatest for higher milligram strength tablets.	*"After the OxyContin reformulation, calls to poison centers involving abuse, therapeutic errors affecting patients, and accidental exposures decreased for OxyContin, but not for comparator opioids. Abuse-deterrent formulations of opioid analgesics can reduce abuse but switching to other accessible non abuse-deterrent opioids might occur. During the study period, other interventions to reduce opioid abuse occurred. However, these have shown small effects and do not explain a drop for OxyContin exposures but not for other opioids."*	-Shorter study period does not allow for assessment of maintenance of effect over time -Only assessed two opioid comparator groups -Did not statistically compare comparator opioid changes to OxyContin -Did not conduct sensitivity analyses to assess the impact of other interventions around the time of the reformulation -Did not assess changes in calls related to oral versus non-oral routes of abuse
Coplan et al. 2016* *_this publication was based on selected analyses from the Purdue's 2014 labeling supplement submission (later withdrawn; See section 1_)	Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System Poison Center Program (PCP) National Poison Data System (NPDS) covering all US poison centers	One year before versus three years after introduction of reformulated OxyContin (3Q2009- 2Q2010 vs 1Q2011- 4Q2013)	**RADARS PCP data**: Population-based rates of misuse declined 43% for OxyContin and 6% for "other schedule II opioids" (composite category), but only OxyContin's decline was statistically significant; prescription-based rates declined 29% and 12%, respectively (both statistically significant). Population-based abuse (any route) (55%, CI: 47 to 61%), oral abuse (52%, CI: 36 to 64%), and non-oral abuse (74%, CI: 68 to 79%)	*"In conclusion, after the introduction of reformulated OxyContin with abuse-deterrent properties, there were decreases in associated abuse, overdose diagnoses, and diversion that occurred consistently across 10 studies that used different measures of abuse and its consequences. Decreases in observations of abuse began within a few months after the introduction of reformulated OxyContin and persisted over the 3-year assessment period. There were*	-Shorter study period does not allow for assessment of maintenance of effect over time -Only one composite comparator was used to compare to OxyContin -Prescription-adjusted analyses were not used to directly compare abuse call rates for OxyContin and "other schedule II opioids" despite known changes in utilization over this period

| | | | calls for OxyContin all declined, and those percent changes were statistically significantly different than "other schedule II opioids" for abuse by any route (-7%, CI:-20 to 9%) and non-oral (3%, CI: -26 to 43%) abuse calls, but not oral (-15%, CI: -32 to 7%).

Prescription-adjusted rates for OxyContin and "other schedule II opioids" were not compared directly, but only the change for OxyContin (-44%) was significant.

NPDS data:

Population-based abuse (any route) (55%, CI: 50 to 60%), oral abuse (54%, CI: 48 to 60%), and non-oral abuse (63%, CI: 54 to 70%) calls for OxyContin all declined, and those percent changes were all statistically significantly different than "other schedule II opioids" (abuse by any route -4%, [CI: -7 to 0%], oral route -8%, [CI: -11 to -4%, and non-oral route +35% [CI: 24 to 50%])

Prescription-adjusted rates for OxyContin and "other schedule II opioids" were not compared directly, but both OxyContin (-48%) and "other schedule II opioids" (-9%) declined significantly. | *reductions in both nonoral and oral abuse of OxyContin, although greater decreases were observed for nonoral abuse, consistent with the physicochemical abuse-deterrent properties. The decreases for OxyContin were both larger and occurred earlier than that for comparator opioids without abuse-deterrent properties, suggesting that the decreases for OxyContin were not due to general opioid interventions such as prescription monitoring programs or environmental trends such as less opioid prescribing."**

* this conclusion was not solely based on poison center data | |
| Dart et al., 2015 | Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System Poison Center Program (PCP)

General population data (2010) | Eight years before versus three years after introduction of reformulated OxyContin (4Q2002-2Q2009 vs 3Q2009- 4Q2013)*

* this study did not compare periods statistically (only visually compared trends in rates over time) | In the Poison Center Program, the quarterly abuse call rate for all opioid analgesics increased from 0.20 per 100,000 population in 2003 to 0.56 in 2010 and then decreased to 0.35 by the end of 2013.

There were increasing heroin abuse calls around the same time as decreasing calls involving extended-release oxycodone (OxyContin and generics), which all appeared to coincide with the introduction of an abuse-deterrent formulation. | *"The introduction of abuse-deterrent OxyContin coincided with a flattening of the trajectory of opioid analgesic prescriptions but occurred after the increase in reported heroin use became apparent. Given that 79.5% of new heroin initiates in the National Survey on Drug Use and Health reported that their initial drug was a prescription opioid and that reported heroin use by patients in a substance-abuse program nearly doubled after the introduction of abuse-deterrent OxyContin, it seems likely that the* | -Only used heroin as a comparator

-Did not rely on statistical comparisons (only visual descriptive trend figures)

-Did not adjust for utilization changes with respect to ER oxycodone products (OxyContin and generic) |

				reformulation of extended-release oxycodone in 2010 has contributed to the increase in reported heroin use." * * *this conclusion was not solely based on poison center data*	
Severtson et al, 2013	Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System Poison Center Program (PCP) SDI health (now IQVIA) utilization data	Two years before versus two years after introduction of reformulated OxyContin (10/2008-9/2010 vs 10/2010- 9/2012)	After the reformulation, OxyContin abuse exposures declined 38% (95% CI: 31–45) per general population and 32% (95% CI: 24–39) per unique recipients of dispensed drug (URDD). Unintentional therapeutic error exposures for OxyContin declined 24% (95% CI: 15–31) per population and 15% (95% CI: 6–24) per URDD. Comparing the pre- and post-reformulation periods, abuse exposures for all other prescription opioids decreased ~9% (p=0.002) per URDD; that group decreased ~8% (p=0.008) for unintentional therapeutic errors. Per general population, changes were no longer statistically significant.	*"This article indicates that the abuse, therapeutic errors, and diversion of ERO declined following the introduction of a tamper-resistant reformulation of the product. Reformulating abused prescription opioids to include tamper-resistant properties may be an effective approach to reduce abuse of such products."* * * *this conclusion was not solely based on poison center data*	-Shorter study period does not allow for assessment of maintenance of effect over time -Did not exclude a transition period -No individual opioid comparators; only assessed one opioid composite comparator -Use of URDD denominator to account for availability is problematic because this captures the number of patients dispensed the drug, not the amount dispensed per patient which can vary significantly across patients and prescriptions -Did not assess changes in calls related to oral versus non-oral routes of abuse

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of OxyContin Postmarketing Requirement (PMR) 3051-3
Final Study Report

Date: August 2020

Reviewer: Celeste Mallama, Ph.D., M.P.H., Epidemiology Reviewer
                                         Division of Epidemiology II

Secondary Reviewer: Jana McAninch, M.D., M.P.H., M.S., Senior Medical
                                         Epidemiologist
                                         Division of Epidemiology II

Associate Office Director: Judy Staffa, Ph.D., R.Ph., Associate Director for Public
                                         Health Initiatives
                                         Office of Surveillance and Epidemiology

Subject: OxyContin Postmarketing Final Study Report 3051-3

Drug Name(s):   OxyContin (oxycodone hydrochloride extended-release)

Application Type/Number: NDA 022272/IND 029038

Applicant/sponsor: Purdue Pharma L.P.

OSE RCM #:   2016-732

TABLE OF CONTENTS

ABBREVIATIONS:

-1y/3y: 1-year pre-period before reformulation (3Q2009-2Q2010) vs. 3-year post-period after reformulation (1Q2011-4Q2013), excluding transition period

-2y/5y: 2-year pre-period before reformulation (3Q2008-2Q2010) vs. 5-year post-period after reformulation (1Q2011-4Q2015), excluding transition period

ADF: Abuse Deterrent Formulation

AIC: Akaike Information Criteria

APAP: Acetaminophen (or paracetamol)

ASI-MV: Addiction Severity Index-Multimedia Version

CDC: Centers for Disease Control

CI: Confidence Interval

DEA: Drug Enforcement Administration

DEPI: Division of Epidemiology II

ER: Extended Release

FDA: Food and Drug Administration

IR: Immediate Release

ITS: Interrupted Time Series

LA: Long Acting

mg: Milligram

NA: Not Applicable

NAVIPPRO®: National Addictions Vigilance Intervention and Prevention Program

NDA: New Drug Application

NOS: Not Otherwise Specified

NPA: National Prescription Audit

ORF: Reformulated Oxycontin

OTP: Opioid Treatment Program

PMR: Postmarketing Requirement

Q: Yearly Quarter (3-month period)

RADARS: Researched Abuse, Diversion and Addiction-Related Surveillance

RAPID: Researchers and Participants Interaction Directly

REMS: Risk Evaluation and Mitigation Strategy

RORR: Ratio of Rate Ratios

SAP: Statistical Analysis Plan

SE: Single Entity

SKIP: Survey of Key Informants' Participants

TIRF: Transmucosal IR Fentanyl

US: United States

1   EXECUTIVE SUMMARY

Background

The objective of this review is to determine whether findings from postmarketing requirement (PMR) study 3051-3 (hereafter, PMR 3051-3) provide evidence that OxyContin®'s (hereafter, OxyContin) reformulation reduced abuse of OxyContin among adults enrolling in methadone maintenance treatment programs (Opioid Treatment Program [OTP]) and adults entering general substance abuse treatment programs who endorsed an opioid as their primary drug of abuse (Survey of Key Informants' Patients [SKIP]).

The study conducted by Purdue Pharma (hereafter, the sponsor) to fulfill PMR 3051-3 is one of four studies the United States (US) Food and Drug Administration (FDA) required of the sponsor to evaluate the impact of OxyContin's 2010 reformulation on "real-world" abuse and overdose associated with this product. Specifically, PMR study 3051-3 aimed to assess the effect of OxyContin's reformulation on rates of OxyContin abuse in a large sample of individuals entering treatment centers who endorsed opioids as their main drug of abuse. This data source did not collect information on route of abuse at the time of OxyContin's reformulation, so the study was only able to examine overall abuse (via any route).

Overview of Study Methods

This study analyzed data from RADARS® (hereafter, RADARS) Treatment Center Programs (TCP). TCP is comprised of the OTP and SKIP programs, which survey persons entering treatment for opioid use disorders about their recent drug use. The OTP program collects information primarily from public facilities that use medication-assisted treatment, while the SKIP includes primarily private facilities that do not use medication-assisted treatment. Each patient is offered the opportunity to complete an anonymous, standardized, self-administered paper-based questionnaire that solicits information on specific prescription drugs "used to get high" in the past 30 days. Another data source, the IQVIA National Prescription Audit,™ (hereafter, NPA) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, and long-term care facilities into the hands of consumers via formal prescriptions in the US. Data from IQVIA were used in this study to estimate the number of dosage units dispensed for a given drug or drug group within the study coverage area.

The main study period included a pre-reformulation, baseline period of July 2008-June 2010, a 6-month transition period, and a post-reformulation period of January 2011-December 2015. The study used a pre- vs. post-period "difference-in-differences" design, comparing changes in mean abuse rates and an interrupted time series (ITS) approach, comparing slope and level change for OxyContin to those for a pre-specified set of comparator products. The study used three primary comparator opioids to approximate

background trends in abuse rates (i.e., unrelated to the reformulation) to aid in causal inference. Additional, secondary comparators provided contextual information and contributed to the overall interpretation of study findings.

This study provided descriptive data and used Poisson regression models to estimate and compare changes in rates of abuse of OxyContin and comparators. There is no single, standard scientifically agreed-upon denominator or modeling approach to estimate abuse rates. Therefore, the study generated estimates using a population-based model (model 1: number of respondents included in the denominator [i.e., offset]), a utilization-based model (model 2: dosage units dispensed used as the denominator), and utilization-adjusted (model 3: dosage units dispensed included as a covariate). The main analyses for this review used the following variable definitions: 1) Any treatment center submitting at least one assessment during the study period, 2) OxyContin abuse cases only (no generic ER oxycodone), 3) entire US geographic region, and 4) 2 year pre-period and 5 year post-period (-2y/5y). In addition, due to the inherent uncertainties associated with these data and this design (e.g., potential for bias due to misclassification, use of a dynamic study sample in which treatment centers can drop in and out of the network over time), a number of sensitivity analyses were conducted, including varying the time period (e.g., -1y/3y), definition of an OxyContin abuse case (e.g., any ER oxycodone), site inclusion criteria (e.g., centers submitting ≥1 assessment per year, centers submitting ≥1 assessment per quarter), and geographic area (e.g., entire US excluding Florida, restricted to western census region). Together, these different models and sensitivity analyses were used to estimate a range of possible effect sizes and assess robustness of the overall study findings with regard to the effect of reformulation on abuse rates in this population.
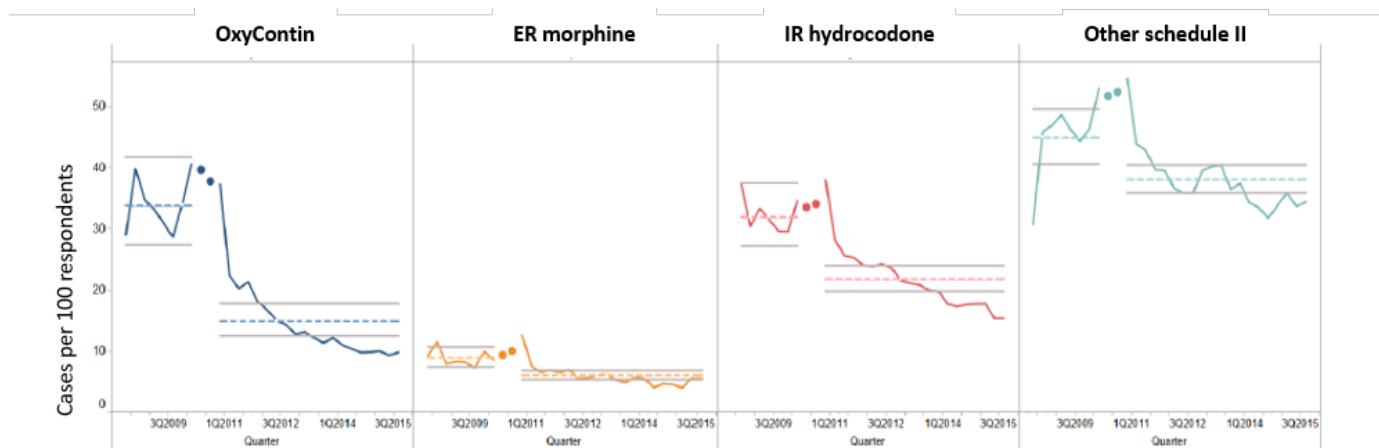
Selected Key Study Findings

Utilization Data: The average number of OxyContin tablets dispensed per month decreased -24.5% from the pre-period to the post-period. In contrast, primary comparators extended release (ER) morphine, immediate release (IR) hydrocodone and "other schedule II opioids" (a composite category composed of IR oxycodone SE and combination products, IR hydrocodone combination products, ER hydrocodone, ER and IR morphine, ER and IR oxymorphone, and ER and IR hydromorphone), all showed increased utilization across the study period, as did the secondary comparator IR oxycodone. Methadone (prescribed for analgesia) was the only comparator to show a decrease in dispensing.

Descriptive Trends of Abuse Rates: Visual inspection of trends in quarterly abuse rates per 100 respondents (Figure A) suggests a decline in rates of abuse for OxyContin and all primary comparators following introduction of reformulated OxyContin, with OxyContin showing a particularly sharp decrease immediately following the transition period. In the pre-period, OxyContin's rates were higher than those of ER morphine, comparable to IR hydrocodone, and lower than the composite "other schedule II opioids" category. In the

post-period, the rate of OxyContin abuse remained below "other schedule II opioids" and dropped below IR hydrocodone, but remained higher than the rate of ER morphine abuse.

Figure A: Observed and estimated (95% CI) rate of abuse cases per 100 respondents over time for OxyContin and primary comparators (3Q2008-4Q2015), RADARS OTP and SKIP combined (Model 1)
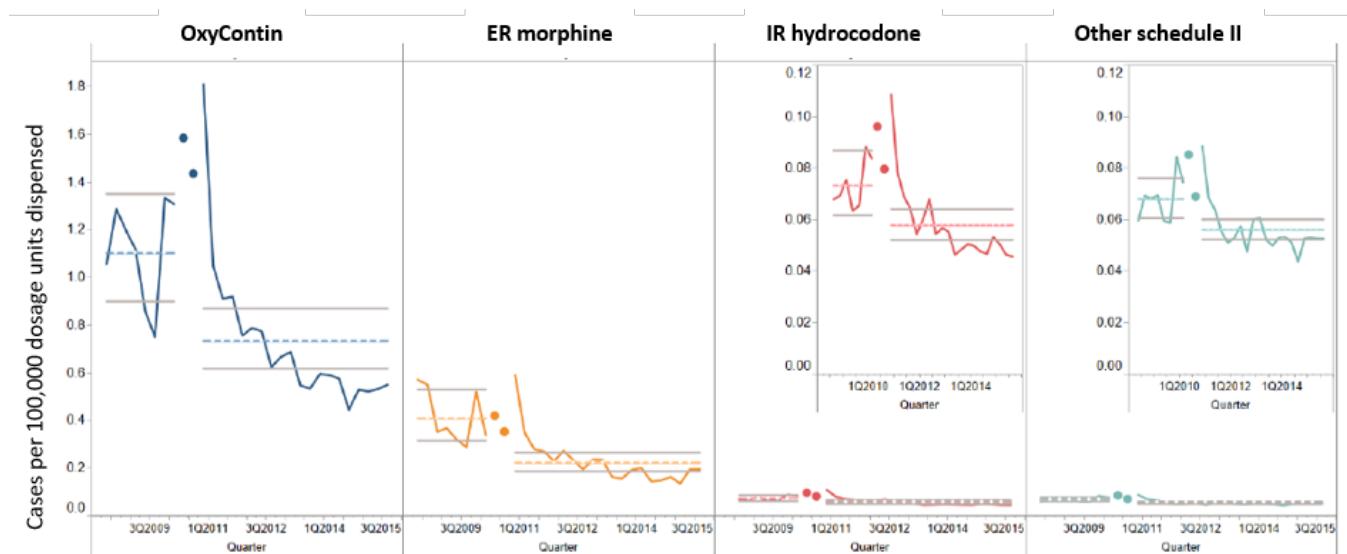
(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Figure 7-5 Descriptive trend figure of observed and model-estimated (95% CI) abuse (3Q2008-4Q2015) for Model 1: rate of abuse per number of respondents, for OxyContin and primary comparators. P. 60.)

Key: ER: Extended Release; IR: Immediate Release; Solid line shows the observed values and the dashed lines represent the model-estimated values for each quarter. 95% confidence intervals are shown as the gray solid line. Observed values for the transition period are shown as points. Model 1 models abuse rate per respondents.

Visual inspection of trends in quarterly rates of abuse per 100,000 dosage units dispensed (Figure B) suggest a decrease in OxyContin's rate that is comparable to that of comparators. Throughout the pre- and post-periods, the rate of abuse cases for OxyContin per 100,000 dosage units dispensed was substantially higher than the rates for ER morphine, IR hydrocodone, and "other schedule II opioids".

Figure B: Observed and model estimated (95% CI) rate of abuse cases per 100,000 dosage units dispensed over time for OxyContin and primary comparators (3Q2008-4Q2015)), RADARS OTP and SKIP combined, (Model 2) *Note different y-axes in insets*

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Descriptive trend figure of observed and model-estimated (95% CI) abuse (3Q2008-4Q2015) for Model 2: rate of abuse per dosage units dispensed, for OxyContin and primary comparators P. 61.)

Key: ER: Extended Release; IR: Immediate Release; Solid line shows the observed values and the dashed lines represent the model-estimated values for each quarter. 95% confidence intervals are shown as the gray solid line. Observed values for the transition period are shown as points. Model 2 models abuse rate per tablets dispensed.

Pre-post means analyses: As shown in Figure C, population-based analyses (model 1) demonstrated that OxyContin had the largest decrease in abuse rates from the pre- to post-period, while utilization-based analyses (models 2 and 2a) showed that ER morphine had the largest decrease.

Figure C: Percent change (95% CI) in mean past-month abuse rate after introduction of reformulated OxyContin, for OxyContin and primary comparators, RADARS OTP/SKIP combined, OTP, and SKIP separately, -2y/5y

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Figure 7-3. Percent change (95% CI) in overall abuse of OxyContin and primary comparators after introduction of reformulated OxyContin for the combined population, OTP population and SKIP population using different modeling approaches, -2y/5y. P. 54.)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondents; Model 2 models abuse rate per tablets dispensed, Model 2a models abuse rate per tablets dispensed, adjusted for respondents as a covariate

Sensitivity analyses based on site inclusion criteria, definition of OxyContin, time period, geographic region, and regression model produced estimates of change in OxyContin abuse ranging from +80.5% to -63.2% for the OTP, SKIP, and combined populations. Estimates in percent change were influenced particularly by model and OxyContin definition: model 3, which adjusted for utilization as a covariate, in combination with the OxyContin definition that included all ER oxycodone products estimated a large increase in percent change for abuse of OxyContin in the OTP population. These estimates ranged considerably and were not qualitatively consistent in showing declines in abuse of OxyContin.
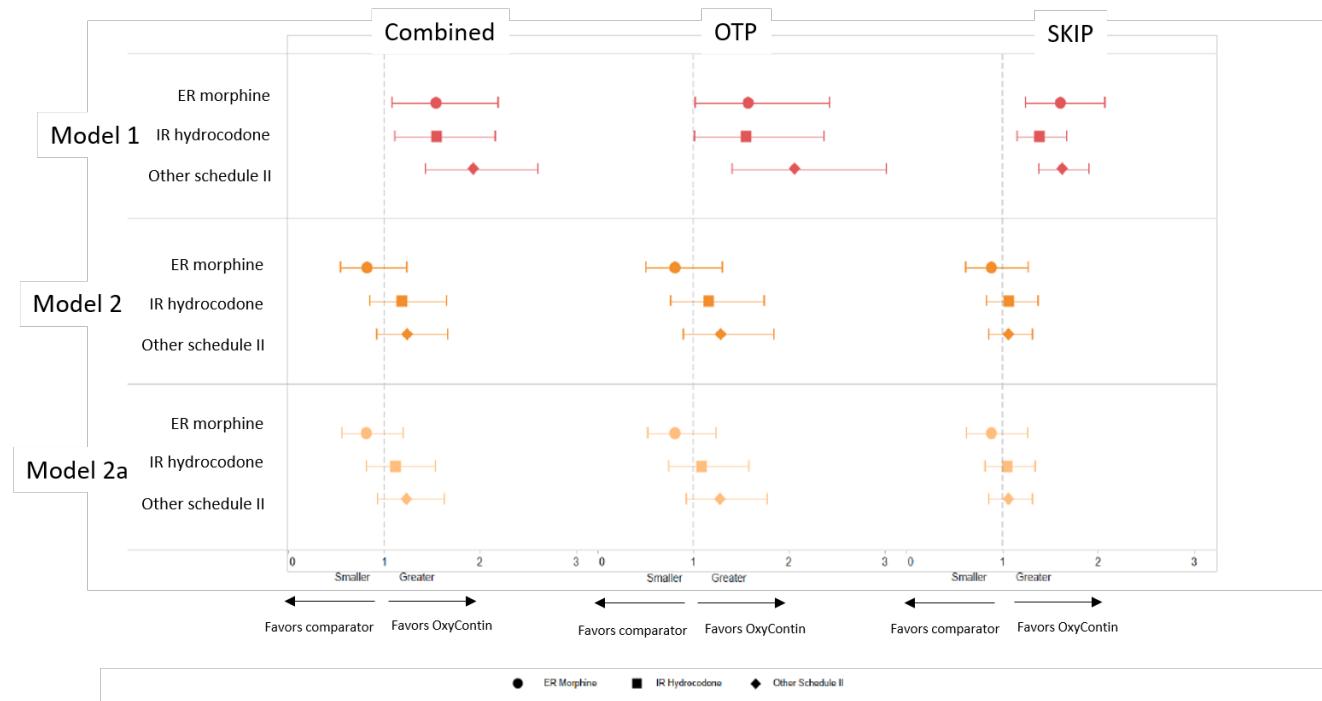
Comparative (difference-in-difference) means analyses: A ratio of rate ratios (RORR) was used to compare OxyContin's pre- to post-period change in mean abuse rate (rate ratio [RR]) to the comparator's change (RORR = [comparator RR] / [OxyContin RR]). An RORR >1 reflects a more favorable change in abuse rates for OxyContin relative to that of a comparator; in this context, favorable could mean a greater reduction or a smaller increase in abuse rates for OxyContin relative to comparators, or no change for

OxyContin but increasing abuse rates for comparators. An RORR <1 indicates a more favorable change for the comparator.

As shown in Figure D, the decrease in mean OxyContin abuse rate from the pre- to post-period per 100 respondents (model 1) was significantly larger than the decrease in the abuse rate for comparators. However, the decrease in mean OxyContin abuse rate per 100,000 dosage units dispensed (models 2 and 2a) from the pre- to post- period was not significantly larger than the decrease observed for any comparators, in OTP or SKIP separately, or in the combined population; the point estimate for ER morphine was <1 using these models.

Figure D: Ratios of Rate Ratios (95% CIs): Pre-post change in abuse rates of primary comparators versus OxyContin, in the RADARS combined, OTP and SKIP populations, -2y/5y

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Figure 7-4. Ratio of risk ratios (95% CI) of overall abuse risk of primary comparators versus overall abuse risk of OxyContin after introduction of reformulated OxyContin for the combined population, OTP population and SKIP population using different modelling approaches -2y/5y. P. 56.)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondents; Model 2 models abuse rate per tablets dispensed, Model 2a models abuse rate per tablets dispensed, adjusted for respondents as a covariate

Interrupted Time Series (ITS) Analyses: Figure E shows results of the ITS analyses for OxyContin and primary comparators, using rates per 100 respondents. Immediate shift (i.e., 'level change')[a] in abuse of OxyContin showed a -26.7% decrease, and there was a -

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[a] Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomization is not an option: interrupted time series analysis. *BMJ* 2015;350:h2750 doi: 10.1136/bmj.h2750

7.5% decrease in slope (i.e., quarterly trend). Comparative ITS (CITS) analyses, an analogous approach to the difference-in-difference means analyses (RORRs) above, compared the pre- to post-period changes in slope of quarterly abuse rates and immediate shift for OxyContin to those for comparators. OxyContin's decrease in slope and immediate shift were both significantly greater than those for IR hydrocodone but were not significantly different from those for ER morphine or "other schedule II opioids."

Figure E: ITS analysis for population-based (per 100 respondents) abuse rates of OxyContin and primary comparators, model 5, RADARS OTP and SKIP populations combined

	Immediate shift Percent change (95% CI)	P value immediate shift	Slope change Percent change (95% CI)	P value slope change
OxyContin	-26.7% (-41.0%, -8.9%)	Ref	-7.5% (-11.5%, -3.4%)	Ref
ER morphine	0.2% (-23.7%, 31.7%)	0.08	-2.2% (-7.5%, 3.4%)	0.12
IR hydrocodone	-1.3% (-13.6%, 12.8%)	0.02	-2.6% (-5.9%, 0.8%)	0.07
Other schedule II	-13.4% (-24.9%, -0.1%)	0.21	-5.7% (-8.5%, -2.8%)	0.47
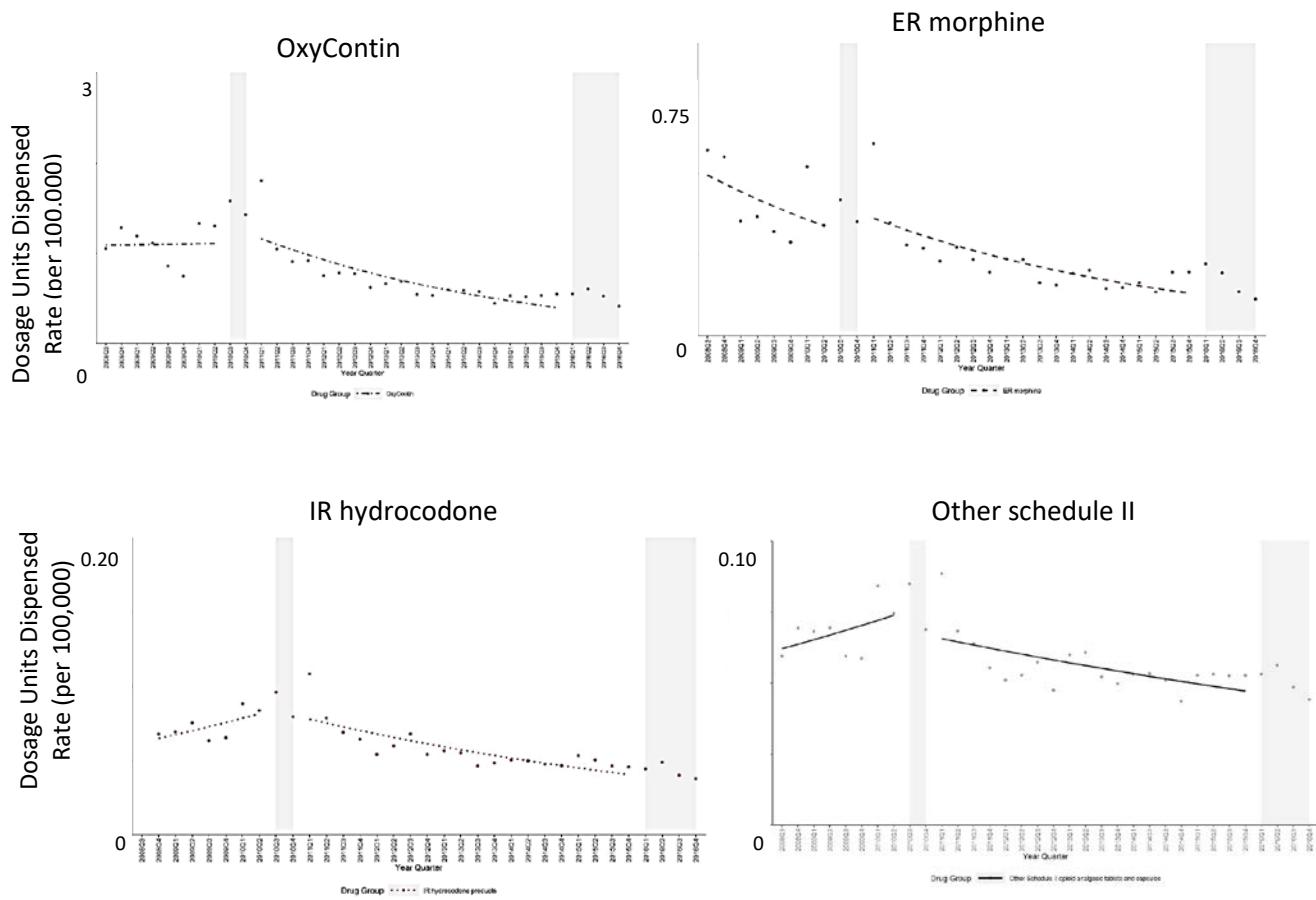
(Source: Purdue Pharma/RADARS® System RADARS® System OxyContin® PMR 3051-2 and 3051-3 Information Request Responses from FDA Received September 2019 (Part 3) Received March 6, 2020. P. 936-1014.)

Key: Points on graph are observed abuse rates. Lines are modeled ITS analyses. ER: Extended Release; IR: Immediate Release

Figure F shows ITS analysis for OxyContin and comparators' abuse rates per 100,000 dosage units dispensed. The immediate shift shows a slight increase in OxyContin abuse rate, while slope shows a modest decrease after the transition period. Neither of these changes is significantly different from the changes for any comparator.

Figure F: ITS analysis for utilization-based (per 100,00 dosage units dispensed) abuse rates of OxyContin and primary comparators, model 6, RADARS OTP and

SKIP populations combined

OxyContin

ER morphine

IR hydrocodone

Other schedule II

	Immediate shift, Percent change (95% CI)	P value Immediate shift	Slope change, Percent change (95% CI)	P value Slope change
OxyContin	4.9% (-21.4%, 39.9%)	Ref	-5.7% (-11.0%, -0.03%)	Ref
ER morphine	6.6% (-26.8%, 55.3%)	0.9	0.05% (-7.4%, 8.1%)	0.2
IR hydrocodone	-4.5% (-22.9%, 18.5%)	0.6	-6.9% (-11.9%, -1.7%)	0.7
Other schedule II	-11.1% (-26.9%, 8.0%)	0.4	-4.1% (-8.1%, 0.02%)	0.7

(Source: Purdue Pharma/RADARS® System RADARS® System OxyContin® PMR 3051-2 and 3051-3 Information Request Responses from FDA Received September 2019 (Part 3) Received March 6, 2020. P. 936-1014.)

Key: Points on graph are observed abuse rates. Lines are modeled ITS analyses. ER: Extended Release; IR: Immediate Release

Analyses of concomitant abuse: Figure G depicts results from an analysis published previously as a RADARS technical report, but that was included as part of the PMR 3051-3 final study report. This analysis examined trends in reported past 30-day abuse of comparator opioids, with and without concomitant reporting of past 30-day OxyContin

abuse. The analysis found that endorsements of ER morphine declined during the study period, particularly in the OTP population, but that the decline was driven by decreases in the percent of respondents endorsing abuse of both OxyContin and ER morphine in the past 30 days (middle panel), rather than in those endorsing abuse of ER morphine without endorsing OxyContin abuse (right panel). This pattern was similar for IR hydrocodone.

Figure G: Percent of respondents endorsing past 30-day abuse of ER morphine tablets/capsules with and without OxyContin in the RADARS System OTP and SKIP Programs (July 2009 to December 2015)

Source: Severtson SG et al (2016) RADARS System Technical Report, 2016-Q2. Available at: http://www.radars.org/Portals/1/TechReports/2016%202Q%20RADARS%20System%20QTR.pdf?ver=2016-09-19-085818-767&timestamp=1482174903929
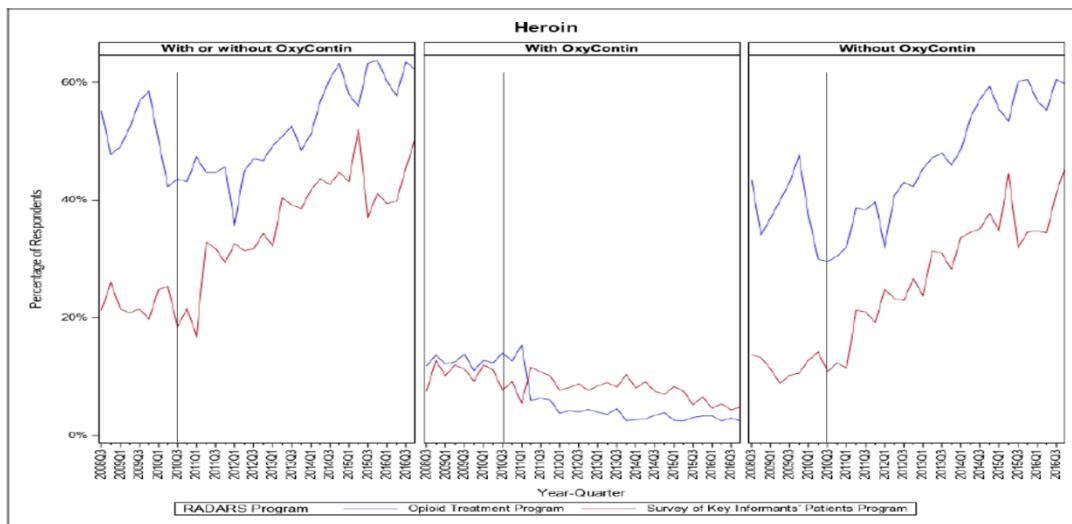
(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Percent of respondents endorsing past 30-day abuse of ER morphine tablets/capsules with and without OxyContin in the RADARS System OTP and SKIP Programs (July 2009 to December 2015). P. 130.)

Key: OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Vertical line denotes OxyContin reformulation, ER: Extended Release

While abuse of primary comparators generally decreased in the post-period, endorsements of heroin abuse increased, particularly in the SKIP population. As shown in Figure H, this increase was predominantly driven by individuals reporting past 30-day abuse of heroin without endorsing OxyContin abuse (right panel). Endorsements of heroin abuse without OxyContin abuse appeared to begin increasing in mid-2011.

Figure H: Percent of respondents endorsing past 30-day abuse of heroin with and without OxyContin in the RADARS System OTP and SKIP programs (2008-2016)

(Source: Results for OxyContin Information Request from FDA received December 5, 2019. Title: Figure 10. Heroin abuse with, without and total abuse with or without OxyContin during the study period for the Opioid Treatment Program (OTP) and the Survey of Key Informants' Patients (SKIP). P. 51)

Key: OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Vertical line denotes time of OxyContin reformulation

Discussion

Overall, the findings of PMR 3051-3 are mixed regarding whether OxyContin's reformulation had a meaningful effect on its rate of abuse among adults with opioid use disorders enrolling in methadone maintenance programs or in general substance abuse treatment programs. The lack of route-specific data limited the ability of this study to detect any changes in route-specific abuse patterns for OxyContin or comparators, as OxyContin was designed to deter only non-oral routes of abuse.

Descriptive quarterly trend figures suggested that, in the combined OTP and SKIP populations, the abuse rate peaked for OxyContin and all comparators during and shortly after the transition period, followed by a decline in the post-period. Model-estimated percent changes in mean abuse rates for OxyContin in the combined population showed a consistent decrease using the main models and variable definitions, but this was not true for all sensitivity analyses. In sensitivity analyses using different definitions of OxyContin (e.g., any ER oxycodone), geographic region restriction, site inclusion criteria, and time period, estimates of percent change for OxyContin ranged from +80.5% to -63.2%. As with comparator opioids, model 3, which adjusted for utilization as a covariate, produced estimates with large increases in abuse rates and very wide confidence intervals. Excluding model 3, estimated percent change for OxyContin ranged from -63.2% to +26.6%.

Comparative means analyses (RORRs) demonstrated significantly larger decreases in abuse rates for OxyContin than for primary comparators for model 1 only, which modeled the pre-post change in the mean abuse rates per 100 respondents. Using models 2 and 2a, which modeled pre-post change in mean abuse rates per 100,000 dosage units dispensed (without and with additional adjustment for the number of assessments, respectively), RORRs were not significant for any of the primary comparators, meaning that the decrease in the mean rate of OxyContin abuse per number of tablets dispensed in the community was not significantly different from the change observed for any of the primary comparators. Finally, ITS analyses of quarterly rates per 100 respondents found that the immediate decrease (i.e., level change) in abuse of OxyContin and the change in slope were both significantly greater than those for IR hydrocodone but not ER morphine or "other schedule II opioids." ITS analyses of utilization-based quarterly rates found that the immediate shift decrease and change in slope in OxyContin abuse rates were not significantly different from any of the primary comparators.

Consistent with the hypothesis that the reformulation reduced OxyContin abuse, the observed declines in population-based OxyContin abuse rates were significantly greater than those for primary comparators; however, decreases were not significantly larger for OxyContin than for comparators in utilization-based analyses (per dosage unit dispensed). It remains unclear how much of the change in prescription patterns was a direct result of the reformulation's impact on abuse liability (versus other factors such as the OxyContin REMS, law enforcement actions, and changes in insurance policies) and why decreases were observed in abuse rates for multiple comparator prescription opioids, particularly in the OTP population, following OxyContin's reformulation. Therefore, it is difficult to determine how much, if any, of the observed decline in OxyContin abuse reports in this population was directly caused by the reformulation.

The data also demonstrated a high prevalence of polysubstance abuse in this population, with the median number of drugs endorsed ranging from 5 to 11 drugs. Although this study was not designed to examine the impact of OxyContin's reformulation on the abuse of either prescription or illicit (heroin), opioids, the data do suggest some shifts in abuse patterns for other opioids that reflect the dynamic nature of substance use patterns and possibly, at least to some degree, some effect of the reformulation on these patterns. Post-hoc analyses, including some derived from a recent RADARS technical report, showed that the proportion of individuals abusing ER morphine or IR hydrocodone in addition to OxyContin decreased but there was no apparent change in the percentage of respondents who reported abusing these opioids without OxyContin. This was not the case for heroin, where there was a decrease in co-endorsement of OxyContin with heroin, but a marked increase in individuals endorsing abuse of heroin without OxyContin. This pattern suggests that some individuals who were abusing OxyContin along with other prescription opioids may have shifted their use to different prescription opioids or heroin following the reformulation.

This was an ecological study that compared aggregate measures of abuse across time periods. This type of study has particular limitations compared to studies that link an exposure/intervention and an outcome at the individual level.[b] Associations and patterns seen at the aggregate or group level may not reflect associations at the individual level—here, the likelihood, or risk, that an individual exposed to a product will abuse it. Therefore, caution is warranted in drawing inferences from an observed reduction in aggregate abuse prevalence or rates about the risk of people abusing a product, of transitioning from one route to another, or of progressing to more severe opioid use disorder.

A number of papers published in the scientific literature describe the changes in abuse of OxyContin and comparators during the time of the reformulation, and six of these studies analyzed RADARS OTP and SKIP data. Overall, these studies found decreases in OxyContin abuse rates after reformulation, consistent with the findings from PMR 3051-3; however, the decreases in OxyContin abuse rates reported in these publications were generally of greater magnitude than what was found in the PMR study and were significantly larger than the change observed for comparators. The differences between the published studies and PMR study estimates appeared to be related to differences in the time period assessed, regression model used to generate estimates, and choice of comparators. Follow-up interviews from a sample of SKIP participants found that respondents who abused OxyContin reported preferring the original formulation. Of those who had abused the original formulation, some reported switching from non-oral to oral abuse of OxyContin after it was reformulated, others reported defeating the abuse-deterrent properties to continue to abuse it non-orally, while others reporting substituting other opioids, commonly heroin. This last finding is generally consistent with the co-endorsement data from PMR 3051-1.

Conclusions

The findings of PMR 3051-3 were mixed and did not provide compelling evidence that the reformulation meaningfully reduced OxyContin abuse among adults with opioid use disorders enrolling in treatment programs. However, the lack of route-specific data limited the ability of this study to detect any potential changes in route-specific, particularly non-oral, abuse. OxyContin's reformulation was followed by an increase in heroin abuse, primarily in the SKIP population, although this study was not designed to assess whether the reformulation contributed causally to this increase. Per dosage units dispensed, OxyContin abuse rates remained higher than primary comparator opioids after reformulation; however, such comparisons must be made cautiously due to the inherent limitations of these data. These study results also illustrate the dynamic and inter-related

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[b] Morgenstern H. Ecologic Studies in Epidemiology: Concepts, Principles, and Methods. Annu Rev. Public Health. 1995. 16: 61-81.

nature of polysubstance abuse and the challenges of measuring and making causal inferences about the impacts of a single intervention on drug abuse patterns in this context.

2   INTRODUCTION

Postmarket required (PMR) study 3051-3 is one of four studies the United States (US) Food and Drug Administration (FDA) required to evaluate the impact of OxyContin®'s (hereafter, OxyContin) reformulation (August 2010) on its abuse. In brief, PMR study 3051-3 aimed to assess the effect of OxyContin's reformulation on overall abuse of OxyContin among individuals either entering methadone maintenance-based opioid use disorder treatment programs or individuals entering general substance abuse treatment programs who endorsed an opioid as a primary drug of abuse. OxyContin (oxycodone hydrochloride, controlled release; New Drug Application [NDA] 022272) was reformulated with physicochemical properties that are intended to deter tablet manipulation for the purposes of abuse primarily via insufflation (snorting) and injection. The reformulation incorporated a high molecular weight polymer (polyethylene oxide) matrix with the intention of making the tablet more difficult to manipulate for the purposes of misuse or abuse. Based on review of *in vitro* and clinical study data, in 2013 FDA concluded reformulated OxyContin had "abuse-deterrent" characteristics, and the label[c] was updated with its current language:

"The in vitro data demonstrate that OXYCONTIN has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the in vitro data, also indicate that OXYCONTIN has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OXYCONTIN by these routes, as well as by the oral route, is still possible."

Observational studies, including PMR study 3051-3, were required to provide further information on the ability of reformulated OxyContin to deter abuse and reduce abuse-related harms in the postmarket setting. Study 3051-3 used two sources of serial cross-sectional data to measure changes in the rates of overall abuse of OxyContin, as reported by individuals entering substance use disorder treatment, comparing the pre-reformulation period of OxyContin marketing to the post-reformulation period, relative to reporting of abuse of comparable opioid analgesic drugs marketed during that time. The three additional required studies evaluate changes from the pre- to post-reformulation in: 1) opioid abuse in a sentinel population of adults who were assessed for substance use disorder and treatment planning, using data from the National Addictions Vigilance Intervention and Prevention Program® (NAVIPPRO®) Addiction Severity Index-Multimedia Version (ASI-MV) surveillance system (PMR 3051-1); 2) opioid abuse-related exposure calls to US poison control centers, using data from the RADARS® Poison Control Program (PMR 3051-2); and 3) fatal and non-fatal opioid overdose among patients prescribed OxyContin or comparator opioids (PMR 3051-4).

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[c] https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022272s027lbl.pdf

The objective of this review is to determine whether data from PMR study 3051-3 support OxyContin's reformulation causing a reduction in abuse of OxyContin among individuals entering methadone maintenance-based opioid use disorder treatment programs or general substance abuse treatment programs.

In conjunction with the other PMR studies (3051-1, 2, and 4) and other relevant information, the findings of this study can be used to help inform the overarching question of whether OxyContin's reformulation meaningfully reduced its abuse and associated harms. While each study can alone provide important information on the impact of the reformulation, it is ultimately necessary to evaluate the totality of evidence from all sources to answer this question. (See OSE Summary Memo)

3   REVIEW METHODS AND MATERIALS

FDA approved a final study protocol for PMR 3051-3 in May 2017, and the sponsor submitted a final report for the study in April 2019. PMR 3051-3 assesses the changes in rates of overall abuse of OxyContin among participants in the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®, hereafter, RADARS) Survey of Key Informants' Patients (SKIP) and Opioid Treatment Program (OTP) programs.

To prepare this document, Department of Epidemiology (DEPI) reviewed:
- PMR study 3051-3 final study report (EPI8029ORF) - "*Assessment of the Effect of Reformulated OxyContin on Reported Abuse of OxyContin among Patients Treated in Substance Abuse Treatment Centers Using the RADARS® System Treatment Center Programs Combined.*" (received April 2019)
  - Study protocol
  - Statistical Analysis Plan (SAP)
  - Study results, including all appendices
- Sponsor submitted responses to information requests (received September 2019, December 2019) and teleconferences (January 2020) related to study 3051-3.
  - Received November 2019
  - Received January 2020
  - Received February 2020
  - Received March 2020

In brief, this review document provides a critical review of study 3051-3, including a summary of the study methods and main findings, as well as discussion of relevant methodological issues, analyses to try to address them, and how these impact inferences that can be made based on the study results. The findings of this review, along with the findings from the other PMRs and the literature, will be used to inform the broader

question of whether OxyContin's reformulation was effective in reducing abuse and associated harms (See OSE Summary Memo).

DEPI also conducted a review of published studies that used RADARS Treatment Center Program data (including OTP and/or SKIP) that may provide context or supplemental information to aid the interpretation of PMR study 3051-3; search terms and strategy are described in DEPI's comprehensive review of the published literature (Ref Lit Review). Six studies were identified that used the same data sources or study participants as PMR study 3051-3, and these were reviewed for any additional information that could inform our interpretation of the findings of PMR study 3051-3.

3.1.1 Overarching Methodological Considerations

RADARS OTP and SKIP allow estimation of the prevalence of abuse of OxyContin and comparator opioids within a geographically diverse but non-representative convenience sample of patients entering treatment for opioid use disorders. The complex and evolving nature of the opioid crisis, as well as inherent limitations of the data source, required a number of overarching methodologic considerations that informed the design and analytic approaches used in this study. Foremost among these were changes in the prescribing/dispensing of opioid analgesics over time, other population-based interventions occurring during the study period, the potential for product misclassification and changes to the survey instrument during the study period, and potential bias introduced by the use of a non-representative and dynamic sample of treatment program sites. Due to the inherent uncertainties associated with these data and the lack of a standard approach to defining all parameters of the analysis, a range of estimates were produced by varying these parameters.

3.2   STUDY OVERVIEW

PMR study 3051-3 assesses the change in self-reported past month abuse of selected opioids before and after OxyContin reformulation, in a population of adults enrolling in methadone maintenance treatment programs (OTP population) and a population of adults entering general substance abuse treatment programs who endorsed an opioid as their primary drug of abuse (SKIP population). Comparator opioids included in this evaluation aid in causal inference by approximating the counterfactual scenario (i.e., what would have been expected to happen with OxyContin abuse trends had the drug not been reformulated) and to provide contextual information on broader abuse trends unrelated to the reformulation. Due to the inherent uncertainties associated with these data and this study design (e.g., product misclassification and changes made to the survey instrument during the study period, the use of a dynamic convenience sample, and potential for confounding by secular trends) a number of different analyses were conducted, including varying the time period, the definition of OxyContin, the site inclusion criteria, and the

models and offsets/covariates used to estimate abuse rates and account for changes in drug utilization over time. These varied approaches assess the robustness of the overall study findings with regard to the effect of the reformulation on abuse rates in this population.

3.3 STUDY OBJECTIVES/SPECIFIC AIMS/SCOPE

Primary objectives

1. Assess the changes in rate of overall abuse of OxyContin in SKIP, OTP, and combined populations, two years before reformulation versus (vs.) five years after the reformulation (-2y/5y)
2. Assess the changes in rate of overall abuse of OxyContin in SKIP, OTP, and combined populations, relative to changes in abuse of primary comparator opioids (-2y/5y)
3. Assess the changes in rate of overall abuse of OxyContin in SKIP, OTP, and combined populations, one year before reformulation vs. three years after reformulation (-1y/3y)
4. Assess the changes in rate of overall abuse of OxyContin relative to changes in abuse of primary comparator opioids (-1y/3y)

Secondary Objectives

1. Assess the changes in trends in abuse of OxyContin and comparator opioids using descriptive and interrupted times series analytic methods
2. Assess the changes in rate of overall abuse of OxyContin relative to secondary comparator opioids (-2y/5y)
3. Assess the changes in rate of overall abuse of OxyContin relative to secondary comparator opioids (-1y/3y)
4. Evaluation of survey changes

3.4 STUDY METHODS

3.4.1 Design & Setting

3.4.1.1 Study Design

Ecological times series using serial cross-sectional survey data.

3.4.1.2 Databases

RADARS Treatment Center Program (TCP)

The RADARS TCP is comprised of the OTP and SKIP programs, which record the specific prescription opioids reported by persons entering treatment for opioid use disorders. The OTP program collects information primarily from public facilities that use medication-assisted treatment, while the SKIP includes primarily private facilities that do not use medication-assisted treatment. Each patient is offered the opportunity to complete

an anonymous, standardized, self-administered paper-based questionnaire that solicits information on specific prescription drugs "used to get high" in the past 30 days.

IQVIA National Prescription Audit™

The IQVIA National Prescription Audit™ (hereafter, NPA) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, and long-term care facilities into the hands of consumers via formal prescriptions in the US; data for the NPA audit are a national level estimate of the drug activity from these three channels. The pharmacies in the database account for most retail pharmacies and represent ~92% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data are also collected from approximately 60 – 86% (varies by class and geography) of mail service pharmacies and approximately 75 – 83% of long-term care pharmacies.

3.4.2 Drug Utilization

Nationwide trends in monthly tablets dispensed were estimated for OxyContin, primary comparators, and secondary comparators using IQVIA (formerly known as IMS Health or QuintilesIMS) National Prescription Audit (NPA) data. These trends were used to understand differences in dispensing patterns of OxyContin and comparators over the entire time period. Estimates generated from the IQVIA NPA data source were used additionally as covariates in regression models that used dosage units dispensed as either an offset or a covariate.
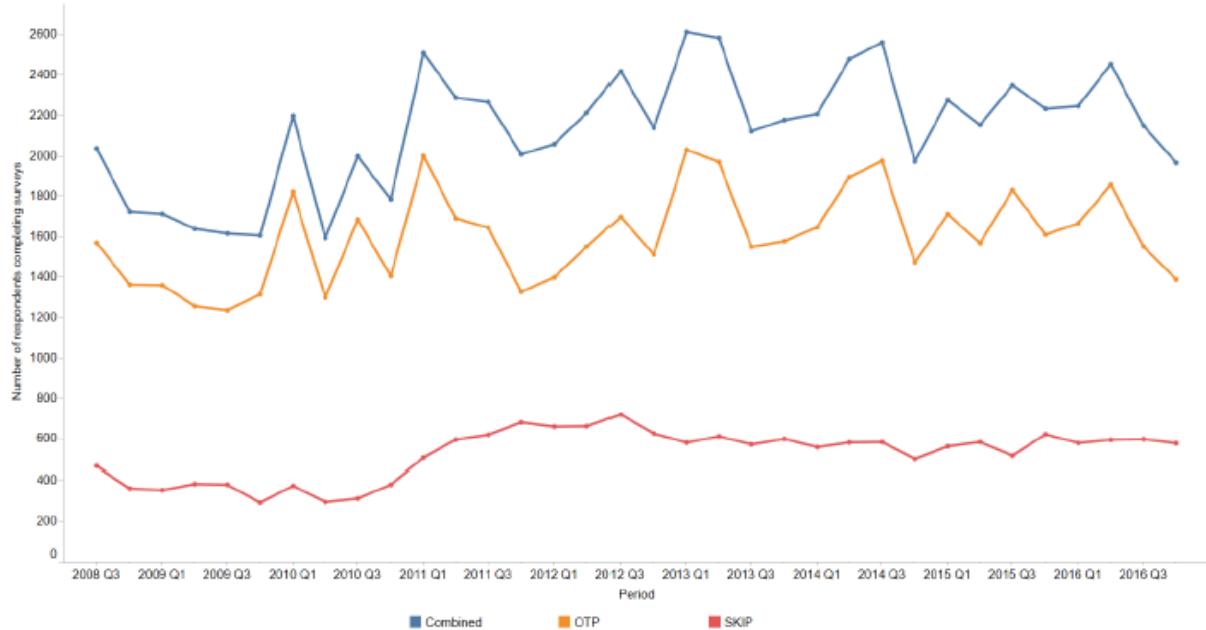
3.4.3 Population

The study population for PMR 3051-3 is a combination of two separate groups of adults treated in substance abuse treatment centers for opioid use disorder across RADARS System centers. The OTP program surveys adults enrolling in methadone maintenance treatment programs and the SKIP program surveys adults entering general substance abuse treatment programs who endorsed an opioid as their primary drug of abuse.

The study population represents a dynamic convenience sample; the geographic distribution of participating sites, relative contribution of OTP and SKIP sites, and the number and demographics of individuals being surveyed changes over time. Figure 1 below shows the number of respondents completing surveys by quarter in the study period for the OTP population, SKIP population, and combined. The OTP population is larger than the SKIP population, and is more heavily weighted in the combined population, but the SKIP population increases in 2011, and therefore the percentage of

the combined population composed of SKIP respondents changes over time. To better understand how this affects the estimated abuse rates, most analyses present results stratified by OTP and SKIP, in addition to the combined populations.

Figure 1: Number of respondents completing surveys across treatment centers by quarter for the RADARS combined population, OTP population, and SKIP population (3Q2008-4Q2016)

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Number of respondents completing surveys across treatment centers by quarter for the combined population, OTP population and SKIP population (3Q2008-4Q2016). P. 21.)

Key: OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients;

The number of eligible assessments meeting the study inclusion criteria varied by quarter. The main analyses used site inclusion criteria of ≥1 assessment during the study period. Site inclusion criteria for main analysis and sensitivity analyses are listed below:

- Site inclusion criteria:
  o Sites contributing at least one assessment during the study period (**main**)
  o Sites contributing at least one assessment per quarter
  o Sites contributing at least one assessment per year (excluding those contributing at least one assessment per quarter)
  o Sites that contributed <1 assessment per year

Analyses with site inclusion criteria of at least 1 assessment/quarter maintain a consistent set of sites and number of assessments (although with substantially reduced sample size and geographic coverage). The subsequent site inclusion criteria categories are mutually exclusive, and aid our understanding of which sites are not consistently contributing assessments, and how they might differ from the core set of sites that are contributing consistently.

Table 1 below provides number of OTP sites and surveys for the main -2y/5y time period.

Table 1: Sites/surveys included in OTP and SKIP samples
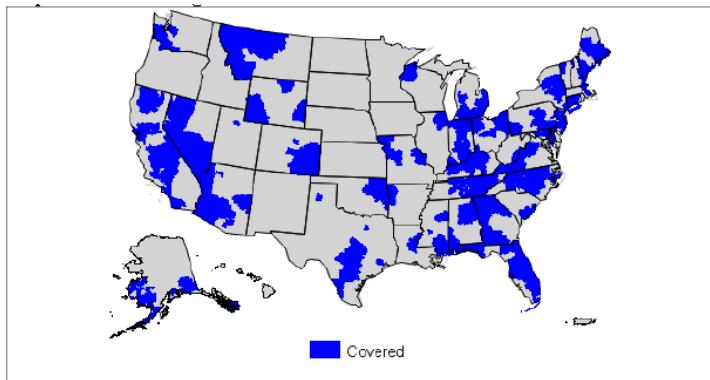
Label	Description	Number OTP sites and surveys	Number SKIP sites and surveys
-2y/5y	2-year pre-reformulation (3Q2008-2Q2010)/ 5-year post-reformulation (1Q2011-4Q2015)	• Pre-period: up to 64 sites/year • Post-period: up to 76 sites/year • 35 states • ~6,400 surveys annually	• Pre-period: up to 58 sites/year • Post-period: up to 154 sites/year • 50 states • ~2,100 surveys annually

(Source: FDA generated table from final study report PMR 3051-3)

Key: OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients
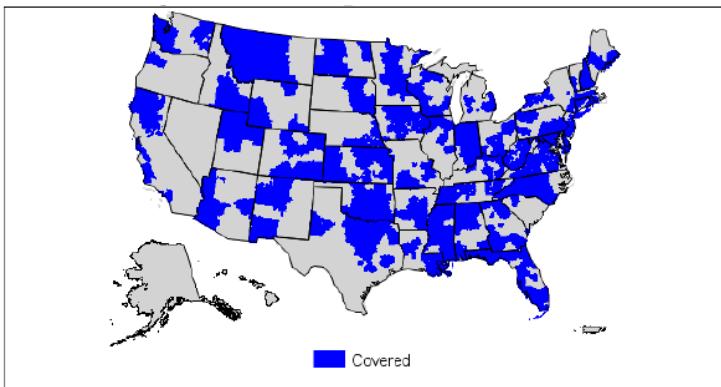
Figure 2-4 below shows geographic coverage for the OTP, SKIP, and combined populations. Combined, these two populations have considerable coverage across the entire US, although the coverage is not consistent across study quarter or years.

Figure 2: RADARS system opioid treatment program (OTP) coverage based on respondents' three-digit ZIP code - 2015
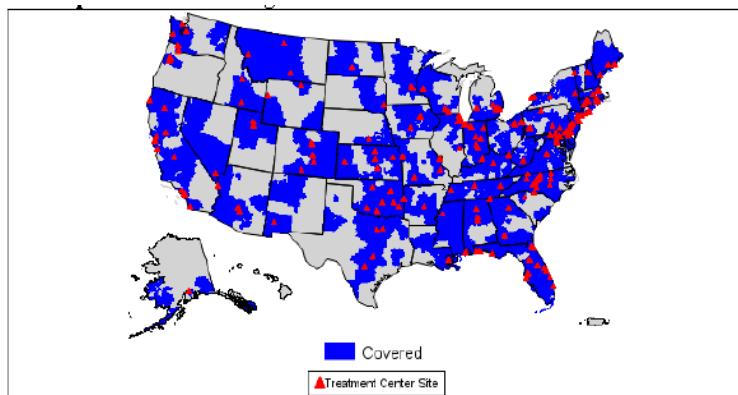
(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: RADARS System Opioid Treatment Program Coverage Based on Respondents' Three-Digit ZIP code – 2015. P. 107.)

Figure 3: RADARS system survey of key informants' patients (SKIP) coverage based on the respondents' three-digit ZIP code - 2015

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: RADARS® System Survey of Key Informants' Patient Coverage Based on the Respondents' Three-Digit ZIP code - 2015. P. 108.)

Figure 4: RADARS system treatment center programs combined (OTP and SKIP), coverage based on the respondents' three-digit ZIP code; and participating treatment center sites - 2015
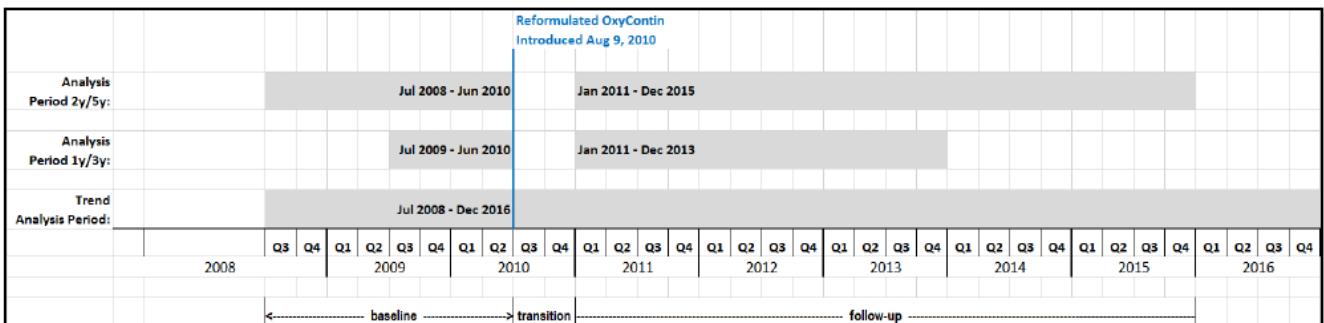
(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: RADARS System Treatment Center Programs Combined (Opioid Treatment Program/Survey of Key Informants' Patients) Coverage Based on the Respondents' Three-Digit ZIP code - 2015. P. 108.)

3.4.4   Time Period

The study period for PMR 3051-3 is broken down into three components: 1) pre-period before OxyContin reformulation, 2) transition period during the transition from original OxyContin to reformulated OxyContin, and 3) post-period after OxyContin reformulation. Two time periods were selected, a -2y/5y period (main), and a -1y/3y period (sensitivity) (Figure 5).

Figure 5: Study time periods

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Study analyses time periods. P. 19.)

3.4.5   Outcome Measurement and Definition of OxyContin

In this study, the primary outcome is past-month abuse of OxyContin or comparator opioids, and time period (i.e., before vs. after introduction of reformulated OxyContin) serves as the "exposure". The RADARS OTP and SKIP surveillance programs use paper-based surveys to examine drug abuse by asking respondents to select the names of specific prescription drugs that they used "to get high" in the past month before entering treatment.[d]

The surveys for both programs underwent a number of revisions during the study period, with several major survey changes occurring early in the post-reformulation period. Survey changes that occurred during the study period are described below:

- In 2Q2011:
    - The Opioid Treatment Program (OTP) survey was changed from a one-sided to a two-sided survey
    - In both programs (OTP and SKIP), the text "to get high" was added to each section of the drug matrix rather than in a header
    - Oxycodone was moved from the second block of the first page to the second to last block on the last page (page 2 in the OTP survey. Similarly, the block location of oxycodone was moved in the SKIP survey.)
- In 4Q2010:
    - In both programs, "Oxycodone, type unknown" was moved to the first position within the oxycodone block
- From 4Q2011 to 1Q2013
    - The wording within the IR oxycodone question was changed from "Oxycodone Immediate Release tablets (such as Percocet or Percodan)" to "Oxycodone Immediate Release tablets"

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[d] In previous regulatory documents, FDA has defined *abuse* as the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. In this review, we use RADARS' definition of abuse as described here. FDA recognizes that the term *abuse* has been identified as potentially stigmatizing to individuals with substance use disorders. This is in no way our intent; rather, we are using the term abuse to describe a specific behavior as defined in the PMR study.

In analyses supported by FDA to better understand the quality of information collected in these admission surveys, RADARS found that endorsement for specific opioids were affected by changes to question wording and/or formatting. Findings from this research also showed that the proportion of endorsements for brand vs. generic did not correlate with prescription dispensing data, indicating that misclassification of generic as brand occurs differentially (i.e., brand is more likely to be endorsed than generic, the "Kleenex" effect). These analyses also identified "careless responders", defined as any survey that endorsed nine or more consecutive items in a column or endorsed more than 23 opioid products in the past 30-days. In the PMR 3051-3 final report, "careless responders" were excluded.

To understand the effect of misclassification of self-reporting of OxyContin in these surveys, two different exposure definitions were included, as described below:

- o OxyContin (any) (main)*
- o ER oxycodone (sensitivity)

The first definition is the most specific and provides the abuse rate for OxyContin only. The second definition includes OxyContin, specific oxycodone generics, and any unknown ER oxycodone endorsements. In the pre-period, no ER oxycodone product, brand or generic, had abuse deterrent properties. After the reformulation, virtually all ER oxycodone dispensed was brand OxyContin, formulated with abuse deterrent properties. Due to this difference in the proportion of brand vs. generic tablets dispensed in the pre- and post-reformulation periods, and the possibility of clients selecting the well-known, brand-name tablet over the generic tablet, this sensitivity analysis was conducted to understand how misclassification of generic oxycodone and brand OxyContin might affect the change in abuse rates from the pre- to post-reformulation period.

In the OTP and SKIP surveys, there was never a distinction between original and reformulated OxyContin. The only option for OxyContin was labeled OxyContin tablet, and this could be selected regardless of formulation. Therefore, all definitions of OxyContin in this study include both original and reformulated OxyContin as one category, with different interpretation in the pre- vs post-periods.

3.4.6 Comparators

Primary and secondary comparator opioids (table 2) were selected to assess percent change in abuse of opioids on the market contemporaneously with OxyContin. These opioids are expected to be similarly affected by concurrent interventions and secular trends but are theoretically not (directly) influenced by OxyContin reformulation, and therefore serve as an approximation of the counterfactual (i.e., what would have happened with OxyContin abuse rates had it not been reformulated). Extended release

(ER) morphine, immediate release (IR) hydrocodone-combination products, and a composite "other schedule II opioids" category were chosen as primary comparators for the study. ER morphine and IR hydrocodone-combination products were chosen as primary comparators because of their large and stable market shares, and because they are captured in a consistent manner in the OTP and SKIP programs throughout the study period. The composite "other schedule II opioids" category was included as an additional primary comparator in an attempt to approximate utilization and abuse trends for a broader group of opioid analgesics; however, "other schedule II opioids" is a composite category whose composition changes over time and whose trends are driven heavily by products with large market shares, predominantly IR hydrocodone and oxycodone products. For example, dispensing of IR oxycodone single entity (SE) increased +78.0% from the pre- to post-reformulation time periods, comprising a larger proportion of this composite comparator in the post-period, and ER hydromorphone was only approved for marketing in 2010, so it was not available during the pre-period.

Table 2: Summary of comparators

Primary Comparators	Secondary Comparators
ER morphine	IR oxycodone
IR hydrocodone-acetaminophen combination products	Methadone
"Other schedule II" opioid analgesic tablets and capsules: • IR oxycodone SE and combination products • IR hydrocodone combination products • ER hydrocodone • ER and IR morphine • ER and IR oxymorphone • ER and IR hydromorphone	Heroin

(Source: FDA generated table from final study report 3051-3)
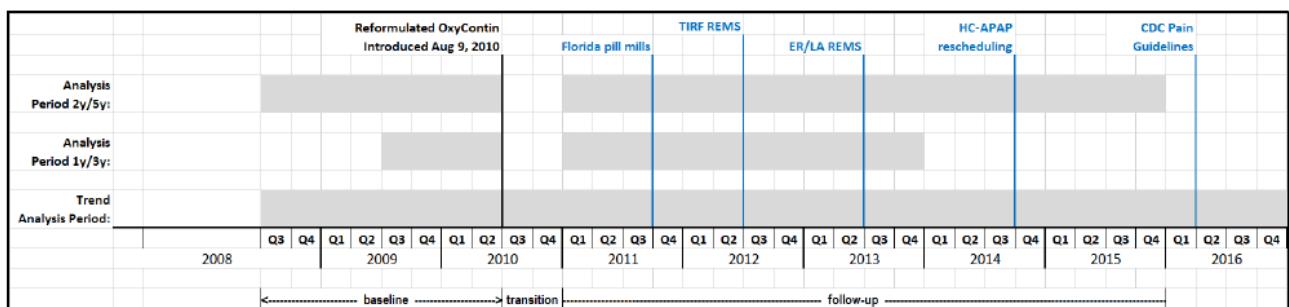
Key: ER: Extended Release; IR: Immediate Release; SE: Single Entity

3.4.7   Additional Analyses to Explore the Possible Effects of other Opioid Interventions

To understand the causal association between reformulation and change in abuse rate of OxyContin, it is necessary to isolate the effect of the abuse deterrent formulation (ADF) properties from that of other interventions in a changing landscape of opioid use and abuse. Below is a description of concurrent population-based opioid interventions that might have affected OxyContin abuse rates.

Acknowledging the potential for various other interventions to affect trends in opioid use and abuse, the sponsor included Figure 6, based on a 2017 publication, which depicts a timeline of *some* population-based opioid interventions occurring during and following the three study time periods. For example, multifaceted legislation in Florida, was enacted in June 2011 (as noted in the timeline below), intended to eliminate pill mills in one state where they had proliferated, supplying prescription drugs to other states through interstate trafficking (Surrat, 2014)[e]. However, not noted in the sponsor's figure were the Drug Enforcement Administration's (DEA) major law enforcement actions beginning earlier, most notably "Operation Oxy alley" in February 2010 and Operation Pill Nation, which was implemented from February (Q1) 2011 -August (Q3) 2012 to arrest pill mill owners, physicians, and staff and seizing assets (Kennedy-Hendricks, 2016)[f]. Also noted are the transmucosal IR fentanyl (TIRF) risk evaluation and mitigation strategy (REMS) and the extended release/long acting (ER/LA) REMS, both of which had the goal of reducing serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of these classes of prescription opioids. In 3rd quarter 2014 hydrocodone combination products were rescheduled by the DEA from schedule III to schedule II of the controlled substances act, and in 1st quarter of 2016 the Centers for Disease Control (CDC) released their pain guideline that gave expert-consensus recommendations for opioid prescribing for the treatment of chronic pain in primary care. Of note, a REMS for OxyContin was approved in 2010, and is not included in the figure.

Figure 6: Timeline of examples of population-based opioid interventions

Reference: (Dart et al., 2017); Florida Pill Mills = multifaceted legislation in Florida, enacted June 2011, was designed to eliminate "pill mills" (medical practices suspected of irresponsibly prescribing opioid analgesics for dubious health benefit) and are hypothesized to have had an effect beyond Florida due to interstate diversion. TIRF REMS = transmucosal IR fentanyl risk evaluation and mitigation strategy. ER/LA REMS = extended release/long-acting risk evaluation and mitigation strategy. HC-APAP rescheduling = rescheduling of hydrocodone-acetaminophen combination products from Schedule III to Schedule II (DEA, 2014); CDC Pain Guideline = Centers for Disease Control and Prevention (Dowell et al., 2016).

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Study analyses time periods. P. 19.)

As described above, a number of population-based opioid interventions were occurring at the same time as OxyContin reformulation. A number of important law enforcement and

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[e] Surratt HL, O'Grady C, Kurtz SP, Stivers Y, Cicero TJ, Dart RC, et al. Reductions in prescription opioid diversion following recent legislative interventions in Florida. *Pharmacoepidemiol Drug Saf*. 2014;23(3):314–20.

[f] Kennedy-Hendricks A, Richey M, McGinty EE, Stuart EA, Barry CL, Webster DW. "Opioid Overdose Deaths and Florida's Crackdown on Pill Mills", *American Journal of Public Health* 2016;106(2):291-297.

interventions and legislative actions in 2010 and 2011 to address the proliferation of unregulated pain clinics, or "pill mills" were focused on the state of Florida, but may have had effects in a broader area through trafficking and diversion of dispensed drugs. To understand the effect of this intervention on OxyContin abuse rates, a number of stratifications were conducted by geographic region. These three geographic region definitions are described below:

- Entire coverage area (main)
- Entire coverage area excluding Florida
- West census region only

The main analyses used treatment centers in the entire coverage area of the US to create estimates for the change in overall abuse rates. To isolate the effect of this intervention from the effect of OxyContin reformulation, a second analysis excluded Florida, and a third analysis included the western census region only. The western census region isolates states geographically distinct from Florida and that therefore may be less likely to be impacted by Florida's legislative and law enforcement actions.

3.4.8 Statistical Models and Covariates

There is no single, standard denominator or modeling approach to estimate abuse rates. Using total assessments as a denominator (population-based analyses) allows us to understand the prevalence, or proportion, of abuse of particular products within a surveyed population of individuals with opioid use disorder. Using dosage units dispensed as a denominator (utilization-based analyses) allows us to understand the rate of abuse of a specific drug, relative to the prescribed availability of that drug in communities. Prescribed availability is important to account for when comparing abuse rates across different drugs and time periods, as a drug has to be available in the community to be abused; however, this does not take into consideration that desirability for abuse might also drive prescribing and dispensing of a drug. Therefore, in this study both population- and utilization-based or adjusted abuse estimates were used to analyze change in rates over time, incorporating utilization metrics (here, number of tablets dispensed in the coverage area), as either an offset (i.e., modeling the change in utilization-based rate) or a covariate (i.e., adjusting for the independent contribution of utilization to abuse estimates). Table 3 below presents the models used in this analysis.

Table 3: Summary of statistical regression models

Model Number	Regression Structure	Offset	Covariate	Objective
Model 1	Poisson regression model	Number respondents	NA	Pre-post means analysis, descriptive trend analysis

Model 1a*	Poisson regression model	Number respondents	Dosage Units Dispensed	Pre-post means, descriptive trend analysis
Model 2	Poisson regression model	Dosage Units Dispensed	NA	Pre-post means, descriptive trend analysis
Model 2a	Poisson regression model	Dosage Units Dispensed	Number respondents	Pre-post means, descriptive trend analysis
Model 3	Poisson regression model	NA	Dosage Units Dispensed	Pre-post means, descriptive trend analysis
Model 3a	Poisson regression model	NA	Dosage Units Dispensed, Number respondents	Pre-post means, descriptive trend analysis
Model 4a	Poisson regression model	NA	Dosage Units Dispensed (categorical), Number respondents	Pre-post means, descriptive trend analysis
Model 5	Interrupted Time Series Poisson	Number respondents	NA	Interrupted time series (ITS), immediate shift and change in slope
Model 5a*	Interrupted Time Series Poisson	Number respondents	Dosage units dispensed	ITS, immediate shift and change in slope
Model 6	Interrupted Time Series Poisson	Dosage Units Dispensed	NA	ITS, immediate shift and change in slope
Model 6a*	Interrupted Time Series Poisson	Dosage Units Dispensed	Number respondents	ITS, immediate shift and change in slope
Model 7	Interrupted Time Series Poisson	NA	Dosage units dispensed	ITS, immediate shift and change in slope
Model 7a	Interrupted Time Series Poisson	NA	Dosage units dispensed, number respondents	ITS, immediate shift and change in slope
Model 8a	Interrupted Time Series Poisson	NA	Dosage Units Dispensed (categorical), number respondents	ITS, immediate shift and change in slope

*Model 1a, 5a, and 6a were not included in the protocol or SAP and are not reported here.

Model 3a has potential collinearity issue between period and dosage units dispensed.

Model 4a was not run due to high collinearity of dosage units dispensed and period.

Model fit diagnostics are included in appendix 6.1.

A note on terminology - in the final study report, the sponsor refers to a "ratio of risk ratios" to assess changes in abuse rate for OxyContin versus comparators. It is important to keep in mind that this is an ecological study using serial cross-sectional data and does not assess risk in the traditional sense, i.e., the probability of an event occurring as a

function of time, as in a cohort study where well-defined populations at risk for an outcome are followed through time to estimate the incidence of an event of interest over a particular time period. Instead this study measures the number of reports of abuse of specific drugs over defined periods of time and can be conceptualized as either a proportion or prevalence (e.g., percent of total surveys endorsing a specific drug) or a rate or even a ratio (e.g., abuse reports per units of drug dispensed during a time period). **In this review, we use the term "rate" in a general manner to refer to the various estimates produced by regression models, and to RORR as "ratio of rate ratios".**

3.5   STUDY RESULTS

3.5.1   Drug Utilization

As shown in Figure 7, there was a sharp decline in OxyContin tablets dispensed in January 2005 following temporary loss of the patent, and a corresponding increase in generic ER oxycodone tablets. The OxyContin patent was reinstated in 2007, after which the number of dispensed OxyContin tablets increased to similar levels as those before the patent was lost. However, some generics remained on the market until all patent lawsuits were settled and generics exited the market in 2011. There was a rapid transition from original to reformulated OxyContin after introduction of the reformulated product in August 2010, followed by a steady decrease in OxyContin dispensing.

Figure 7: OxyContin tablets dispensed per quarter between 1Q2005 and 4Q2014 as assessed in the IQVIA database
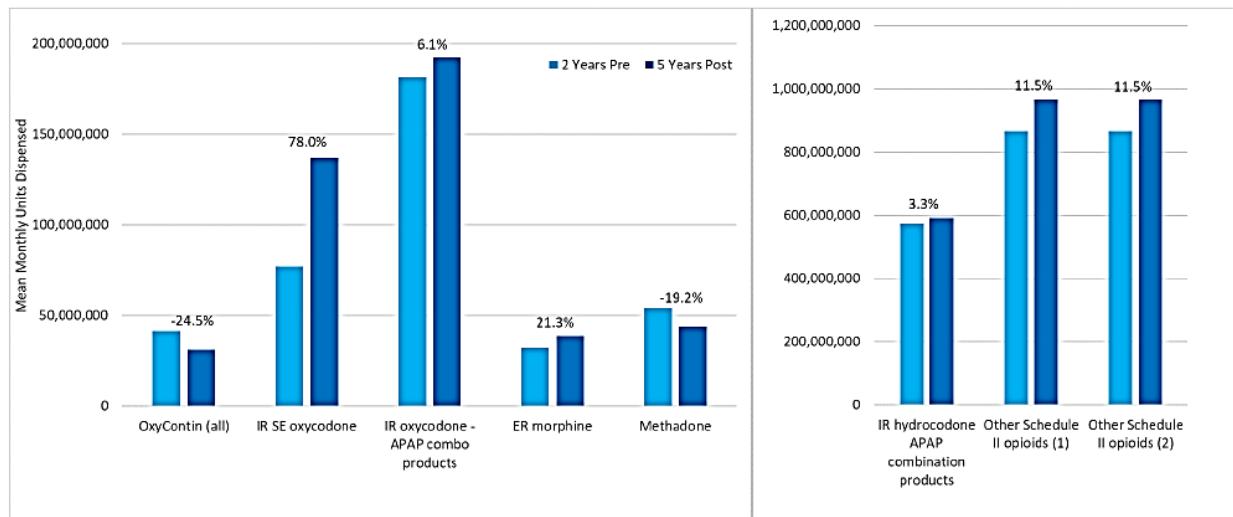
All OxyContin= original and reformulated OxyContin; Note: the all OxyContin line (black) covers the original OxyContin line (solid blue) in the pre-reformulation period and covers the reformulated OxyContin line (dashed blue) in the post-reformulation period

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Appendix Figure 4-1. OxyContin tablets per quarter between 1Q2005 and 4Q2014 as assessed by retail pharmacy dispensing in the IQVIA database. P. 180.)

Key: ER: Extended Release

OxyContin and methadone showed a decrease from the pre- to post-period, while all other comparators (IR SE oxycodone, IR oxycodone-APAP products, ER morphine, IR hydrocodone APAP products, and "other schedule II opioids") showed increases from pre- to post-period (see Figure 8 below).

Figure 8: Percent change in dosage units dispensed for OxyContin and comparator opioids, IQVIA, -2y/5y
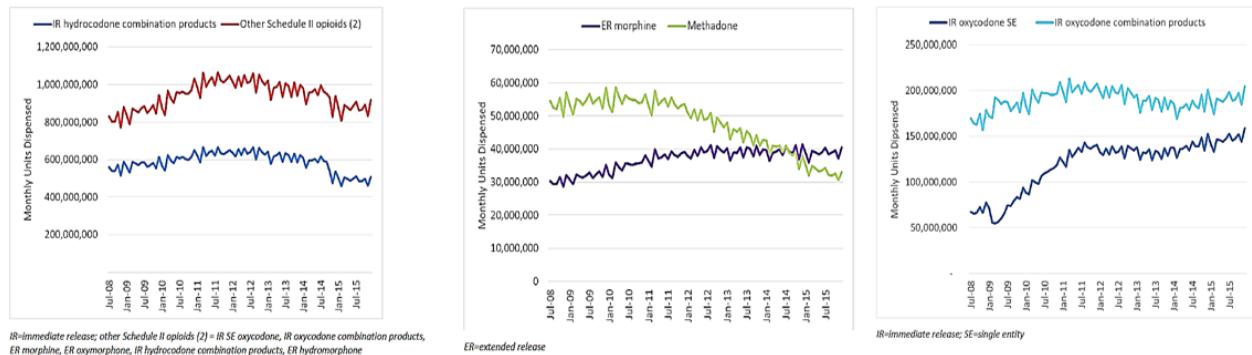
IR=immediate release; SE=single entity; ER=extended release; other Schedule II opioids (1) = IR SE oxycodone, IR oxycodone combination products, ER morphine, ER oxymorphone, IR hydrocodone combination products; other Schedule II opioids (2) = IR SE oxycodone, IR oxycodone combination products, ER morphine, ER oxymorphone, IR hydrocodone combination products, ER hydromorphone (This definition was used in the study.)

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Appendix Figure 4-2. Percent change in dosage units dispensed for OxyContin and comparator opioids -2y/5y. P. 182.)

Key: ER: Extended Release; IR: Immediate Release; SE: Single Entity

Figure 9 below shows monthly dosage units dispensed for IR hydrocodone, "other schedule II opioids", ER morphine, methadone, IR oxycodone SE, and IR oxycodone combination products. "Other schedule II opioids" and IR hydrocodone each show an increase in dispensing from 2008 to 2010, then plateau in 2011, at which point dispensing declines. ER morphine dispensing increased consistently through 2012 and then plateaus, while methadone was stable through 2010 and then dispensing began decreasing in 2011 and continued to decrease through 2015. IR oxycodone SE increased sharply from 2009 to the beginning of 2012, and then increased slightly more through 2015, capturing an increasing proportion of the oxycodone market from the beginning to the end of the study period. IR oxycodone combination products increased until 2011 and then plateaued and declined slightly.

Figure 9: Monthly dosage units dispensed for IR hydrocodone combination products, other schedule II opioids, methadone, ER morphine, IR oxycodone SE, and IR oxycodone combination products from IQVIA July 2008-December 2015

(Source FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Appendix Figure 4-4. Monthly dosage units dispensed for IR hydrocodone combination products and other schedule II opioids (2) from July 2008-December 2015. P. 184 (left). Title: Appendix Figure 4-6. Monthly dosage units for methadone and ER morphine opioids from July 2008-December 2015. P. 186. (middle). Title: Appendix figure 4-5. Monthly dosage units dispensed for IR oxycodone single entity and IR oxycodone combination products from July 2008-December 2015. P. 185 (right).)

Key: ER: Extended Release; IR: Immediate Release; SE: Single Entity

3.5.1.1 Descriptive Characteristics of Patients Included in OTP and SKIP Study Populations

Table 4 shows descriptive demographic data for patients in the combined population included during the study period, stratified into pre- and post-periods. Descriptive demographic data for the OTP and SKIP populations are presented separately in appendix 6.2. In the combined population, respondents endorsing OxyContin, ER morphine, IR hydrocodone, and "other schedule II opioids" were mostly white, with mean age in their early 30's. Slightly greater than 50% were male. The median number of drugs endorsed for those endorsing OxyContin or IR hydrocodone combination products was 8, median number of drugs endorsed for those endorsing "other schedule II opioids" was 7, and median number of drugs endorsed for those endorsing ER morphine was 11. The demographics of the population endorsing these opioids did not change substantially from the pre- to post-periods, although the median number of endorsed products decreased slightly in each category, to 5 for those who endorsed "other schedule II opioids", 6 for those who endorsed IR hydrocodone combination products, 7 for those who endorsed OxyContin, and 9 for those who endorsed ER morphine.

These population demographics were most heavily influenced by the OTP population because the majority of respondents come from in the OTP program. The SKIP population was similar to the OTP population in gender and age but had a slightly higher

percentage of non-white respondents, and the median number of drugs endorsed increased in the post-reformulation period (Tables 14-15, appendix 6.2).

Table 4: Characteristics of the RADARS combined population stratified by OxyContin and primary comparator opioids in the 2-year <u>pre-period (left)</u> and 5-year <u>post-period (right)</u>

Value	OxyContin	ER Morphine	IR Hydrocodone	Other Schedule II
Gender[1]				
Male [Frequency (%)]	2,567 (53.75)	679 (54.23)	1,791 (49.46)	3,174 (50.06)
Female [Frequency (%)]	1,899 (39.76)	481 (38.42)	1,561 (43.11)	2,735 (43.13)
Age				
Mean (SD)	31.14 (9.59)	32.68 (10.35)	33.2 (10.35)	33.05 (10.38)
Median (IQR)	28 (24, 36)	30 (25, 38)	30 (25, 40)	30 (25, 39)
N	4,645	1,208	3,519	6,156
Race[2]				
White [Frequency (%)]	4,224 (88.44)	1,128 (90.10)	3,049 (84.20)	5,422 (85.51)
Latino [Frequency (%)]	196 (4.10)	45 (3.59)	210 (5.80)	340 (5.36)
African-American [Frequency (%)]	154 (3.22)	34 (2.72)	196 (5.41)	293 (4.62)
Native American [Frequency (%)]	106 (2.22)	29 (2.32)	99 (2.73)	161 (2.54)
Asian or Pacific Islander [Frequency (%)]	26 (0.54)	9 (0.72)	15 (0.41)	32 (0.50)
Other [Frequency (%)]	75 (1.57)	12 (0.96)	57 (1.57)	97 (1.53)
Number of Items Endorsed				
Mean (SD)	8.80 (5.02)	11.37 (5.62)	9.04 (5.23)	8.28 (4.87)
Median (IQR)	8 (5, 12)	11 (7, 15)	8 (5, 12)	7 (5, 11)
N	4,776	1,252	3,621	6,341

[1]Respondents with unknown values for gender were not included in this table, therefore percentages for gender do not add to 100%. [2]Respondents could mark more than one race, therefore frequencies may add to more than 100%. SD: standard deviation; IQR: interquartile range; ER=extended release; IR=immediate release; IR Hydrocodone=IR hydrocodone combination products.

Value	OxyContin	ER Morphine	IR Hydrocodone	Other Schedule II
Gender[1]				
Male [Frequency (%)]	3,621 (53.39)	1,475 (53.93)	5,044 (50.83)	8,835 (50.88)
Female [Frequency (%)]	3,073 (45.31)	1,222 (44.68)	4,785 (48.22)	8,349 (48.08)
Age				
Mean (SD)	32.56 (9.65)	33.5 (9.69)	33.52 (9.88)	33.04 (9.81)
Median (IQR)	30 (25, 38)	31 (26, 39)	31 (26, 39)	31 (26, 38)
N	6,735	2,715	9,874	17,266
Race[2]				
White [Frequency (%)]	5,909 (87.13)	2,480 (90.68)	8,470 (85.35)	15,076 (86.81)
Latino [Frequency (%)]	270 (3.98)	81 (2.96)	435 (4.38)	690 (3.97)
African-American [Frequency (%)]	326 (4.81)	86 (3.14)	578 (5.82)	924 (5.32)
Native American [Frequency (%)]	205 (3.02)	76 (2.78)	335 (3.38)	509 (2.93)
Asian or Pacific Islander [Frequency (%)]	46 (0.68)	16 (0.59)	65 (0.65)	106 (0.61)
Other [Frequency (%)]	93 (1.37)	29 (1.06)	146 (1.47)	254 (1.46)
Number of Items Endorsed				
Mean (SD)	8.30 (5.25)	10.20 (5.57)	7.70 (5.00)	6.71 (4.62)
Median (IQR)	7 (4, 11)	9 (6, 14)	6 (4, 10)	5 (3, 9)
N	6,782	2,735	9,924	17,366

[1]Respondents with unknown values for gender were not included in this table, therefore percentages for gender do not add to 100%. [2]Respondents could mark more than one race, therefore frequencies may add to more than 100%. SD: standard deviation; IQR: interquartile range; ER=extended release; IR=immediate release; IR Hydrocodone=IR hydrocodone combination products.
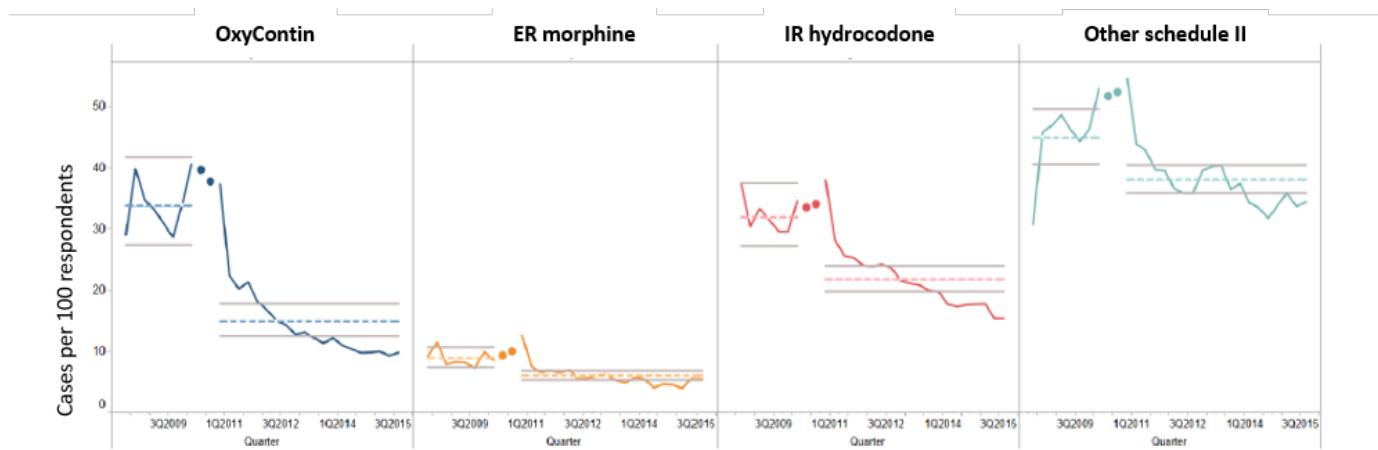
(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Table 7-1. Demographic characteristics of the combined population stratified by OxyContin and primary comparator opioids (3Q2008-2Q2010). P. 42. Title: Table 7-2. Demographic characteristics of the combined population stratified by OxyContin and primary comparator opioids (1Q2011-4Q2015). P. 43.)

Key: ER: Extended Release; IR: Immediate Release

3.5.2 Descriptive Trend Analyses

Figure 10 below shows observed quarterly and estimated mean abuse rates per 100 respondents. OxyContin and the three comparators show declines immediately following introduction of reformulated OxyContin; however, OxyContin shows the sharpest decrease immediately following the transition period. These plots also show that OxyContin rates of abuse per 100 respondents were higher than ER morphine, comparable to IR hydrocodone, and lower than the composite "other schedule II opioids" category in the pre-period. In the post period, the rate of OxyContin abuse dropped below "other schedule II opioids" and IR hydrocodone but remained higher than ER morphine.

Figure 10: Observed and model 1 estimated (95% CI) rate of abuse cases per 100 respondents over time for OxyContin and primary comparators (3Q2008-4Q2015), RADARS OTP and SKIP combined

CI: confidence interval. The solid line shows the observed values and the dashed line represents the model-estimated values for each quarter. 95% CIs are shown as the grey solid line. Observed values for the transition period (3Q2010 and 4Q2010) are shown as points. ER=Extended release; IR=Immediate release; IR Hydrocodone=IR hydrocodone combination products

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Figure 7-5 Descriptive trend figure of observed and model-estimated (95% CI) abuse (3Q2008-4Q2015) for Model 1: rate of abuse per number of respondents, for OxyContin and primary comparators. P. 60.)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondents; Parameters: entire US region, sites contributing >1 assessment during the study period, any OxyContin

Figure 11 shows observed quarterly and estimated mean abuse rates for OxyContin and primary comparators, per 100,000 dosage units dispensed. Here, a pronounced peak is evident for OxyContin and comparators in abuse rates during the transition period as well as the first quarter of the post-period, followed by a sharp decline. Throughout the pre- and post-periods, the rate of abuse cases for OxyContin per 100,000 dosage units dispensed was substantially higher than ER morphine, IR hydrocodone, and "other schedule II opioids".

Figure 11: Observed and model 2 estimated (95% CI) rate of abuse cases per 100,000 dosage units dispensed over time for OxyContin and primary comparators (3Q2008-4Q2015), RADARS OTP and SKIP combined, *note difference in y-axis scale for insets*

CI: confidence interval. The solid line shows the observed values and the dashed line represents the model-estimated values for each quarter. 95% CIs are shown as the grey solid line. Observed values for the transition period (3Q2010 and 4Q2010) are shown as points. ER=Extended release; IR=Immediate release; IR Hydrocodone=IR hydrocodone combination products

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Descriptive trend figure of observed and model-estimated (95% CI) abuse (3Q2008-4Q2015) for Model 2: rate of abuse per dosage units dispensed, for OxyContin and primary comparators P. 61.)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 2 models abuse rate per tablets dispensed; Parameters: entire US region, sites contributing ≥1 assessment during the study period; any OxyContin

Figure 12 shows observed and model-estimated trend plots for the rate of abuse per 100,000 dosage units dispensed adjusting for number of respondents for OxyContin and primary comparators. Again, each opioid group showed a peak during the reformulation period, with a subsequent decline in abuse rates. OxyContin had the highest rate of abuse per 100,000 dosage units dispensed adjusting for number of respondents as compared with ER morphine, IR hydrocodone, and "other schedule II opioids".

Figure 12: Observed and model 2a estimated (95% CI) rate of abuse cases per 100,000 dosage units dispensed over time for OxyContin and primary comparators, adjusted for number of respondents (3Q2008-4Q2015)[g], RADARS OTP and SKIP combined

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[g] Model 1 and Model 2 include one predictor variable for each time period (pre- and post-periods), with population or drug utilization adjusted for as offset variables. With an offset adjustment, the expected rate is the same each quarter during the time period. With an offset adjustment, quarterly differences in the denominator correspond to proportional changes in the expected numerator value so that the expected rate remains the same across quarters within the time period.

Model 2a includes an offset variable, but also includes an all pharmaceutical exposures in addition to time period as predictor variables. Model 3 and Model 3a include variables other than time period (e.g. dosage units dispensed, all pharmaceutical exposures) as covariates in the regression model. Unlike Model 1 and Model 2, the expected value will be different if the covariate value is different each quarter.
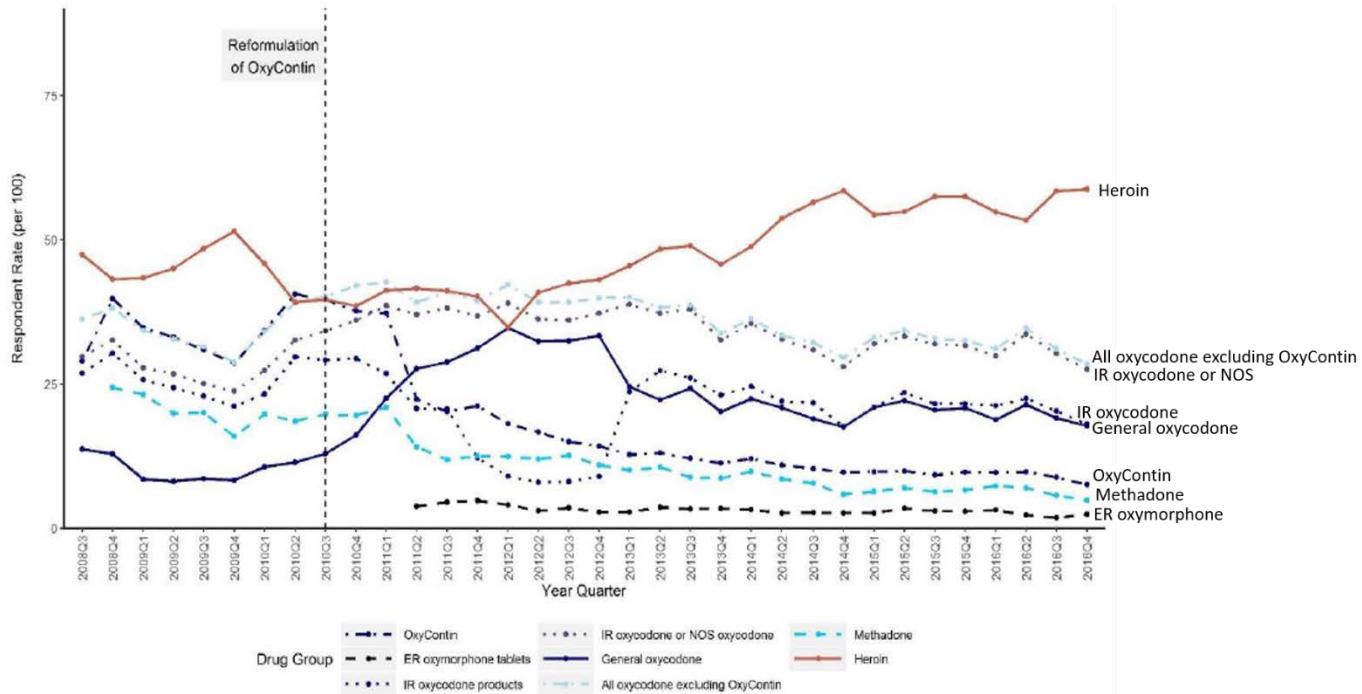
CI: confidence interval. The solid line shows the observed values and the dashed line represents the model-estimated values for each quarter. 95% CIs are shown as the grey solid line. Observed values for the transition period (3Q2010 and 4Q2010) are shown as points. ER=Extended release; IR=Immediate release; IR Hydrocodone=IR hydrocodone combination products

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Descriptive trend figure of observed and model-estimated (95% CI) abuse (3Q2008-4Q2015) for Model 2a: rate of abuse per dosage units dispensed and adjusting for the number of respondents, for OxyContin and primary comparators P. 61.)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 2 models abuse rate per tablets dispensed; Parameters: entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

Figure 13 shows observed quarterly trends for OxyContin and secondary comparators per 100 respondents. General oxycodone began to rise in 3Q2010 and plateaued in 1Q2012, while heroin began to rise in 1Q2012 and continued to increase. IR oxycodone and not otherwise specified (NOS) oxycodone began to increase in 4Q2009 and plateaued in 1Q2011. IR oxycodone decreased from 4Q2010 until 4Q2012 when it rose and plateaued in 2Q2013.

Figure 13: Observed rate of abuse for OxyContin and secondary comparators per 100 respondents, RADARS OTP and SKIP combined population
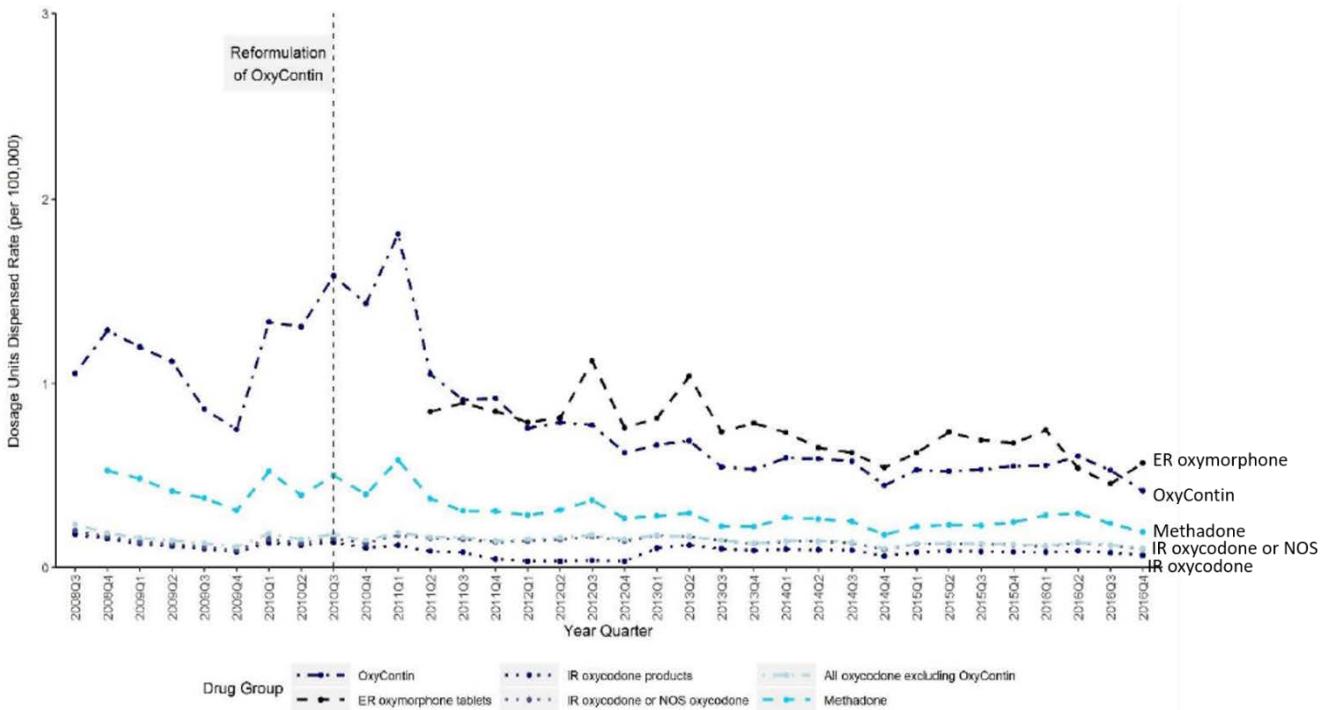
(Source: Purdue Pharma/RADARS® System RADARS® System OxyContin® PMR 3051-2 and 3051-3 Information Request Responses from FDA received September 2019 (Part 3) received March 6, 2020. Title: observed respondent rate. P. 684.)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondents; Parameters: entire US region, sites contributing ≥1 assessment during the study period

Figure 14 shows observed quarterly rates of abuse for OxyContin and comparators per dosage units dispensed. Utilization-based rates of abuse for OxyContin were higher than all secondary comparators until 2Q2012 when the rate of ER oxymorphone abuse became higher.

Figure 14: Observed rate of abuse for OxyContin and secondary comparators per 100,000 dosage units dispensed, RADARS OTP and SKIP combined population

(Source: Purdue Pharma/RADARS® System RADARS® System OxyContin® PMR 3051-2 and 3051-3 Information Request Responses from FDA received September 2019 (Part 3) received March 6, 2020. Title: b) observed dosage unit dispensed rate. P. 685.)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 2 models abuse rate per tablets dispensed; Parameters: entire US region, sites contributing >1 assessment during the study period

3.5.3 Pre- and Post-period Past Month Abuse of OxyContin and Primary Comparators

Table 5 below presents mean quarterly model-estimated rates of abuse for OxyContin and primary comparators per 100 respondents (model 1), per 100,000 dosage units dispensed (model 2), or per 100,000 dosage units dispensed adjusted for number of respondents (model 2a) for the combined population and stratified by OTP and SKIP. The mean OxyContin abuse rate dropped from 33.8 endorsements per 100 respondents to 14.9 endorsements per 100 respondents in the combined population, a decrease of approximately 50%, which is more than the decrease for any primary comparator. The decrease in the mean Oxycontin abuse rate in SKIP was substantially smaller than in OTP. In utilization-based analyses (model 2), the mean OxyContin abuse rate decreased from 1.1 endorsements per 100,000 dosage units dispensed to 0.7 in the combined population, a decrease of approximately 30% which is smaller than the decrease observed for ER morphine. Again, the decrease for OxyContin was substantially smaller in SKIP compared to OTP.

Table 5: Pre- and post-period, mean quarterly model-estimated abuse rates for OxyContin, ER morphine, IR hydrocodone, and "other schedule II opioids", RADARS OTP, SKIP, and combined populations (-2y/5y)

		Model 1 Mean quarterly estimated abuse cases/100 respondents		Model 2 Mean quarterly estimated abuse cases/100,000 dosage units dispensed		Model 2a Mean quarterly estimated abuse cases /100,000 dosage units dispensed, adjusted for number respondents	
		Pre-period mean	Post-period mean	Pre-period mean	Post-period mean	Pre-period mean	Post-period mean
OxyContin	Combined	33.8	14.9	1.1	0.7	1.3	0.7
	OTP	33.9	12.5	1.2	0.7	1.3	0.7
	SKIP	33.5	21.6	0.6	0.5	0.6	0.5
ER morphine	Combined	8.9	6.0	0.4	0.2	0.5	0.2
	OTP	9.2	5.3	0.5	0.2	0.5	0.2
	SKIP	7.7	8.0	0.2	0.1	0.2	0.1
IR hydrocodone	Combined	31.9	21.8	0.1	0.1	0.1	0.1
	OTP	30.4	17.3	0.1	0.1	0.1	0.0
	SKIP	38.1	34.3	0.0	0.0	0.1	0.0
Other schedule II opioids	Combined	44.9	38.1	0.1	0.1	0.1	0.1
	OTP	43.6	33.1	0.1	0.1	0.1	0.1
	SKIP	49.8	52.2	0.0	0.0	0.0	0.0

(Source: FDA generated table from 3051-3 Final Study Report. Data from appendix 12.)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: -2y/5y, entire US region, sites contributing $\geq$1 assessment during the study period, any OxyContin

Figure 15 (and table 16 in appendix 6.3) show the percent change in overall abuse of OxyContin and primary comparators post-reformulation for the combined population, and separately for the OTP and SKIP populations. While OxyContin had a larger decrease in rate of abuse post-reformulation compared to competitors in population-based analyses (model 1), ER morphine demonstrated the largest decrease in rate of abuse in utilization-based analyses (model 2) and in utilization-based analyses adjusting for number of respondents (model 2a). The OTP populations had a larger percent decrease for OxyContin abuse compared to the SKIP population regardless of the model. Figure 34

in appendix 6.4 shows percent change for OxyContin alone, without comparators, and shows similar changes.

Figure 15: Percent change (95% CI) in mean past-month abuse rate after introduction of reformulated OxyContin, for OxyContin and primary comparators, RADARS OTP/SKIP combined, OTP, and SKIP separately, -2y/5y

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Figure 7-3. Percent change (95% CI) in overall abuse of OxyContin and primary comparators after introduction of reformulated OxyContin for the combined population, OTP population and SKIP population using different modeling approaches, -2y/5y. P. 54.)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: -2y/5y, entire US region, sites contributing ≥ 1 assessment during the study period, any OxyContin

Figure 16 (and table 17 appendix 6.3) show ratios of rate ratios (RORRs) for OxyContin and primary comparators. RORR is a type of difference-in-differences model[1] whereby an interaction term tests for a statistically significant relative difference in rate ratios comparing OxyContin's rate ratio to each comparator opioids rate ratio, further referred to as a ratio of rate ratios (RORR). The RORR parameter can be interpreted as relative

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[1] https://www.annualreviews.org/doi/full/10.1146/annurev-publhealth-040617-013507

comparison in the rates (null=1) whereby an RORR>1 favors OxyContin with respect to the change in post- to pre-reformulation periods, and an RORR<1 favors the comparator.

RORR for all primary comparators for all populations are significant in population-based analyses (model 1) indicating a larger decrease in overall abuse of OxyContin compared to the primary comparators. None of the RORRs for primary comparators were significant using models 2 and 2a, which are utilization-based. RORRs for models 3 and 3a, which adjust for utilization as a covariate, are presented in appendix 6.3. These models produced mixed results.

Figure 16: Ratios of Rate Ratios (95% CIs): Pre-post change in abuse rates of primary comparators versus OxyContin, in the RADARS combined, OTP, and SKIP populations, -2y/5y

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Figure 7-4. Ratio of risk ratios (95% CI) of overall abuse risk of primary comparators versus overall abuse risk of OxyContin after introduction of reformulated OxyContin for the combined population, OTP population and SKIP population using different modelling approaches -2y/5y. P. 56.)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: -2y/5y, entire US region, sites contributing >1 assessment during the study period, any OxyContin

3.5.3.1   Sensitivity analysis: additional <u>regression models</u>

Table 6 below presents percent change estimates of mean quarterly abuse rates for OxyContin and comparators using model 3 (no offset, covariate dosage units dispensed), and model 3a (no offset, covariate dosage units dispensed and number respondents).

Overall, model 3 produced percent change estimates with very wide confidence intervals, which often include zero, indicating that this model provides estimates with low precision. Model 3a also had low precision for ER morphine. This model had potential collinearity issues between period and dosage units dispensed.

Table 6: Percent change (95% CI) in mean past-month abuse rate of OxyContin and primary comparators for models 3, and 3a, RADARS combined population, -2y/5y

	OxyContin	ER morphine	IR hydrocodone	"Other schedule II opioids"
Model 3	-20.0% (-44.7% to 15.8%)	63.6% (-5.7% to 183.7%)	-21.3% (-40.4% to 3.9%)	-19.4% (-42.8% to 13.4%)
Model 3a	-40.7% (-59.5% to -13.2%)	32.7% (-14.4% to 105.9%)	-35.3% (-50.6% to -15.3%)	-27.9% (-46.6% to -2.8%)
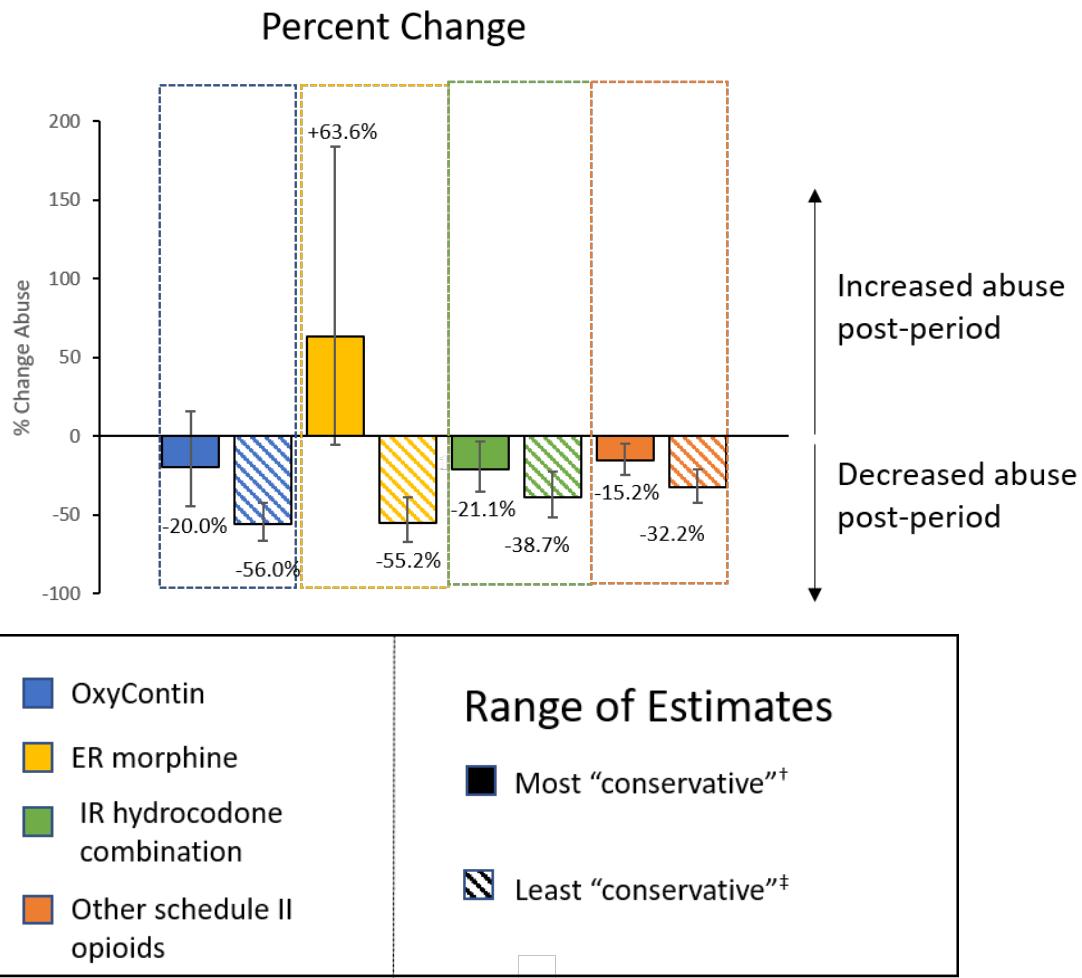
(Source: FDA generated table from Final Study Report 3051-3)

Key: ER: Extended Release; IR: Immediate Release; Model 3 models abuse rate adjusted for tablets dispensed as a covariate; Model 3a models abuse rate adjusted for tablets dispensed and respondents as covariates; Parameters: -2y/5y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

3.5.3.2   Range of estimates for percent change in mean quarterly abuse rates and RORRs

Figure 17 below presents the most and least "conservative" estimates (i.e., the smallest pre-post reduction [or largest increase] and largest pre-post reduction [or smallest increase] in abuse rates, respectively) for percent change in mean quarterly abuse of OxyContin and primary comparators in the analyses described above. Range figures below contain estimates from models 1, 2, 2a, 3, and 3a. OxyContin, IR hydrocodone, and "other schedule II opioids" all show decreased rates of abuse for their most and least "conservative" estimates. The least "conservative" estimates (i.e., largest estimated reductions) for OxyContin and ER morphine are comparable, with slightly smaller reductions for IR hydrocodone and "other schedule II opioids." The most "conservative" estimate of change for OxyContin is comparable to the decrease for IR hydrocodone and "other schedule II opioids". For ER morphine, models 3, and 3a produced estimates with large confidence intervals, which is why an increase is observed for the most "conservative" estimate.

Figure 17: Most and least "conservative" values for estimated percent change in OxyContin and primary comparator mean quarterly abuse rates with main parameters* and all regression models for RADARS combined population

Percent Change

(Source: FDA generated figure from Information Request Response)

Key: ER: Extended Release; IR: Immediate Release; †Most "Conservative": Smallest pre-post reduction (or largest increase) in abuse; ‡Least "Conservative": Largest pre-post reduction (or smallest increase) in abuse; *Main parameters: -2y/5y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

Figure 18 below shows the most and least "conservative" RORR estimates (i.e., the smallest RORR values, and the largest RORR values) for change in abuse rate for primary comparators vs. OxyContin. The most "conservative" estimates for ER morphine, IR hydrocodone, and "other schedule II opioids" are 1.0 or below, indicating no significant difference between the percent decrease observed for OxyContin and the percent decrease observed for comparators. The least "conservative" RORR estimates demonstrate a significantly larger decrease in abuse for OxyContin than that observed in primary comparators. In general, the most "conservative" RORR estimates are those that are utilization-based or adjust for utilization, while the least "conservative" RORR estimates are those that are population-based.

Figure 18: Most and least conservative values for estimated RORRs for primary comparators vs. OxyContin with main parameters* and all regression models for RADARS <u>combined population</u>

(Source: FDA generated figure from Information Request Response)

Key: ER: Extended Release; IR: Immediate Release; †Most "Conservative": Smallest pre-post reduction (or largest increase) in OxyContin abuse relative to comparator's change; ‡Least "Conservative": Largest pre-post reduction (or smallest increase) in OxyContin abuse relative to comparator's change; *Main parameters: -2y/5y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

Table 20 in appendix 6.5 presents the models associated with these estimates.

Figure 19 below presents the range of estimates produced by primary variables for all regression models for percent change in abuse of OxyContin and primary comparators in

the OTP population. Percent change in OxyContin abuse ranged from +1.9% to -63.2%, while all estimates for abuse of primary comparators showed a decrease.

Figure 19: Most and least conservative values for estimated percent change in OxyContin and primary comparator mean quarterly abuse rates with main parameters* and all regression models for RADARS <u>OTP population</u>

(Source: FDA generated figure from Information Request Response)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; †Most "Conservative": Smallest pre-post reduction (or largest increase) in abuse; ‡Least "Conservative": Largest pre-post reduction (or smallest increase) in abuse; *Main parameters: -2y/5y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

Figure 20 below presents range of RORRs produced for change in abuse of primary comparators vs. OxyContin, for main variable definitions with all models, in the OTP population. The most "conservative" RORR estimates produced non-significant RORRs that showed a larger decrease in comparator abuse than OxyContin, while the least "conservative" RORR estimates showed a significantly larger decrease in OxyContin

abuse than comparators. In general, the most "conservative" RORR estimates were produced by models that are utilization-based, while the least conservative RORR estimates were produced by models that are population-based.

Figure 20: Most and least conservative values for estimated RORRs for primary comparators vs. OxyContin with main parameters* and all regression models for RADARS® <u>OTP population</u>

Ratio of Rate Ratios

(Source: FDA generated figure from Information Request Response)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; †Most "Conservative": Smallest pre-post reduction (or largest increase) in OxyContin abuse relative to comparator's change; ‡Least "Conservative": Largest pre-post reduction (or smallest increase) in

OxyContin abuse relative to comparator's change; *Main parameters: -2y/5y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

Table 21 in appendix 6.5 presents the models associated with these estimates.

Figure 21 below presents range of estimates for percent change in OxyContin abuse and abuse of comparators for the SKIP population, with main variable definitions and all models. Unlike the OTP population, where all comparators showed a decrease in percent abuse for all models, the most "conservative" estimates for percent decrease in comparators all showed an increase in abuse. OxyContin showed a decrease for the most and least "conservative" estimates. Generally, decrease in abuse of OxyContin and comparators is more apparent in the OTP population than the SKIP population.

Figure 21: Most and least "conservative" values for estimated percent change in OxyContin and primary comparator mean quarterly abuse rates with main parameters* and all regression models for RADARS <u>SKIP population</u>
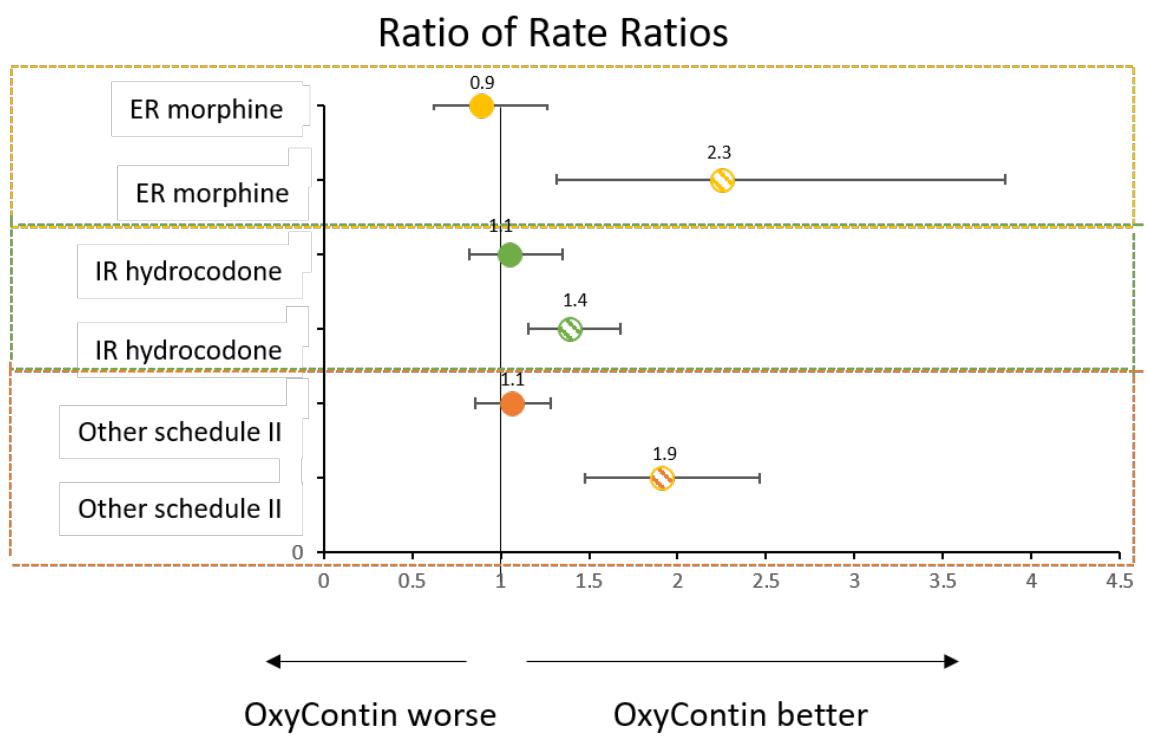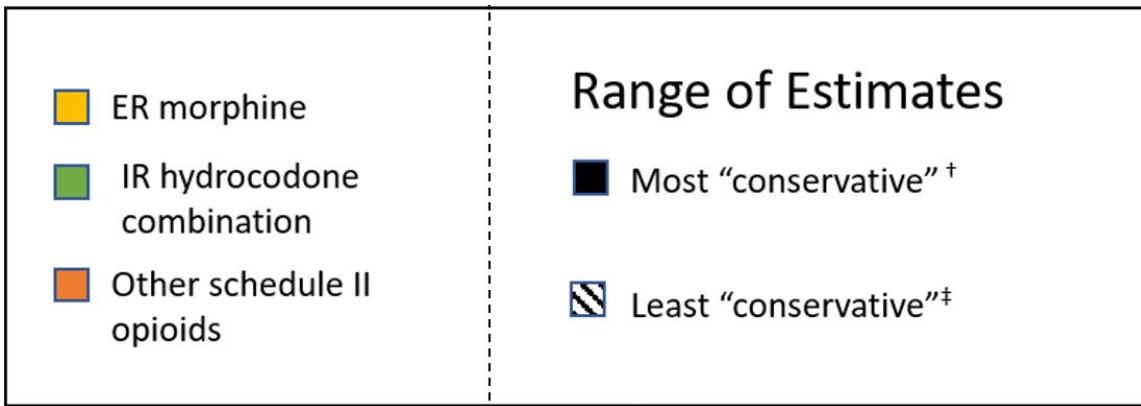
(Source: FDA generated figure from Information Request Response)

Key: ER: Extended Release; IR: Immediate Release; SKIP: Survey of Key Informants' Patients; †Most "Conservative": Smallest pre-post reduction (or largest increase) in abuse; ‡Least "Conservative": Largest pre-post reduction (or smallest increase) in abuse; *Main parameters: -2y/5y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

Figure 22 below presents the most and least "conservative" RORR estimates for primary comparators vs. OxyContin in the SKIP population, using the main variable definitions and all regression models. Again, the most "conservative" estimates of abuse show non-significant RORRs for primary comparators vs. OxyContin, while the least "conservative" estimates show a significantly greater decrease in abuse of OxyContin than comparators.

Figure 22: Most and least "conservative" values for estimated RORRs for primary comparators vs. OxyContin with main parameters* and all regression models for RADARS SKIP population

(Source: FDA generated figure from Information Request Response)

Key: ER: Extended Release; IR: Immediate Release; Survey of Key Informants' Patients; †Most "Conservative": Smallest pre-post reduction (or largest increase) in OxyContin abuse relative to comparator's change; ‡Least "Conservative": Largest pre-post reduction (or smallest increase) in OxyContin abuse relative to comparator's change; *Main parameters: -2y/5y, entire US region, sites contributing >1 assessment during the study period, any OxyContin

Table 22 in appendix 6.5 presents the models associated with these estimates.

3.5.3.3 Sensitivity analysis for OxyContin definition to explore impact of misclassification

Table 7 below presents percent change estimates using different definitions of OxyContin, 1) any OxyContin (original or reformulated) and 2) any ER oxycodone. Before OxyContin's reformulation, generic ER oxycodone was dispensed at low rates relative to brand OxyContin, and then decreased to a trivial level of dispensing shortly after the reformulation. Examining changes in any ER oxycodone abuse, particularly in analyses adjusting for dispensed tablets, helps explore the potential impact of misclassification between OxyContin and generic ER oxycodone in pre- and post-reformulation time periods.

Estimates for percent change in overall abuse of OxyContin range from -33.4% to -56.0% for the first definition of OxyContin (brand only) and range from -11.1% to -50.3% for the second definition of OxyContin (all ER oxycodone). Percent change estimates for the broader ER oxycodone definition, compared to the more specific OxyContin definition, were attenuated, more so for the models that include dispensed tablets in the denominator.

Table 7: Percent change (95% CI) in mean past-month abuse rate of OxyContin and primary comparators after introduction of reformulated OxyContin, for different OxyContin definitions, RADARS combined population -2y/5y

	Model 1 % change (95% CI)	Model 2 % change (95% CI)	Model 2a % change (95% CI)
OxyContin	-56.01% (-66.59%, -42.08%)	-33.43% (-48.94%, -13.21%)	-45.08% (-58.15%, -27.91%)
ER Oxycodone	-50.25% (-60.89%, -36.70%)	-11.12% (-28.44%, 10.39%)	-27.05% (-41.77%, -8.61%)
ER Morphine	-32.33% (-45.73%, -15.61%)	-45.48% (-60.07%, -25.57%)	-55.30% (-67.04%, -39.38%)
IR Hydrocodone	-31.82% (-43.46%, -17.79%)	-21.10% (-35.33%, -3.73%)	-38.90% (-51.42%, -23.16%)
Other Schedule II	-15.16% (-24.56%, -4.60%)	-17.59% (-27.92%, -5.79%)	-32.45% (-42.11%, -21.18%)

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Table 6-2. OxyContin definition sensitivity analysis for Primary Objective 2, percent change (95% CI) -2y/5y. P. 203.)

Key: CI: Confidence Interval; ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: -2y/5y, entire US region, sites contributing ≥1 assessment during the study period

Is it also important to note that endorsements for Oxycodone, type unknown increased dramatically in 1Q2011, increasing ~50%, when oxycodone, type unknown was moved to the first choice in the oxycodone block.

3.5.3.4 Sensitivity analysis (region definition) to explore impact of Florida pill mill interventions

Table 8 below presents estimates of percent change in abuse for OxyContin and primary comparators in three regions: 1) entire coverage area, 2) western census region only, and 2) entire coverage area excluding Florida. The second and third region definitions were chosen to better understand the possible confounding effect of the Florida pill mill interventions on the percent change in abuse rates for OxyContin and comparators. The western census region was used as an isolated coverage area to exclude states in close proximity to Florida that might also have been influenced by the effect of pill mills and the resulting legislation. Percent change estimates for OxyContin were similar for all three region definitions, although the western census region generally produced the largest estimates of decrease. This was true across the comparators as well.

Table 8: Percent change (95% CI) in mean past-month abuse rate of OxyContin and primary comparators after introduction of reformulated OxyContin, in different geographic regions, RADARS combined population, -2y/5y

	Model 1 % change (95% CI)	Model 2 % change (95% CI)	Model 2a % change (95% CI)
OxyContin			
Entire Coverage Area	-56.01% (-66.59%, -42.08%)	-33.43% (-48.94%, -13.21%)	-45.08% (-58.15%, -27.91%)
Western Census	-57.63% (-69.39%, -41.36%)	-46.81% (-60.44%, -28.50%)	-45.17% (-59.20%, -26.31%)
Excluding Florida	-54.83% (-66.01%, -39.99%)	-35.77% (-51.28%, -15.32%)	-45.03% (-58.68%, -26.88%)
ER Morphine			
Entire Coverage Area	-32.33% (-45.73%, -15.61%)	-45.48% (-60.07%, -25.57%)	-55.15% (-66.97%, -39.10%)
Western Census	-42.78% (-56.91%, -24.02%)	-62.17% (-73.18%, -46.65%)	-61.24% (-72.16%, -46.04%)
Excluding Florida	-34.72% (-49.43%, -15.74%)	-47.40% (-62.76%, -25.72%)	-55.14% (-68.16%, -36.80%)
IR Hydrocodone			
Entire Coverage Area	-31.82% (-43.46%, -17.79%)	-21.10% (-35.33%, -3.73%)	-38.65% (-51.30%, -22.70%)
Western Census	-41.37% (-54.62%, -24.24%)	-48.62% (-60.79%, -32.67%)	-48.40% (-60.37%, -32.80%)
Excluding Florida	-31.81% (-43.95%, -17.04%)	-23.33% (-37.73%, -5.60%)	-37.46% (-50.90%, -20.33%)
Other Schedule II Opioids			
Entire Coverage Area	-15.16% (-24.56%, -4.60%)	-17.59% (-27.92%, -5.79%)	-32.22% (-42.02%, -20.77%)
Western Census	-28.32% (-40.75%, -13.28%)	-48.71% (-58.36%, -36.82%)	-47.43% (-57.06%, -35.64%)
Excluding Florida	-16.15% (-26.35%, -4.55%)	-22.79% (-33.50%, -10.37%)	-34.08% (-44.64%, -21.51%)

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Table 6-3 Sensitivity analyses by region for Primary Objective 2, percent change (95% CI) -2y/5y. P. 205.)

Key: CI: Confidence Interval; ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: -2y/5y, sites contributing ≥1 assessment during the study period, any OxyContin

3.5.3.5   Sensitivity analysis for site inclusion criteria

Table 9 below presents percent change estimates of abuse rate for OxyContin and comparators using the following site inclusion criteria: 1) all sites, 2) sites contributing at least one assessment per quarter (n=15), 3) sites contributing at least one assessment per year excluding those in site group 2 (n=31), 4) sites that didn't meet the criterion of at least one assessment per year (n=362). Overall, results of these sensitivity analyses were similar to the main analysis (all sites), despite the fact that the additional region definitions (>1 assessment/quarter, >1 assessment/year, and other sites) are mutually exclusive, and no site from one category is included in another. The most restrictive, and

most consistent set of sites (≥ 1 assessment per quarter) produced the largest estimates of decrease in OxyContin abuse for models 1 and 2.

Table 9: Percent change (95% CI) in mean past-month abuse rate of OxyContin and primary comparators after introduction of reformulated OxyContin, using different site inclusion criteria, RADARS combined population, -2y/5y

	Model 1 % change (95% CI)	Model 2 % change (95% CI)	Model 2a % change (95% CI)
All Sites			
OxyContin	-56.01% (-66.59% to -42.08%)	-33.43% (-48.94% to -13.21%)	-45.08% (-58.15% to -27.91%)
ER Morphine	-32.33% (-45.73% to -15.61%)	-45.48% (-60.07% to -25.57%)	-55.15% (-66.97% to -39.10%)
IR Hydrocodone	-31.82% (-43.46% to -17.79%)	-21.10% (-35.33% to -3.73%)	-38.65% (-51.30% to -22.70%)
Other Schedule II	-15.16% (-24.56% to -4.60%)	-17.59% (-27.92% to -5.79%)	-32.22% (-42.02% to -20.77%)
Sites with ≥ 1 Assessment per Quarter			
OxyContin	-66.08% (-75.93% to -52.20%)	-47.92% (-62.05% to -28.55%)	-47.83% (-60.72% to -30.71%)
ER Morphine	-36.93% (-48.78% to -22.33%)	-44.10% (-56.82% to -27.65%)	-44.16% (-55.28% to -30.28%)
IR Hydrocodone	-40.79% (-55.26% to -21.64%)	-27.51% (-45.99% to -2.72%)	-31.68% (-47.55% to -11.01%)
Other Schedule II	-25.44% (-36.27% to -12.77%)	-24.44% (-35.47% to -11.54%)	-24.56% (-34.51% to -13.11%)
Sites with ≥ 1 Assessment per Year			
OxyContin	-59.84% (-69.29% to -47.48%)	-38.84% (-50.47% to -24.47%)	-37.56% (-49.58% to -22.68%)
ER Morphine	-35.76% (-48.36% to -20.09%)	-52.31% (-62.23% to -39.79%)	-51.55% (-61.69% to -38.72%)
IR Hydrocodone	-36.44% (-47.41% to -23.19%)	-31.39% (-42.48% to -18.17%)	-31.91% (-42.63% to -19.18%)
Other Schedule II	-16.98% (-27.60% to -4.80%)	-23.86% (-32.86% to -13.65%)	-22.56% (-31.20% to -12.84%)
Other Sites			
OxyContin	-50.25% (-62.53% to -33.94%)	-24.21% (-46.32% to 7.01%)	-62.45% (-74.28% to -45.18%)
ER Morphine	-27.35% (-44.32% to -5.22%)	-39.32% (-61.03% to -5.50%)	-69.81% (-80.61% to -53.00%)
IR Hydrocodone	-26.72% (-38.63% to -12.49%)	-18.10% (-36.20% to 5.13%)	-61.99% (-73.09% to -46.32%)
Other Schedule II	-12.32% (-21.03% to -2.65%)	-13.59% (-28.83% to 4.92%)	-57.20% (-67.61% to -43.46%)
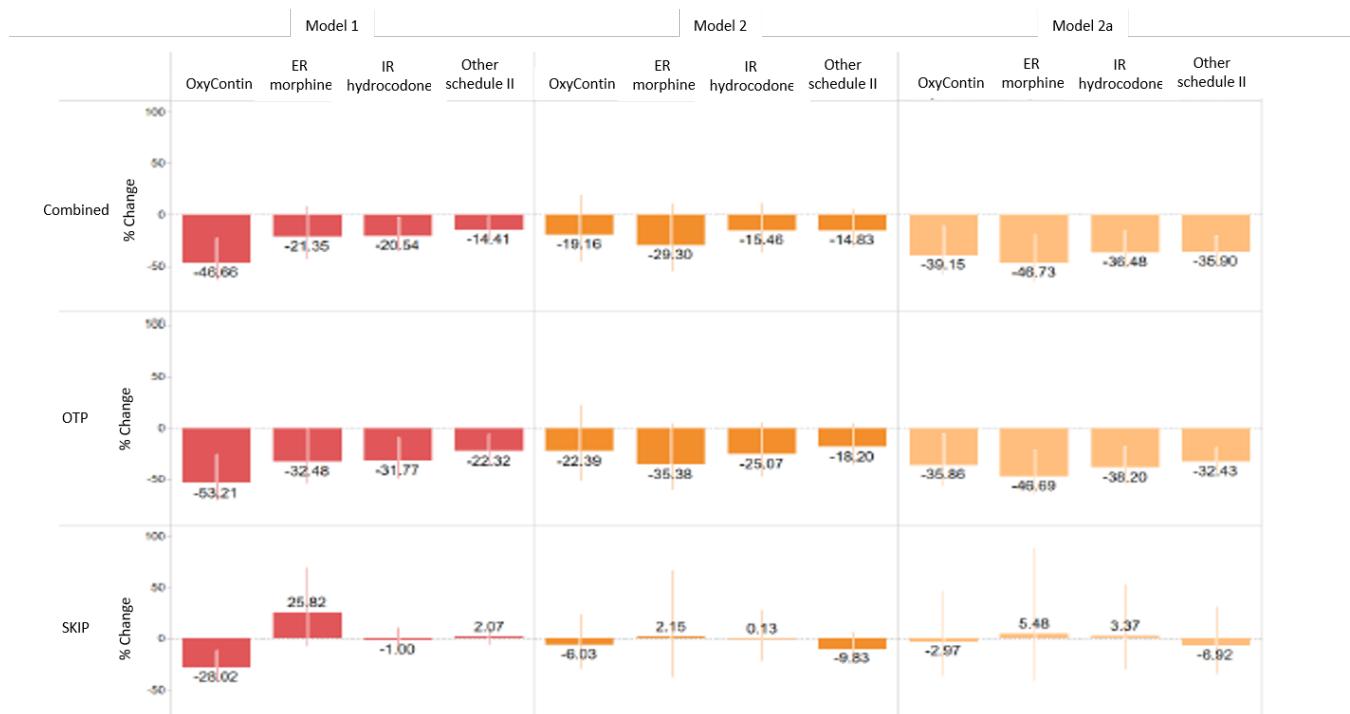
(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Table 6-4 Sensitivity analyses by site inclusion criteria for Primary Objective 2, percent change (95% CI) -2y/5y. P. 207.)

Key: CI: Confidence Interval; ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: -2y/5y, entire US region, any OxyContin

3.5.3.6 Sensitivity analysis using alternative time periods

Figure 23 below (and table 23 in appendix 6.6) shows percent change estimates of mean quarterly abuse rates for OxyContin and comparators for a -1y/3y time period (3Q2009-2Q2010/1Q2011-4Q2013). Estimated percent decreases in OxyContin abuse rates for the -1y/3y time period generally agreed with the estimates produced by the -2y/5y time period, although they were more modest. Estimates for the combined population for the -1y/3y time period ranged from -19.2% to -46.7%, while estimates for the -2y/5y time period ranged from -33.4% to -56.0%. Estimates for decrease in OxyContin abuse in the stratified OTP and SKIP populations were also smaller for the -1y/3y period compared to the -2y/5y period. Results from this analysis for OxyContin alone are presented in appendix 6.7. Percent change estimates are very similar to those presented here.

Figure 23: Percent change (95% CI) in mean past-month abuse rate of OxyContin and primary comparators after introduction of reformulated OxyContin, RADARS OTP, SKIP, and combined populations, -1y/3y
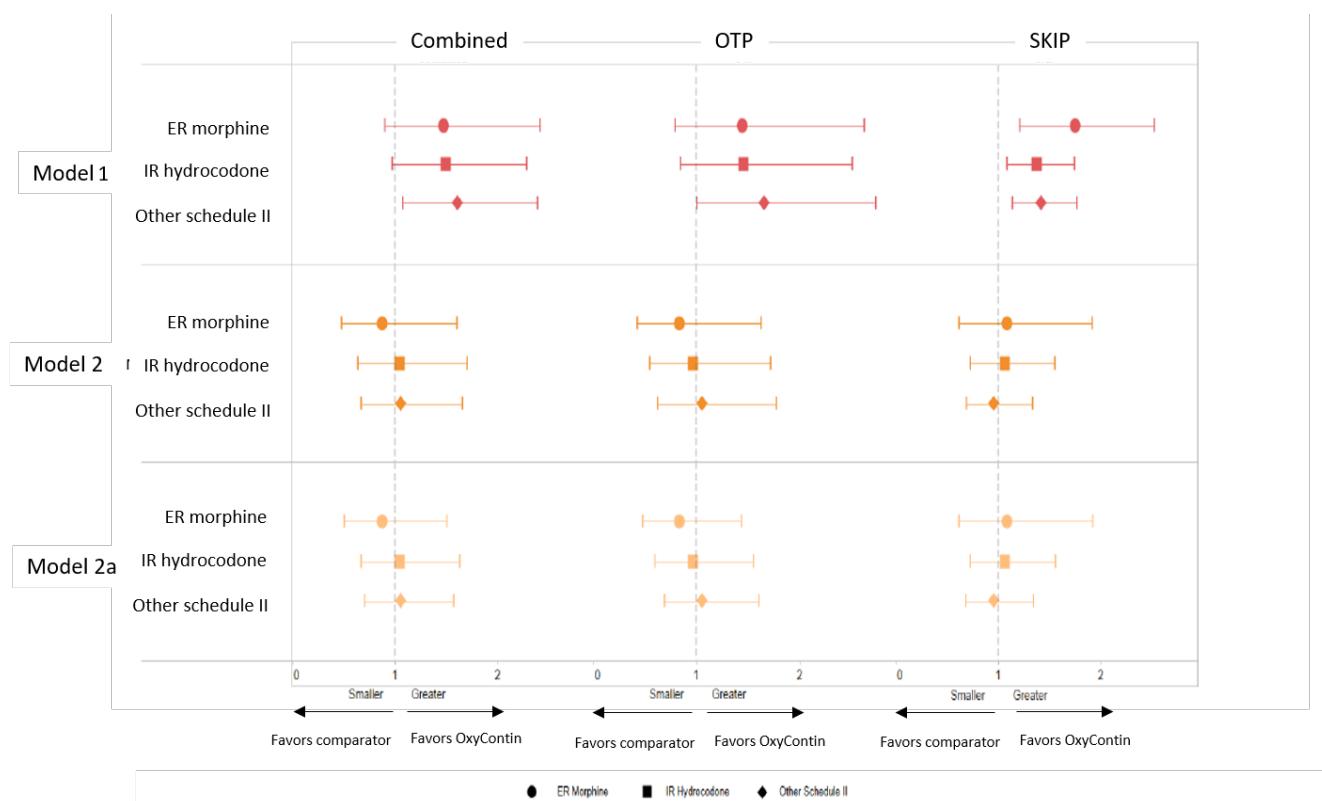
(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Figure 7-10. Percent change (95% CI) in overall abuse of OxyContin and primary comparator opioids after introduction of reformulated OxyContin for combined population, OTP population and SKIP population, -1y/3y. P. 68.)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per

tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: entire US region, sites contributing >1 assessment during the study period, any OxyContin

RORRs for OxyContin and the primary comparators during the -1y/3y period are presented in figure 24 (and table 24 in appendix 6.6). In the combined populations, RORRs are not significant for primary comparators vs. OxyContin for any models except for model 1 for the "other schedule II opioids" comparator. No RORRs were significant for OTP, and RORRs for model 1 were all significant for SKIP.

Figure 24: RORRs for OxyContin and primary comparators, RADARS OTP, SKIP, and combined populations, -1y/3y

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Appendix Figure 7-3. Ratio of risk ratios (95% CI) of past-month abuse risk for the primary comparator opioids relative to OxyContin -1y/3y. P. 219.)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: entire US region, sites contributing >1 assessment during the study period, any OxyContin

3.5.4 Range of Sensitivity Analyses

Table 10 below presents the range of estimates produced for percent change in mean quarterly abuse from pre- to post-period, and RORR for comparators vs. OxyContin, for the -2y/5y time period. In general, the most "conservative" estimates for RORR were those produced with the OxyContin definition that included all ER oxycodone, and the least conservative estimates were those produced by the OxyContin only definition.

Table 10: Range of estimates for percent change and RORR, -2y/5y, RADARS OTP and SKIP populations separately, and combined

	Percent change (95% CI)		RORR (95% CI)	
	Most "conservative"†	Least "conservative"‡	Most "conservative"ᵡ	Least "conservative"ᵞ
OxyContin	80.5% (9.8% to 196.6%)[1]	-63.2% (-74.1% to -47.8%)[2]	Ref	Ref
ER morphine	99.2% (5.5% to 276.1%)[3]	-62.2% (-73.2% to -46.7%)[4]	0.4 (0.2 to 0.9)[9]	2.5 (1.4 to 4.5)[10]
IR hydrocodone	17.00% (-11.23% to 54.21%)[5]	-48.6% (-60.8% to -32.7%)[6]	0.4 (0.2 to 0.7)[11]	1.3 (0.9 to 1.8)[12]
Other schedule II	41.06% (14.60% to 73.64%)[7]	-48.7% (-58.4% to -36.8%)[8]	0.5 (0.3 to 0.8)[13]	2.1 (1.4 to 3.0)[14]

(Source: FDA generated table from information request response)

1) Model 3; OTP population; entire US; -2y/5y; ER oxycodone 2) Model 1; OTP population; entire US, -2y/5y; OxyContin 3) Model 3; SKIP population; entire US; -2y/5y; 4) Model 2; combined population; western census region only; -2y/5y; 4) Model 2; combined population; western region only; -2y/5y; 5) Model 3; SKIP population; entire US; -2y/5y; 6) Model 2; combined population; western region only; -2y/5y; 7) Model 3; SKIP population; entire US; -2y/5y; 8) Model 2; combined population; western region only; -2y/5y; 9) Model 3; OTP population; entire US; -2y/5y; ER oxycodone; 10) Model 3a; combined population; excluding Florida; -2y/5y; OxyContin; 11) Model 3; OTP population; entire US; -2y/5y; ER oxycodone; 12) Model 3; SKIP population; entire US; -2y/5y; OxyContin; 13) Model 3; combined population; entire US; -2y/5y; ER oxycodone; 14) Model 1; OTP population; entire US; -2y/5y; OxyContin

Key: CI: Confidence Interval; ER: Extended Release; IR: Immediate Release; †Most "Conservative" percent change: Smallest pre-post reduction (or largest increase) in abuse; ‡Least "Conservative" percent change: Largest pre-post reduction (or smallest increase) in abuse; ᵡMost "Conservative" RORR: Smallest pre-post reduction (or largest increase) in OxyContin abuse relative to comparator's change; ᵞLeast "Conservative" RORR: Largest pre-post reduction (or smallest increase) in OxyContin abuse relative to comparator's change
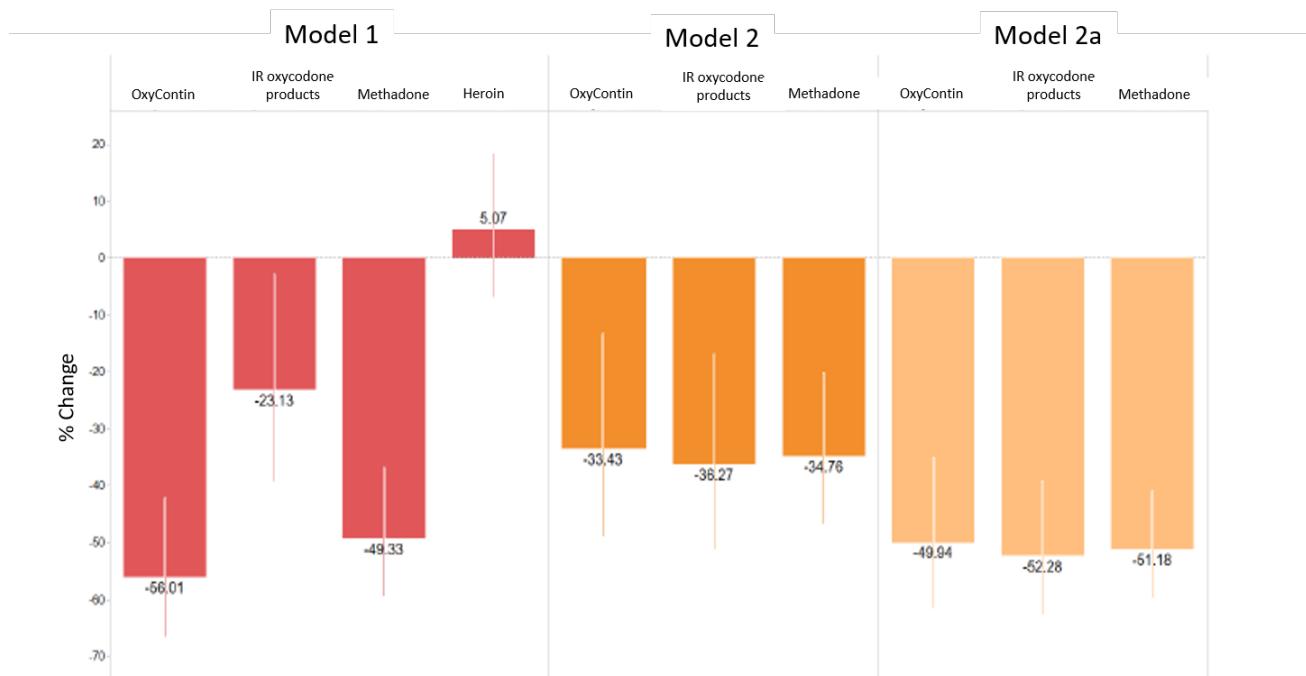
3.5.5 Pre- and Post-period Past Month Abuse of OxyContin and Secondary Comparators

Figure 25 (and table 26 in appendix 6.8) presents changes in mean rate of abuse for OxyContin and secondary comparators for the OTP and SKIP populations combined.

Model 1, which uses number respondents as a denominator, showed a similar decrease in abuse for OxyContin and methadone and a smaller decrease for IR oxycodone products. Heroin was assessed with model 1 only, because dosage units dispensed cannot be tracked for this illicit substance, and showed a +5.1% increase

Models 2 and 2a, which both use dosage units dispensed as a denominator, showed similar levels of percent decrease in overall abuse for OxyContin, IR oxycodone products, and methadone.

Figure 25: Percent change (95% CI) in mean past-month abuse rate of OxyContin and secondary comparators after introduction of reformulated OxyContin, -2y/5y, RADARS OTP and SKIP populations combined

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Percent change (95% CI) in overall abuse for OxyContin and the secondary comparator opioids after introduction of reformulated OxyContin -2y/5y. P. 69.)

Key: IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: -2y/5y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

Changes in mean rates of abuse for OxyContin and secondary comparators for the -1y/3y time period are presented in appendix 6.9.

Table 11 below presents percent change for secondary comparators and OxyContin, stratified by OTP and SKIP populations. Generally, a larger decrease is seen in the OTP

population than the SKIP population, for OxyContin and comparators. This is especially apparent for heroin, where there is only a +0.6% increase in the OTP population, while there is a +62.8% increase in the SKIP population.

Table 11: Percent change (95% CI) in mean past-month abuse rate of OxyContin and secondary comparators after introduction of reformulated OxyContin, -2y/5y, <u>stratified by RADARS combined, OTP, and SKIP populations</u>

|	Model 1			Model 2			Model 2a		
	Combined	OTP	SKIP	Combined	OTP	SKIP	Combined	OTP	SKIP
OxyContin	-56.0% (-66.6%, -42.1%)	-63.2% (-74.1%, -47.8%)	-35.5% (-44.2%, -25.3%)	-33.4% (-48.9%, -13.2%)	-39.5% (-56.2%, -16.2%)	-17.7% (-31.0%, -1.8%)	-49.9% (-61.5%, -34.9%)	-49.0% (-62.3%, -31.4%)	-32.4% (-45.1%, -16.8%)
IR oxycodone	-23.1% (-39.2%, -2.8%)	-32.1% (-46.4%, -13.9%)	-0.7% (-26.9%, 35.1%)	-36.3% (-51.2%, -16.8%)	-37.8% (-52.8%, -18.0%)	-35.1% (-51.7%, -12.7%)	-52.3% (-62.6%, -39.1%)	-47.8% (-58.8%, -33.8%)	-46.8% (-61.7%, -26.0%)
Methadone	-49.3% (-59.4%, -36.8%)	-49.7% (-60.0%, -36.7%)	-45.5% (-55.9%, -32.8%)	-34.8%	Not provided*	Not provided*	-51.2%	Not provided*	Not provided*
Heroin	5.1% (-6.8%, 18.5%)	0.6% (-10.4%, 12.8%)	62.8% (32.0%, 100.8%)	NA	NA	NA	NA	NA	NA

(Source: FDA generated table from information request response)
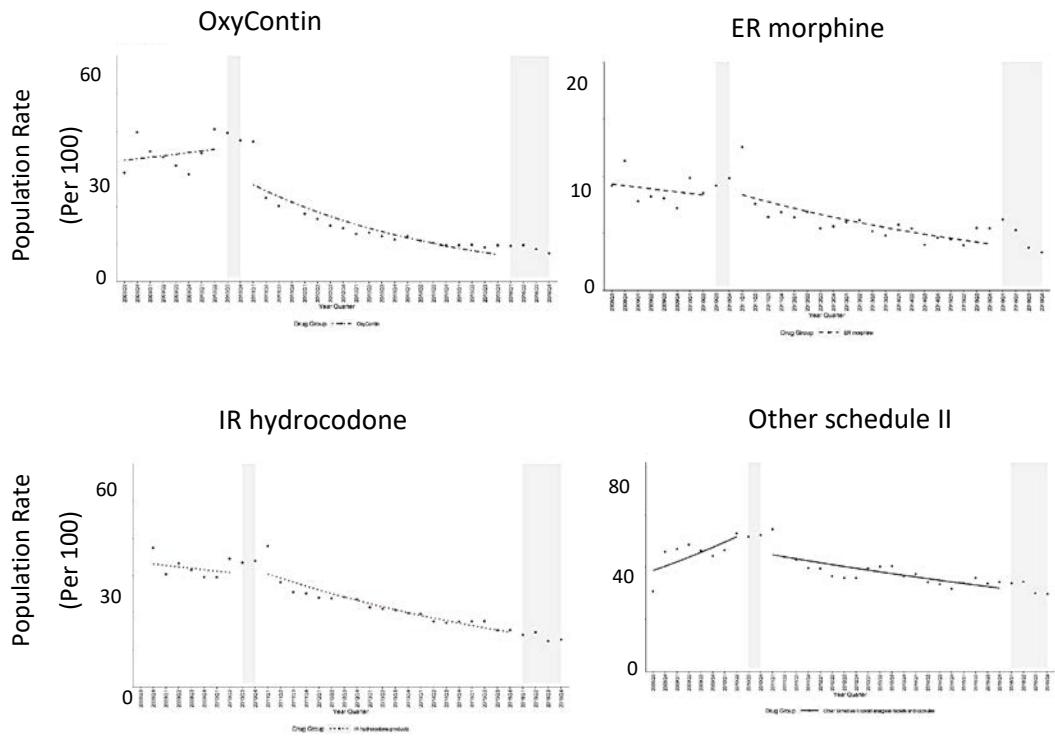
Key: IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: -2y/5y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

3.5.6   Interrupted Time Series Analysis

Figure 26 below shows ITS analysis for OxyContin and primary comparators per 100 respondents. Immediate shift (or 'level change')[h] in abuse of OxyContin shows a -26.7% decrease and change in slope shows a -7.5% decrease. These are both significant when compared to changes in immediate shift and slope for IR hydrocodone but are not significant compared to ER morphine or "other schedule II opioids".

Figure 26: ITS analysis for <u>population-based (per 100 respondents)</u> abuse rates of OxyContin and primary comparators, model 5, RADARS OTP and SKIP populations combined

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[h] Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomization is not an option: interrupted time series analysis. *BMJ* 2015;350:h2750 doi: 10.1136/bmj.h2750

OxyContin

ER morphine

IR hydrocodone
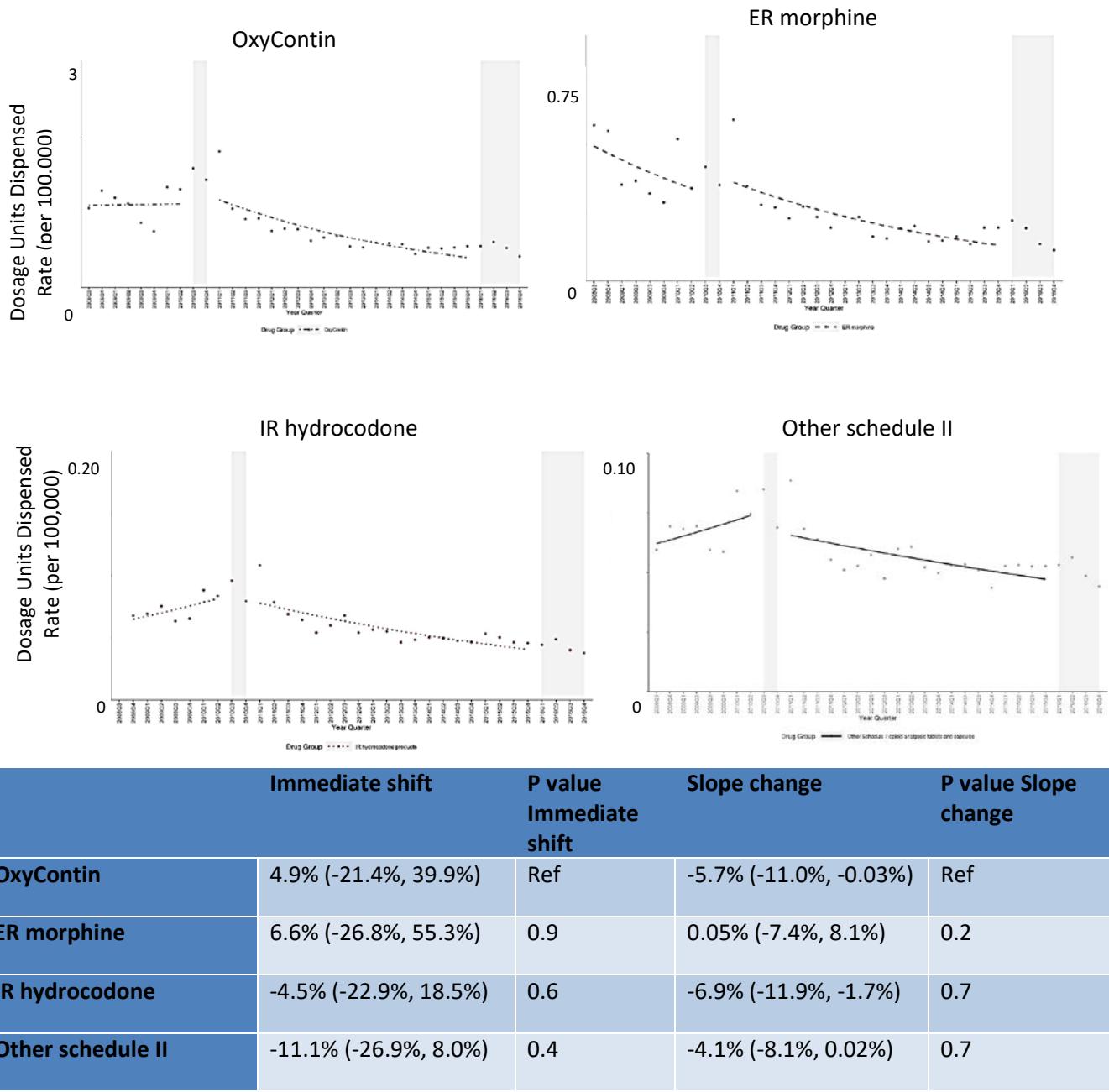
Other schedule II

	Immediate shift (95% CI)	P value immediate shift	Slope change (95% CI)	P value slope change
OxyContin	-26.7% (-41.0%, -8.9%)	Ref	-7.5% (-11.5%, -3.4%)	Ref
ER morphine	0.2% (-23.7%, 31.7%)	0.08	-2.2% (-7.5%, 3.4%)	0.12
IR hydrocodone	-1.3% (-13.6%, 12.8%)	0.02	-2.6% (-5.9%, 0.8%)	0.07
Other schedule II	-13.4% (-24.9%, -0.1%)	0.21	-5.7% (-8.5%, -2.8%)	0.47

(Source: Figure: Purdue Pharma/RADARS® System RADARS® System OxyContin® PMR 3051-2 and 3051-3 Information Request Responses from FDA Received September 2019 (Part 3) Received March 6, 2020. P. 936-1014. FDA generated table from final study report 3051-3.)

Key: CI: Confidence Interval; ER: Extended Release; IR: Immediate Release; Points on graph are observed abuse rates. Lines are modeled ITS analyses; Parameters: -2y/5y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

Figure 27 below shows ITS analysis for OxyContin and comparators per 100,000 dosage units dispensed. Immediate shift shows a slight increase for OxyContin abuse while slope change shows a modest decrease. Neither of these changes is significantly different than the changes for any comparator.

Figure 27: ITS analysis for <u>utilization-based (per 100,00 dosage units dispensed)</u> abuse rates of OxyContin and primary comparators, model 6, RADARS OTP and SKIP populations combined

OxyContin

ER morphine

IR hydrocodone

Other schedule II

	Immediate shift	P value Immediate shift	Slope change	P value Slope change
OxyContin	4.9% (-21.4%, 39.9%)	Ref	-5.7% (-11.0%, -0.03%)	Ref
ER morphine	6.6% (-26.8%, 55.3%)	0.9	0.05% (-7.4%, 8.1%)	0.2
IR hydrocodone	-4.5% (-22.9%, 18.5%)	0.6	-6.9% (-11.9%, -1.7%)	0.7
Other schedule II	-11.1% (-26.9%, 8.0%)	0.4	-4.1% (-8.1%, 0.02%)	0.7

(Source: Purdue Pharma/RADARS® System RADARS® System OxyContin® PMR 3051-2 and 3051-3 Information Request Responses from FDA Received September 2019 (Part 3) Received March 6, 2020. P. 936-1014. FDA generated table from final study report 3051-3.)

Key: CI: Confidence Interval; ER: Extended Release; IR: Immediate Release; Points on graph are observed abuse rates. Lines are modeled ITS analyses. Parameters: -2y/5y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

3.5.7 Evaluation of Survey Changes

The OTP and SKIP survey tools underwent a number of changes (see methods section) during the study period that could have influenced the reported results.

In an attempt to better understand the effect of the change from a one-page survey to a two-sided survey in the OTP program on abuse endorsement rates, the sponsor examined changes in abuse rates for OxyContin and comparators for one-sided OTP surveys only, compared to SKIP and combined population abuse rates (results are presented in appendix 6.11). This analysis was uninterpretable due to the comparison between the very brief post-reformulation timeframe in which one-sided surveys were present (they were phased out beginning in 2Q2011) and the full 5-year post-period for SKIP and the combined population. In particular, the sharp peak in abuse rates continuing into the early post-period makes the comparison of different time periods uninformative for assessing the impact of the survey changes.

A second sensitivity analysis was conducted to understand the effect of the removal of Percocet and Percodan as examples of IR oxycodone in 4Q2011, and the subsequent restoration of these examples in 1Q2013. Removal of the Percocet and Percodan examples resulted in a decline in endorsement of IR oxycodone and a subsequent increase in endorsements for not otherwise specified oxycodone, however it is difficult to ascertain the overall effect of this change, as the time frame for the sensitivity analysis was conducted over the entire time period, in which the examples were included, removed, and then restored (appendix 6.10).
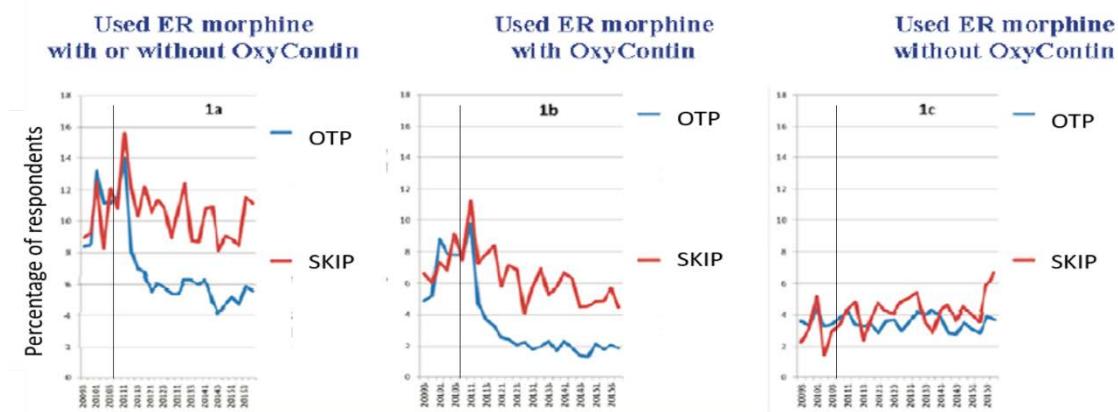
As part of an FDA-supported research project, RADARS submitted data that demonstrated changes in endorsement odds for certain opioids after survey changes. The magnitude and direction of these changes were dependent upon the survey change and the opioid, but the analyses did indicate that changes in survey wording or formatting can substantially change odds of endorsements, creating the potential for differential misclassification of products endorsed.

3.5.8 Changes in Comparator Abuse Rates Stratified by Co-endorsement of Past 30-day Abuse of OxyContin

In additional data that were not pre-specified in the study protocol, the sponsor submitted analyses of changes in comparator abuse rates stratified by concurrent abuse of OxyContin, derived from RADARS System technical reports. Figure 28 below presents past 30-day abuse rates for ER morphine, with and without co-endorsement of past 30-day abuse of OxyContin. There was a decline in ER morphine abuse in the OTP population, but not in the SKIP population, overall. This decline occurred primarily in the population that endorsed both ER morphine and OxyContin, indicating that the overall

decrease seen for ER morphine was driven by a reduction in OTP cases where both ER morphine and OxyContin abuse were reported. This pattern was similar for IR hydrocodone (Figure 29).

Figure 28: Percent of respondents endorsing past 30-day abuse of ER morphine tablets/capsules with and without OxyContin in the RADARS System OTP and SKIP Programs (July 2009 to December 2015)

Source: Severtson SG et al (2016) RADARS System Technical Report, 2016-Q2. Available at: http://www.radars.org/Portals/1/TechReports/2016%202Q%20RADARS%20System%20QTR.pdf?ver=2016-09-19-085818-767&timestamp=1482174903929
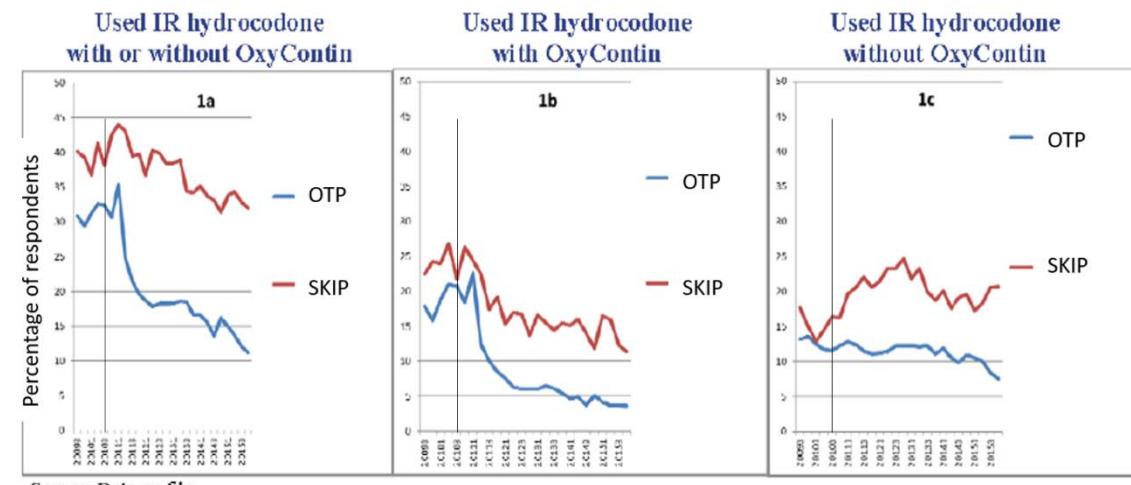
(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Percent of respondents endorsing past 30-day abuse of ER morphine tablets/capsules with and without OxyContin in the RADARS System OTP and SKIP Programs (July 2009 to December 2015). P. 130.)

Key: ER: Extended Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Vertical line denotes OxyContin reformulation

Figure 29: Percent of respondents endorsing past 30-day abuse of IR hydrocodone tablets/capsules with and without OxyContin in the RADARS System OTP and SKIP Programs (July 2009 to December 2015)
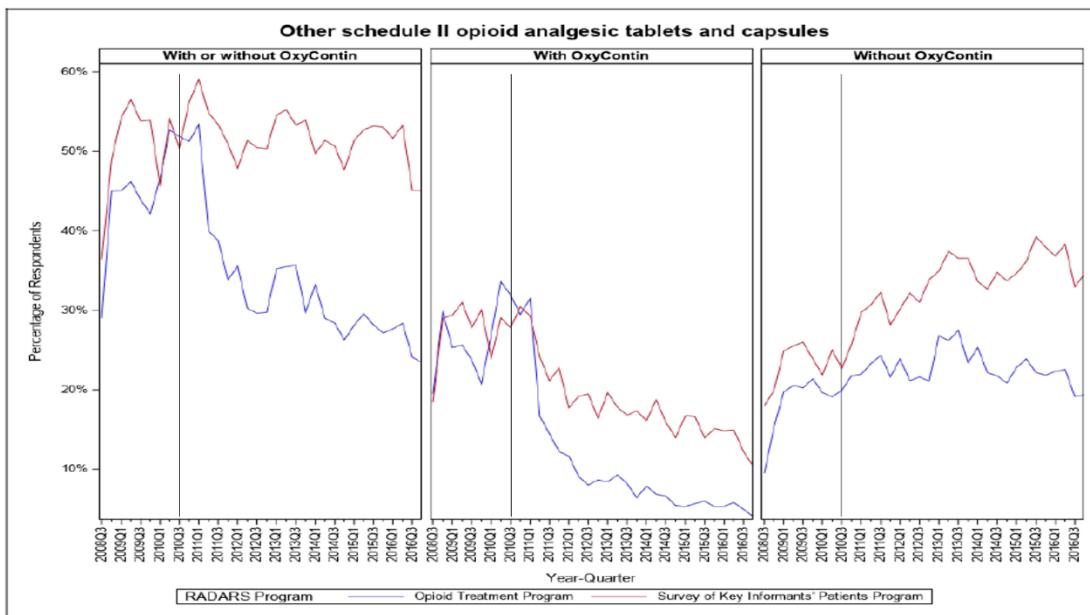
Source: Data on file

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Percent of respondents endorsing past 30-day abuse of IR hydrocodone tablets/capsules with and without OxyContin in the RADARS System OTP and SKIP Programs (July 2009 to December 2015). P. 130.)

Key: IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Vertical line denotes OxyContin reformulation

In order to better understand change in abuse of all comparators stratified by concurrent endorsement of OxyContin, FDA requested graphs for percent of respondents endorsing past-30 day abuse of all comparators with and without OxyContin in the RADARS system. A different trend is evident in co-endorsement of "other schedule II opioids" and OxyContin than ER morphine or IR hydrocodone. While endorsements of both "other schedule II opioids" and OxyContin decreases for both OTP and SKIP participants for this drug category, as seen above, there is a subsequent increase in abuse of "other schedule II" opioids with no endorsement of OxyContin, especially for SKIP (Figure 30).

Figure 30: Percent of respondents endorsing past 30-day abuse of "other schedule II opioids" with and without OxyContin in the RADARS System OTP and SKIP programs (2008-2016)
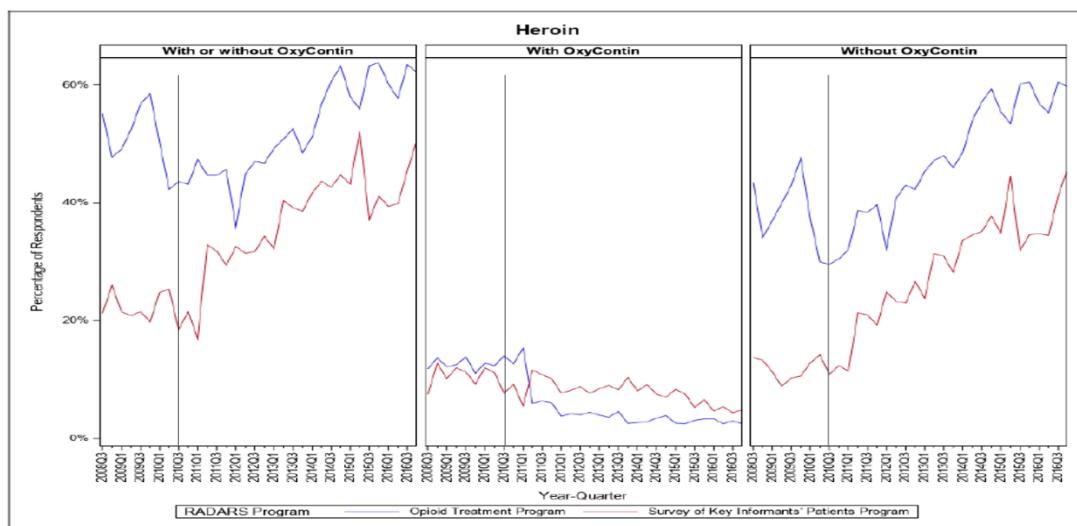
(Source: Results for OxyContin Information Request from FDA received December 5, 2019. Title: Figure 3. Other Schedule II opioids abuse with, without and total abuse with or without OxyContin during the study period for the Opioid Treatment Program (OTP) and the Survey of Key Informants' Patients (SKIP). P. 44)

Key: Vertical line denotes OxyContin reformulation

There was an upward trend in heroin abuse in both the OTP and SKIP populations (Figure 31). The percentage of cases reporting both heroin and OxyContin abuse declined in 4Q2010 in the OTP population, and shows a less prominent and gradual decline over the entire time period in the SKIP population. The percentage reporting past 30-day abuse

of heroin with no OxyContin endorsement begins to increase in both programs around 3Q2011.

Figure 31: Percent of respondents endorsing past 30-day abuse of heroin with and without OxyContin in the RADARS System OTP and SKIP programs (2008-2016)

(Source: Results for OxyContin Information Request from FDA received December 5, 2019. Title: Figure 10. Heroin abuse with, without and total abuse with or without OxyContin during the study period for the Opioid Treatment Program (OTP) and the Survey of Key Informants' Patients (SKIP). P. 51)

Key: Vertical line denotes OxyContin reformulation

Figures of abuse estimates for remaining secondary comparators stratified by endorsement of OxyContin can be found in appendix 6.11. Abuse of ER oxymorphone showed an upward trend in SKIP and a downward trend in OTP. Both populations showed a downward trend of endorsements for OxyContin and ER oxymorphone. Abuse of IR oxycodone and OxyContin generally decreased in both populations, while abuse of IR oxycodone without an endorsement for OxyContin generally increased. Methadone endorsements decreased for those also endorsing OxyContin and for those endorsing methadone in the absence of oxycodone. General oxycodone endorsements increased rapidly in 1Q2011 and then plateaued and began to modestly decrease, regardless of OxyContin endorsements.

Descriptive analyses for observed yearly abuse rate by injection for part of the post-period (2012-2016) for OxyContin and primary comparators is presented in appendix 6.12.

3.6   SPONSOR'S STUDY CONCLUSIONS

The sponsor concludes that the results of this study are consistent with the hypothesis that the introduction of reformulated OxyContin with abuse deterrent properties has resulted in a meaningful and sustained reduction in overall OxyContin abuse in a population of individuals seeking treatment for opioid use disorders. The reduction in overall OxyContin abuse is statistically differentiated from the comparator opioids using the population rate, however, the utilization rate varies and is not always statistically differentiated. They note that the abuse deterrent properties in reformulated OxyContin primarily target non-oral routes of abuse. The change in overall abuse (using any route) as measured in this study, may underestimate the effectiveness of reformulated OxyContin.

4   DISCUSSION

4.1   FDA INTERPRETATION OF STUDY FINDINGS

4.1.1   Introduction

This is an ecological study that compares aggregate measures of abuse across time periods. This type of study has particular limitations compared to studies that link an exposure/intervention and an outcome at the individual level.[i] Associations and patterns seen at the aggregate or group level may not reflect associations at the individual level — here, the likelihood, or risk, that an individual exposed to a product will abuse it. Therefore, caution is warranted in drawing inferences from an observed reduction in aggregate abuse prevalence or rates about the risk of people abusing a product, of transitioning from one route to another, or of progressing to more severe opioid use disorder.

 It is also important to keep in mind that these data were all collected from individuals with ongoing opioid use disorder requiring treatment, so changes observed over time represent the relative use of various opioids within this highly selected population rather than the prevalence of use of these drugs in the general population.

4.1.2   Estimated Effect of Oxycontin's Reformulation on Abuse Rates (Main Analyses)

Given the potential for both sampling and misclassification bias, as well as differing ways to consider the amount of drug dispensed in the community, this study employed multiple analytic models with differing assumptions. For the most part, these assumptions are not testable, making it difficult to determine the most valid results.

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[i] Morgenstern H. Ecologic Studies in Epidemiology: Concepts, Principles, and Methods. Annu Rev. Public Health. 1995. 16: 61-81.

Furthermore, several comparator opioids were used to approximate the expected changes in OxyContin abuse rates had it not been reformulated (i.e., the counterfactual scenario). This is an important consideration when attempting to draw causal inferences from a study, that is to conclude that changes seen in OxyContin abuse rates were *caused* by the reformulation (rather than simply temporally associated with it) and not caused instead by the various other exogenous factors and changes in survey instruments that may have driven changes in observed abuse patterns and trends during the study period. Unfortunately, no comparator was ideal for this purpose, and so multiple, imperfect primary comparators were used, with additional (secondary) comparators included to provide further contextual information.

Finally, in a time series analysis, the selection of time periods can impact results, and results of trend analyses may differ from those of means analyses.

Below, we discuss the range of results from the varied analyses conducted as part of this study. We believe that this range represents a reasonable estimate of plausible effect sizes for the abuse-deterrent properties of OxyContin on overall OxyContin abuse rates in a population of individuals entering treatment for opioid use disorder in the US.

4.1.2.1 Quarterly Trends in Abuse

Descriptive quarterly trend information can help us understand changes in abuse rates throughout the study period. These figures demonstrated that, in the combined OTP and SKIP populations, the abuse rate appeared to peak for OxyContin and all comparators during the transition period, with the high rates continuing into the first period of the post-period, followed by a decline in abuse rate in the post-period.

4.1.2.2 Pre-Post Mean Analyses

Model-estimated percent changes in abuse rates for OxyContin from the main analyses in the combined population generally showed a decrease across all models, populations, and parameters, ranging from -20.0% to -56.0%. Model-estimated changes in abuse rates for IR hydrocodone and "other schedule II opioids" were similar, ranging from -21.2% to -38.7% and -15.2% to -32.2%, respectively. ER morphine had a larger range, from +63.6% to -55.2%.

In the OTP population, percent change in OxyContin abuse ranged from +1.9% to -63.2%. Percent decrease in primary comparators were fairly similar to each other: range of decrease for ER morphine was -22.9% to -58.5%, IR hydrocodone was -29.9% to -44.2% and "other schedule II opioids" was -22.2% to -35.8%.

In the SKIP population, percent change in OxyContin abuse ranged from -8.2% to -36.3%, ER morphine ranged from +99.2% to -33.4%, IR hydrocodone ranged from +17.0% to -21.2%, and other schedule II opioids ranged from +41.1% to -20.2%.

Generally, all opioids showed a larger decrease in the OTP population than the SKIP population.

Generally, in the combined, OTP and SKIP populations, RORR for primary comparators vs. OxyContin demonstrated a significant difference between OxyContin and comparators for model 1, which modeled the pre-post change in the mean abuse rates per 100 assessments. Using models 2 and 2a, which modeled pre-post change in mean abuse rates per 100,000 dosage units dispensed (without and with additional adjustment for the number of assessments, respectively), RORRs were not significant for any of the primary comparators, meaning that the decrease in the mean rate of OxyContin abuse per number of pills dispensed in the community was not significantly larger than that of any of the primary comparators. Results from model 3 and model 3a, which estimated abuse cases adjusted for utilization, but not per unit of utilization, produced mixed results.

Interpreting the differing results from these models involves addressing questions that do not have simple answers. For example, a decrease in OxyContin prescribing will make less drug available for abuse but could have occurred for a number of reasons. If this decrease was driven solely by decreased desirability of OxyContin for abuse due to the reformulation, then adjusting for the change in dosage units dispensed would be unnecessary as the decreased dispensing would lie in the causal pathway from reformulation to decreased abuse. However, if the decrease in prescription volume was driven, even in part, by other factors, such as changes in insurance or formulary coverage, prescriber preference, or crackdowns on rogue prescribing and dispensing (i.e., pill mills), then it is important to control for these changes when evaluating the causal relationship between the reformulation and changes in abuse rates.

In all likelihood, decreased demand of OxyContin for the purposes of diversion and abuse was one, but not the only, driver of declining prescription volume. Therefore, Model 1 (not utilization-based) may overestimate the effect of the reformulation, while Models 2 and 2a (utilization-based) may underestimate the effect.

Analyses using the secondary comparators of IR oxycodone products and methadone products showed a range of estimated change in abuse rates from -0.7% in the SKIP population to -52.3% in the combined population for IR oxycodone, and -34.8% in the combined population to -51.2% in the combined population for methadone. It is likely that part of the decrease in IR oxycodone endorsements was due to the change in survey wording, where the examples of Percocet and Percodan were removed from the 'oxycodone immediate release tablets' question. Change in abuse of heroin was estimated as increasing +5.1% for OTP and SKIP combined; however, this change was heavily weighted by the lack of change in the OTP population. In the SKIP population, there was a +62.8% increase in heroin use that appeared to begin around 2Q2011.

4.1.2.3 Interrupted Time Series results

Interrupted time series analyses can help us understand how ongoing trends affect changes in abuse, as opposed to means analyses which simply take the mean quarterly abuse rate in the pre-period and compare it to the mean quarterly abuse rate in the post-period. If abuse rates were decreasing coming into the pre-period and continued to decrease at the same rate into the post-period, means analyses might still show a decrease in pre vs. post, while ITS analysis would not indicate a change in immediate effect or change in slope. In population-based analyses, immediate decrease in abuse of OxyContin was significant when compared to IR hydrocodone, but neither immediate shift or slope change were significant against ER morphine and "other schedule II opioids". In utilization-based analyses, the pre-specified transition period of 6 months appeared to be inadequate to isolate the transition period, in which abuse rates increased sharply for reasons that are not entirely clear, and the first quarter of the post-period included these increased rates. Therefore, for utilization-based analyses, the ITS analyses were difficult to interpret with regard to the change in level (immediate shift) or slope (trajectory) of OxyContin and comparator abuse rates and the causal association with the reformulation

4.1.3 Estimated Effect of Oxycontin's Reformulation on Abuse Rates (Sensitivity analyses)

A large number of parameters were included in sensitivity analyses in part due to the complicated nature of these data sources. There is yet no standard approach to defining all parameters of the analysis, and therefore a number of sensitivity analyses, exploring the definition of OxyContin, region, treatment site inclusion criteria, model, and time periods were used to assess the robustness of the main findings and to better understand how these parameters influence the results of the study. These are described below.

Misclassification Bias and measurement of OxyContin abuse

Misclassification can occur in a survey setting when a respondent is unsure of which product he or she abused, because it looks or sounds similar to the abused product, due to misinterpretation of the question (e.g., confusion about the referent time frame or what is being asked) or literacy issues, or because of survey fatigue. In the OTP and SKIP tools, the following options are provided for individuals to report abuse of an ER oxycodone product:

-   OxyContin
-   oxycodone ER, not listed above
-   oxycodone ER, not sure of name
-   oxycodone, type unknown

During the study period, the other options for oxycodone products beside those listed above changed and included oxycodone extended release; generic "OxyContin",

oxycodone extended release; generic "OxyContin" by Mallinckrodt, extended release tablets by Mallinckrodt, Xartemis XR tablets, and Targiniq ER tablets (which was never marketed). To better understand the possible effect of product misclassification within the ER oxycodone category, an OxyContin definition "any ER oxycodone" was used that included specific ER oxycodone generics and any unspecified ER oxycodone endorsements. Given that the vast majority of generic ER oxycodone dispensing occurred in the pre-period, and dispensing dropped to trivial levels in the post-period, misclassification of ER oxycodone as OxyContin could have artificially increased abuse rates in the pre-period, leading to an apparently larger decrease in abuse rates in the post-period. The addition of ER oxycodone attenuated the percent decrease in OxyContin abuse in the post-period, primarily for utilization-based estimates, which changed from -33.4% with the main definition of OxyContin, to -11.1% for all ER oxycodone. While this is a substantial change for the estimates per dosage unit dispensed, the RORR for these analyses (generated with model 2) were already non-significant compared to all primary comparators.

Time-Frame

Because the length of the pre- and post-periods can impact both the mean abuse rates, influence of other interventions and secular trends, study site inclusion, and precision of estimates, an additional time period definition was explored in addition to the -2y/5y pre- and post-periods used for the main analysis. These sensitivity analyses were conducted using a shorter, 1-year baseline with a 3-year post-period. In general, using this shorter time period yielded attenuated decreases in the percent changes for OxyContin and primary comparators, regardless of the model used. RORRs for primary comparators vs. OxyContin were also attenuated. Whereas RORRs for the -2y/5y time period were significant for model 1 for the combined, OTP, and SKIP populations, only the SKIP population had significant RORRs for primary comparators vs. OxyContin for the -1y/3y time period, as well as the combined population for "other schedule II opioids".

Site inclusion criteria and study population

OTP and SKIP are both non-representative and dynamic samples of patients entering treatment for opioid use disorder (with or without other substance use disorders). Therefore, in both of these populations, while patients might be abusing other drugs, opioids are the primary drug of abuse. In this sense, this sample is a fairly restricted and perhaps more homogenous sample than other populations being assessed for substance abuse problems (for example, the ASI-MV sample from PMR 3051-1). For this reason, and because restricting the sample to a consistent set of sites (i.e., those contributing at least on survey per quarter) severely reduces the sample size, the main site inclusion criteria for this review was all sites that contributed at least one assessment during the study period. Still, opioid abuse patterns may vary considerably across geographic regions, and also between the OTP and SKIP populations. In addition, the number of

SKIP respondents increased during the study period, and therefore the proportion of the combined population comprised of SKIP to OTP changed. Therefore, main results were stratified by OTP vs. SKIP, and sensitivity analyses were conducted to assess the impact of changes in site distribution.

In general, results from these sensitivity analyses showed that sites contributing data in every quarter had similar results to sites that contributed assessments at least annually, and estimated changes in abuse from these sites were similar to the estimates from the main analysis including all sites. The largest decrease for percent change in OxyContin abuse was observed when restricting sites to those with ≥ 1 assessment per quarter.

Results in the OTP population demonstrated consistently larger decreases in abuse of OxyContin and all primary comparator opioids compared to SKIP. Since the OTP population is larger and thus more heavily weighted in the combined results, percent change estimates for the combined population were larger than for the SKIP population alone. The reasons for the observed differences in the OTP and SKIP results are not clear; they could reflect true differences in abuse patterns and behaviors in the two groups or perhaps be a result of different geographic distributions or nuanced differences in the survey formats.

<u>Geographically restricted analyses to explore potential impact of Florida pill mill actions</u>

To better understand how the legislative and law enforcement actions on Florida pill mills might have affected changes in abuse of OxyContin and comparators, analyses were stratified by geographic region: 1) entire coverage area, 2) entire coverage area excluding Florida, and 3) the western census region. Generally, percent change estimates for OxyContin were similar for all three region definitions, although the western census region generally produced the largest estimate of decrease, suggesting that the Florida intervention did not have a major effect on changes in OxyContin abuse rates in the OTP and SKIP populations.

4.1.4   Comparators and Causal Inference

In making causal inferences, it is important to consider the effects of concurrent interventions and market changes, as described above, as well as potential bias due to changes in the survey format and wording that occurred during the study period. To understand how reformulation, specifically, influenced OxyContin abuse rates, a group of comparators were selected to approximate these "background" trends. None of these comparators, however, likely represent a perfect negative control, or counterfactual. For example, ER morphine's utilization increased during the study period, whereas OxyContin's decreased. IR hydrocodone may serve as a good approximation of general trends, but its relatively low levels of abuse via non-oral routes make it a poor comparator for trends related to these routes of abuse. And the composition of the "other schedule II

opioids" category changes over time (see appendix 6.13 for additional detail on primary and secondary comparator selection and characteristics). Finally, the use of multiple comparators, each with multiple models, becomes difficult to interpret statistically, due to multiple comparisons and the increased likelihood of significant findings due to chance alone. Although these comparisons are not considered independent (which would likely require some statistical correction), the multiple comparisons with often disparate results nonetheless create complexity that make quantitative conclusions about causal relationships challenging.

In addition, the quarterly trend data for comparators with and without past 30-day concurrent abuse of OxyContin suggests that changes in abuse of OxyContin, either due to the reformulation or due to other factors, might not have been independent from abuse trends for comparators. The co-endorsement figures (see section 3.4.9) demonstrate that the decrease in abuse of ER morphine and IR hydrocodone occurred mostly in individuals who also endorsed OxyContin in the past month. It is possible that the reformulation of OxyContin also affected abuse of these drugs, but the interpretation of these findings remains somewhat unclear.

4.2 SUBSTITUTION EFFECTS AND POLYSUBSTANCE ABUSE

Although this study was not specifically designed to examine the impact of OxyContin's reformulation on the abuse of either prescription or illicit (heroin), the data do suggest some shifts in abuse patterns for other opioids that may reflect, at least to some degree, the effect of the reformulation as opposed to background trends. Data on the number of drugs endorsed by survey respondents (ranging from 5 to 11) indicate that polysubstance abuse is common in these populations, and the co-endorsement data help us understand how individuals might have used OxyContin in the context of comparators. As described above, in post-hoc analyses derived from RADARS technical reports, the proportion of individuals abusing ER morphine or IR hydrocodone in addition to OxyContin decreased but there was no apparent decrease (or subsequent increase) in the percentage of respondents who reported abusing these opioids and not OxyContin. This was not the case for "other schedule II opioids" or heroin, where there was a decrease in co-endorsement of OxyContin with these comparators, but an increase in individuals abusing these drugs without OxyContin, especially for heroin. Although the interpretation of these data is not entirely clear, the patterns suggest that some individuals who were abusing OxyContin along with other opioids may have shifted their use to other prescription opioids or heroin that were accessible to them following the reformulation.

4.3 STUDY STRENGTHS AND LIMITATIONS

The conclusions that can be drawn from this study are impacted by its methodological strengths and limitations. A study using the combined OTP and SKIP data resource was

selected as part of the suite of PMR studies evaluating the impact of OxyContin's reformulation because of the unique strengths of the data resource, as summarized below. However, as with all the other studies, this one has considerable limitations, many of which have been noted previously and are summarized below.

Strengths:

- Provides product-specific reporting of recent drug abuse behaviors
- Use of an enriched, drug-experienced population increases numbers of events and study power
- Availability of multiple comparators provides contextual information to help interpret changes in OxyContin abuse rates
- Has information covering time period before and after OxyContin reformulation
- Combined, OTP, and SKIP sites have considerable geographic coverage across the US
- OTP and SKIP cover two different groups of patients with substance abuse: patients enrolling in methadone maintenance programs and those entering substance abuse treatment programs other than methadone clinics

Limitations:

- Route of abuse information was not collected during the study period. Therefore, these data can only inform our understanding of the change in overall abuse rates for OxyContin and comparators. This is an important limitation, since the abuse deterrent properties in reformulated OxyContin were only designed to prevent non-oral routes of abuse, and not necessarily abuse overall.
- Self-report of products abused is subject to misclassification that may substantially affect prevalence estimates. The degree of misclassification may vary across products and across time in ways that are difficult to quantify and are likely influenced by changes in design of the survey tool. Distinguishing among different oxycodone products may be particularly challenging for respondents.
- OTP and SKIP are not able to assess the prevalence of clinical outcomes consequent to abuse of specific drug products, including overdose, addiction, or death
- Data captured in OTP and SKIP are a convenience sample, not a random sample, and thus may in part reflect regional differences in drug abuse patterns
- Data do not measure the prevalence of abuse of drugs in the general population, only among those entering treatment. Therefore, it can only be used to study the shifts in opioid abuse patterns in a sample of people requiring treatment for opioid use disorder.

4.4 REVIEW OF RELATED PUBLISHED LITERATURE

Overview:

A number of papers have been published in the scientific literature describing the changes in abuse of OxyContin and comparators during the time of OxyContin reformulation. Six of these studies analyzed RADARS OTP and SKIP data; these articles are abstracted in a table in appendix 6.14 and are discussed below. Overall, these studies found decreases in OxyContin abuse rates after reformulation, which agrees with the findings from PMR 3051-3; however, the decreases reported in these publications generally were larger than what was found in the PMR study, and significantly larger than comparators. The differences between the published study and PMR estimates appeared to be related to differences in time period assessed, regression model used to generate estimates, and choice of comparators. Follow-up interviews from a sample of SKIP participants found that respondents who abused OxyContin reported preferring the original formulation, and some, but not all, switched to another opioid, commonly heroin, after OxyContin was reformulated. This finding is generally consistent with the co-endorsement data from PMR 3051-3. Other participants reported switching from non-oral to oral abuse while others reported defeating the abuse-deterrent properties to continue to abuse OxyContin non-orally.

Summary of individual studies:

Cicero et al. published two studies, one in 2012 and another in 2015, focusing on a subset of SKIP respondents who indicated their willingness to participate in the Researchers And Participants Interacting Directly (RAPID) interview program, and who had indicated any lifetime abuse of the original formulation of OxyContin. The 2012 analysis of 103 interviewees showed that of all opioids used to get high in the past 30 days, OxyContin fell from 47.4% of respondents to 30% from 4Q2009 to 1Q2012, while heroin doubled. Interviews with patients who abused both formulations of OxyContin (original and reformulated) demonstrated unanimous preference for the older version. Of the patients interviewed who had abused both formulations of OxyContin, 24% found a way to defeat the tamper-resistant properties, and 66% reported switching to another opioid, most commonly heroin.

The 2015 study followed up with 153 RAPID participants who indicated any lifetime abuse of the original formulation of OxyContin. These 153 interviewees were questioned about the impact of reformulation on their subsequent choice of drugs: a third indicated that the reformulation had no effect on their drug selection and continued to use OxyContin, another third indicated that they had replaced OxyContin with other drugs as a result of the reformulation, 30% indicated that they did not use OxyContin enough to change their drug of choice, and 3.3% indicated that the reformulation influenced their decision to stop abusing drugs altogether. Eighty-eight (57.5%) respondents indicated using both formulations of OxyContin, and these respondents were questioned about route of abuse upon reformulation: 43% reported that they switched from primarily

injecting/inhaling OxyContin to swallowing it whole, 34% reported that they were able to defeat the reformulated OxyContin and continued to inject/inhale the drug as primary route, and the remaining 23% primarily swallowed the original formulation of OxyContin, and continued to do so with reformulated OxyContin. Among the 33.3% of respondents who indicated that reformulation led them to switch their drug choices, with 70% of these switching to heroin, due to the desire for a more intense high, as well as heroin being readily available and cheaper than opioid analgesics.

In a third study, Cicero et al. (2016) analyzed abuse of OxyContin and an ER oxymorphone product that used similar mechanisms to deter abuse through intranasal and intravenous routes. The study conducted follow up interviews with small samples of SKIP participants who had indicated abusing both formulations of each respective drug, asking about how their abuse patterns had changed after the reformulations. Based on participants' historical recall, there was a -50% reduction in injection, a -64.1% decrease in snorting, and a +49.2% increase in oral abuse of OxyContin. Again, based on participants' historical recall, there was a -14.3% reduction in injection, a -53.6% decrease in snorting, and a +5.0% increase in oral abuse of ER oxymorphone, although the number of individuals who reported injecting but not snorting the product increased. This study demonstrated that although these two opioid products had the same abuse deterrent properties, disparate outcomes resulted from the introduction of these abuse deterrent formulations, which indicates that the effect of ADFs may be drug-specific.

Coplan et al. (2016) reported selected results of a number of investigations of changes in OxyContin abuse rates following reformulation. The data sources included poison control data, information from individuals entering substance abuse treatment, diversion reports from law enforcement, and fatality reports. Using population adjusted rates, OxyContin showed a -30% decrease in abuse in SKIP and a -43% decrease in OTP. "All schedule II opioids" was included as the only comparator for these data sources and showed a +16% increase in SKIP data and a +9% increase in OTP data. Using prescription-based rates, OxyContin showed a -32% decrease in SKIP and a -33% decrease in OTP. "All other schedule II opioids" showed a +5% increase in SKIP, and a 0% increase in OTP. The decreases reported for OxyContin in this article are considerably larger than the decreases reported in PMR 3051-3 for the -1y/3y time period that corresponds to the time period reported in the article, particularly for the prescription-adjusted rates. Decreases in abuse rate for "other schedule II opioids" reported in PMR 3051-3 are larger than those reported in the article. The reasons for these discrepancies are not entirely clear. One possible reason is that the published study used prescription-based rates, while PMR 3051-3 used dosage units dispensed-based rates, which FDA believes to be a more appropriate denominator for these analyses due to potential variation in prescription size and because each tablet represents an opportunity for abuse or diversion. Another difference between Coplan et al. and PMR 3051-3 is the choice of comparator: the authors of the study chose

"other schedule II opioids" only as the comparator, while PMR 3051-3 included this composite category as well as ER morphine and IR hydrocodone.

Severtson et al. (2016) reported on OxyContin abuse in OTP and SKIP in the year prior to reformulation compared to 2Q2015 to understand the durability of the initial reductions in abuse five years later. This study found that OxyContin had a -82.6% decrease in population adjusted abuse by 2Q2015, while the "other opioid group" (which consisted of oral dosage forms of hydrocodone, hydromorphone, morphine, oxymorphone, tramadol, tapentadol, and IR oxycodone) had a decrease of -32.0% in the OTP program. In the SKIP program, OxyContin had a -53.9% decrease in population adjusted abuse, while "other opioids" had a -7.2% decrease. For prescription adjusted abuse rate, OxyContin showed a -72.8% decrease from pre-reformulation to 2Q2015, while "other opioids" had a -30.9% decrease in OTP. In SKIP, OxyContin had a -34.8% decrease in abuse while "other opioids" had a +10.8% increase in abuse. These estimates of decrease are larger than those reported in PMR 3051-3. One major difference between this study and PMR 3051-3, is the time period under investigation, PMR 3051-3 assessed changes in abuse rates over a 2-year pre-period and 5-year post-period, whereas Severtson et al. compared pre-reformulation abuse rates to the estimated rate in 2Q2015. Another difference between the two studies is that PMR 3051-3 used dosage unit dispensed-based rates while the Severtson study used prescription-based rates.

Dart et al. (2015) used endorsements from OTP and SKIP for prescription opioids (oxycodone, hydrocodone, hydromorphone, fentanyl, morphine, and tramadol) to estimate quarterly event rate per 100,000 population and predicted the time of the maximum value of the curve. In a secondary analysis, Dart et al. compared the rate of heroin use and OxyContin abuse adjusted per 100,000 population. In OTP, the rate of prescription opioid abuse increased from 1.6 per 100,000 population in 2005 to 7.3 in 2010 and then decreased to 3.5 by the end of 2013. In the SKIP program, the rate of prescription opioid abuse increased from 1.5 per 100,000 population in 2008 to 3.8 in 2011 and then decreased to 2.8 by the end of 2013. In OTP, the rate of heroin use was relatively flat for the period from 2005 through 2013, and the rate of abuse of reformulated ER oxycodone decreased after 2010. In the SKIP program, the rate of heroin use increased in 2011 and remained increased, whereas the rate of abuse of reformulated ER oxycodone decreased. One major difference between the analysis in the Dart et al., study and PMR 3051-3 is that descriptive trends in PMR 3051-3 were adjusted for population and dosage units dispensed, while the Dart study adjusted only for population. Another major difference was the choice of comparator for OxyContin abuse rates: in PMR 3051-3 the main comparators were ER morphine, IR hydrocodone, and "other schedule II opioids", while the main comparator in Dart et al. was heroin. Finally, the time periods for this comparison in Dart et al. were 1Q2005-4Q2013 for OTP and 1Q2008-4Q2013 for SKIP.

4.5 OVERALL SYNTHESIS OF FINDINGS

Overall, PMR 3051-3 found that OxyContin abuse rates did decrease after reformulation in two populations of individuals entering treatment for opioid use disorders. The reductions were substantially attenuated when adjusted for changes in utilization (number of tablets dispensed), however, and results were mixed as to whether this decrease was larger than the decrease observed for comparators, making it difficult to definitively attribute the observed decreases to OxyContin's abuse-deterrent properties. In population-based analyses (i.e., per 100 respondents), the decreases in OxyContin abuse rates were significantly larger than the decreases for primary comparators (although this was not consistently true when using the shorter 1-year pre-period and 3-year post-period). In utilization-based analyses (i.e., per 100,000 dosage units dispensed); however, the decreases for OxyContin were not significantly larger than for comparators. Descriptive analyses showed similar trends for OxyContin and comparators: a peak in abuse rates shortly after reformulation (particularly for the utilization-based estimates), followed by declining rates in the post-period.

One could hypothesize several reasons why abuse rates for comparators (particularly ER morphine and IR hydrocodone) showed a decrease after reformulation: (1) comparator abuse rates decreased due to exogenous secular trends such as evolving drug preferences or changes in availability or price of other drugs such as heroin; (2) Changes in the survey or study sample contributed to the observed decreases across multiple drugs; (3) OxyContin's reformulation could have directly impacted abuse patterns in this population such that abuse of these comparators decreased along with OxyContin. This could have occurred, for instance, if some patients who had previously abused OxyContin along with comparator opioids shifted their use to another drug, such as heroin, leading to decreasing rates in OxyContin as well as comparators after reformulation. The trends in ER morphine, IR hydrocodone, and heroin use with/without OxyContin support this third possibility to some extent. Finally, it is possible that the observations are explained by some combination of these reasons. If scenario three is correct, even to some extent, this raises questions about the ability of these comparators to serve as good negative controls, because they may also be influenced by the reformulation.

Means analyses demonstrated a significantly larger decrease for OxyContin in population-based analyses, but not in utilization-based analyses. This is demonstrative of some of these comparators having increasing trends in utilization during the study period, while OxyContin dispensing was decreasing. Making causal inferences based on these findings requires consideration of several possible reasons for the decline in OxyContin dispensing. The first reason lies within the causal pathway from the ADF to a reduction in abuse rates: OxyContin dispensing decreased due to the reformulation's causing a decrease in desirability and demand for this drug for abuse or diversion. The second reason does not lie within the causal pathway but is instead a confounder of the causal

association between the ADF and changes in abuse rates: OxyContin dispensing decreased due to reasons other than the reformulation, for example, changes in formularies or insurance coverage, the 2010 OxyContin REMS, law enforcement actions, or prescriber or patient preference unrelated to abuse of the drug. The third, and most likely, explanation is that some combination of both of these scenarios lead to decreases in OxyContin dispensing (and possibly changes in utilization trends for comparator opioids). The relative contribution of these two causal pathways is unknown, which makes it difficult to determine which estimate—population or utilization adjusted—lies closer to the true effect of the reformulation.

The two published studies reporting data from follow-up interviews conducted with SKIP participants provide some additional information that aid in interpretation of the PMR findings. Although using small, convenience samples, these investigators found that individuals who had abused original OxyContin did report changing their abuse behaviors as a result of the reformulation, with a substantial minority changing to using this drug through oral routes (although they could still be abusing other drugs via non-oral routes), others substituting heroin or different prescription opioids, and still others circumventing the abuse-deterrent properties to continue to abuse OxyContin via non-oral routes, and a very small fraction attempting to stop abusing opioids. A shift from non-oral abuse to oral abuse of OxyContin is consistent with an effect of the reformulation, although this change would not be captured in the main SKIP or OTP data, as information on route of abuse was not collected at the time of reformulation. The substitution/switching findings are also largely consistent with those of PMR 3051-3, which suggest that polysubstance use is the norm, and that drug choices are dynamic, inter-related, and vary across treatment populations.

Finally, it is worth noting that, per dosage unit dispensed, OxyContin abuse rates remained higher than comparator opioids after reformulation. Such comparisons must be made cautiously, as this is not a nationally representative sample, and relative abuse rates may also be substantially affected by design of the survey instrument, the order in which products are presented, and other sources of product misclassification.

5   CONCLUSIONS

The findings of PMR 3051-3 were mixed and did not provide compelling evidence that the reformulation meaningfully reduced OxyContin abuse among adults with opioid use disorders enrolling in treatment programs. However, the lack of route-specific data limited the ability of this study to detect any potential changes in route-specific, particularly non-oral, abuse. OxyContin's reformulation was followed by an increase in heroin abuse, primarily in the SKIP population, although this study was not designed to assess whether the reformulation contributed causally to this increase. Per dosage units dispensed, OxyContin abuse rates remained higher than primary comparator opioids after

reformulation; however, such comparisons must be made cautiously due to the inherent limitations of these data. These study results also illustrate the dynamic and inter-related nature of polysubstance abuse and the challenges of measuring and making causal inferences about the impacts of a single intervention on drug abuse patterns in this context.

6 APPENDIX

6.1 MODEL FIT DIAGNOSTICS

Figure 32: AIC model fit statistic values for percent changes in overall abuse of OxyContin based on the RADARS population

Model	AIC model fit statistic
Model 1	1420
Model 2	1339.9
Model 2a	1249.9
Model 3	1257.1
Model 3a	1200.0

(Source: Results for OxyContin Information Request from FDA received February 11 2020. "Table Shells PMR 3051-3_11FEB2020_RMPDS.xlsx".)

Key: Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Model 3 models abuse rate adjusted for tablets dispensed as a covariate; Model 3a models abuse rate adjusted for tablets dispensed and respondents as covariates

Figure 33: AIC model fit statistic values for percent changes in overall abuse for OxyContin relative to primary comparators based on the RADARS population

Model	AIC model fit statistic
Model 1	3305.0
Model 2	3583.3
Model 2a	3281.7
Model 3	3300.2
Model 3a	2972.5

(Source: Results for OxyContin Information Request from FDA received February 11 2020. "Table Shells PMR 3051-3_11FEB2020_RMPDS.xlsx".)

Key: Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Model 3 models abuse

rate adjusted for tablets dispensed as a covariate; Model 3a models abuse rate adjusted for tablets dispensed and respondents as covariates

6.2   DEMOGRAPHIC CHARACTERISTICS OF SKIP AND OTP PATIENTS

Table 12: Demographic characteristics of RADARS OTP population stratified by OxyContin and primary comparator opioids (3Q2008-2Q2010)

Value	OxyContin	ER Morphine	IR Hydrocodone	Other Schedule II
Gender[1]				
Male [Frequency (%)]	2,062 (54.26)	555 (53.99)	1,396 (50.62)	2,477 (50.65)
Female [Frequency (%)]	1,480 (38.95)	387 (37.65)	1,150 (41.70)	2,066 (42.25)
Age				
Mean (SD)	30.56 (9.21)	32.18 (10.11)	32.64 (9.96)	32.42 (10)
Median (IQR)	28 (24,35)	29 (25,38)	30 (25,39)	30 (25,38)
N	3,685	987	2,664	4,730
Race[2]				
White [Frequency (%)]	3,474 (91.42)	942 (91.63)	2,418 (87.67)	4,313 (88.20)
Latino [Frequency (%)]	142 (3.74)	36 (3.50)	156 (5.66)	256 (5.24)
African-American [Frequency (%)]	86 (2.26)	23 (2.24)	111 (4.02)	190 (3.89)
Native American [Frequency (%)]	35 (0.92)	15 (1.46)	33 (1.20)	52 (1.06)
Asian or Pacific Islander [Frequency (%)]	19 (0.50)	8 (0.78)	9 (0.33)	23 (0.47)
Other [Frequency (%)]	53 (1.39)	10 (0.97)	42 (1.52)	70 (1.43)
Number of Items Endorsed				
Mean (SD)	8.91 (5.01)	11.45 (5.53)	9.37 (5.25)	8.50 (4.85)
Median (IQR)	8 (5, 12)	11 (7, 15)	8 (5, 12)	8 (5, 11)
N	3,800	1,028	2,758	4,890

[1]Respondents with unknown values for gender were not included in this table, therefore percentages for gender do not add to 100%. [2]Respondents could mark more than one race, therefore frequencies may add to more than 100%. SD: standard deviation; IQR: interquartile range; OTP: Opioid Treatment Program (medication-assisted treatment). ER=extended release; IR=immediate release; IR Hydrocodone=IR hydrocodone combination products.

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Table 7-3 Demographic characteristics of OTP population stratified by OxyContin and primary comparator opioids (3Q2008-2Q2010). P. 44)

Table 13: Demographic characteristics of RADARS OTP population stratified by OxyContin and primary comparator opioids (1Q2011-4Q2015)

Value	OxyContin	ER Morphine	IR Hydrocodone	Other Schedule II
Gender[1]				
Male [Frequency (%)]	2,279 (54.30)	957 (53.64)	3,021 (51.80)	5,677 (51.01)
Female [Frequency (%)]	1,847 (44.01)	797 (44.67)	2,737 (46.93)	5,307 (47.68)
Age				
Mean (SD)	32.61 (9.43)	33.62 (9.66)	33.58 (9.56)	33.09 (9.53)
Median (IQR)	30.5 (26,37)	31 (26,39)	32 (26,39)	31 (26,38)
N	4,162	1,769	5,797	11,061
Race[2]				
White [Frequency (%)]	3,785 (90.18)	1,656 (92.83)	5,148 (88.27)	9,953 (89.42)
Latino [Frequency (%)]	170 (4.05)	50 (2.80)	273 (4.68)	452 (4.06)
African-American [Frequency (%)]	144 (3.43)	36 (2.02)	271 (4.65)	481 (4.32)
Native American [Frequency (%)]	69 (1.64)	38 (2.13)	91 (1.56)	169 (1.52)
Asian or Pacific Islander [Frequency (%)]	22 (0.52)	11 (0.62)	36 (0.62)	58 (0.52)
Other [Frequency (%)]	40 (0.95)	16 (0.90)	73 (1.25)	139 (1.25)
Number of Items Endorsed				
Mean (SD)	7.77 (4.98)	9.48 (5.46)	7.36 (4.71)	6.31 (4.29)
Median (IQR)	7 (4, 11)	9 (5, 13)	6 (4, 10)	5 (3, 8)
N	4,197	1,784	5,832	11,130

[1]Respondents with unknown values for gender were not included in this table, therefore percentages for gender do not add to 100%. [2]Respondents could mark more than one race, therefore frequencies may add to more than 100%. SD: standard deviation; IQR: interquartile range; OTP: Opioid Treatment Program (medication-assisted treatment). ER=extended release; IR=immediate release; IR Hydrocodone=IR hydrocodone combination products.

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Table 7-4 Demographic characteristics of OTP population stratified by OxyContin and primary comparator opioids (1Q2011-4Q2015). P. 45)

Table 14: Demographic characteristics of RADARS SKIP population stratified by OxyContin and primary comparator opioids (3Q2008-2Q2010)

Value	OxyContin	ER Morphine	IR Hydrocodone	Other Schedule II
Gender[1]				
Male [Frequency (%)]	505 (51.74)	124 (55.36)	395 (45.77)	697 (48.04)
Female [Frequency (%)]	419 (42.93)	94 (41.96)	411 (47.62)	669 (46.11)
Age				
Mean (SD)	33.37 (10.64)	34.93 (11.07)	34.96 (11.3)	35.14 (11.31)
Median (IQR)	31 (25,39)	33 (26,42)	32 (26,42)	32 (26,43)
N	960	221	855	1,426
Race[2]				
White [Frequency (%)]	750 (76.84)	186 (83.04)	631 (73.12)	1,109 (76.43)
Latino [Frequency (%)]	54 (5.53)	9 (4.02)	54 (6.26)	84 (5.79)
African-American [Frequency (%)]	68 (6.97)	11 (4.91)	85 (9.85)	103 (7.10)
Native American [Frequency (%)]	71 (7.27)	14 (6.25)	66 (7.65)	109 (7.51)
Asian or Pacific Islander [Frequency (%)]	7 (0.72)	1 (0.45)	6 (0.70)	9 (0.62)
Other [Frequency (%)]	22 (2.25)	2 (0.89)	15 (1.74)	27 (1.86)
Number of Items Endorsed				
Mean (SD)	8.40 (5.06)	10.99 (6.05)	7.98 (5.01)	7.54 (4.87)
Median (IQR)	7 (5, 11)	10 (6, 15)	6 (4, 11)	6 (4, 10)
N	976	224	863	1,451

[1]*Respondents with unknown values for gender were not included in this table, therefore percentages for gender do not add to 100%.* [2]*Respondents could mark more than one race, therefore frequencies may add to more than 100%. SD: standard deviation; IQR: interquartile range; SKIP: Survey of Key Informants' Patients Program (non-medication-assisted treatment). ER=extended release; IR=immediate release; IR Hydrocodone=IR hydrocodone combination products.*

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Table 7-5 Demographic characteristics of SKIP population stratified by OxyContin and primary comparator opioids (3Q2008-2Q2010). P. 46)

Table 15: Demographic characteristics of RADARS SKIP population stratified by OxyContin and primary comparator opioids (1Q2011-4Q2015)

Value	OxyContin	ER Morphine	IR Hydrocodone	Other Schedule II
Gender[1]				
Male [Frequency (%)]	1,342 (51.91)	518 (54.47)	2,023 (49.44)	3,158 (50.64)
Female [Frequency (%)]	1,226 (47.43)	425 (44.69)	2,048 (50.05)	3,042 (48.78)
Age				
Mean (SD)	32.49 (9.99)	33.29 (9.76)	33.43 (10.32)	32.96 (10.28)
Median (IQR)	30 (25,38)	31 (26,40)	31 (26,40)	31 (25,39)
N	2,573	946	4,077	6,205
Race[2]				
White [Frequency (%)]	2,124 (82.17)	824 (86.65)	3,322 (81.18)	5,123 (82.15)
Latino [Frequency (%)]	100 (3.87)	31 (3.26)	162 (3.96)	238 (3.82)
African-American [Frequency (%)]	182 (7.04)	50 (5.26)	307 (7.50)	443 (7.10)
Native American [Frequency (%)]	136 (5.26)	38 (4.00)	244 (5.96)	340 (5.45)
Asian or Pacific Islander [Frequency (%)]	24 (0.93)	5 (0.53)	29 (0.71)	48 (0.77)
Other [Frequency (%)]	53 (2.05)	13 (1.37)	73 (1.78)	115 (1.84)
Number of Items Endorsed				
Mean (SD)	9.17 (5.55)	11.57 (5.52)	8.18 (5.34)	7.43 (5.08)
Median (IQR)	8 (5, 13)	11 (7, 16)	7 (4, 11)	6 (4, 10)
N	2,585	951	4,092	6,236

[1]Respondents with unknown values for gender were not included in this table, therefore percentages for gender do not add to 100%. [2]Respondents could mark more than one race, therefore frequencies may add to more than 100%. SD: standard deviation; IQR: interquartile range; SKIP: Survey of Key Informants' Patients Program (non-medication-assisted treatment). ER=extended release; IR=immediate release; IR Hydrocodone=IR hydrocodone combination products.

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Table 7-6 Demographic characteristics of SKIP population stratified by OxyContin and primary comparator opioids (1Q2011-4Q2015). P. 47)

6.3 PRE- AND POST-PERIOD PAST MONTH ABUSE OF OXYCONTIN AND PRIMARY COMPARATORS (COMBINED AND OTP AND SKIP SEPARATELY), -2Y/5Y

Table 16: Percent change (95% CI) in mean past-month abuse rate after introduction of reformulated OxyContin, for OxyContin and primary comparators, RADARS OTP/SKIP combined, OTP, and SKIP separately, -2y/5y

		Model 1 % change (95% CI)	Model 2 % change (95% CI)	Model 2a % change (95% CI)
OxyContin	Combined	-56.01% (-66.59%, -42.08%)	-33.43% (-48.94%, -13.21%)	-45.08% (-58.15%, -27.91%)
	OTP	-63.20% (-74.08%, -47.75%)	-39.45% (-56.24%, -16.23%)	-48.58% (-62.06%, -30.30%)
	SKIP	-35.45% (-44.20%, -25.33%)	-17.65% (-30.96%, -1.76%)	-25.01% (-40.83%, -4.96%)
ER Morphine	Combined	-32.33% (-45.73%, -15.61%)	-45.48% (-60.07%, -25.57%)	-55.15% (-66.97%, -39.10%)
	OTP	-42.17% (-55.26%, -25.25%)	-50.88% (-65.14%, -30.78%)	-58.50% (-69.64%, -43.28%)
	SKIP	3.47% (-16.12%, 27.64%)	-26.81% (-46.52%, 0.17%)	-33.43% (-52.97%, -5.78%)
IR Hydrocodone	Combined	-31.82% (-43.46%, -17.79%)	-21.10% (-35.33%, -3.73%)	-38.65% (-51.30%, -22.70%)
	OTP	-42.95% (-55.11%, -27.50%)	-29.92% (-45.42%, -10.02%)	-44.21% (-56.29%, -28.79%)
	SKIP	-10.15% (-19.78%, 0.63%)	-11.75% (-25.74%, 4.88%)	-21.18% (-39.08%, 1.98%)
Other Schedule II	Combined	-15.16% (-24.56%, -4.60%)	-17.59% (-27.92%, -5.79%)	-32.22% (-42.02%, -20.77%)
	OTP	-24.16% (-34.79%, -11.80%)	-22.21% (-33.73%, -8.69%)	-34.19% (-43.20%, -23.75%)
	SKIP	4.75% (-2.48%, 12.50%)	-12.32% (-22.24%, -1.13%)	-20.21% (-34.80%, -2.35%)

Model 1: rate of abuse per number of respondents; Model 2: rate of abuse per dosage units dispensed; Model 2a: rate of abuse per dosage units dispensed and adjusting for the number of respondents. ER=extended release; IR=immediate release; IR Hydrocodone= IR hydrocodone combination products; CI: confidence interval; OTP: Opioid Treatment Program (medication-assisted treatment); SKIP: Survey of Key Informants' Patients Program (non-medication-assisted treatment).

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Table 7-8. Percent change (95% CI) in overall abuse for OxyContin and primary comparators after introduction of reformulated OxyContin for the combined population, OTP population and SKIP population using different modelling approaches, -2y/5y P. 55.)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: -2y/5y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

Table 17: RORR (95% CI): Pre-post change in abuse rates of primary comparators vs. OxyContin, in the RADARS combined, OTP, and SKIP populations, -2y/5y
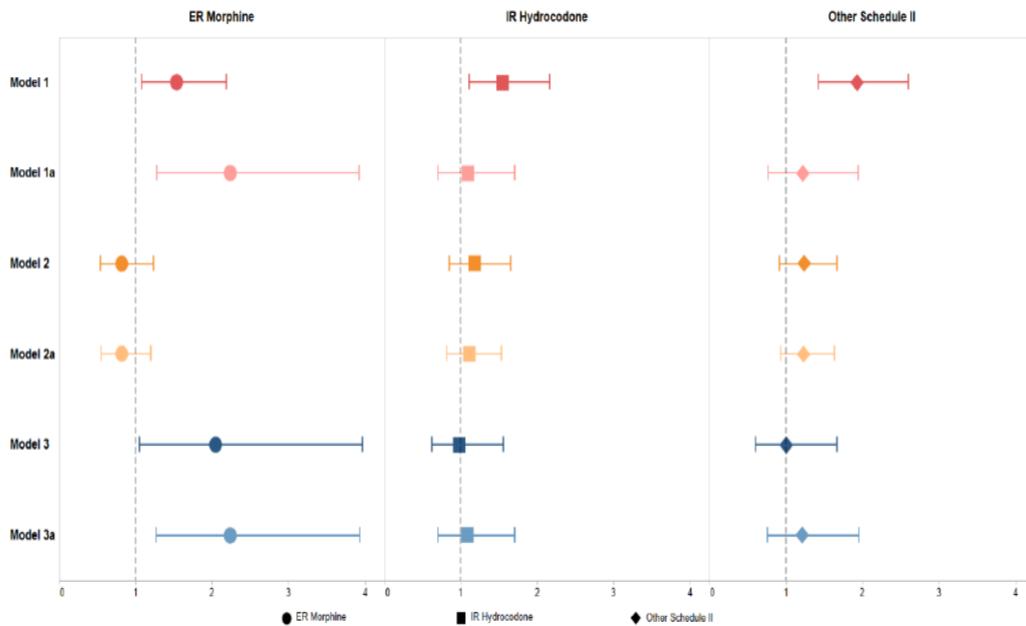
		Model 1 *RORR* (95% CI)	Model 2 *RORR* (95% CI)	Model 2a *RORR* (95% CI)
ER Morphine	Combined	1.538 (1.081, 2.189)	0.819 (0.544, 1.233)	0.817 (0.557, 1.198)
	OTP	1.571 (1.018, 2.426)	0.811 (0.506, 1.301)	0.807 (0.527, 1.235)
	SKIP	1.603 (1.242, 2.070)	0.889 (0.620, 1.274)	0.888 (0.623, 1.266)
IR Hydrocodone	Combined	1.550 (1.111, 2.162)	1.185 (0.851, 1.651)	1.117 (0.813, 1.536)
	OTP	1.550 (1.014, 2.370)	1.157 (0.768, 1.744)	1.085 (0.746, 1.578)
	SKIP	1.392 (1.157, 1.674)	1.072 (0.837, 1.372)	1.051 (0.820, 1.348)
Other Schedule II	Combined	1.929 (1.430, 2.601)	1.238 (0.920, 1.666)	1.234 (0.934, 1.631)
	OTP	2.061 (1.407, 3.018)	1.285 (0.895, 1.845)	1.280 (0.926, 1.770)
	SKIP	1.623 (1.380, 1.908)	1.065 (0.860, 1.318)	1.064 (0.858, 1.319)

Model 1: rate of abuse per number of respondents; Model 2: rate of abuse per dosage units dispensed; Model 2a: rate of abuse per dosage units dispensed and adjusting for the number of respondents. Ratio of risk ratios (RORR)=(comparator risk ratio)/(OxyContin risk ratio); ER=extended release; IR=immediate release; IR Hydrocodone= IR hydrocodone combination products; CI: confidence interval; OTP: Opioid Treatment Program (medication-assisted treatment); SKIP: Survey of Key Informants' Patients Program (non-medication-assisted treatment).

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Table 7-9. Ratio of risk ratios (95% CI) of overall abuse risk of primary comparators versus overall abuse risk of OxyContin after introduction of reformulated OxyContin for the combined population, OTP population and SKIP population using different modelling approaches, -2y/5y. P. 57.)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: -2y/5y, entire US region, sites contributing $\geq$1 assessment during the study period, any OxyContin

Table 18: RORR (95% CI): Pre-post change in abuse rates of primary comparators vs. OxyContin for all models, RADARS combined population
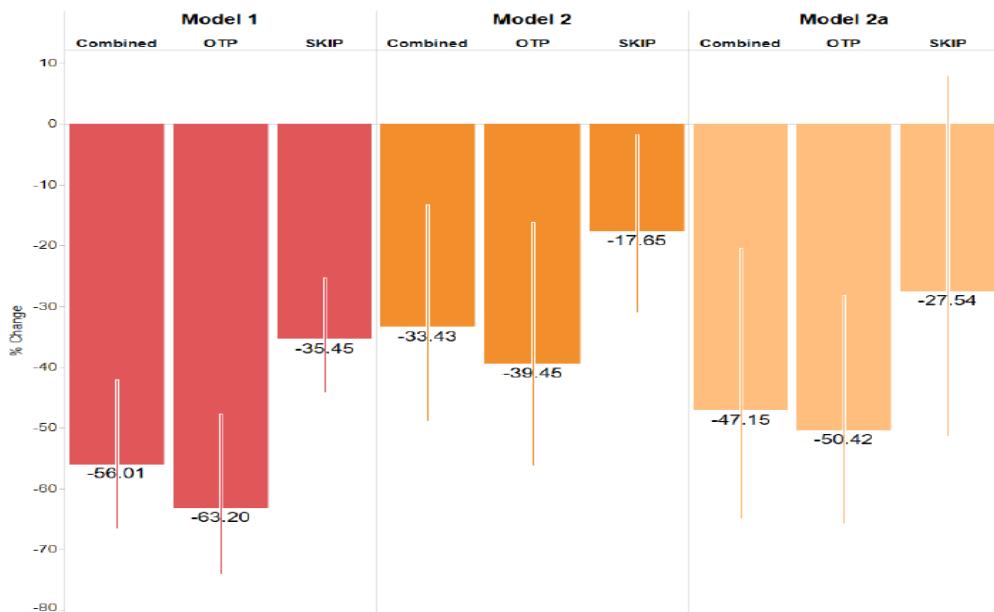
Drug Group: IR Hydrocodone = IR hydrocodone products; Other Schedule II = Other Schedule II opioid analgesic tablets and capsules

(Source: Purdue Pharma/RADARS® System RADARS® System OxyContin® PMR 3051-2 and 3051-3 information request responses from FDA received September 2019 (Part 3), submitted March 6, 2020. Title: Figure 2.25. Poisson regression 2 years pre-reformulation vs. 5 years post-reformulation for past 30 day abuse of OxyContin (original + reformulated) and primary comparator opioids using the entire coverage area in the treatment centers combined population. P. 655.)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Model 3 models abuse rate adjusted for tablets dispensed as a covariate; Model 3a models abuse rate adjusted for tablets dispensed and respondents as covariates; Parameters: -2y/5y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

6.4   PRE- AND POST-PERIOD PAST MONTH ABUSE OF OXYCONTIN ALONE (COMBINED AND OTP AND SKIP SEPARATELY), -2Y/5Y

Figure 34: Percent change (95% CI) in mean past-month abuse of OxyContin after introduction of reformulated OxyContin for the RADARS combined population, OTP population, and SKIP population, -2y/5y

Model 1: rate of abuse per number of respondents; Model 2: rate of abuse per dosage units dispensed; Model 2a: rate of abuse per dosage units dispensed and adjusting for the number of respondents. CI: confidence interval; OTP: Opioid Treatment Program (medication-assisted treatment); SKIP: Survey of Key Informants' Patients Program (non-medication-assisted treatment).

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Percent change (95% CI) in overall abuse of OxyContin after introduction of reformulated OxyContin for the combined population, OTP population, and SKIP population using different modeling approaches -2y/5y. P. 49.)

Key: OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: -2y/5y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

Table 19: Percent change (95% CI) in OxyContin abuse for the RADARS® combined population, OTP population, and SKIP population, -2y/5y

OxyContin	Model 1 % change (95% CI)	Model 2 % change (95% CI)	Model 2a % change (95% CI)
Combined	-56.01% (-66.59%, -42.08%)	-33.43% (-48.94%, -13.21%)	-47.15% (-64.88%, -20.45%)
OTP	-63.20% (-74.08%, -47.75%)	-39.45% (-56.24%, -16.23%)	-50.42% (-65.76%, -28.21%)
SKIP	-35.45% (-44.20%, -25.33%)	-17.65% (-30.96%, -1.76%)	-27.54% (-51.40%, 8.04%)

Model 1: rate of abuse per number of respondents; Model 2: rate of abuse per dosage units dispensed; Model 2a: rate of abuse per dosage units dispensed and adjusting for the number of respondents. CI: confidence interval; OTP: Opioid Treatment Program (medication-assisted treatment); SKIP: Survey of Key Informants' Patients Program (non-medication-assisted treatment).

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Percent change (95% CI) in OxyContin abuse for the combined population, OTP population and SKIP population using different modeling approaches -2y/5y. P. 50.)

Key: OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per

tablets dispensed adjusted for respondents as a covariate; Parameters: -2y/5y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

6.5   RANGES FOR PERCENT CHANGE AND RORR FOR OXYCONTIN AND PRIMARY COMPARATORS

Table 20: Range of pre-post relative change estimates for OxyContin and primary comparators for primary variable definitions and all models, RADARS® <u>combined population</u>

	Range: Pre-post relative change (95% CI)		Range: RORR (95% CI)	
	Most "conservative"	Least "Conservative"	Most "conservative"	Least "conservative"
OxyContin	-20.0% (-44.7% to 15.8%)[1]	-56.0% (-66.6% to -42.1%)[2]	Ref	Ref
ER morphine	63.6% (-5.7% to 183.7%)[3]	-55.2% (-67.0% to -39.1%)[4]	0.8 (0.6 to 1.2)[9]	2.2 (1.3 to 3.9)[10]
IR hydrocodone	-21.1% (-35.3% to -3.7%)[5]	-38.7% (-51.3% to -22.7%)[6]	1.0 (0.6 to 1.6)[11]	1.6 (1.1 to 2.2)[12]
Other schedule II	-15.2% (-24.6% to -4.6%)[7]	-32.2% (-42.0% to -20.8%)[8]	1.0 (0.6 to 1.7)[13]	1.9 (1.4 to 2.6)[14]

(Source: FDA generated table from information request response)

1) Model 3, 2) Model 1, 3) Model 3, 4) Model 2a, 5) Model 2, 6) Model 2a, 7) Model 1, 8) Model 2a, 9) Model 2a, 10) Model 3a, 11) Model 3, 12) Model 1 13) Model 3, 14) Model 1

Table 21: Range of pre-post relative change estimates for OxyContin and primary comparators for primary variable definitions and all models, RADARS <u>OTP population</u>

	Range: Pre-post relative change (95% CI)		Range: RORR (95% CI)	
	Most "conservative"	Least "conservative"	Most "conservative"	Least "conservative"
OxyContin	1.9% (-37.2% to 65.5%)[1]	-63.2% (-74.1% to -47.8%)[2]	Ref	Ref
ER morphine	-22.9% (-53.9% to 29.0%)[3]	-58.5% (-69.6% to -43.3%)[4]	0.8 (0.4 to 1.5)[9]	1.6 (1.0 to 2.4)[10]
IR hydrocodone	-29.9% (-45.4% to -10.0%)[5]	-44.2% (-56.3% to -28.8%)[6]	0.7 (0.4 to 1.1)[11]	1.6 (1.0 to 2.4)[12]
Other schedule II	-22.2% (-33.7% to -8.7%)[7]	-35.8% (-46.3% to -23.1%)[8]	0.7 (0.4 to 1.1)[13]	2.1 (1.4 to 3.0)[14]

(Source: FDA generated table from information request response)

1) Model 3, 2) Model 1, 3) Model 3, 4) Model 2a, 5) Model 2, 6) Model 2a, 7) Model 2, 8) Model 3a, 9) Model 3, 10) Model 1, 11) Model 3, 12) Model 1, 13) Model 3, 14) Model 1

Table 22: Range of pre-post relative change estimates for OxyContin and primary comparators for primary variable definitions and all models, RADARS <u>SKIP population</u>

	Range: Pre-post relative change (95% CI)		Range: RORR (95% CI)	
	Most "conservative"	Least "conservative"	Most "conservative"	Least "conservative"
OxyContin	-8.2% (-26.0% to 13.9%)[1]	-36.3% (-48.3 to -21.4%)[2]	Ref	Ref
ER morphine	99.2% (5.5% to 276.1%)[3]	-33.4% (-53.0% to -5.8%)[4]	0.9 (0.6 to 1.3)[9]	2.3 (1.3 to 3.9)[10]
IR hydrocodone	17.00% (-11.23% to 54.21%)[5]	-21.2% (-39.1% to 2.0%)[6]	1.1 (0.8 to 1.3)[11]	1.4 (1.2 to 1.7)[12]
Other schedule II	41.1% (14.6% to 73.6%)[7]	-20.2% (-34.8% to -2.4%)[8]	1.1 (0.9 to 1.3)[13]	1.9 (1.5 to 2.5)[14]

(Source: FDA generated table from information request response)

1) Model 3, 2) Model 3a, 3) Model 3, 4) Model 2a, 5) Model 3, 6) Model 2a, 7) Model 3, 8) Model 2a, 9) Model 2a, 10) Model 3a, 11) Model 2a, 12) Model 1, 13) Model 2a, 14) Model 3a

6.6 PRE- AND POST-PERIOD PAST MONTH ABUSE OF OXYCONTIN AND PRIMARY COMPARATORS: COMBINED AND OTP AND SKIP SEPARATELY, -1Y/3Y

Table 23: Percent change (95% CI) in abuse of OxyContin and primary comparator opioids after introduction of reformulated OxyContin, RADARS combined, OTP, and SKIP populations, -1y/3y

		Model 1 % change (95% CI)	Model 2 % change (95% CI)	Model 2a % change (95% CI)
OxyContin	Combined	-46.66% (-63.21%, -22.66%)	-19.16% (-45.68%, 20.31%)	-39.15% (-58.69%, -10.39%)
	OTP	-53.21% (-70.55%, -25.64%)	-22.39% (-51.03%, 23.01%)	-35.86% (-56.74%, -4.88%)
	SKIP	-28.02% (-41.44%, -11.52%)	-6.03% (-29.16%, 24.67%)	-2.97% (-36.08%, 47.30%)
ER Morphine	Combined	-21.35% (-43.07%, 8.67%)	-29.30% (-55.29%, 11.80%)	-46.73% (-65.11%, -18.67%)
	OTP	-32.48% (-53.88%, -1.16%)	-35.38% (-60.36%, 5.37%)	-46.69% (-63.97%, -21.13%)
	SKIP	25.82% (-7.09%, 70.39%)	2.15% (-37.52%, 67.01%)	5.48% (-40.96%, 88.45%)
IR Hydrocodone	Combined	-20.54% (-35.45%, -2.18%)	-15.46% (-36.38%, 12.32%)	-36.48% (-52.51%, -15.03%)
	OTP	-31.77% (-48.71%, -9.25%)	-25.07% (-46.97%, 5.87%)	-38.20% (-53.66%, -17.57%)
	SKIP	-1.00% (-12.10%, 11.50%)	0.13% (-22.04%, 28.62%)	3.37% (-30.41%, 53.54%)
Other Schedule II	Combined	-14.41% (-25.77%, -1.30%)	-14.83% (-31.47%, 5.87%)	-35.90% (-48.48%, -20.25%)
	OTP	-22.32% (-36.06%, -5.63%)	-18.20% (-36.29%, 5.04%)	-32.43% (-43.69%, -18.91%)
	SKIP	2.07% (-5.86%, 10.67%)	-9.83% (-24.34%, 7.46%)	-6.92% (-34.50%, 32.27%)

Model 1: rate of abuse per number of respondents; Model 2: rate of abuse per dosage units dispensed; Model 2a: rate of abuse per dosage units dispensed and adjusting for the number of respondents. ER=extended release; IR=immediate release; IR Hydrocodone=IR hydrocodone combination products; CI=confidence interval; OTP: Opioid Treatment Program (medication-assisted treatment); SKIP: Survey of Key Informants' Patients Program (non-medication-assisted treatment).

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Percent change (95% CI) in overall abuse of OxyContin and the primary comparator opioids after introduction of reformulated OxyContin -1y/3y. P. 218.)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: -1y/3y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

Table 24: Ratio of rate ratios (95% CI): Pre-post change in abuse rates of primary comparator versus Oxycontin, in RADARS combined, OTP, and SKIP populations, -1y/3y

		Model 1 RORR (95% CI)	Model 2 RORR (95% CI)	Model 2a RORR (95% CI)
ER Morphine	Combined	1.474 (0.901, 2.413)	0.875 (0.477, 1.604)	0.876 (0.509, 1.505)
	OTP	1.443 (0.792, 2.629)	0.833 (0.425, 1.630)	0.831 (0.481, 1.438)
	SKIP	1.748 (1.211, 2.522)	1.087 (0.617, 1.917)	1.087 (0.615, 1.920)
IR Hydrocodone	Combined	1.490 (0.973, 2.280)	1.046 (0.641, 1.705)	1.044 (0.669, 1.630)
	OTP	1.458 (0.846, 2.512)	0.966 (0.543, 1.717)	0.964 (0.597, 1.556)
	SKIP	1.375 (1.084, 1.745)	1.066 (0.730, 1.554)	1.065 (0.728, 1.558)
Other Schedule II	Combined	1.605 (1.078, 2.389)	1.054 (0.670, 1.658)	1.053 (0.705, 1.575)
	OTP	1.660 (1.004, 2.743)	1.054 (0.624, 1.780)	1.053 (0.689, 1.610)
	SKIP	1.418 (1.136, 1.770)	0.960 (0.688, 1.338)	0.959 (0.686, 1.341)
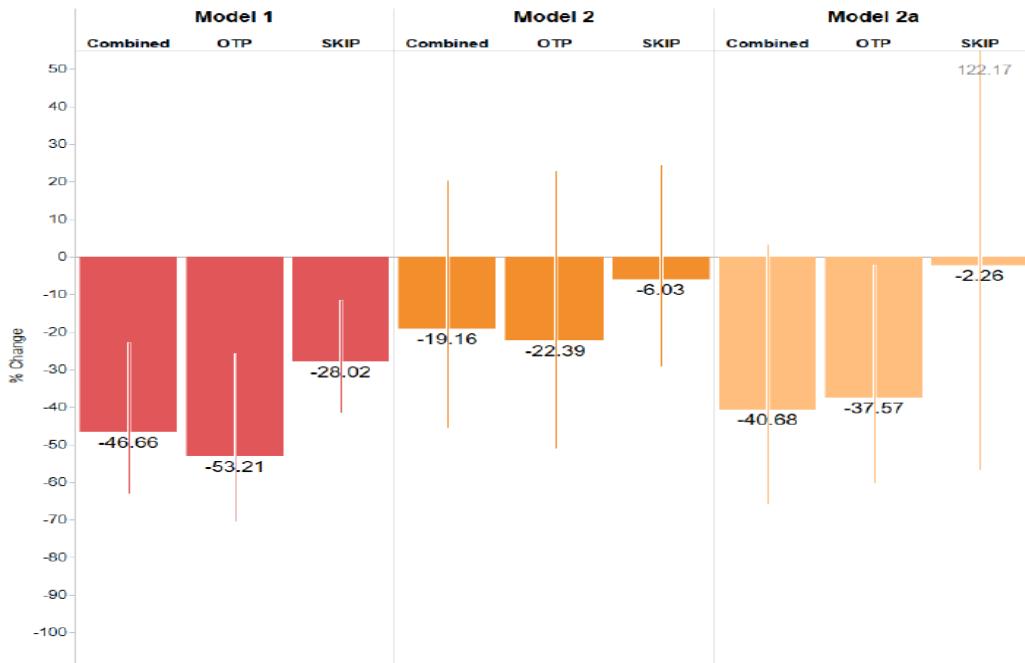
Model 1: rate of abuse per number of respondents; Model 2: rate of abuse per dosage units dispensed; Model 2a: rate of abuse per dosage units dispensed and adjusting for the number of respondents. Ratio of risk ratios (RORR)=(comparator risk ratio)/(OxyContin risk ratio); ER=extended release; IR=immediate release; IR Hydrocodone=IR hydrocodone combination products; CI=confidence interval; OTP: Opioid Treatment Program (medication-assisted treatment); SKIP: Survey of Key Informants' Patients Program (non-medication-assisted treatment).

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Ratio of risk ratios (95% CI) of past-month abuse risk for the primary comparator opioids relative to OxyContin, -1y/3y. P. 68.)

Key: ER: Extended Release; IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: -1y/3y, entire US region, sites contributing >1 assessment during the study period, any OxyContin

6.7 PRE- AND POST-PERIOD PAST MONTH ABUSE OF OXYCONTIN ALONE: COMBINED AND OTP AND SKIP SEPARATELY, -1Y/3Y

Figure 35: Percent change (95% CI) in mean past-month abuse of OxyContin after introduction of reformulated OxyContin for RADARS combined population, OTP population, and SKIP population, -1y/3y

Model 1: rate of abuse per number of respondents; Model 2: rate of abuse per dosage units dispensed; Model 2a: rate of abuse per dosage units dispensed and adjusting for the number of respondents. CI=Confidence interval; OTP: Opioid Treatment Program (medication-assisted treatment); SKIP: Survey of Key Informants' Patients Program (non-medication-assisted treatment).

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Percent change (95% CI) in overall abuse of OxyContin after introduction of reformulated OxyContin for combined population, OTP population, and SKIP population, -1y/3y. P. 67.)

Key: OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: -1y/3y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

Table 25: Percent change (95% CI) in mean past-month abuse rate of OxyContin after introduction of reformulated OxyContin for RADARS combined population, OTP population, and SKIP population, -1y/3y

	Model 1 % change (95% CI)	Model 2 % change (95% CI)	Model 2a % change (95% CI)
Combined	-46.66% (-63.21%, -22.66%)	-19.16% (-45.68%, 20.31%)	-40.68% (-65.95%, 3.36%)
OTP	-53.21% (-70.55%, -25.64%)	-22.39% (-51.03%, 23.01%)	-37.57% (-60.17%, -2.17%)
SKIP	-28.02% (-41.44%, -11.52%)	-6.03% (-29.16%, 24.67%)	-2.26% (-57.00%, 122.17%)

Model 1: rate of abuse per number of respondents; Model 2: rate of abuse per dosage units dispensed; Model 2a: rate of abuse per dosage units dispensed and adjusting for the number of respondents. CI=confidence interval; OTP: Opioid Treatment Program (medication-assisted treatment); SKIP: Survey of Key Informants' Patients Program (non-medication-assisted treatment).

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Percent change (95% CI) in overall abuse of OxyContin after introduction of reformulated OxyContin for combined population, OTP population, and SKIP population, -1y/3y. P. 214.)

Key: OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: -1y/3y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

6.8 PRE- AND POST-PERIOD PAST MONT ABUSE OF OXYCONTIN AND SECONDARY COMPARATORS, COMBINED POPULATION, -2Y/5Y

Table 26: Percent change (95% CI) in mean past-month abuse rate of OxyContin and secondary comparator opioids after introduction of reformulated OxyContin, RADARS combined population, -2y/5y

	Model 1 % change (95% CI)	Model 2 % change (95% CI)	Model 2a % change (95% CI)
OxyContin	-56.01% (-66.59%, -42.08%)	-33.43% (-48.94%, -13.21%)	-49.94% (-61.51%, -34.88%)
IR Oxycodone Products	-23.13% (-39.23%, -2.75%)	-36.27% (-51.15%, -16.84%)	-52.28% (-62.63%, -39.05%)
Methadone	-49.33% (-59.38%, -36.80%)	-34.76% (-46.74%, -20.07%)	-51.18% (-59.76%, -40.77%)
Heroin	5.07% (-6.83%, 18.48%)	--[1]	--[1]
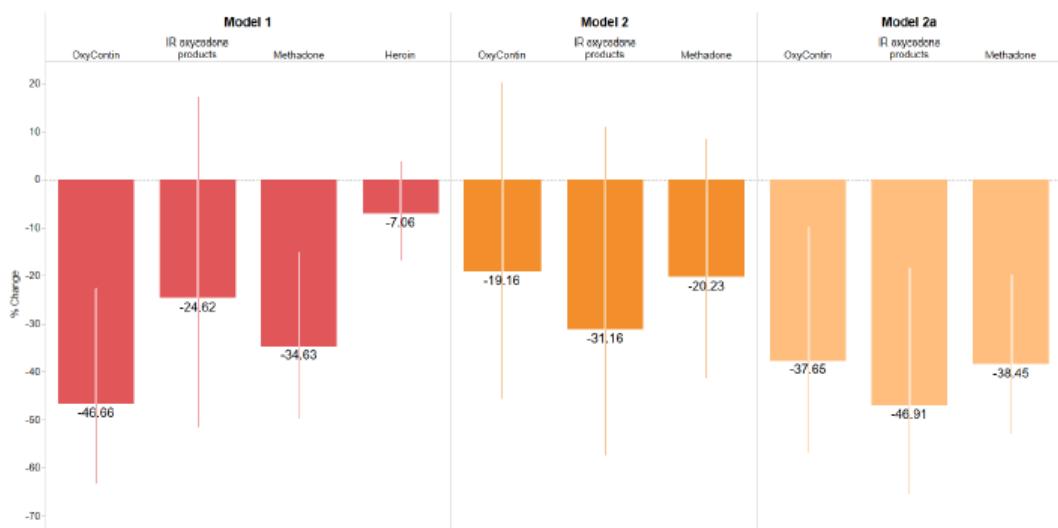
Model 1: rate of abuse per number of respondents; Model 2: rate of abuse per dosage units dispensed; Model 2a: rate of abuse per dosage units dispensed and adjusting for the number of respondents. IR=immediate release; CI=confidence interval. [1] Heroin is an illicit drug and therefore can only be evaluated in Model 1.

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Percent change (95% CI) in overall abuse for OxyContin and the secondary comparator opioids after introduction of reformulated OxyContin -2y/5y. P. 234.)

Key: IR: Immediate Release; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: -2y/5y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

6.9 PRE- AND POST-PERIOD PAST MONTH ABUSE OF OXYCONTIN AND SECONDARY COMPARATORS, COMBINED POPULATION, -1Y/3Y

Figure 36: Percent change (95% CI) in mean past-month abuse rate for OxyContin and the secondary comparator opioids after introduction of reformulated OxyContin, RADARS combined population, -1y/3y

Model 1: rate of abuse per number of respondents; Model 2: rate of abuse per dosage units dispensed; Model 2a: rate of abuse per dosage units dispensed and adjusting for the number of respondents. IR=immediate release; CI: confidence interval.

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Percent change (95% CI) in overall abuse for OxyContin and the secondary comparator opioids after introduction of reformulated OxyContin -1y/3y. P. 70.)

Key: IR: Immediate Release; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate; Parameters: -1y/3y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

Table 27: Percent change (95% CI) in mean past-month abuse rate of OxyContin and secondary comparator opioids after introduction of reformulated OxyContin, RADARS combined population, -1y/3y

	Model 1 % change (95% CI)	Model 2 % change (95% CI)	Model 2a % change (95% CI)
OxyContin	-46.66% (-63.21%, -22.66%)	-19.16% (-45.68%, 20.31%)	-37.65% (-56.87%, -9.86%)
IR Oxycodone Products	-24.62% (-51.58%, 17.33%)	-31.16% (-57.36%, 11.13%)	-46.91% (-65.44%, -18.43%)
Methadone	-34.63% (-49.66%, -15.11%)	-20.23% (-41.40%, 8.57%)	-38.45% (-52.80%, -19.74%)
Heroin	-7.06% (-16.82%, 3.84%)	_-[1]	_-[1]

Model 1: rate of abuse per number of respondents; Model 2: rate of abuse per dosage units dispensed; Model 2a: rate of abuse per dosage units dispensed and adjusting for the number of respondents. IR=immediate release; CI=confidence interval. [1] Heroin is an illicit drug and therefore can only be evaluated in Model 1.

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title Percent change (95% CI) in overall abuse of OxyContin and secondary comparator opioids after introduction of reformulated OxyContin -1y/3y. P. 237.)

Key: IR: Immediate Release; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate;

Parameters: -1y/3y, entire US region, sites contributing ≥1 assessment during the study period, any OxyContin

6.10 EVALUATION OF SURVEY CHANGES

Table 28: Assessment of survey change: Percent change in abuse after introduction of reformulated OxyContin, RADARS combined, SKIP, and OTP 1-page survey populations, -2y/5y

	Model 1 % Change (95% CI)	Model 2 % Change (95% CI)	Model 2a % Change (95% CI)
OxyContin			
All Surveys	-56.01% (-66.59%, -42.08%)	-33.43% (-48.94, -13.21%)	-45.08% (-58.15%, -27.91%)
SKIP	-35.45% (-44.20%, -25.33%)	-17.65% (-30.96%, -1.76%)	-25.01% (-40.83%, -4.96%)
1-page Survey	15.09% (-9.49%, 46.36%)	65.69% (15.52%, 137.66%)	58.63% (13.44%, 121.84%)
ER Morphine			
All Surveys	-32.33% (-45.73%, -15.61%)	-45.48% (-60.07%, -25.57%)	-55.15% (-66.97%, -39.10%)
SKIP	3.47% (-16.12%, 27.64%)	-26.81% (-46.52%, 0.17%)	-33.43% (-52.97%, -5.78%)
1-page Survey	43.38% (12.78%, 82.29%)	41.40% (-8.69%, 118.94%)	34.48% (-12.85%, 107.51%)
IR Hydrocodone			
All Surveys	-31.82% (-43.46%, -17.79%)	-21.10% (-35.33%, -3.73%)	-38.65% (-51.30%, -22.70%)
SKIP	-10.15% (-19.78%, 0.63%)	-11.75% (-25.74%, 4.88%)	-21.18% (-39.08%, 1.98%)
1-page Survey	21.32% (4.28%, 41.13%)	48.73% (13.38%, 95.11%)	38.93% (11.14%, 73.68%)
Other Schedule II			
All Surveys	-15.16% (-24.56%, -4.60%)	-17.59% (-27.92%, -5.79%)	-32.22% (-42.02%, -20.77%)
SKIP	4.75% (-2.48%, 12.50%)	-12.32% (-22.24%, -1.13%)	-20.21% (-34.80%, -2.35%)
1-page Survey	23.75% (-2.82%, 57.58%)	27.12% (-0.14%, 61.82%)	21.37% (-1.80%, 49.99%)

ER=extended release; IR=immediate release; IR Hydrocodone=IR hydrocodone combination products; CI=confidence interval; Model 1: Rate of abuse/Number of respondents. Model 2: Rate of abuse/Dosage units dispensed. Model 2a: Rate of abuse/Dosage units dispensed adjusting for number of respondents.

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Assessment of survey change: Percent change in abuse after introduction of reformulated OxyContin -2y/5y. P. 246.)

Key: OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; ER: Extended Release; IR: Immediate Release; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate

Table 29: Assessment of survey change for IR oxycodone abuse: RORR after introduction of reformulated OxyContin, RADARS combined population, -1y/3y

	Model 1 RORR (95% CI)	Model 2 RORR (95% CI)	Model 2a RORR (95% CI)
IR Oxycodone	1.413 (0.793, 2.518)	0.852 (0.457, 1.587)	0.852 (0.487, 1.489)
IR Oxycodone & Oxycodone NOS	2.563 (1.749, 3.755)	1.545 (1.007, 2.369)	1.545 (1.062, 2.246)
General Oxycodone	5.279 (3.234, 8.619)	--[1]	--[1]

RORR=ratio of risk ratios; IR=immediate release; NOS=not otherwise specified formulation (IR or extended release); CI=confidence interval; Model 1: Rate of abuse/Number of respondents. Model 2: Rate of abuse/Dosage units dispensed. Model 2a: Rate of abuse/Dosage units dispensed adjusting for number of respondents. [1]A denominator could not be determined because the type of oxycodone was unknown.

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Assessment of survey change for IR oxycodone abuse: RORR after introduction of reformulated OxyContin -1y/3y. P. 248.)

Key: OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; IR: Immediate Release; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate

Table 30: Assessment of survey change for IR oxycodone abuse: RORR after introduction of reformulated OxyContin, RADARS combined population, -2y/5y

	Model 1 RORR (95% CI)	Model 2 RORR (95% CI)	Model 2a RORR (95% CI)
IR Oxycodone	1.748 (1.217, 2.510)	0.957 (0.658, 1.394)	0.953 (0.678, 1.341)
IR Oxycodone & Oxycodone NOS	2.827 (2.118, 3.773)	1.549 (1.144, 2.096)	1.542 (1.170, 2.032)
General Oxycodone	5.472 (3.766, 7.951)	--[1]	--[1]

RORR=ratio of risk ratios; IR=immediate release; NOS=not otherwise specified formulation (IR or extended release); CI=confidence interval; Model 1: Rate of abuse/Number of respondents. Model 2: Rate of abuse/Dosage units dispensed. Model 2a: Rate of abuse/Dosage units dispensed adjusting for number of respondents. [1]A denominator could not be determined because the type of oxycodone was unknown.

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Assessment of survey change for IR oxycodone abuse: RORR after introduction of reformulated OxyContin -2y/5y. P. 248.)

Key: OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; IR: Immediate Release; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate

Table 31: Assessment of survey change: Percent change in abuse after introduction of reformulated OxyContin, RADARS combined, SKIP and 1-page OTP populations, -1y/3y

	Model 1 % Change (95% CI)	Model 2 % Change (95% CI)	Model 2a % Change (95% CI)
OxyContin			
All Surveys	-46.66% (-63.21%, -22.66%)	-19.16% (-45.68%, 20.31%)	-39.15% (-58.69%, -10.39%)
SKIP	-28.02% (-41.44%, -11.52%)	-6.03% (-29.16%, 24.67%)	-2.97% (-36.08%, 47.30%)
1-page Survey	15.21% (-13.72%, 53.86%)	75.25% (3.53%, 196.67%)	68.66% (3.76%, 174.15%)
ER Morphine			
All Surveys	-21.35% (-43.07%, 8.67%)	-29.30% (-55.29%, 11.80%)	-46.73% (-65.11%, -18.67%)
SKIP	25.82% (-7.09%, 70.39%)	2.15% (-37.52%, 67.01%)	5.48% (-40.96%, 88.45%)
1-page Survey	46.39% (10.73%, 93.53%)	54.51% (-4.30%, 149.48%)	47.85% (-8.91%, 139.98%)
IR Hydrocodone			
All surveys	-20.54% (-35.45%, -2.18%)	-15.46% (-36.38%, 12.32%)	-36.48% (-52.51%, -15.03%)
SKIP	-1.00% (-12.10%, 11.50%)	0.13% (-22.04%, 28.62%)	3.37% (-30.41%, 53.54%)
1-page Survey	23.83% (9.37%, 40.21%)	41.28% (0.80%, 98.03%)	35.35% (1.33%, 80.80%)
Other Schedule II			
All Surveys	-14.41% (-25.77%, -1.30%)	-14.83% (-31.47%, 5.87%)	-35.90% (-48.48%, -20.25%)
SKIP	2.07% (-5.86%, 10.67%)	-9.83% (-24.34%, 7.46%)	-6.92% (-34.50%, 32.27%)
1-page Survey	16.31% (-0.58%, 36.08%)	24.27% (-12.80%, 77.09%)	19.34% (-12.40%, 62.60%)
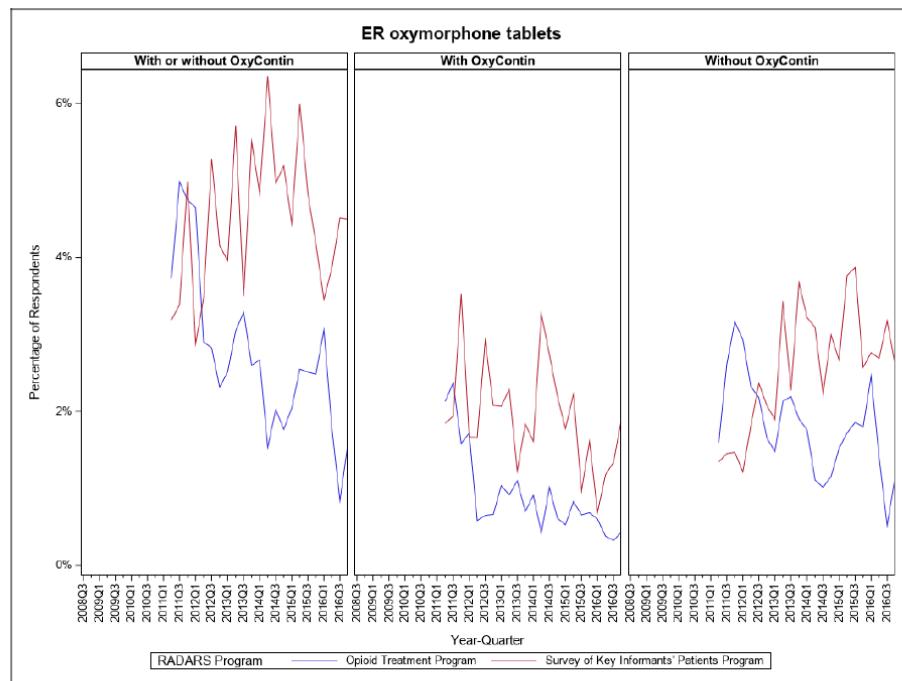
ER=extended release; IR=immediate release; IR Hydrocodone=IR hydrocodone combination products; CI=confidence interval; Model 1: Rate of abuse/Number of respondents. Model 2: Rate of abuse/Dosage units dispensed. Model 2a: Rate of abuse/Dosage units dispensed adjusting for number of respondents.

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Assessment of survey change: Percent change in abuse after introduction of reformulated OxyContin -1y/3y. P. 247.)

Key: OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; ER: Extended Release; IR: Immediate Release; Model 1 models abuse rate per respondent; Model 2 models abuse rate per tablets dispensed; Model 2a models abuse rate per tablets dispensed adjusted for respondents as a covariate

6.11 CHANGES IN COMPARATOR ABUSE RATES STRATIFIED BY CO-ENDORSEMENT (PAST 30-DAY) ABUSE OF OXYCONTIN

Figure 37: Percent of respondents endorsing past 30-day abuse of ER oxymorphone with and without OxyContin in the RADARS System OTP and SKIP programs (2008-2016)
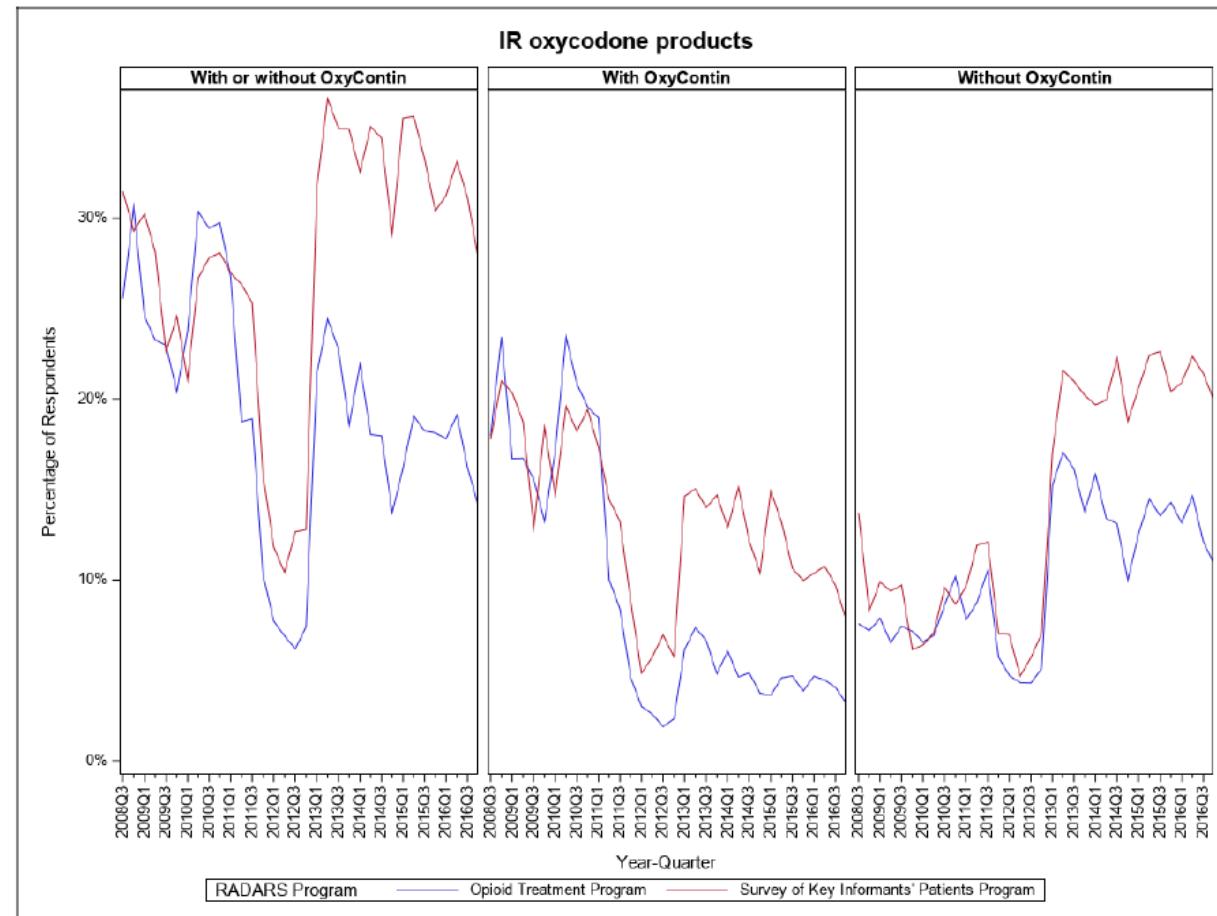
ER=extended release

(Source: Results for OxyContin Information Request from FDA received December 5, 2019. Title: Figure 4. ER oxymorphone abuse with, without and total abuse with or without OxyContin during the study period for the Opioid Treatment Program (OTP) and the Survey of Key Informants' Patients (SKIP). P. 45)

Key: ER: Extended Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients

Figure 38: Percent of respondents endorsing past 30-day abuse of IR oxycodone products with and without OxyContin in the RADARS System OTP and SKIP programs (2008-2016)

IR=immediate release

Key: IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients

Figure 39: Percent of respondents endorsing past 30-day abuse of IR oxycodone or NOS oxycodone products with and without OxyContin in the RADARS System OTP and SKIP programs (2008-2016)

IR=immediate release; NOS=not otherwise specified (formulation)

Key: IR: Immediate Release; OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients; NOS: Not Otherwise Specified
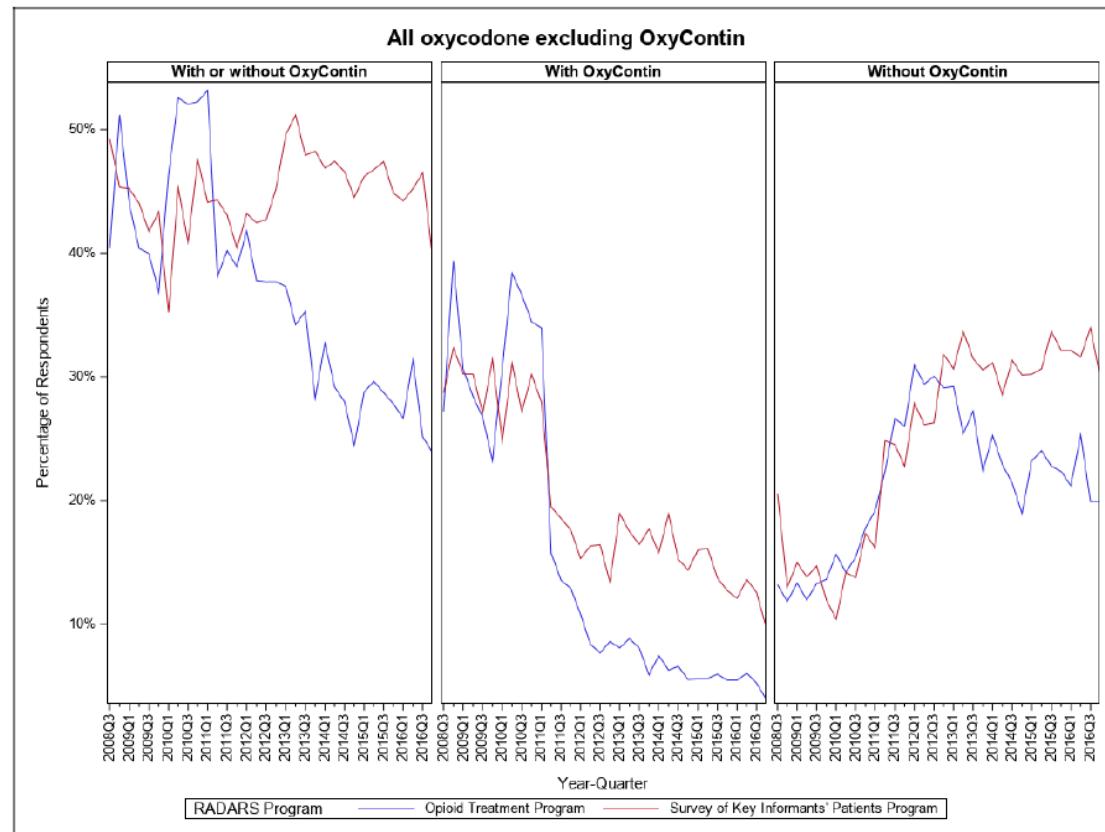
Figure 40: Percent of respondents endorsing past 30-day abuse of general oxycodone products with and without OxyContin in the RADARS System OTP and SKIP programs (2008-2016)

(Source: Results for OxyContin Information Request from FDA received December 5, 2019. Title: Figure 5. General oxycodone abuse with, without and total abuse with or without OxyContin during the study period for the Opioid Treatment Program (OTP) and the Survey of Key Informants' Patients (SKIP). P. 48)

Key: OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients
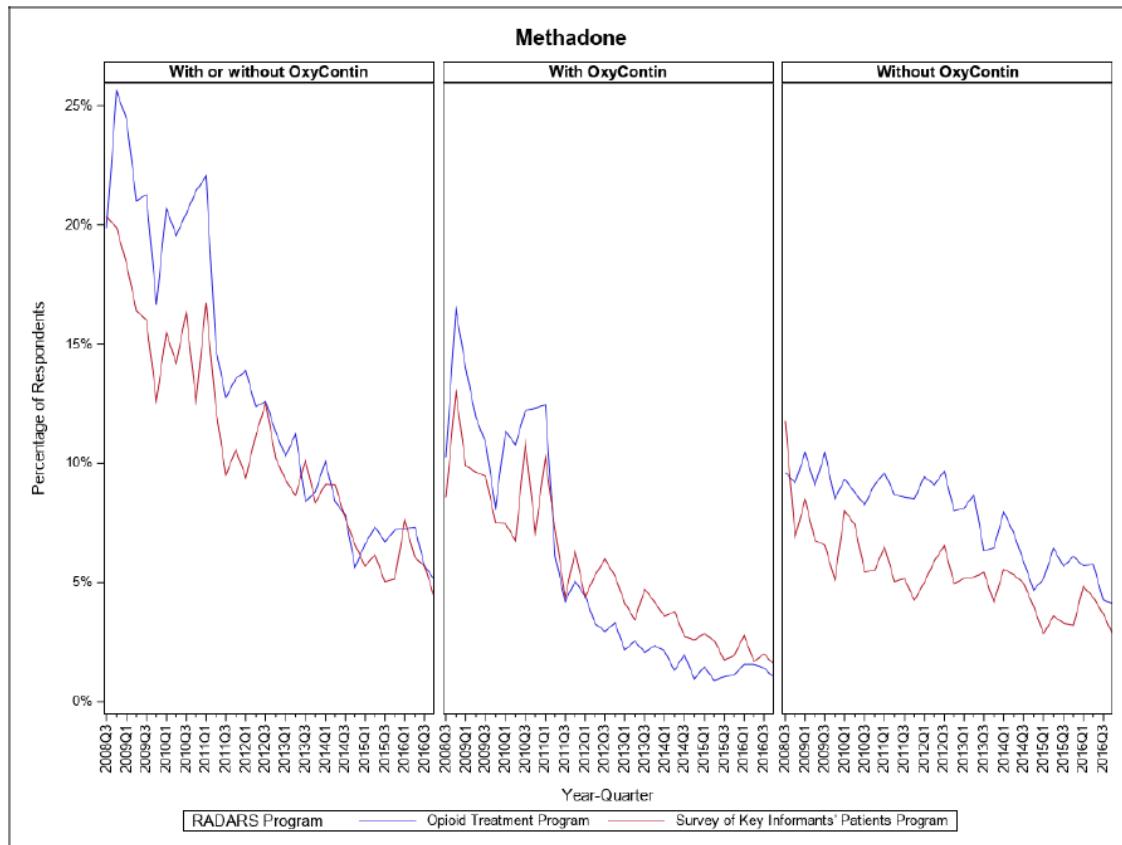
Figure 41: Percent of respondents endorsing past 30-day abuse of all oxycodone products (excluding OxyContin) with and without OxyContin in the RADARS System OTP and SKIP programs (2008-2016)

(Source: Results for OxyContin Information Request from FDA received December 5, 2019. Title: Figure 5. General oxycodone excluding OxyContin abuse with, without and total abuse with or without OxyContin during the study period for the Opioid Treatment Program (OTP) and the Survey of Key Informants' Patients (SKIP). P. 49)

Key: OTP: Opioid Treatment Program; SKIP: Survey of Key Informants' Patients

Figure 42: Percent of respondents endorsing past 30-day abuse of methadone with and without OxyContin in the RADARS System OTP and SKIP programs (2008-2016)
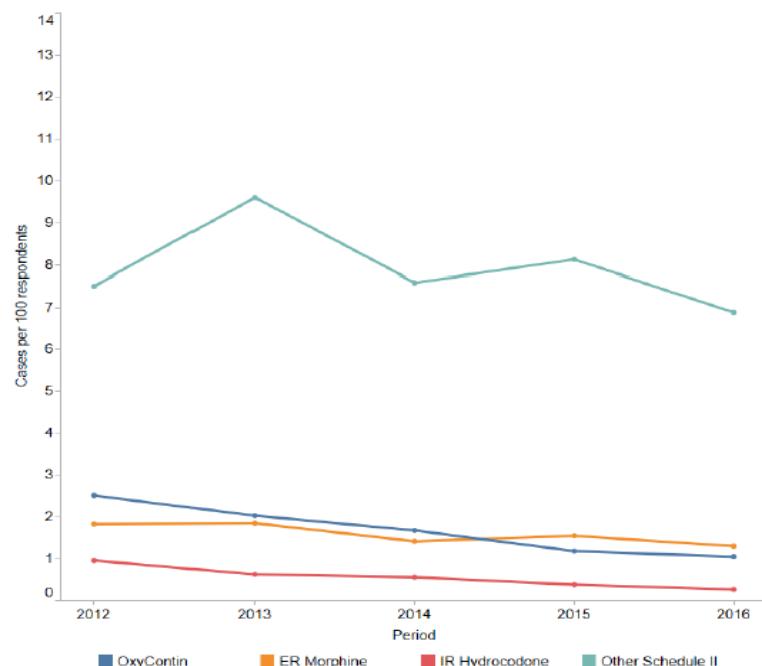
(Source: Results for OxyContin Information Request from FDA received December 5, 2019. Title: Figure 5. Methadone abuse with, without and total abuse with or without OxyContin during the study period for the Opioid Treatment Program (OTP) and the Survey of Key Informants' Patients (SKIP). P. 50)

6.12 DESCRIPTIVE ANALYSIS OF CHANGES IN INJECTION ABUSE FOR OXYCONTIN AND PRIMARY COMPARATORS

Figure 43: Observed yearly abuse rate by injection route for OxyContin and primary comparator opioids (2012-2016), RADARS combined population
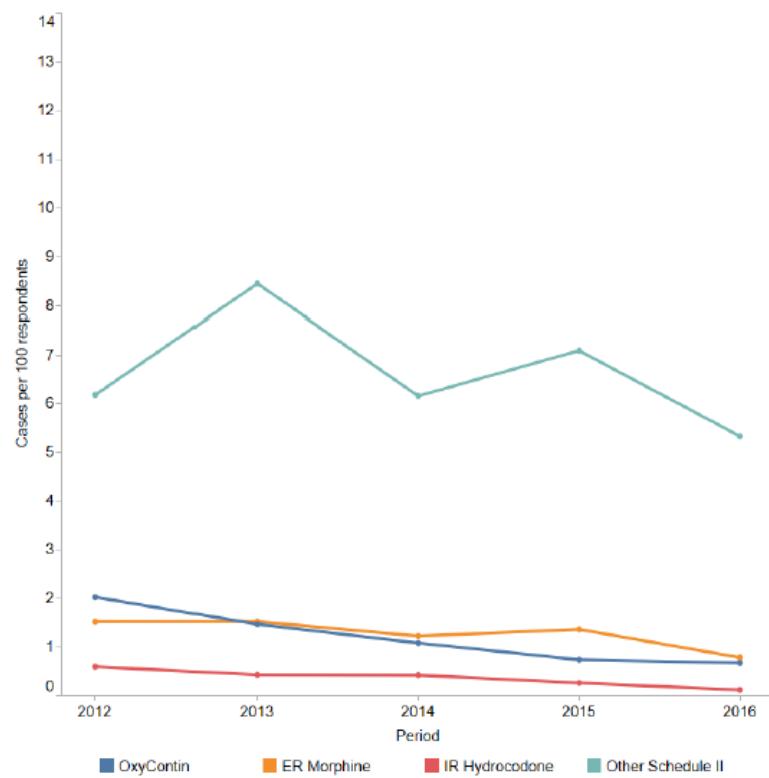
ER=extended release; IR=immediate release; IR Hydrocodone= IR hydrocodone combination products.

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title Observed yearly abuse rate by injection route for OxyContin and primary comparator opioids (2012-2016), combined population. P. 223.)

Figure 44: Observed yearly abuse rate by injection route for OxyContin and primary comparator opioids (2012-2016), RADARS OTP population
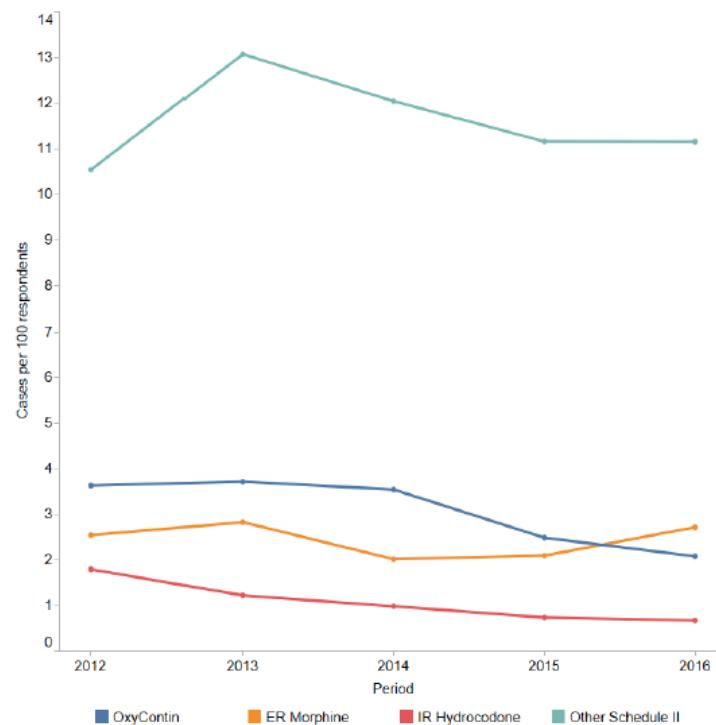
ER=extended release; IR=immediate release; IR Hydrocodone= IR hydrocodone combination products; OTP: Opioid Treatment Program (medication-assisted treatment).

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Observed yearly abuse rate by injection route for OxyContin and primary comparator opioids (2012-2016), OTP population. P. 223.)

Key: ER: Extended Release; IR: Immediate Release

Figure 45: Observed yearly abuse rate by injection route for OxyContin and primary comparator opioids (2012-2016), RADARS SKIP population

ER=extended release; IR=immediate release; IR Hydrocodone= IR hydrocodone combination products; SKIP: Survey of Key Informants' Patients Program (non-medication-assisted treatment).

(Source: FDA Postmarketing Requirement Study 3051-3 Final Report. Title: Observed yearly abuse rate by injection route for OxyContin and primary comparator opioids (2012-2016), SKIP population. P. 225.)

Key: ER: Extended Release; IR: Immediate Release

6.13 COMPARATORS AND CAUSAL INFERENCE

ER morphine, IR hydrocodone, and the composite "other schedule II opioids" were included as primary comparators. These were intended for direct comparison with OxyContin, in order to understand if decreases in OxyContin abuse were larger than the decreases seen in these primary comparators. During the study period, ER morphine had a large and relatively stable market share, was subject to ER/LA opioid analgesic regulatory actions such as the ER/LA opioid analgesic REMS, and is classified as a Schedule II product, as is OxyContin. It is also commonly abused via non-oral routes. However, utilization was increasing for ER morphine in the post-period, while utilization was decreasing for OxyContin, making it important to compare changes in abuse rates of these two products both adjusting for and unadjusted for utilization. IR hydrocodone combination products had a large and relatively stable market share during the study period, however unlike OxyContin, this category is composed almost exclusively of immediate release combination products (with acetaminophen), and therefore does not have similar abuse patterns to OxyContin, and in particular has very low rates of injection. For the majority of the study period these products were categorized as schedule III; in October 2014, hydrocodone combination products were changed to schedule II. "Other schedule II opioids" is a composite category combining ER and IR formulations of hydrocodone combination products, ER and IR oxymorphone, ER and IR hydromorphone, ER and IR morphine, and IR oxycodone. The advantage of this composite category is that the large number of products included create a more stable drug utilization pattern, and therefore allows for an adjusted rate that is not affected by fluctuations in utilization. However, composite categories like this one include drugs that vary widely with respect to market share, length of time on the market, and trends in utilization and abuse. This composite category is more heavily influenced by products with relatively larger market shares and higher numbers of abuse reports, and changes in rates of abuse for products with smaller market shares or lower numbers of abuse reports will be obscured. In addition, several opioids in this composite category underwent specific changes in formulation or question formatting in the OTP and SKIP surveys. For example, the wording for IR oxycodone in the OTP/SKIP survey tools changed in 4Q2011 from "Oxycodone immediate release tablets such as Percocet or Percodan" to "Oxycodone immediate release tablets." After this change, there was a subsequent decrease in IR oxycodone endorsement and an increase in endorsement of oxycodone, not otherwise specified. ER hydromorphone was approved in 2010, and a reformulated version of brand ER oxymorphone was introduced in 2012.

Secondary comparators were intended to include contextual information on changes in the patterns of opioid abuse around the time of OxyContin reformulation. Secondary comparators included methadone, IR oxycodone, and heroin. Methadone was the only comparator with a decrease in utilization similar to OxyContin, however it is used for both pain management and for treatment of opioid addiction and is therefore difficult to interpret as a comparator. Only the methadone that is prescribed and dispensed for pain is captured in drug utilization databases and counted as part of the denominator in utilization-adjusted analyses; however, methadone dispensed at opioid treatment centers may also be diverted and abused, and therefore captured as part of the numerator but not the denominator in these studies. Although IR oxycodone, particularly SE oxycodone, has potential value as a comparator for OxyContin because it contains the same opioid molecule as OxyContin, IR oxycodone was a problematic comparator in this study because of the change to the wording of this question in the OTP and SKIP tools, and subsequent decrease in rates of abuse, as described above. ER oxymorphone is an appealing comparator, as it is a high potency, single-entity, extended-release opioid that is commonly abused via non-oral routes. ER oxymorphone trends are difficult to interpret, however, because it was relatively new to the market at the beginning of the study period and had a small and rapidly increasing market share, followed by introduction of a reformulated product (designed to deter non-oral abuse not approved by FDA to be labeled as abuse-deterrent) as well as generics during the study period. Heroin is another drug that is commonly abused via non-oral routes; however, it is an illicit opioid with complex and multifactorial drivers of availability and abuse. This drug can, however, help us understand the context of changes in OxyContin abuse following reformulation. Concerns have been raised about the reformulation of OxyContin having a substitution effect, resulting in a shift to heroin and an increase in heroin overdoses. This study was not designed to evaluate this phenomenon or assess the impact of OxyContin's reformulation on heroin abuse; however, understanding these changing patterns remains important to evaluating the overall impact of the ADF.

6.14 SUMMARY TABLE OF PUBLISHED LITERATURE RELATED TO PMR 3051-1

Publication Year (Funding source)	Data Source	Study Design/Type	Study Period	Methods	Results	Strengths	Limitations
Cicero, 2012 (Denver Health and Hospital Authority (RADARS®))	RADARS® SKIP and RAPID	Observational, cross-sectional. Interviews.	July 1, 2009-March 31, 2012	Assessment of percentage of respondents selecting target opioids. Follow-up qualitative interviews.	Selection of OxyContin as a primary drug of abuse decreased from 35.6% of respondents in the pre-period to 12.8% in 1Q2012. Selection of hydrocodone and other oxycodone increased slightly during this time period and selection of other opioids (including fentanyl and hydromorphone) increased. Of all opioids used to get high in the past 30 days, OxyContin fell from 47.4% of respondents to 30.0%. Heroin doubled. Interviews with patients who abused both formulations of OxyContin demonstrated unanimous preference for the older version. 24% found a way to defeat the tamper-resistant properties. 66% reported switching to another opioid, most commonly heroin.	(+) Qualitative interviews allow for follow-up with patients to better understand abuse patterns	(-) Small, selected sample size (-) No adjustment for prescription volume

Cicero, 2016 (Washington University and RADARS®)	RADARS® SKIP and RAPID	Observational, cross-sectional. Interviews.	OxyContin: 1Q2009-4Q2014, Opana ER: 2Q2011-4Q2014 (each with a 2 quarter transition period)	Analyzed SKIP data for OxyContin and Opana ER endorsements to produce time-related trends of abuse pre- and post-reformulation. Conducted qualitative follow-up interviews with RAPID participants to capture route of administration (ROA). Logistic regression to estimate time-related trends in abuse rates of OxyContin and Opana ER.	OxyContin showed a 50% reduction in injection, and a 64.1% reduction in snorting, and showed a 49.2% increase in oral abuse. ER oxymorphone showed a 14.3% reduction in injection, and a 53.6% decrease in snorting, with a 5% increase in oral abuse. The number of individuals who reported injecting but not snorting the product increased.	(+) Conducted follow-up interviews with RAPID patients to capture information on ROA	(-) Small, selected sample size

Coplan, 2016 (Purdue Pharma L.P.)	RADARS® SKIP and OTP	Observational, cross-sectional	3Q2009-4Q2013 (transition period: 3Q2010-4Q2010)	Used endorsements from SKIP and OTP to estimate population-based and prescription-based abuse rate for OxyContin and comparators. Poisson regression and model utilizing abuse cases as the dependent variable, with time, opioid groups, and opioid group by time as the covariates, and log census population or prescription numbers as offset.	OxyContin abuse decreased-30% in RADARS SKIP data, and -43% in RADARS OTP data, using population rates. OxyContin abuse decreased -32% in RADARS SKIP and -33% in RADARS OTP, using prescription-based rates. All schedule II opioids increased +16% in RADARS SKIP and +9% in RADARS OTP. All schedule II opioids increased +5% in RADARS SKIP and 0% in RADARS OTP.	(+) Includes results from multiple surveillance systems	(-) Difficult to understand which sites were included in analysis (-) Only composite "other schedule II opioids" included as comparator

Author (Year)	Database	Study design	Time period	Methods	Results	Strengths	Limitations
Severtson, 2016 (RADARS®)	RADARS® SKIP and OTP	Observational, cross-sectional	July 2009-June 2010, January 2011-June 2015 (transition period: 3Q2010-4Q2010)	Used endorsements from SKIP and OTP to estimate abuse rate for OxyContin and other opioids adjusting for population and 1,000 prescriptions dispensed. Generalized linear modeling to compare differences in mean population intentional abuse rates in the year prior to reformulation to the estimated rate for 2015 quarter based upon the trend (slope) of the post-reformulation rates. Poisson regression analysis was used to calculate the expected rates and 95% confidence bands for each time period and drug group. "Other opioid" group composed of oral dosage forms of opioid analgesics: hydrocodone, hydromorphone, morphine, oxymorphone, tramadol, tapentadol, and immediate release oxycodone.	Population-based abuse OTP, pre-reformulation vs. 2Q2015: OxyContin:-82.6% (-86.7, -77.1) "Other opioid" group: -32.0% (-40.1, -22.9) Population-based abuse OTP, average quarterly rate change: OxyContin: -9.4% (-11.1, -7.6) "Other opioid" group: -3.5% (-4.3, -2.7) Population-based abuse SKIP, pre-reformulation vs 2Q2015: OxyContin: -53.9% (-64.1, -40.7) "Other opioid" group: -7.2% (-19.4, +6.9) Population-based abuse SKIP, average quarterly rate change: OxyContin: -4.0% (-5.5, -2.4) "Other opioid" group: -1.5% (-2.3, -0.7) Utilization-based abuse OTP, pre-reformulation vs. 2Q2015: OxyContin: -72.8% (-80.6, -62.0) "Other opioid" group: -30.9% (-40.4, -19.8) Utilization-based abuse OTP, average quarterly rate change: OxyContin: -8.2% (-10.4, -6.0) "Other opioid" group: -3.2% (-4.2, -2.3) Utilization-based abuse SKIP, pre-reformulation vs. 2Q2015: OxyContin: -34.8% (-48.4, -17.7) "Other opioid" group: +10.8% (-5.1, +29.5) Utilization-based abuse SKIP, average quarterly rate change: OxyContin: -2.6% (-4.0, -1.1) "Other opioid" group: -0.3% (-1.1, +0.5)	(+) Analyzes both population-based and prescription-based abuse estimates (+) Stratifies by OTP and SKIP (+) Includes average quarterly change	(-) Limited details on methods (-) Only comparator was composite category

| Dart 2015 (Denver Health and Hospital Authority) | RADARS® SKIP and OTP | Observational, cross-sectional | OTP: 2005-2013, SKIP: 2008-2013 | Used endorsements from OTP and SKIP (for Rx opioids: oxycodone, hydrocodone, hydromorphone, fentanyl, morphine, and tramadol and for heroin) to estimate quarterly event rate per 100,000 population for prescription opioids and heroin. Poisson regression model with linear and quadratic terms for time. Computed the time of the maximum predicted value of the curve. | In OTP, the rate of prescription opioid abuse increased from 1.6 per 100,000 population in 2005 to 7.3 in 2010 and then decreased to 3.5 by the end of 2013. In the SKIP program, the rate of prescription opioid abuse increased from 1.5 per 100,000 population in 2008 to 3.8 in 2011 and then decreased to 2.8 by the end of 2013. In OTP, the rate of heroin use was flat for the period from 2005 through 2013, and the rate of abuse of OxyContin decreased after 2010. In the SKIP program, the rate of heroin use increased in 2011 and remained increased, whereas the rate of abuse of OxyContin decreased. | (+) Describes rate of Rx opioid use and heroin use. (+) Incorporates data from multiple data sources. | (-) Does not adjust for utilization for prescription opioids. |

| Cicero, 2015 (Denver Health and Hospital Authority and Washington University) | RADARS® SKIP and RAPID | Observational, cross-sectional, interviews | January 2009-June 2014 | Used endorsements from SKIP data (150 sites in 48 states) for clients 18+. 82% response rate. Subset of respondents participated in interview based Researchers and Participants Interacting Directly (RAPID) program to supplement and add context to SKIP survey (response rate 55.6%). SKIP and RAPID gathered information on sociodemographic and all opioid compounds used for nontherapeutic/recreational purposes. RAPID interviews included formulations used, routes of administration, and effect of introduction of ADF. Chi square tests used for trend to measure differences in abuse rates over time in SKIP sample and chi square goodness-of-fit test used to analyze differences in the routes of administration in RAPID sample. | 45% of clients entering treatment from 2009-2010 indicated non-medical use of OxyContin in the past 30 days. Upon introduction of the ADF, this number decreased to 26%, but reached a plateau at 25%-30% of new patients entering treatment with no further decreases from 2012-2014.

Of the 153 RAPID participants who indicated any lifetime abuse of the original formulation of OxyContin, 33% indicated that the reformulation had no effect on drug selection and continued to use OxyContin and 33% indicated that they had replaced OxyContin with other drugs as a result of the reformulation. Five respondents (3.3%) indicated that the reformulation influenced their decision to stop abusing drugs altogether. The remaining respondents (30.1%) indicated that they did not use OxyContin enough to change their choice of drug.

Eighty-eight RAPID participants indicated using both formulations of OxyContin – of these, 43% reported that they switched from primarily injecting/inhaling the drug to swallowing it whole. Thirty-four percent reported that they were able to defeat the reformulated OxyContin and continued to inject or inhale the drug as primary route. The remaining 23% of participants primarily swallowed the previous formulation of OxyContin, and the reformulation had no effect on continued oral route. Among these respondents, significantly more individuals selected oral routes after reformulation (80.7% vs. 55.4%) while the opposite was observed for nonoral routes (92.8% vs 50.6%).

Among RAPID respondents who indicated that reformulation led them to shift their drug choices, 37 had codable responses, of which 70% indicated heroin. Far fewer participants shifted to other prescription opioids. Participants who switched to heroin indicated a desire for a more intense high and heroin being readily available and cheaper than opioid analgesics as motivations. | (+) Qualitative interview data help gain understanding of trends in switching and motivations for switching | (-) Small, selective subsample of RADARS participants willing to undergo follow-up interview, not necessarily representative of SKIP population generally |

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Department of Health and Human Services Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

OxyContin® Postmarketing Requirement (PMR) 3051-4 Final Study Report

Date:	August 7th, 2020
Reviewer(s):	Alex Secora, PhD Epidemiology Reviewer Division of Epidemiology II Christina Greene, PhD Epidemiology Reviewer Division of Epidemiology II
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Subject	Review of OxyContin PMR 3051-4 final study report – *Changes in Fatal and Non-fatal Overdose among Individuals Dispensed OxyContin after its Reformulation with Abuse-deterrent Properties – A Healthcare Database Analysis with Linkage to the National Death Index*
Drug Name(s):	OxyContin (oxycodone hydrochloride extended-release)
Application Type/Number:	NDA 022272/IND 029038
Applicant/sponsor:	Purdue Pharma L.P.

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ABBREVIATIONS:

-2y/2y Two-year period before (3Q2008-2Q2010) compared to the two-year period after the introduction of reformulated OxyContin (1Q2011 to 4Q2012) excluding the transition period

-2y/5y Two-year period before (3Q2008-2Q2010) compared to the five-year period after the introduction of reformulated OxyContin (1Q2011- 3Q2015), excluding the transition period

ADF Abuse-deterrent formulation
aRR Adjusted rate ratio
BOE Basis of eligibility
CI Confidence interval
CMS Centers for Medicare and Medicaid Services
ER Extended-release
FDA United States Food and Drug Administration
FFS Fee-for-Service
HIRD HealthCore Integrated Research Database®
ICD-9-CM International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM International Classification of Diseases, Tenth Revision, Clinical Modification
IR Immediate-release
IRR Incidence rate ratio
LA Long-acting
MAX Medicaid Analytical eXtract
N/A Not applicable
NDI National Death Index
NOS Not otherwise specified
OUD Opioid use disorder
PMR Postmarketing requirement
PPV Positive predictive value
PS Propensity score
REMS Risk evaluation and mitigation strategy
RORR Ratio of rate ratios
RR Rate ratio
SAP Statistical analysis plan
SD Standard deviation
SE Single-entity
TD Transdermal

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EXECUTIVE SUMMARY

Postmarketing requirement (PMR) study 3051-4 is one of four studies the United States Food and Drug Administration (FDA) required of the sponsor, Purdue Pharma, to evaluate the impact of OxyContin's reformulation on its abuse. Specifically, PMR study 3051-4 aimed to assess the impact of the reformulation on overdose rates among patients dispensed OxyContin. This study included data from three administrative claim databases and required new linkages to mortality data to capture fatal overdose. In conjunction with the other PMR studies (3051-1, 2, and 3) and other relevant information, the findings of this study can be used to help inform the overarching question of whether OxyContin's reformulation meaningfully reduced its abuse and associated harms, like overdose.

Overview of study methods:

In brief, the study assessed the change in any fatal or non-fatal opioid overdose rates (hereafter, overdose rates) among patients dispensed OxyContin, comparing the two years before (3Q2008-2Q2010, hereafter pre-period) to the five years after OxyContin's reformulation (1Q2011-3Q2015, hereafter post-period)[i], excluding a market transition period (3Q2010-4Q2010) immediately following the marketing of reformulated OxyContin. The study included analyses in three separate administrative claims databases to evaluate the consistency of results across databases and patient populations: 1) HealthCore Integrated Research Database® (hereafter, HIRD), 2) MarketScan Commercial and Medicare Supplemental Claims and Encounters database (hereafter, MarketScan), and 3) Medicaid Analytic eXtract (MAX): National Medicaid Database (hereafter, Medicaid). These databases were linked to the National Death Index (NDI) to capture fatal opioid overdoses.

Outside of the fatal opioid overdoses captured in NDI, all opioid overdose outcomes were identified using a validated code-based diagnostic algorithm developed for use in administrative claims databases. In a published portability study, the opioid overdose algorithm that differentiated intentionality did not perform reliably across other claims databases, most notably in Tennessee's Medicaid data. Because of the superior performance of the any opioid overdose (unintentional and intentional) algorithm compared to the intentional opioid overdose algorithm, we considered results using the any opioid overdose algorithm to be primary, and these are the focus of this review. FDA views the unintentional opioid overdose analyses in PMR study 3051-4 to be exploratory.

The study included information on overdose rates among those dispensed other opioid analgesics to aid in causal inference. Three primary comparators (extended-release [ER] morphine tablets or capsules, transdermal fentanyl, and methadone tablets or capsules) were used as negative controls (i.e., "counterfactuals") for OxyContin, intended to approximate expected changes in overdose rates among those dispensed OxyContin in the absence of the reformulation; several secondary comparators were also included to provide additional context.

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[i] Two years after OxyContin reformulation were available in Medicaid database (1Q2011-4Q2012) at time of analysis

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Preliminary analyses of utilization data found that a large majority of patients dispensed OxyContin received overlapping prescriptions for other opioid analgesics. Immediate-release (IR) opioid analgesics were the most commonly dispensed with OxyContin, particularly IR formulations of hydrocodone and oxycodone. Concomitancy with other opioid analgesics complicates our ability to make causal inferences about the effect of OxyContin's reformulation. Therefore, overdose rates associated with OxyContin and comparators were calculated using several different exposure group definitions. The main cohort included exposure time in which patients received OxyContin or the comparator either with or without concomitant opioid analgesics. Additional analyses used cohorts that included time in which the patient received concomitant IR opioid analgesics only and also more restricted cohorts that only included time in which the patient received OxyContin or the comparator without any concomitant opioid analgesics.

Treatment episodes in the pre- and post-periods were defined as continuous patient-level opioid analgesic exposure periods (in person-months), calculated using the drug dispensing dates and the estimated number of days dispensed in patients' administrative pharmacy claims. Unadjusted and adjusted overdose incidence rates and 95% confidence intervals (CI) were modeled using Poisson regression. Adjusted analyses included demographic characteristics, clinical characteristics, and other comorbidities ascertained using administrative claims.

Investigators calculated overdose rate ratios (RR) by comparing the overdose rates of the pre- and post-periods for OxyContin and each of the comparator opioid analgesic exposure groups (RR = [overdose incidence rate post-period] / [overdose incidence rate pre-period]). A ratio of rate ratios (RORR) was then used to compare the changes in overdose rates between the pre- and post-periods comparing patients dispensed OxyContin to those dispensed a comparator opioid analgesic (RORR = [comparator RR] / [OxyContin RR]). In these types of difference in difference models, an RORR >1 reflects a more favorable pre-post change in overdose rates among those dispensed OxyContin relative to any changes in overdose rates in patients dispensed a comparator; in this context, favorable could mean a greater pre-post reduction or a smaller increase in overdose rates among those dispensed OxyContin relative to those dispensed a comparator, or even no change in overdose rates among those dispensed OxyContin but an increase in overdose rates among those dispensed a comparator. An RORR <1 indicates a more favorable change for among those dispensed a comparator. A random-effects meta-analysis was also used to compute meta-analyzed (combined) RRs and RORRs for the two commercial databases (MarketScan and HIRD).

Due to the inherent uncertainties associated with these data and their interpretation, multiple analyses were conducted to assess robustness of the study findings. For example, the analytic cohorts were restricted to incident use periods only. Using an incident user cohort can help minimize biases that result from including those with experience using the drug but it also substantially reduces sample size and power. Investigators also conducted additional analyses stratified by fee-for-service (FFS) and managed care Medicaid plan types to ensure that data capture and results were consistent across coverage plans. Finally, to explore additional methods for adjusting for relevant characteristics of patients with opioid analgesic use, the investigators used propensity score weighted Poisson regression models for some analyses.

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Summary of results:

Summary of eligible patients and descriptive analyses

Approximately 25% of the total U.S. Medicaid membership during the study period was eligible after applying the data usability criteria; all eligible patients dispensed an opioid analgesic of interest were linkable to NDI (N=445,118). In the commercial claims databases, ~40% of the eligible patients dispensed an opioid analgesic of interest were linkable to NDI in MarketScan (N=288,645), while ~60% of the eligible patients linkable to NDI in HIRD (N=201,801).

Overall, the mean ages were older in commercial claims populations compared to the Medicaid population. The Medicaid population had higher proportions of patients with nearly all comorbidities compared to the commercial claims populations, but in aggregate (across the entire study period) there were no substantial differences in measured clinical characteristics comparing those dispensed OxyContin and those dispensed primary comparators in any of the databases.

The sponsor's pre-study preliminary analyses found some notable changes in patient characteristics across the study period. There were geographic shifts in the population of patients dispensed OxyContin in MarketScan, but not Medicaid. In MarketScan, median age and arthritis[ii] and chronic pain diagnoses all increased among patients dispensed OxyContin; there were also minor increases in substance use disorder diagnoses. There were large declines in the number of higher strength tablets dispensed over the period — notably the 80 milligram tablets.

Changes in opioid overdose rates among patients dispensed OxyContin

In the commercial claims combined incident and prevalent user cohorts (see Table 1), there were modest reductions in opioid overdose rates among patients dispensed OxyContin with or without other opioid analgesics concomitantly, and when restricted to person-time dispensed OxyContin with any immediate-release (IR) opioid analgesic concomitantly. These reductions were not seen in the Medicaid cohort. None of the adjusted overdose rate ratios for these cohorts were statistically significant. When restricted to person-time dispensed OxyContin alone (with no other opioid analgesics), there were larger reductions in opioid overdose rates among OxyContin recipients across all databases, but the changes were only statistically significant in one database (HIRD).

[ii] "Arthritis" includes arthropathies, osteoarthritis and musculoskeletal pain

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Table 1: Adjusted overdose rate ratios among those dispensed OxyContin across databases, by concomitancy with other opioid analgesics

OxyContin exposure group	Medicaid			MarketScan			HIRD		
	Pre-period rate per 1,000 PMs (ref)	Post-period rate per 1,000 PMs	Adjusted rate ratio (CI)	Pre-period rate per 1,000 PMs (ref)	Post-period rate per 1,000 PMs	Adjusted rate ratio (CI)	Pre-period rate per 1,000 PMs (ref)	Post-period rate per 1,000 PMs	Adjusted rate ratio (CI)
Any OxyContin use[i]	1.80	1.86	1.00 (0.89-1.12)	0.82	0.80	0.90 (0.75-1.08)	0.93	0.85	0.84 (0.65-1.09)
Concomitant use[ii] with any IR opioid analgesic	1.89	2.02	1.04 (0.91-1.19)	0.93	0.96	0.95 (0.77-1.17)	0.93	0.75	0.74 (0.54-1.02)
OxyContin use alone	1.65	1.42	0.85 (0.68-1.06)	0.60	0.44	0.72 (0.50-1.04)	0.91	0.48	**0.52 (0.32-0.83)***

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *= statistically significant (p<0.05); [i]=excludes periods dispensed OxyContin or primary comparator concomitantly; [ii]=includes only periods dispensed an IR opioid analgesics concomitantly, excluding periods dispensed OxyContin or primary comparator opioid analgesics concomitantly; person-months (PMs); confidence interval (CI); adjusted for variables in section 3.4.5; for all databases, the pre-period is two years before the reformulation, but the post-period for Medicaid analyses is two years after the reformulation and the post-period for MarketScan/HIRD analyses is five years after the reformulation

Overall, the incident only cohorts were smaller with substantially reduced aggregate exposure time across databases compared to analyses from combined cohorts. Overdose rate ratios using incident only cohorts were generally similar to those of the combined cohort but were not statistically significant for any of the OxyContin exposure groups.

Overdose rate changes for OxyContin compared to primary comparators

In Medicaid analyses, with the exception of fentanyl, the adjusted ratio of rate ratios (RORR) favored the comparators (i.e., RORR < 1) over OxyContin among patients with or without other opioid analgesics dispensed concomitantly, but the RORR was only statistically significant for methadone (see Table 2). Adjusted RORRs also favored comparators when restricted to person-time dispensed any IR opioid analgesic concomitantly, with statistically significant RORRs for ER morphine and methadone. In the commercial claims analyses (MarketScan and HIRD), the adjusted RORRs all generally favored OxyContin when looking at those dispensed the comparators with or without other opioid analgesics concomitantly, or when restricted to person-time dispensed with an IR opioid analgesic concomitantly, but no RORR was statistically significant for any comparator. Meta-analyzed comparative results from the commercial claims databases were generally consistent with results of the commercial claims analyzed separately, except that the RORRs were statistically significant for methadone (favoring OxyContin) when analyzed separately.

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When restricted to person-time dispensed OxyContin or comparators alone, all adjusted RORRs favored OxyContin, but only in the commercial claims databases were some adjusted RORRs statistically significant: ER morphine in the HIRD data, and fentanyl and methadone in the MarketScan data. Meta-analyzed results from the commercial claims databases were also generally consistent with results when analyzed separately, except that all RORRs were statistically significant (favoring OxyContin) when meta-analyzed.

Table 2: Adjusted ratios of rate ratios among those dispensed primary comparators compared to those dispensed OxyContin, by database and concomitancy with other opioid analgesics

Opioid analgesic exposure group	Exposure period category	Medicaid	MarketScan	HIRD
		Adjusted ratio of rate ratio (CI)[iii]	Adjusted ratio of rate ratio (CI)[iii]	Adjusted ratio of rate ratio (CI)[iii]
ER morphine	Any use[i]	0.91 (0.80-1.04)	1.12 (0.86-1.46)	1.09 (0.78-1.53)
Fentanyl	(**with or without** concomitant opioid analgesic use periods)	1.05 (0.90-1.22)	1.19 (0.93-1.53)	1.04 (0.73-1.49)
Methadone		**0.85 (0.74-0.98)***	1.32 (0.97-1.79)	1.20 (0.83-1.74)
ER morphine	Concomitant IR opioid analgesic use[ii]	**0.84 (0.72-0.99)***	1.00 (0.74-1.35)	1.01 (0.66-1.56)
Fentanyl	(**with** concomitant IR opioid analgesic use periods)	0.98 (0.83-1.17)	1.09 (0.81-1.45)	1.17 (0.74-1.83)
Methadone		**0.80 (0.67-0.96)***	1.08 (0.73-1.59)	1.19 (0.73-1.92)
ER morphine	Use alone	1.17 (0.90-1.52)	1.62 (0.97-2.72)	**2.20 (1.18-4.10)***
Fentanyl	(**without** concomitant opioid analgesic use periods)	1.27 (0.95-1.69)	**1.68 (1.02-2.78)***	1.40 (0.73-2.70)
Methadone		1.03 (0.79-1.33)	**1.94 (1.14-3.29)***	1.76 (0.98-3.17)

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *= statistically significant (p<0.05); [i]=excludes periods dispensed OxyContin or primary comparator concomitantly; [ii]=includes only periods dispensed an IR opioid analgesic concomitantly, excluding periods dispensed OxyContin or primary comparator opioid analgesics concomitantly; [iii]= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); person-months (PMs); confidence interval (CI); adjusted for variables in section 3.4.5; reference for this table is OxyContin adjusted rate ratio (see Table 1); for all databases, the pre-period is two years before the reformulation, but the post-period for Medicaid analyses is two years after the reformulation and the post-period for MarketScan/HIRD analyses is five years after the reformulation

The adjusted RORR point estimates using the incident user only cohort were generally similar to those using the combined cohort, but the RORRs were not statistically significant, with the exception of methadone which was statistically significant (favoring OxyContin) among patients with or without other opioid analgesics dispensed concomitantly. When the Medicaid analyses were stratified by plan type (FFS or managed

care),[iii] some adjusted RORR estimates were qualitatively different from each other, notably for fentanyl, but RORRs in both cohorts were mostly not significant.

The RORR estimates using the unintentional opioid overdose algorithm were similar to the RORR estimates using the primary any opioid overdose algorithm. Overall, the number of fatal overdoses was much lower than non-fatal overdose, and the proportion of overdoses that were fatal did not change across time periods, either for OxyContin or any comparator group.

<u>**Methodological considerations:**</u>

Patient characteristics and sample selection

PMR study 3051-4 assessed opioid overdose rates among patients directly dispensed opioid analgesics through traditional channels of distribution and reimbursed by Medicaid or commercial insurance. While important to study with respect to the impact of the reformulation, patients who receive an insurance-reimbursed prescription for opioid analgesics may not be representative of the populations where non-oral abuse and overdose are most common. This type of patient-based study population receiving prescription opioid analgesics paid for by health insurance may be at an inherently lower risk for opioid abuse and overdose than individuals who obtain prescription opioids using cash (who are not included in commercial claims data) or through diversion (i.e., from other sources like friends or illicit channels). Those who obtain opioids from sources other than their own prescription may be particularly at risk for abuse and overdose via non-oral routes which are *a priori* expected to be affected the most by OxyContin's reformulation.

Many otherwise eligible patients could not be included in PMR study 3051-4 due to lack of data linkage capability and other data quality issues, but these exclusions likely did not bias the comparative analyses. In MarketScan and HIRD, not all eligible opioid-analgesic-dispensed patients could be linked to the NDI; however, demographic characteristics and comorbidities were similar when comparing those who were linkable to those who were not. In Medicaid, only a minority of all beneficiaries had data deemed usable, but there did not appear to be meaningful differences in the results of stratified analyses by Medicaid coverage type.

Sensitivity analyses were conducted using an incident user cohort to help minimize potential selection biases resulting from including prevalent (ongoing) users. Prevalent users had to survive long enough to be included in the study and thus may be at a potentially lower risk for the outcome, although it is also possible that the likelihood of the outcome *increases* with greater exposure time. Nevertheless, because of the way "incident" use was defined in this study, incident and prevalent users were fairly comparable, as both can have prior experience with non-study opioid analgesics and can contribute multiple treatment episodes. Despite the greater statistical uncertainty in the incident user only analyses, the point estimates using the combined user cohort (incident and prevalent) and incident user only cohort were very similar.

[iii] This was only conducted using the unintentional opioid overdose algorithm

Challenges with exposure and outcome measurement in administrative claims data

Drug exposure can be difficult to accurately characterize in claims-based observational studies, particularly for opioid analgesics. While opioid analgesic drugs can be taken routinely like antihypertensives, they are also taken as needed or sporadically. This variability in use patterns creates uncertainty with respect to measuring exposure time and defining time at risk for the outcome, and therefore many assumptions are needed to calculate exposure time. For example, the actual use patterns by the patient may not be well represented by the days' supply, which is a variable input by the pharmacist based on a combination of factors. The dose taken by the patient may also not be captured well in claims data, but this can be an important risk factor for overdose. Neither daily dose nor tablet strength were included in comparative analyses in this study.

Because of the potential for lagged outcomes in this study, overdose rates associated with some opioid analgesics may be underestimated. In this study, leftover opioid analgesic tablets from the previous dispensing were ignored in exposure time calculations, excluding what could have been additional "at risk" exposure time. At the same time, "stockpiled" leftover drug and frequent changes in opioid analgesic regimens create challenges in accurately allocating exposure time, and thus correctly attributing overdose outcomes to a particular dispensed opioid analgesic. Furthermore, unobservable factors may affect drug continuation, for example, prescriber concerns about aberrant behaviors and risk of overdose. This type of informative censoring can also bias relative comparisons between opioid analgesic and time periods.

Finally, without reliable ascertainment of intentionality, route-specific information, or information on the specific opioid(s) involved in an overdose, PMR study 3051-4 was unable to examine specific subsets of overdose cases likely most relevant to understanding the impact of the reformulation (i.e., unintentional overdose involving non-oral abuse of OxyContin). While it is unknown what opioid(s) specifically precipitated each overdose in this study, the event is attributed to the last opioid analgesic the patient was dispensed, and therefore, some inaccurate attribution of overdoses to specific opioid analgesics is likely (e.g., a patient overdoses on multiple drugs, including heroin, after being dispensed ER morphine).

Adjusting for potential confounders

a) Risk factors for overdose

Without sufficient adjustment for all important confounders it is difficult to say whether observed changes in overdose rates for OxyContin (relative to comparators) were due to the effect of the reformulation on overdose risk in patients receiving the drug, or shifts in the risk profiles of patients receiving the drug. Preliminary data suggested that there were indeed some differences in the patients dispensed OxyContin comparing the pre- and post-periods, including potentially relevant comorbidities. It is unclear, however, whether confounding was adequately addressed in this study.

Risk factors like opioid use disorder (OUD) and prior overdose were considered for adjustment in the models but doing so comes with challenges. The sponsor viewed OUD as a potential mediator in the causal pathway between opioid analgesic dispensing and

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overdose, and thus, did not adjust for it in primary models. However, while the proportion of patients with OUD diagnosis codes was relatively similar when comparing those dispensed OxyContin to the primary comparators in aggregate (across the entire study period), it is not clear whether there was differential prescribing of specific opioid analgesics to patients with OUD diagnosis codes by period, as those data were not provided. Any systematic differential opioid analgesic prescribing by OUD diagnosis and study period could bias results considerably. At the same time, OUD diagnosis codes in claims data are not a reliable indicator of the presence or absence of OUD, which limits their utility as a covariate in this study.

Prior opioid overdose was found to be, by far, the strongest risk factor for subsequent overdose. The prevalence of prior opioid overdose was relatively balanced when comparing those dispensed OxyContin to the primary comparators in aggregate, but it was included in all adjusted models as a time-varying covariate to account for its strong association with the outcome of interest. Time-varying covariates can introduce time-varying confounding and bias associations, but from the sponsor's perspective it was nevertheless important to account for the within-person correlation from patients' contributing multiple overdose events over the study period. Given the study design and the definition/algorithm's demonstrated validity, including a time-varying "any prior overdose" variable is appropriate.

The sponsor argued that other potentially important risk factors like major depressive disorder, alcohol use disorder, or other substance use disorders are also better operationalized as mediators in the causal pathway rather than adjusted for as confounders. The sponsor did not submit any data to support this position. To be mediators these conditions would have to occur as a result of starting a specific opioid analgesic therapy, but many of the conditions are common and likely to be present before treatment initiation. In other words, these types of variables may be confounders, or even effect modifiers, of the association between the OxyContin reformulation and overdose.

Concomitant benzodiazepine use is a known risk factor for opioid overdose, but it was not adjusted for in any primary analyses as the sponsor again viewed this as a potential mediator. Overall, benzodiazepine use was comparable in patients dispensed OxyContin and other comparator opioid analgesics in aggregate (across the entire study period), but to better understand the potential impact of benzodiazepine use on study results, FDA requested additional analyses. Subsequently submitted data suggest that any benzodiazepine dispensing changes from the pre- to post-periods were likely nondifferential by opioid analgesic and that adjusting for baseline benzodiazepine use did not meaningfully impact results in HIRD and Medicaid. Nor was benzodiazepine use found to be a statistically significant effect modifier. Given these results, and the relative balance in benzodiazepine dispensing rates across opioid analgesic exposure groups and time periods, relative comparisons between opioid analgesics were likely not substantially biased by concomitant benzodiazepine use. Nonetheless, because benzodiazepines and opioids are often obtained through means other than one's own (insurance reimbursed) prescription, it is unknown whether there was actual differential use of other substances across time periods or comparators.

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b) Adequacy of adjusted models in controlling for confounding

To account for differences in the patient populations before and after the reformulation and to mitigate the impact of confounding, some Poisson models used covariate adjustment, while others were weighted by the propensity score (PS),[iv] but the results were not substantively different from unadjusted results. This may be due, in part, to limited and incomplete adjustment for some important potential confounders, as discussed above. Adequately adjusting for confounders in claims-based analyses is often challenged by incomplete data (e.g., current alcohol and substance use, socioeconomic status), and a lack of validated diagnosis codes known to accurately reflect important medical conditions (e.g., OUD). Nonetheless, adjusted analyses that control for patient characteristics, including demographic information and certain conditions that are more reliably captured using claims-based diagnosis codes, are still preferable to unadjusted analyses, however limited.

Even after adjusting for measurable potential confounders, it is likely that channeling bias was still relevant in this study, and this type of selection bias can be particularly challenging to address using administrative claims data alone. Because the reformulation was specifically designed to deter tablet manipulation for the purposes of abuse, it is possible that prescribers differentially prescribed ("channeled") reformulated OxyContin to patients they perceived to have a higher risk of abusing the drug. This could introduce imbalances in the overdose risk profile of patients comparing the two periods, potentially attenuating any true benefit of the reformulation.

An alternative scenario must also be considered, however, wherein patients seeking to abuse OxyContin "self-selected" *not* to receive the product after reformulation, requesting and receiving different opioid analgesics without abuse-deterrent properties, or transitioning to non-prescribed opioids (e.g., heroin or diverted prescription opioids), thus creating a *lower* risk cohort of OxyContin users following reformulation. In this scenario, results would show a more favorable impact of the reformulation on overdose risk. The overall decline in OxyContin dispensing, and particularly of the 80 milligram tablets, may in part reflect such a migration away from OxyContin by individuals seeking to abuse it by non-oral routes. Although it is unclear to what extent that ultimately explains the decreased dispensing, it does at least indicate some significant changes in prescribing patterns for OxyContin that could substantially affect the risk profile of patients receiving the product.

Interpretation of PMR Study 3051-4 Findings:

Effect of OxyContin's reformulation on <u>overdose rates among those dispensed any OxyContin</u> (i.e., with or without other opioid analgesics concomitantly):

The results of PMR 3051-4 do not demonstrate that the reformulation reduced the risk of opioid overdose in patients dispensed OxyContin, overall (i.e., including exposure with or without other opioid analgesics). A conclusion that OxyContin's reformulation actually reduced opioid overdose risk in these patients would be supported by robust and statistically significant reductions in overdose rates that were temporally associated with the intervention, largely consistent across databases, and unlikely to be explained by either

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[iv] Note this was only using the unintentional overdose outcome

systematic or random error. In HIRD, the overdose rates among OxyContin recipients appeared to decrease modestly immediately after the reformulation but the decline was not sustained, and there was no discernable decline in overdose rates among those dispensed OxyContin in either the Medicaid or MarketScan databases. Small changes are more likely to be completely explained by residual confounding, particularly when we are not confident that confounding was adequately controlled for, given the limited adjustment for some potentially important covariates and limited ability to measure others. Furthermore, most changes across time periods were not statistically significant, indicating that random chance cannot be ruled out as an explanation either.

To account for potential confounding by calendar time (i.e., secular trends), changes in opioid overdose rates among those dispensed OxyContin should also differ meaningfully from any changes observed in those dispensed comparator opioid analgesics. In the commercial claims populations, changes in opioid overdose rates among patients dispensed OxyContin compared to the changes among patients dispensed primary comparators modestly favored OxyContin, but they were not significantly different from each other. In fact, the results of Medicaid data analyses among users of any OxyContin or OxyContin with IR opioid analgesics concomitantly were actually *unfavorable* to OxyContin with respect to changes in overdose rates after the reformulation, in that reductions in overdose rates among those dispensed ER morphine and methadone were observed but there was no change among those dispensed OxyContin.

Concomitant dispensing and switching from one opioid analgesic to another creates challenges in disentangling the marginal effect of one opioid analgesic on overdose risk in the context of multiple concurrent opioid analgesic exposures, but the use of multiple opioid analgesics concurrently was more the rule than the exception in these populations. Although it complicates causal inference, studying the effect of the reformulation in settings in which the drug is most commonly used (i.e., with other opioid analgesics) is still important. One possible explanation for the lack of an observed effect in this cohort is that the reformulation actually had little or no effect on overall opioid overdose because opioid analgesic use and abuse patterns are complex and dynamic, in some cases including both prescription and illicit opioids. Opioid analgesic concomitancy patterns in patients dispensed OxyContin also changed over the study period, with increased concomitant prescribing overall and changes in the types of opioid analgesics used with OxyContin. It is therefore perhaps not unexpected that changing a single product's formulation did not appear to result in an overall reduction in opioid overdose.

Although this study did not show that the reformulation reduced overdose risk in insured patients receiving OxyContin, the findings also do not preclude this possibility. While certainly important to study, this study cohort may not reflect the population most likely to abuse or experience an overdose involving OxyContin. It is possible that effects of reformulation might have been detected in higher risk groups,[v] including those obtaining OxyContin from sources other than their own prescription or using cash to purchase prescription opioid analgesics, and those abusing opioids by non-oral routes. However,

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[v] PMR study 3051-1 and study 3051-3 targeted higher risk groups like those being specifically assessed for opioid treatment, but overdose outcomes were not assessed in those studies

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these groups are generally not distinguishable in data sources capable of linking a specific drug exposure to overdose outcomes, while controlling for other confounding factors.

Effect of OxyContin's reformulation on <u>overdose rates among those dispensed OxyContin alone</u> (i.e., without other opioid analgesics concomitantly):

When restricting analyses to patients dispensed OxyContin or comparators alone, results were somewhat more favorable with respect to the impact of the reformulation on opioid overdose risk, although this was true only in the commercial claims populations, and not in Medicaid. The implications and generalizability of this finding are not entirely clear. Analyses that only include patients using one opioid analgesic product at a time are simpler from a causal inference perspective, as noted above, but OxyContin use without the concomitant dispensing of any other opioid analgesics—primarily IR opioid analgesics— is much less common than dispensing of OxyContin with at least intermittent use of other opioid analgesics and represents a relatively small subset of OxyContin use in real-world settings.

Bi-annual overdose rate data were not provided for this smaller cohort so it was not possible to determine the exact timing of declines in overdose rates relative to the reformulation. While the results were more favorable with respect to the impact of the reformulation, they were not entirely consistent across databases, or across comparators, and there was greater uncertainty in the estimates due to the reduced exposure time. When restricted to person-time dispensed OxyContin alone, reductions in opioid overdose rates were modest and only significant in one commercial claims database (HIRD). Overall, changes in opioid overdose rates when restricted to person-time dispensed OxyContin alone differed favorably from changes in comparators, to varying degrees. Statistical significance varied across comparators in the two commercial claims databases, and the differences were not significant in Medicaid. When the results of the commercial claims databases were combined using meta-analytic methods, the point estimates were generally similar to those from analyses conducted separately in each database, but the comparative results were all statistically significant using meta-analysis. At the same time, these results must be interpreted with caution as only two databases (effectively two separate "studies") were combined, and between-study heterogeneity could not be properly evaluated.

It is possible that OxyContin's reformulation reduced the risk of overdose in patients who received this product without any other opioid analgesics, at least among patients with commercial insurance. Given the potential for residual confounding in these analyses, however, it is also important to consider alternative explanations for these findings. It is possible that patients receiving reformulated OxyContin were inherently at lower risk of overdose than those who received original OxyContin. Some "non-exchangeability" of the cohorts would remain if there were important unmeasured differences between these groups. Such differences could be due to increased prescriber awareness of risk of OxyContin abuse in general (e.g., due to the 2010 OxyContin REMS provider communications), or changes in patient selection related specifically to OxyContin's abuse-deterrent properties.

Differences could also be related to patient "self-selection;" for example, if individuals seeking to abuse OxyContin non-orally stopped abusing OxyContin, some perhaps instead seeking out other opioids, either prescription or illicit, when OxyContin was reformulated.

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If this was the case, then post-period OxyContin user cohort might have had a lower risk of overdose. Although this latter explanation would be consistent with reformulated OxyContin having an abuse-deterrent effect, it does not necessarily show that the abuse-deterrent properties conferred a reduced risk of overdose among those exposed to the product, or that those who stopped using OxyContin because of its reformulation (and were therefore not included in the reformulated OxyContin exposure group) were less likely to experience an overdose. In addition, the distribution of dispensed OxyContin tablet strengths skewed lower in the post-period, which could have contributed to the observed declines in overdose rates when restricted to person-time dispensed OxyContin alone relative to comparators, independent of any risks associated with non-oral abuse specifically or the direct ability of the abuse-deterrent properties to reduce these risks. Again, the changes in OxyContin dosage strengths dispensed could reflect some abuse-deterrent effect of the reformulation, with individuals who seek high-strength tablets to manipulate for the purposes of abuse migrating away from OxyContin after its reformulation. It is unclear, though, whether lower overdose rates in a cohort receiving lower doses of OxyContin can reasonably be interpreted as the "abuse-deterrent" properties reducing the risk of overdose.

Conclusions:

The results of PMR 3051-4 do not demonstrate that the reformulation reduced the risk of opioid overdose in patients dispensed OxyContin, overall. When restricted to person-time dispensed OxyContin or comparators *alone* (i.e., without other opioid analgesics), results were somewhat more favorable with respect to the reformulation reducing opioid overdose risk, although this was true only in the commercial claims populations and not the Medicaid cohort. The implications and generalizability of this specific finding are not entirely clear, however, in part because OxyContin use without concomitant dispensing of any other opioid analgesics was relatively uncommon. The interpretation of this finding is further complicated by the potential for unmeasured differences between the prescribed patient populations in the pre- and post-reformulation periods. It is possible that OxyContin's abuse-deterrent properties did confer a reduced risk of overdose among patients using the product without any other opioid analgesics. However, it is also plausible that patients receiving OxyContin alone in the post-reformulation period were inherently at a lower risk of overdose than those who received OxyContin alone during the pre-period, either through changes in OxyContin prescribing practices, or through "self-selection" away from reformulated OxyContin among patients seeking to abuse it via non-oral routes. While the latter explanation may be consistent with reformulated OxyContin having an abuse-deterrent effect, it does not necessarily follow that the abuse-deterrent properties conferred a reduced risk of overdose among those exposed to the product or that those who migrated away from OxyContin because of its reformulation actually had a lower risk of overdose.

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1   INTRODUCTION

Postmarketing requirement (PMR) study 3051-4 is one of four studies the United States Food and Drug Administration (FDA) required of the sponsor, Purdue Pharma, LP (hereafter, the sponsor) to evaluate the impact of OxyContin's reformulation on its abuse and overdose. Specifically, PMR study 3051-4 aimed to assess the impact of the reformulation on risk of overdose among patients dispensed OxyContin. OxyContin (oxycodone hydrochloride, controlled release; New Drug Application [NDA] 022272) was reformulated with physicochemical properties that were intended to deter tablet manipulation for the purposes of abuse primarily via insufflation and injection. The reformulation incorporated a high molecular weight polymer (polyethylene oxide) matrix with the intention of making the tablet more difficult to manipulate for the purposes of non-oral misuse or abuse. Based on review of *in vitro* and clinical study data, in 2013 FDA concluded that reformulated OxyContin had "abuse-deterrent" characteristics, and the label[vi] was updated with its current language:

"The in vitro data demonstrate that OXYCONTIN has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the in vitro data, also indicate that OXYCONTIN has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OXYCONTIN by these routes, as well as by the oral route, is still possible."

Observational studies, including PMR study 3051-4, were required to provide further information on the ability of reformulated OxyContin to deter abuse and reduce abuse-related harms in the postmarket setting. Study 3051-4 used three sources of administrative claims data to measure changes in the rates of overdose among patients dispensed OxyContin, comparing the pre-reformulation period of OxyContin marketing to the post-reformulation period, relative to comparable opioid analgesic drugs marketed during that time. The three additional required studies evaluated changes from the pre- to post-reformulation in: 1) opioid abuse in a sentinel population of adults who were assessed for substance use disorder and treatment planning, using data from the NAVIPPRO® ASI-MV surveillance system (PMR 3051-1); 2) opioid abuse exposure calls to US poison control centers, using data from the RADARS® Poison Control Program (PMR 3051-2); 3) opioid abuse in a sentinel population of adults entering methadone and non-methadone treatment for opioid use disorder, using data from the RADARS Treatment Center Program (PMR 3051-3).

In 2014, the sponsor submitted postmarket studies to support a "real-world" abuse-deterrence labeling claim; these studies were reviewed by the Division of Epidemiology (DEPI) and the Division of Biometrics (DB7), and an Advisory Committee (AC) meeting was scheduled for July 2015 to discuss the studies findings' in a public forum. In June 2015, the sponsor withdrew their labeling supplement and the AC meeting was cancelled. In 2016, FDA issued formal PMR letters to ensure timely study completion and to allow FDA to provide input on study design and methods. With respect to PMR study 3051-4, this study was not a part of the initial 2014 submission and was formally required in the

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[vi] OxyContin label (revised 08/2015):
https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022272s027lbl.pdf

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2016 PMR letter to address a need for an evaluation of the impact of reformulation on non-fatal and fatal overdose associated with OxyContin dispensing.

Unlike the other PMR studies (3051-1,2,3), PMR study 3051-4 required new linkages to mortality data and use of validated claims-based algorithms to ascertain opioid overdose outcomes. In 2016, FDA recommended major modifications to PMR study 3051-4, including, but not limited to, analyzing data from patients with concurrent use of other opioid analgesics in addition to OxyContin, and adding a Medicaid database. FDA also provided input on the protocol and analysis plan to assess the usability of Medicaid data. In 2019, the sponsor submitted the final study report incorporating FDA's recommendations, including a formal assessment of Medicaid data usability by state.

The objective of this review was to determine whether data from PMR study 3051-4 support that OxyContin's reformulation reduced fatal and non-fatal opioid overdose risk among patients dispensed the product.

In conjunction with the other PMR studies (3051-1, 2, and 3) and other relevant information, the findings of this study can be used to help inform the overarching question of whether OxyContin's reformulation meaningfully reduced its abuse and associated harms. While each study can alone provide important information on the potential impact of the reformulation, it is ultimately necessary to evaluate the totality of evidence from all sources to answer this question.

2   REVIEW METHODS AND MATERIALS

To prepare this review document, DEPI reviewed:
- PMR study 3051-4 final study report (EPI8034ORF) - "*Changes in Fatal and Non-fatal Overdose among Individuals Dispensed OxyContin® after its Reformulation with Abuse-deterrent Properties – A Healthcare Database Analysis with Linkage to the National Death Index*" (received August 2019)
  - Study protocol
  - Statistical analysis plan
  - Study results, including all appendices
- Sponsor submitted responses to information requests:
  - Received March 3, 2017
  - Received March 9, 2017
  - Received December 12, 2019
  - Received January 31, 2020
  - Received March 26, 2020
  - Received April 1, 2020

In brief, this review document provides a summary and interpretation of PMR study 3051-4 methods and main findings, including a discussion of relevant methodological issues and how these impact inferences that can be made based on the study's results. The findings of this review will be used to inform the broader question of whether OxyContin's reformulation was effective in reducing abuse and associated harms. DEPI also conducted a review of the literature to identify published studies using administrative claims data that may provide context or supplemental information to aid in the interpretation of PMR study

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3051-4 ([see background document: OSE Literature Review](#)). Two such studies were identified, and these were reviewed for any additional information that could inform our interpretation of the findings of PMR study 3051-4.

To determine whether OxyContin's reformulation reduced overdose rates among patients dispensed the product, PMR study 3051-4 findings were evaluated using FDA's Guidance for Industry, "Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data,"[vii] and fundamental guiding principles of epidemiology, including principles for making causal inferences from observational data.

3 PMR STUDY 3051-4 METHODS

3.1 STUDY OVERVIEW

In PMR study 3051-4, investigators analyzed three administrative claims databases (Medicaid and two commercial claims databases) linked to national mortality data to assess the impact of OxyContin's reformulation on the incidence of fatal or non-fatal opioid overdose ("overdose") among patients dispensed OxyContin. Analyses compared overdose rates in these patients in the two years before (3Q2008-2Q2010) to the five years after (1Q2011-3Q2015) OxyContin reformulation (two years after OxyContin reformulation in Medicaid database [1Q2011-4Q2012]), excluding a transition period (3Q2010-4Q2010). The change in overdose rates among patients dispensed OxyContin was compared to the change observed in patients dispensed selected other opioid analgesics. These comparators were intended to provide contextual information on opioid overdose trends unrelated to the reformulation and to aid in causal inference. Due to the complexity of these data, (e.g., many patients dispensed OxyContin concomitantly with intermittent dispensing of other opioid analgesics, and potential for confounding by patient characteristics) a number of different analyses were conducted to better understand the generalizability of study findings and role of potential biases. For example, some analyses included the use of several exposure categories that included patients dispensed OxyContin with or without other opioid analgesics. In separate analyses, alternative methods were used to adjust for patient-level characteristics. Primary PMR study 3051-4 analyses were conducted in three different administrative claims databases to look for consistency in findings across databases and patient populations.

3.2 STUDY OBJECTIVES

Primary objectives <u>as stated in the protocol</u>:

1) Assess the changes in the rates of unintentional overdose among those dispensed OxyContin, two years before the reformulation versus (vs.) five years after the reformulation (-2 years[y]/5y)
2) Assess the changes in rates of unintentional overdose among those dispensed OxyContin vs. primary comparator opioid analgesics (-2y/5y)

[vii] FDA's Guidance for Industry: https://www.fda.gov/media/79922/download

3) Assess the changes in rates of unintentional overdose among those dispensed OxyContin vs. secondary comparator opioid analgesics (-2y/5y)

Secondary objectives <u>as stated in the protocol</u>:

1) Assess the changes in rates of unintentional and suicide-related (intentional) overdose separately among those dispensed OxyContin vs. primary comparator opioid analgesics (-2y/5y)
2) Assess the changes in rates of unintentional overdose among patients continuously dispensed OxyContin from the pre- to post-period vs. those continuously dispensed primary comparator opioid analgesics from the pre- to post-period (-2y/5y)
3) Describe temporal trends in overdose rates between 2008 and 2015 among those dispensed OxyContin, and primary and secondary comparator opioid analgesics
4) Compare the characteristics of individuals dispensed OxyContin or primary comparator opioids, overall, and stratified by ability to link to the National Death Index (NDI)

3.3 OVERARCHING METHODOLOGICAL CONSIDERATIONS

There are several aspects of the PMR 3051-4 study design and methods that were intended to address concerns with the data quality and potential biases. A number of preliminary descriptive analyses were also conducted to help inform the study design and analytic approach.

Use of multiple claims databases: Three separate administrative claims databases were used in PMR study 3051-4 to broaden the patient population under study and evaluate the consistency of findings in multiple patient populations and data environments. Two databases were commercial claims databases, including only individuals with private insurance, and the other was the Medicaid Analytic eXtract database, including those with subsidized government insurance (see Section 3.4.1.2) and potentially different risk profiles based on their higher prevalence of certain comorbidities.

Use of comparator drugs as negative controls: Three primary comparators (extended-release [ER] morphine, transdermal [TD] fentanyl, and methadone) were used as negative controls, "counterfactuals," for OxyContin, approximating the expected changes in overdose rates among patients dispensed OxyContin had it not been reformulated. The comparators were chosen to reflect a diverse set of ER or long-acting (LA) opioid analgesic products with comparable market share and regulatory requirements (see Section 3.4.3). The primary comparators' in this study have long marketing histories as ER/LA opioid analgesics suggesting that they may be subject to the same longer-term secular trends in patient selection, prescribing practices, abuse profile, and overdose risk as OxyContin. Using comparators can help to account for larger secular trends in the outcome, and published data suggest that there are likely secular trends in opioid overdose that are important to consider. For instance, following sustained annual increases from 1999 to roughly 2011, the rate of increase of opioid overdose deaths involving prescription opioids (natural and semisynthetic) has slowed since 2011, whereas those from heroin and

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synthetic opioids (i.e., illicit fentanyl analogs) have increased dramatically.[viii] These data reflect overdoses in the entire US population and may not reflect trends within the cohorts studied in PMR study 3051-4, but they underscore the importance of controlling for secular trends when making inferences about any changes in overdose rates over time. In addition, changing commercial and state Medicaid coverage policies during the study period could differentially affect population risk profiles and overdose risk across study time periods.

Dispensing trends for OxyContin: The sponsor conducted two analyses (see Appendix 8.1) in response to an information request sent by the Agency in 2017 requesting data on opioid analgesic switching patterns around the time of the reformulation, and the prevalence of OxyContin's use concomitantly with other opioid analgesics. The findings are briefly summarized here:

- **Opioid analgesic switching patterns**: Among patients dispensed original OxyContin, 61% switched to reformulated OxyContin in the MarketScan commercial insurance database, 19% switched to other opioid analgesics, 6% continued to receive original OxyContin, and 14% had no further opioid analgesic claims observed by 3 months after OxyContin reformulation. In the Medicaid database, 65% switched to reformulated OxyContin, 17% switched to other opioid analgesics, 8% continued to receive original OxyContin, and 10% had no further opioid analgesic claims observed. More than 80% of those who switched went on to initiate a generic immediate release (IR) opioid analgesic in both databases. The most common other opioid analgesic that OxyContin users switched to was IR oxycodone (49%). Roughly 42% and 57% of generic ER oxycodone users were subsequently dispensed reformulated OxyContin within 3 months of a defined index prescription date[ix] around when generic ER oxycodone marketing ceased in the commercially-insured and Medicaid populations, respectively. Of note, this analysis did not assess whether these switching and discontinuation patterns (i.e., from OxyContin to other opioid analgesics or discontinuation of opioid analgesics) were different from patterns before the reformulation or attributable specifically to OxyContin's reformulation.

- **Concomitant opioid analgesic use:** In the MarketScan commercial insurance database from 2008 to 2015, only ~10% to ~14% of patients dispensed OxyContin were dispensed OxyContin alone (i.e., without other opioid analgesics) for the duration of their OxyContin dispensing in a given year, while ~80% to ~87% were dispensed OxyContin concomitantly with other opioid analgesics, often mixing periods of both concomitant dispensing and dispensing alone. In the Medicaid database from 2008 to 2012, ~28% to ~34% of patients dispensed OxyContin were only dispensed OxyContin alone for the duration of their OxyContin use in a given year, while ~66% to ~71% were dispensed OxyContin concomitantly with other opioid analgesics, also often mixing periods of both concomitant dispensing and dispensing alone. In both databases, IR opioid analgesics were the most commonly

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[viii] Hedegaard H, Miniño AM, Warner M. Drug overdose deaths in the United States, 1999–2018. NCHS Data Brief, no 356. Hyattsville, MD: National Center for Health Statistics. 2020

[ix] Defined as an active ER oxycodone dispensing on October 1, 2010, or an ER oxycodone dispensing between October 1, 2010 and March 31, 2011.

dispensed with OxyContin among the drugs analyzed, particularly IR formulations of hydrocodone and oxycodone.

- o There were some notable changes in patient characteristics comparing before and after the reformulation (See Appendix 8.1). There were geographic shifts among patients dispensed OxyContin in MarketScan, but not Medicaid, with increases in the Northeast and South and declines in North Central, U.S. Age skewed older comparing periods in MarketScan, but not in Medicaid. Arthritis[x] and chronic pain diagnoses also increased considerably among patients dispensed OxyContin comparing periods in MarketScan, and there were minor increases in diagnoses of substance use disorder[xi]; this was not as clear in Medicaid because the data provided on comorbidities was very limited. Additionally, there were large declines in number of higher strength tablets dispensed over the period analyzed in both MarketScan and Medicaid — notably the 80 milligram tablets.

- Based on the concomitant use data, overdose rates were assessed separately among all OxyContin users, or those with or without other opioid analgesics dispensed concomitantly (including those dispensed IR opioid analgesics, specifically), and specifically during time dispensed OxyContin alone, or without other opioid analgesics dispensed concomitantly. Using multiple distinct exposure groups helps to reflect the various ways patients are dispensed opioid analgesics and improves the generalizability of the study's findings. Comparative analyses of patients using only one opioid analgesic product at a time are simpler from a causal inference perspective, but this does not appear to be the most common treatment practice with respect to OxyContin. At the same time, consistent effects across all exposure groups would suggest a more robust impact of the reformulation on overdose rates and would facilitate a more straightforward interpretation of the study's findings.

Medicaid data usability: Because of the differences in how administrative claims data from fee-for-service (FFS) and comprehensive managed care Medicaid coverage types are collected and reported for patient-level healthcare encounters, separate analyses were conducted to assess the usability (i.e., "completeness") of data from the different plan types across all available states and years (See sub-study methods and results in Appendix 8.3). Based on the results of this evaluation, for PMR study 3051-4 Medicaid overdose analyses the sponsor included only data in a given state/year determined to be usable based on measures of "continuity" and "connectivity" of administrative claims using criteria derived from Li et al.[xii] (See section 3.4.1.2 and Appendix 8.3). Primary results were assembled using a combined cohort of FFS and comprehensive managed care patients in states/years deemed usable, but stratified analyses by coverage type were also conducted as sensitivity analyses.

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[x] "Arthritis" includes arthropathies, osteoarthritis and musculoskeletal pain

[xi] "Substance use disorder" excludes opioid use disorder

[xii] Li et al. (2017) Internal validation of Medicaid Analytic eXtract (MAX) data capture for comprehensive managed care plan enrollees from 2007 to 2010. Pharmacoepidemiology and Drug Safety: 1-10; https://doi.org/10.1002/pds.4365

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Validated outcome ascertainment: Opioid overdose outcomes were identified using the code-based diagnostic algorithm developed for use in administrative claims databases and validated as part of the extended-release/long-acting opioid analgesic (ER/LA OA) PMR study 3033-6, conducted by the Opioid Product Consortium (OPC) (see Section 3.4.6).[xiii] The results of PMR study 3033-6 are described in Green et al, [xiv] along with additional algorithm portability assessments (i.e., their ability to perform consistently across databases) which showed that the "any opioid overdose" algorithm (unintentional and intentional; fatal and non-fatal) was consistently superior in accurately ascertaining cases to the intentional opioid overdose algorithm (fatal and non-fatal) across several claims databases, most notably in TennCare (Tennessee Medicaid data). **Therefore, FDA now views the "any opioid overdose" analyses in PMR study 3051-4 as primary, and while they were originally planned as primary objectives, the unintentional opioid overdose analyses are now viewed as exploratory due to this algorithm's poorer performance in the validation and database portability studies.**

Adjusting for patient differences across periods: Opioid overdose incidence rate ratios were adjusted for patient demographic characteristics, clinical characteristics, and other comorbidities (see Section 3.4.5) using both standard multivariate adjustment, and propensity score weighted Poisson models to help mitigate the potential confounding from important differences in patient-level characteristics in the pre- and post-reformulation periods, or across groups receiving different opioid analgesics. Changes in prescribing practices could bias results if higher risk (with respect to abuse and overdose), or lower risk, patients were "channeled" onto specific opioid analgesics differentially across the study period.

3.4   STUDY METHODS

3.4.1   Design & Setting

3.4.1.1   Study Design

Retrospective, pre- versus post-intervention cohort study

3.4.1.2   Electronic healthcare databases

HealthCore Integrated Research Database (hereafter, HIRD)

HIRD is an administrative healthcare claims database with data on commercially-insured individuals. HIRD includes longitudinal (since 2006) medical and pharmacy claims data from over 50 million commercial and Medicare Advantage Anthem health plan members.

IBM (formerly Truven Health) MarketScan Commercial and Medicare Supplemental Claims and Encounters database (hereafter, MarketScan)

[xiii] ER/LA opioid PMR letter: https://www.fda.gov/media/95546/download ; ClinicalTrials.gov Identifier: NCT02667197, https://clinicaltrials.gov/ct2/show/NCT02667197

[xiv] Green CA, et al. (2019) Identifying and classifying opioid-related overdoses: A validation study. Pharmacoepidemiol Drug Saf;28: 1127–1137. https://doi.org/10.1002/pds.4772

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MarketScan is an administrative healthcare claims database with data on commercially-insured individuals with employer-based health insurance, and their covered family members. Marketscan included longitudinal medical and pharmacy claims data for over 100 million individuals over the study period.

Medicaid Analytic eXtract (MAX): National Medicaid Database (hereafter, Medicaid)

Medicaid MAX is an administrative healthcare claims database available through the Centers for Medicare and Medicaid Services (CMS) with data on individuals with subsidized government insurance. At the time of analysis, these Medicaid data covered beneficiaries in all 50 states and Washington D.C. through 2012 (28 states through 2013), including all medical and pharmacy claims for beneficiaries covered by both FFS and comprehensive managed care Medicaid plans.

For all Medicaid analyses, the sponsor only retained data for patients a given combination of state, year, and basis of eligibility (BOE) group that was determined to be usable, or essentially "complete," based on operationalized measures of "continuity"[xv] and "connectivity"[xvi] for patients' administrative claims over time using criteria derived from Li et al.[xvii] (2017) (See sub-study results in Appendix 8.3):

- For managed care members, there were 12 states that had all data included in the study (all years 2008-2012 for both the adult and disabled populations), while 19 states did not have any years included for either the adult or disabled populations. The other 19 states (and Washington, DC) had a subset of their years included for either the adult and/or disabled BOE groups.
- For FFS patients, there were six states that had all years excluded for the adult population, and two states that had all years excluded for the disabled population. There were 20 states that had all years included in both the adult and disabled populations, and for the other 35 states and Washington DC, most of their data were included.

In sum, approximately 25% of the Medicaid beneficiary population (~24 million of ~95 million) were eligible for this study after applying the data usability criteria from Li et al.

National Death Index (NDI)

All databases were linked to the NDI to ascertain mortality status and cause of death among patients dispensed opioid analgesics. The NDI, maintained by National Center for Health Statistics (NCHS), is a central computerized index of death record information comprised of data from state vital statistics offices.

[xv] "Continuity" is defined by medical treatment that continues after a patient switches from FFS to managed care coverage

[xvi] "Connectivity" is defined by medical treatment that is expected given a specific diagnosis among patients in either FFS or managed care

[xvii] Li et al. (2017) Internal validation of Medicaid Analytic eXtract (MAX) data capture for comprehensive managed care plan enrollees from 2007 to 2010. Pharmacoepidemiology and Drug Safety: 1-10; https://doi.org/10.1002/pds.4365

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3.4.1.3 Time period definitions

2-year baseline (3Q2008-2Q2010), hereafter pre-period: reflects a baseline period with relatively stable utilization of OxyContin[xviii]

6-month transition (3Q2010-4Q2010): excluded from analyses as it represents the transition period (i.e., a period that includes the introduction of reformulated OxyContin to the market, and the decreasing supply and availability of the original OxyContin formulation)

5-years post-reformulation (1Q2011-3Q2015), hereafter post-period**:** provides an estimate of the sustained effect after the reformulation. The last quarter of 2015 was excluded to avoid the use of un-validated ICD-10-CM overdose codes when the US switched from ICD-9 to ICD-10 billing codes.

- **Two-years post-reformulation for Medicaid (1Q2011 to 4Q2012) analyses**: The Medicaid data did not have complete information available from 2013 – 2015 for all states so the post-period was truncated.

3.4.2 Study Population

Inclusion criteria applied to all analyses:

- Individuals aged 16-74 years (aged 16-64 years in Medicaid)
- At least one pharmacy dispensing of an eligible oral or transdermal (TD) opioid analgesic between July 1, 2008 and September 30, 2015
- At least three months of continuous health plan eligibility (prior to an eligible opioid analgesic dispensing)
- Population that is linkable to the NDI (except for Secondary Objective 4)

Patients with prior opioid overdose were included in the study. Approximately 40% of the HIRD, and 66% of MarketScan populations were **not** linkable to the NDI; these patients were excluded.

For the Medicaid population, only treatment episodes from state, year, and BOE groups for FFS and managed care members deemed eligible based on criteria defined by Li et al. were included

3.4.3 Comparators

Primary comparators

These primary comparators were intended to serve as negative controls for OxyContin, reflecting background trends and approximating expected changes in OxyContin overdose rates in the absence of the reformulation but subject to the same secular trends and various public health efforts (i.e., the "counterfactual" scenario). As there is no single ideal comparator, three comparators were chosen to reflect a diverse set of ER or long-acting (LA) opioid analgesic products with market share and settings of use that were similar to

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[xviii] Does not include the large changes in brand versus generic ER oxycodone prescriptions observed in early 2008 after the reinstatement of the OxyContin patent

OxyContin's and that were subject to the same regulatory actions (e.g., ER/LA Opioid Risk Evaluation and Mitigation Strategies) as OxyContin.

- **ER morphine tablets or capsules**: an ER prescription opioid analgesic drug used in chronic pain settings. ER morphine was not reformulated and had a large, relatively stable market share over the study period. While all the primary comparators have some utility, ER morphine may represent the best direct opioid analgesic to compare to OxyContin, with a relative potency and total number of patients dispensed over the study period fairly similar to those of OxyContin.
- **TD fentanyl (hereafter, fentanyl)**: an ER prescription opioid analgesic drug with a long marketing history and used in chronic pain settings. Fentanyl had relatively stable utilization over the study period. The time period for this study largely pre-dates the emergence of illicit fentanyl in the black market, and the subsequent rise in fentanyl-related deaths. It bears mentioning that TD fentanyl underwent a market transition from majority reservoir to matrix TD formulations over the study period, which could have impacted overdose risk associated with these products.
- **Methadone tablets or capsules**: a long-acting prescription opioid analgesic drug that is used in chronic pain settings and was not reformulated. Methadone had gradually declining use but no major fluctuations in utilization over the study period.

Secondary comparators

Secondary comparators were included to provide contextual information to assist the interpretation of observed changes in overdose rates for OxyContin and primary comparators. Secondary comparators included the following, along with the main reasons for not being selected as primary comparators:

- ER oxymorphone tablets: reformulated during the post-period, low market share during the study period
- SE/IR oxycodone tablets: not an ER/LA opioid analgesic, often used in acute pain settings
- IR hydromorphone tablets: not an ER/LA opioid analgesic, often used in acute pain settings
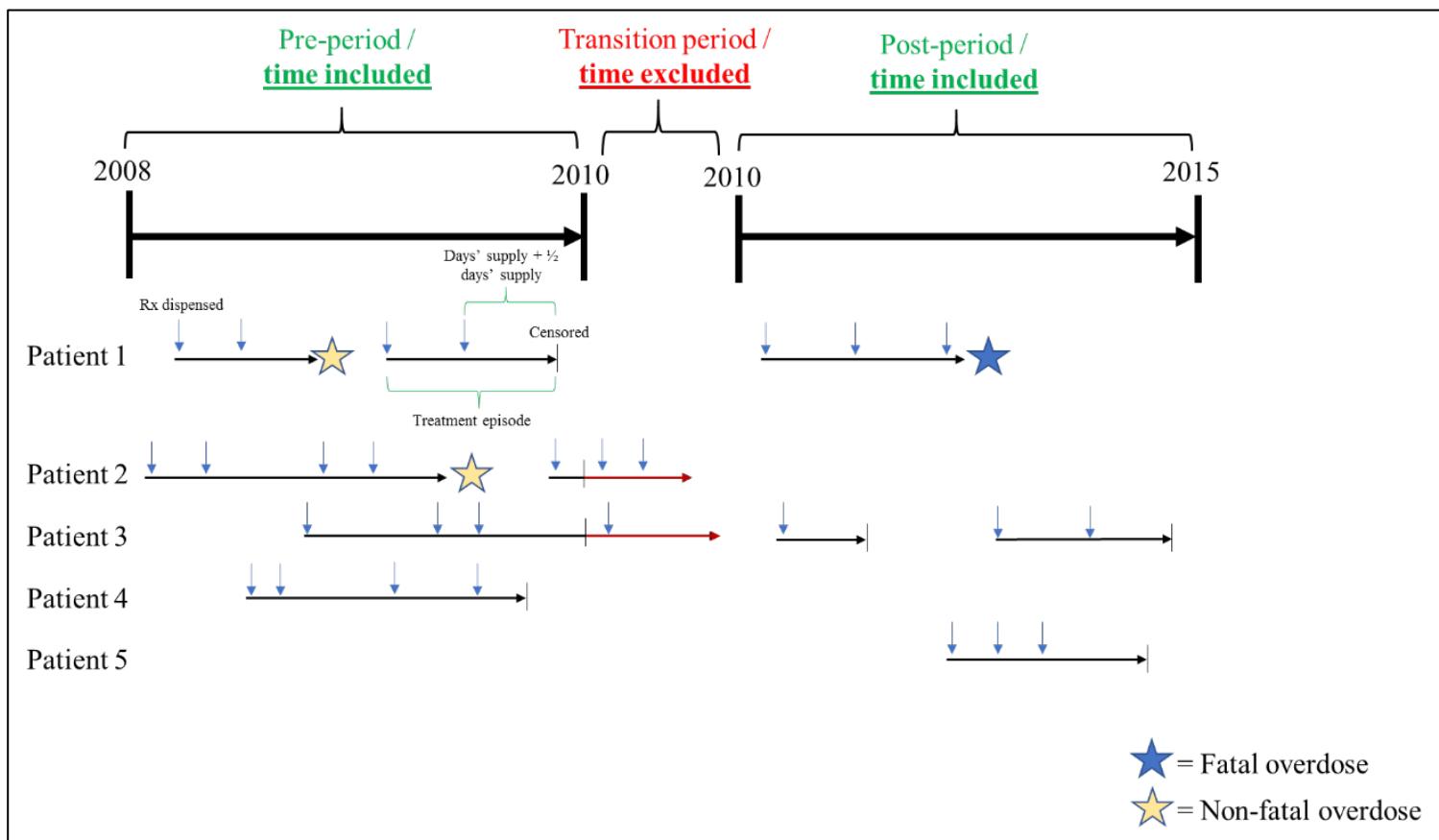
With the exception of single-entity immediate-release (SE/IR) oxycodone, the secondary comparators have lower utilization and more severe fluctuations in their utilization during the study period. SE/IR oxycodone could serve as a direct comparator given it is the same active moiety, but as an IR formulation, patient populations and prescribing practices may be quite different from OxyContin, particularly with regard to opioid analgesic co-prescribing. SE/IR oxycodone is frequently dispensed with OxyContin (see Appendix 8.1) further complicating its use as a comparator.

3.4.4   Exposure Time

Treatment episodes in the pre- and post-periods were defined as continuous patient-level opioid analgesic exposure periods (in person-time [months]) (see Figure 1), calculated using the drug dispensing dates and the number of days dispensed in patients' administrative pharmacy claims. The number of days dispensed is an estimate entered by

the dispensing pharmacist and may be influenced by the prescriber instructions, insurance reimbursement, or other unknown factors. Continuous opioid analgesic exposure time within a treatment episode began on the date of first dispensing of the opioid analgesic and ended at the exhaustion of days' supply plus half of the days' supply of the last dispensing of the opioid analgesic in that treatment episode, including the day of dispensing as an exposed day. Continuous opioid analgesic exposure time ended if there was one or more patient days of discontinuity in opioid analgesic "exposed" time; a treatment episode was censored if an individual discontinued an opioid analgesic of interest, initiated another study opioid analgesic (depending on the analyses), had the outcome of interest (fatal or non-fatal overdose), died, terminated their health plan, or reached the end of a study period (e.g., end of pre-period, post-period, or transition period).

Figure 1: Exposure time schematic

(*FDA generated figure*)

Key: Prescription (Rx); horizontal arrows that are black denote opioid analgesic exposure time periods (i.e., treatment episodes) that would theoretically be included in analyses; horizontal arrows that are red denote time that would not be included as it overlapped the transition period; vertical arrows denote prescription dispensed; note, all overdoses were included (fatal or non-fatal) in final analyses

If an individual obtained a new dispensing of the same opioid analgesic prior to exhausting the days' supply of a prior prescription of that opioid analgesic, the episode was extended using the newest prescription days' supply plus half days' supply. Any overlap between the days' supply of the two prescriptions was ignored. This means that exposure time did

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not account for indefinite "stockpiling" of medications. When there was a dispensing of a different opioid analgesic (i.e., opioid analgesic switch) before the end of the days' supply for the previous dispensing, a new treatment episode was created at the first dispensing of the new opioid analgesic, but this new episode also included any overlapping days' supply of the previous opioid analgesic dispensing, thus it would be concomitant use (of the new opioid analgesic with the old opioid analgesic) until the older prescription ran out.

Exposure groups:

Treatment episodes were categorized by opioid analgesic concomitancy to reflect the various ways patients are dispensed opioid analgesics, and to look for consistency of effect across exposure groups. As described above (Section 3.3 and Appendix 8.5), the sponsor conducted analyses on opioid analgesic switching patterns and concomitancy among patients dispensed OxyContin around the time of the reformulation. Based on these findings, analyses were conducted separately for the following mutually exclusive exposure groups:

- those involving the dispensing an opioid analgesic with or without concomitant opioid analgesics;

- those involving the dispensing of only one opioid analgesic (i.e., no concomitant use);

- those involving the dispensing of several opioid analgesics concomitantly

- o **OxyContin dispensing**
  1. Any OxyContin use: Time dispensed OxyContin, regardless of other opioid analgesic dispensing (including comparators)
  2. Any OxyContin use (without concomitant primary comparator): Time dispensed OxyContin, excluding periods dispensed primary comparators concomitantly
  3. OxyContin use without a concomitant opioid analgesic (CO): Time dispensed OxyContin only, censored at dispensing of another opioid analgesic (comparators or any other)
  4. OxyContin with concomitant IR opioid analgesic: Time dispensed OxyContin and any IR opioid analgesic concomitantly, excluding periods dispensed primary comparator concomitantly
  5. OxyContin with a CO: Time dispensed OxyContin and an IR or ER opioid analgesic concomitantly, excluding periods dispensed primary comparator concomitantly
     - These data were not included in this review. The vast majority of concomitant use was with IR opioid analgesics (#4), therefore the results of these analyses were nearly identical to the results for #4.
- o **Any primary comparator (PC) dispensing**
  1. Any PC use: Time dispensed a PC, regardless of other opioid analgesic dispensing (including comparators)
  2. Any PC use (excluding periods with OxyContin or other PC): Time dispensed a PC, excluding periods dispensed OxyContin or any other PC concomitantly

3. PC use without a CO: Time dispensed a PC only, censored at dispensing of another opioid analgesic (comparators or any other)
4. PC with concomitant IR: Time dispensed a PC and any IR opioid analgesic concomitantly, excluding periods dispensed OxyContin or any other PC concomitantly
5. PC with a CO: Time dispensed a PC and an IR or ER opioid analgesic concomitantly, excluding periods dispensed of OxyContin or any other PC concomitantly
   - These data are not presented. The vast majority of concomitant use is with IR opioid analgesics (#4), therefore the results of these analyses are nearly identical.
- **Any secondary comparator (SC) dispensing**
  1. Any SC use (excluding periods with OxyContin, PC, or other SCs): Time dispensed a SC, excluding periods dispensed OxyContin or any PC or SC concomitantly, permitting dispensing of any non-comparators concomitantly
  2. SC use without a CO: Time dispensed with a SC only, censored at dispensing of another opioid analgesic (comparators or any other)
  3. SC with a CO: Time dispensed a SC and an IR or ER opioid analgesic concomitantly, excluding periods dispensed OxyContin or any PC or SC concomitantly
     - These data are not presented in this review. The results of these analyses were nearly identical to those from #1.

Primary analyses included both treatment episodes defined as existing (prevalent) and new (incident) use episodes analyzed together (i.e., any patient meeting inclusion criteria); this was done to improve statistical power given the rare outcome of overdose. Sensitivity analyses stratified by prevalent and incident use treatment episodes were also conducted (See section 3.4.7.2). For these analyses, "incident use" was defined as having had no recorded dispensing of any study opioid analgesic in at least three months (i.e., 92 days of data coverage) prior to the start of a treatment episode. The population of "incident users" could have taken other opioid analgesics not listed in Section 3.2.3, so patients were not necessarily "new" to recent opioid analgesic use (e.g., patients could have used IR hydrocodone prior to the index date). An individual could re-enter the cohort as an "incident user" at later points in the study if they met the incident use criteria at the beginning of their new treatment episode.

For Secondary Objective 2, which examined overdose rates among patients continuously dispensed OxyContin (without a PC) or a PC opioid analgesic (without OxyContin or other PC) from the pre-period through the post-period, all pre-period treatment episodes that were initially eligible for Primary Objective 2 were included; however, for the post-period, only treatment episodes from the patients who were still dispensed the study opioid analgesic at the end of the pre-period, and continuously dispensed the same opioid analgesic through the transition period, and into the post-period were included in the cohort. Since patient inclusion in these analyses was based on post-reformulation information, patients with continuous opioid analgesic use must have survived without a

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fatal overdose through the pre-period and transition period to be included. Secondary Objective 2 analyses were considered exploratory.

3.4.5   Covariates

Demographic characteristics, clinical characteristics, and other comorbidities were ascertained for each treatment episode using patients' administrative claims, including diagnosis codes from their inpatient and outpatient service claims (See Table 3). These variables were selected based on their availability in the data, and their potential relevancy as a confounder with respect to their association with the choice of opioid analgesic dispensed and the outcome of opioid overdose. The primary clinical covariates (Table 3, comorbidities I) were selected because they were for chronic conditions with diagnosis codes that were expected to be consistently noted for a given patient across the study period; this is important as patients may contribute multiple treatment episodes. Additional variables (Table 3, comorbidities II) were included only in propensity score (PS) weighted analyses (See Section 3.4.7.2) limited to "incident use" periods. The sponsor deemed these additional variables (Table 3, comorbidities II) as potential intermediate ("downstream") variables (or mediators) in the causal pathway (i.e., clinical characteristics potentially caused by the opioid analgesic dispensed) that may obscure the "true" casual effect.

Benzodiazepine use was also deemed an intermediate variable in the causal pathway by the sponsor, and thus was excluded from all analyses; FDA requested the sponsor re-analyze the data with baseline benzodiazepine use (within three months of treatment initiation) as a covariate in the fully-adjusted models and the results were submitted in their April 1, 2020, information request response. FDA also requested the sponsor explore its role as a potential effect modifier in those analyses, testing for statistically significant interactions between baseline benzodiazepine use and opioid analgesic exposure group across the databases, and conducting stratified analyses where necessary.

As noted in section 3.4.2, patients with eligible treatment episodes after a non-fatal overdose were included in analyses. Because patients could have had an overdose and become eligible again, and because past overdose is highly predictive of future overdose, the sponsor also used a time-updated variable for "history of overdose event/poisoning" in adjusted analyses to account for within-person correlation.

The lookback period was three months (i.e., 92 days) prior to each treatment episode for all covariates, except for certain demographic characteristics which were assessed at the first opioid analgesic dispensing (e.g., geographic region), and other select covariates which used a six-month lookback period (these are noted in the table below).

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Table 3: Variables in statistical models

Variables used in all fully-adjusted statistical models		Additional variables used only in propensity score analyses (sensitivity analyses)
Demographic / descriptive characteristics	**Comorbidities / clinical characteristics I**	**Comorbidities / clinical characteristics II**
Age	Abdominal pain	Alcohol use disorder
Gender	Amputation	Generalized anxiety disorder
Geographic region (commercial databases)	Arthritis, arthropathies, osteoarthritis, and musculoskeletal pain	Attention deficit hyperactive disorder (ADHD)
United States (US) state residence (Medicaid database)	Back pain	Bipolar disorder
Calendar year of index date	Chronic pain	Major depressive disorder
Plan type (Health Maintenance Organization [HMO], preferred provider organization [PPO], consumer driver health insurance [CDHP]/high deductible health plan [HDHP])	Fibromyalgia	History of attempted suicide
	Headache	Post-traumatic stress disorder
	Malignancy	Sleep disorder
	Multiple sclerosis	Somatoform disorder
	Neuropathic pain	Opioid Use Disorder
Medicaid coverage type (fee-for-service [FFS], managed care [CMC])	Peripheral vascular disease	Non-OUD Substance Use Disorder
	Stroke	Borderline personality disorder
Medicaid basis of eligibility (basis of eligibility [BOE]) group (disabled, adult)	Liver disease	All-cause office visits in last six months
	Renal disease	All cause emergency department visits in last six months
	Chronic Obstructive Pulmonary Disease (COPD)	All cause hospitalizations in last six months
	Impaired respiratory function	Distinct medication classes in last six months
	Deyo-Charlson-comorbidity index	
	History of overdose/ poisoning*	Prior use of Tramadol (ER or IR)
	Prior use of opioid analgesic (none, extended-release [ER] opioid only, immediate-release [IR] opioid only, ER + IR opioids)	

(*FDA generated table*)

Key: *=time-updated variable at each treatment episode since patients with previous overdose could be included if they were subsequently dispensed an opioid analgesic; extended-release (ER); immediate-release (IR); opioid use disorder (OUD)

3.4.6   Outcome Measures

Opioid overdose outcomes were identified using the code-based diagnostic algorithm developed for use in administrative claims databases and validated as part of the extended-release/long-acting opioid analgesic (ER/LA OA) PMR study 3033-6, conducted by the Opioid Product Consortium (OPC)[xix]; the algorithm also relied on database linkages to the NDI to capture fatal opioid overdose events.

The OPC published the results of PMR study 3033-6[xx] and additional algorithm portability assessments they conducted independently, including testing the algorithms in Tennessee

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[xix] ER/LA opioid PMR letter: https://www.fda.gov/media/95546/download; ClinicalTrials.gov Identifier: NCT02667197: https://clinicaltrials.gov/ct2/show/NCT02667197

[xx] Green CA, et al. (2019) Identifying and classifying opioid-related overdoses: A validation study. Pharmacoepidemiol Drug Saf;28: 1127–1137. https://doi.org/10.1002/pds.4772

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Medicaid data (TennCare). That study demonstrated the any opioid overdose algorithm (unintentional and intentional; fatal and non-fatal) was superior to the intentional opioid overdose algorithm (fatal and non-fatal), with consistently high sensitivity, specificity, positive predictive value, and F scores across databases (See Table 4). The sponsor conducted a partial portability assessment of the algorithms (See Appendix 8.2) as part of PMR 3051-4, evaluating their performance in only the HIRD database where they had access to medical records, and the performance metrics they provided were generally consistent with those presented Green et al.

Because of the superior performance of the any overdose algorithm and the limited portability of the intentional overdose algorithm, particularly in the Tennessee Medicaid data, FDA views the any opioid overdose analyses in PMR study 3051-4 as primary, and analyses differentiating between intentional and unintentional are viewed as exploratory.

Table 4: Performance of the any opioid overdose algorithm and the intentional opioid overdose algorithm from PMR study 3051-4 and Green et al.

Measure	Kaiser Permanente Northwest		HIRD*		Kaiser Permanente Washington		Optum Integrated Database		Tennessee Medicaid data (TennCare)	
	Any opioid overdose	Intentional opioid overdose	Any opioid overdose	Intentional opioid overdose	Any opioid overdose	Intentional opioid overdose	Any opioid overdose	Intentional opioid overdose	Any opioid overdose	Intentional opioid overdose
Sensitivity	97.2	70.5	n/a	66.0	100.0	74.1	96.9	63.2	99.2	44.9
Specificity	84.6	90.2	n/a	96.4	89.2	86.7	100.0	91.0	92.4	87.1
Positive Predictive Value	87.4	78.9	85.0	88.6	84.1	74.1	100.0	81.1	91.9	64.5
Negative Predictive Value	96.5	85.5	n/a	n/a	100	86.7	96.9	80.1	99.2	75.1
F-Score	0.92	0.74	n/a	n/a	0.92	0.74	0.98	0.67	0.95	0.53

(*FDA generated table from PMR 3051-4 study report and Green et al*)

Key: *=These results were provided in the PMR study 3051-4 portability sub-study; all data (but HIRD) were abstracted from Green et al (2019); F-score is a measure of a test's accuracy

In PMR study 3051-4, an overdose was included as an outcome if it occurred during an eligible treatment episode. Thus, patients could have several non-fatal overdose events throughout the study period if they had several eligible treatment episodes and overdoses.

Of note, all overdose algorithms used in PMR 3051-4 include fatal and non-fatal overdoses involving any opioid, including prescription products and/or illicit opioids such as heroin and illicitly manufactured fentanyl.

Primary outcome in PMR study 3051-4

- Any opioid overdose: Intentional or unintentional, fatal or non-fatal opioid overdose

Exploratory outcomes in PMR study 3051-4

- Unintentional fatal or non-fatal opioid overdose
- Intentional fatal or non-fatal opioid overdose

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3.4.7   Statistical Analyses

3.4.7.1   Primary Methods

Primary metrics and statistical models

Unadjusted and adjusted overdose incidence rates and 95% confidence intervals (CI) were modeled using Poisson regression, with person-time (i.e., opioid analgesic exposure time) included as an *offset*, and pre- versus post-reformulation overdose rate ratios (RR) were calculated for OxyContin and comparator opioid analgesic exposure groups, as defined in Section 3.4.4 above. The regression models used repeated-measures Generalized Estimating Equations (GEE) with an independent covariance matrix to account for the correlation between a given patient's multiple eligible treatment episodes; the robust ("sandwich") variance estimator was used to calculate 95% CIs. The expanded model was specified as follows:

$$\ln(Events_i) = \beta_0 + \beta_{Oxy}z_{Oxy} + \beta_{PP}z_{PP} + \beta_{RoR}z_{PP}z_{Oxy} + \overline{\beta}_C\overline{z}_C + \ln(PersonTime_i)$$

The subscript *i* refers to each (mutually exclusive) block of person-time defined by opioid analgesic exposure group, pre- or post-reformulation period, and covariates. The indicator variable Z_{oxy} takes on the values 0 for OxyContin (1 to n for comparator opioid analgesics); Z_{pp} takes on the values 1 for the post-reformulation period (0 for pre-reformulation period). $\overline{\beta}_C\overline{z}_C$ represents the full set of covariates.

Overdose RRs comparing the overdose rates of the pre- and post-periods were calculated for OxyContin and each of the comparator opioid analgesic exposure groups (RR = [overdose incidence rate post-period] / [overdose incidence rate pre-period]). A ratio of rate ratios (RORR) was used to compare the changes in overdose rates between the pre- and post-periods comparing patients dispensed OxyContin to those dispensed a comparator opioid analgesic (RORR = [comparator RR] / [OxyContin RR]). In these types of difference in difference models,[xxi] the RORR is represented by the interaction (β_{RoR}) between time period (binary variable: pre- or post-period) and opioid analgesic exposure group (with OxyContin as the reference drug group). An RORR >1 reflects a more favorable change in overdose rates among those dispensed OxyContin comparing the periods before and after the reformulation relative to any changes in overdose rates for patients dispensed a comparator; in this context, favorable could mean a greater reduction or a smaller increase in overdose rates among those dispensed OxyContin comparing periods relative to those dispensed a comparator, or no change in overdose rates among those dispensed OxyContin but increasing overdose rates among those dispensed a comparator. An RORR <1 indicates a more favorable change for among those dispensed a comparator.

[xxi] Wing C et al. (2018) Designing Difference in Difference Studies: Best Practices for Pubic Health Policy Research. Annual Review of Public Health; 39: 453-469.

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Meta-analytic methods

Analyses were undertaken separately in the three databases, and results are presented separately in the study report; however, DerSimonian and Laird[xxii] random-effects meta-analysis was also used to compute meta-analyzed (combined) RRs and RORRs for the two commercial databases (MarketScan and HIRD). The Medicaid population was not included in these analyses given *a priori* differences in this population compared to the commercially-insured populations and the shorter post-reformulation period available in the Medicaid data.

PMR 3051-4 final study report only included meta-analyzed results for the unintentional overdose (exploratory outcome), which are not shown in this review, but the updated the meta-analyzed results (April 2020 information request response) using the any overdose outcome are described.

3.4.7.2 Sensitivity analyses

1) Incident user only cohort

In a subset of analyses, cohorts were restricted to incident use periods, with "incident" defined as having had no recent (within three months) dispensing of any study opioid analgesic (See Section 3.2.4); separately, prevalent only users were also analyzed (these data are not included in this review). Restricting to incident user only patient cohorts can help minimize selection biases that result from including ongoing users that, by definition, have had some experience with the study drug, and have not had the outcome, or are potentially less susceptible for the outcome. In the case of opioid analgesic use and overdose, it is also possible that the converse is true, in that the likelihood of the outcome increases with exposure time. Selection biases can also be introduced when adjusting for variables after initiation, particularly those that may have been impacted by treatment selection. The results of analyses using the incident user only cohort were compared to the results of analyses using the combined (incident and prevalent user) cohort to better understand the effect of potential selection biases.

2) Fee-for-service versus comprehensive managed care

State-based Medicaid programs generally involve a mix of fee-for-service (FFS) or comprehensive managed care insurance coverage plans, with states transitioning between models over time (See Appendix 8.3). Administrative insurance claims data from Medicaid FFS-covered patients are collected differently than managed care patients, and the state-specific shifts in primary coverage type can challenge longitudinal studies relying on consistent data capture over time. Consistent with the primary analyses using only states/years/basis of eligibility (BOE) combinations with useable (i.e., "complete") FFS or managed care Medicaid data, as a sensitivity analyses the sponsor also conducted stratified analyses to look for differences by coverage type.

[xxii] Borenstein M. et al. (2010) A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods, 1: 97-111. DerSimonian R, and Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials, 7: 177-88. DerSimonian R, and Laird N (2015) Meta-analysis in clinical trials revisited. Contemp Clin Trials, 45: 139-45

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3) Propensity score (PS) weighted analyses

Sensitivity analyses using propensity scores were conducted to explore additional methods for adjusting for relevant characteristics of patients with opioid analgesic use that are more strongly associated with one period (pre- or post-period) over another, and to mitigate the potential for confounding with respect to OxyContin prescribing, or the prescribing of the comparator drugs, around the time of the reformulation.

Overdose rate ratios were estimated using PS-weighted Poisson regression models of only incident user cohorts to best reflect the probability of initiation. In these analyses, the post-period cohort was weighted to match the covariate (demographic, clinical characteristics, and comorbidities) distribution of the pre-period cohort. Each data partner fit separate PS models (i.e., logistic regression models) to estimate the probability that an incident treatment episode was from the post-period versus the pre- period for those involving OxyContin and for those involving each comparator. Weights based on these fitted probabilities were assigned to individual treatment episodes (weight of 1 for treatment episodes in the pre-period; weight of PS_i / $1\text{-}PS_i$ for the post-period). Propensity score distributions were evaluated, and extreme weights were trimmed (non-overlapping distributions). Covariate balance after PS-weighting was assessed using standardized mean differences, using <0.10 difference in prevalence as a threshold for defining "balance".

4   STUDY RESULTS

Notes on terminology:

- FDA has defined the term "*abuse*" as the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. FDA recognizes that this term has been identified as potentially stigmatizing to individuals with substance use disorders. This is in no way our intent; rather, we are using the term abuse as it has been previously defined specifically by FDA to describe a specific set of behaviors, or as it is used in the study(ies) we are reviewing.

  In this review, unless otherwise specified, "<u>overdose rates</u>" are defined as "*rates of combined any (unintentional or intentional) fatal or non-fatal opioid overdose.* In a validation study using medical record review to estimate the predictive performance of claims-based opioid overdose algorithms, the algorithm to ascertain any opioid overdose (intentional or unintentional; fatal or non-fatal) was superior to the algorithm differentiating between intentional and unintentional overdose (See Section 3.4.6). Therefore, FDA views analyses using any opioid overdose as primary.

- When describing overdose rates in different exposure groups—for example, those that include only time in which patients were dispensed OxyContin (or a comparator), without other opioid analgesics concomitantly—we may use the following terminology for simplicity in text, tables, and figures: "*among patients dispensed OxyContin (or comparator) alone*" or "*OxyContin use alone.*" Overdose rates and rate ratios are computed using person-time of exposure, not the number of patients; therefore, a patient can theoretically contribute time to multiple different exposure groups during

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the study period. This does not mean that these patients were only *ever* dispensed OxyContin alone, but rather that the patients contributed exposure time to the analysis for this exposure cohort.

- When using the term "*significant*" or "*significance*" we are referring to statistical significance, not necessarily clinical or public health significance.
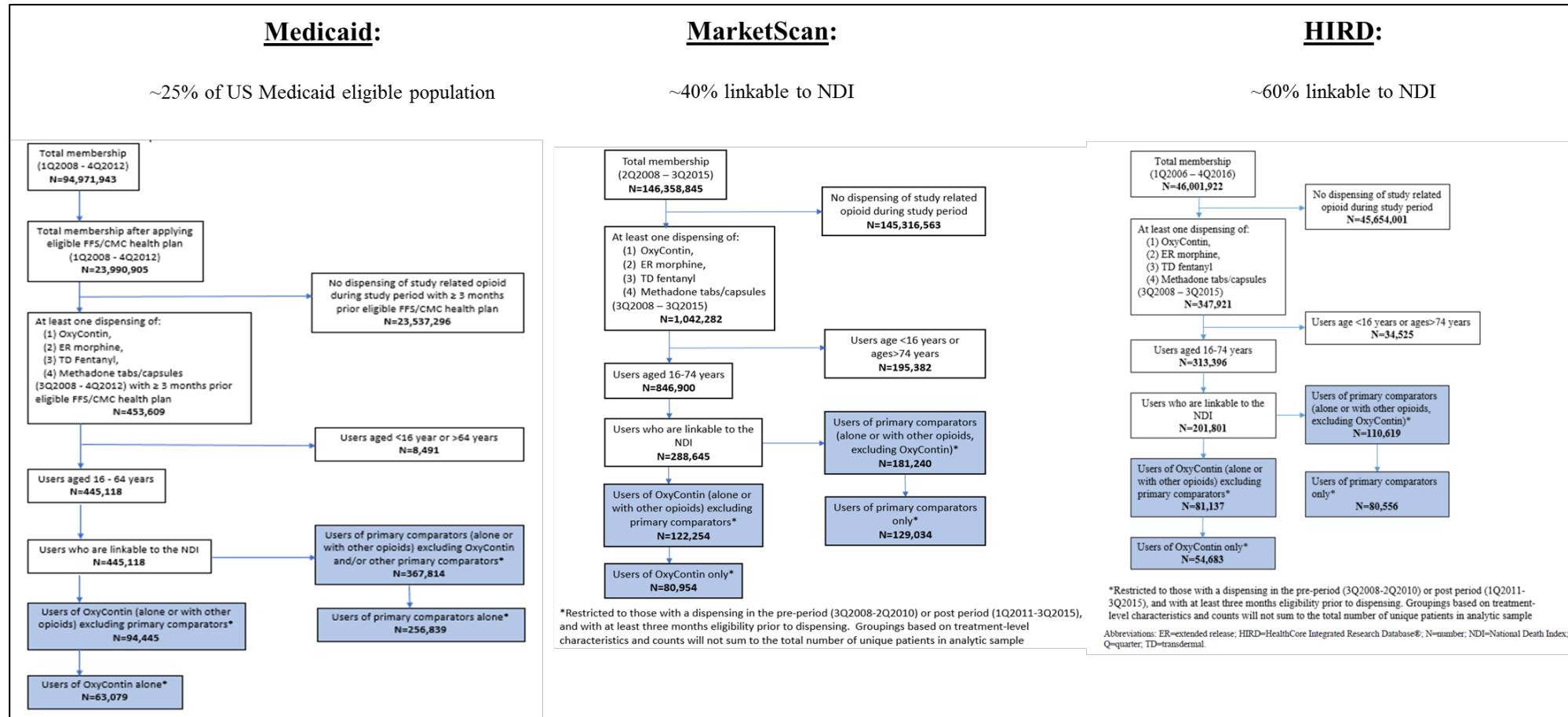
4.1 DESCRIPTIVE COHORT SUMMARY

4.1.1 Study Cohort Summary

Figure 2 shows the total number of available patients in each database, and the total number of excluded patients after applying linkage and inclusion/exclusion criteria; the numbers at the bottom of the flowcharts (blue boxes) reflect the final analytic sets for primary objectives. In Medicaid, ~25% (N= 23,990,905) of the total Medicaid membership during the study period was eligible after applying the Li et al. criteria (data usability criteria); all eligible patients dispensed an opioid analgesic of interest were linkable to NDI (N=445,118), with 94,445 patients dispensed OxyContin alone or with other opioid analgesics over the study period.

In the commercial claims databases, ~40% of the eligible patients dispensed an opioid analgesic of interest were linkable to NDI in MarketScan (N=288,645), while ~60% of the eligible patients were linkable to NDI in HIRD (N=201,801). MarketScan had the most patients dispensed OxyContin alone or with other opioid analgesics over the study period (N=122,254), and HIRD had the least (N=81,137).

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Figure 2: Cohort flowcharts of included patients, by database

Medicaid: ~25% of US Medicaid eligible population

MarketScan: ~40% linkable to NDI

HIRD: ~60% linkable to NDI

Medicaid:

Total membership (1Q2008 - 4Q2012) N=94,971,943

Total membership after applying eligible FFS/CMC health plan (1Q2008 - 4Q2012) N=23,990,905

No dispensing of study related opioid during study period with ≥ 3 months prior eligible FFS/CMC health plan N=23,537,296

At least one dispensing of:
(1) OxyContin,
(2) ER morphine,
(3) TD Fentanyl,
(4) Methadone tabs/capsules (3Q2008 - 4Q2012) with ≥ 3 months prior eligible FFS/CMC health plan N=453,609

Users aged <16 year or >64 years N=8,491

Users aged 16 - 64 years N=445,118

Users who are linkable to the NDI N=445,118

Users of primary comparators (alone or with other opioids) excluding OxyContin and/or other primary comparators* N=367,814

Users of OxyContin (alone or with other opioids) excluding primary comparators* N=94,445

Users of primary comparators alone* N=256,839

Users of OxyContin alone* N=63,079

MarketScan:

Total membership (2Q2008 – 3Q2015) N=146,358,845

No dispensing of study related opioid during study period N=145,316,563

At least one dispensing of:
(1) OxyContin,
(2) ER morphine,
(3) TD fentanyl
(4) Methadone tabs/capsules (3Q2008 – 3Q2015) N=1,042,282

Users age <16 years or ages>74 years N=195,382

Users aged 16-74 years N=846,900

Users who are linkable to the NDI N=288,645

Users of primary comparators (alone or with other opioids, excluding OxyContin)* N=181,240

Users of OxyContin (alone or with other opioids) excluding primary comparators* N=122,254

Users of primary comparators only* N=129,034

Users of OxyContin only* N=80,954

*Restricted to those with a dispensing in the pre-period (3Q2008-2Q2010) or post period (1Q2011-3Q2015), and with at least three months eligibility prior to dispensing. Groupings based on treatment-level characteristics and counts will not sum to the total number of unique patients in analytic sample

HIRD:

Total membership (1Q2006 – 4Q2016) N=46,001,922

No dispensing of study related opioid during study period N=45,654,001

At least one dispensing of:
(1) OxyContin,
(2) ER morphine,
(3) TD fentanyl
(4) Methadone tabs/capsules (3Q2008 – 3Q2015) N=347,921

Users age <16 years or ages>74 years N=34,525

Users aged 16-74 years N=313,396

Users who are linkable to the NDI N=201,801

Users of primary comparators (alone or with other opioids, excluding OxyContin)* N=110,619

Users of OxyContin (alone or with other opioids) excluding primary comparators* N=81,137

Users of primary comparators only* N=80,556

Users of OxyContin only* N=54,683

*Restricted to those with a dispensing in the pre-period (3Q2008-2Q2010) or post period (1Q2011-3Q2015), and with at least three months eligibility prior to dispensing. Groupings based on treatment-level characteristics and counts will not sum to the total number of unique patients in analytic sample

Abbreviations: ER=extended release; HIRD=HealthCore Integrated Research Database®; N=number; NDI=National Death Index; Q=quarter; TD=transdermal.

(*Sponsor figure taken from PMR 3051-4 study report*; reformatted by FDA)

Table 5 shows summary demographic and clinical characteristics of patients dispensed OxyContin (excluding the use of primary comparators) and patients dispensed any primary comparators (excluding the use of OxyContin) in aggregate, combining the pre- and post-periods. Mean exposure time contributed per patient was slightly longer among those dispensed primary comparator opioid analgesics compared to those dispensed OxyContin, particularly in the commercial claims databases. At the same time, the mean exposure time per treatment episode (irrespective of the patient) was similar among those dispensed primary comparator opioid analgesics compared to those dispensed OxyContin (see Appendix 8.4.1-8.4.3), ranging from 1.4 to 2.1 months. A slightly larger proportion of patients dispensed OxyContin were male compared to those dispensed primary comparator opioid analgesics, but the mean ages were similar within databases. Overall, the mean ages were older in commercial claims databases compared to the Medicaid population.

There were no substantial differences in clinical characteristics comparing those dispensed OxyContin and those dispensed primary comparators (see Table 5 and Appendix 8.4.1-8.4.3). Of note, the proportions of those with a history of overdose and opioid type dependence (ICD 9 code: 304.0x) were slightly larger among those dispensed primary comparators; data were not provided by period. Prior benzodiazepine dispensing was also similar comparing exposure groups across databases. In Medicaid (see Appendix 8.7) rates of benzodiazepine dispensing across opioid analgesic exposure groups were largely the same comparing the pre- and post-periods, while in HIRD (see Appendix 8.7) rates of benzodiazepine dispensing decreased similarly from the pre- to post-periods across nearly all opioid analgesic exposure groups. Overall, the Medicaid population had more comorbidities compared to those of the commercial claims databases across opioid analgesic exposure groups.

Table 5: Demographic and clinical characteristics summary for those dispensed OxyContin and other primary comparator opioid analgesics, by database

Variable	Value	Any OxyContin*			Any Primary Comparator Opioids^		
		Medicaid	MarketScan	HIRD	Medicaid	MarketScan	HIRD
Patients		94,445	122,254	81,137	367,814	181,240	110,619
Total person-time per patient in months	Mean (SD)	7.8 (10.0)	6.0 (10.3)	6.1 (11.4)	8.1 (10.3)	8.0 (11.9)	9.5 (13.9)
Treatment Episodes		522,775	561,703	378,441	2,039,232	975,389	654,462
Gender	Female	295,875 (56.6%)	285,366 (50.8%)	189,986 (50.2%)	1,241,520 (60.9%)	560,051 (57.4%)	382,769 (58.5%)
	Male	226,900 (43.4%)	276,337 (49.2%)	188,455 (49.8%)	797,712 (39.1%)	415,338 (42.6%)	271,693 (41.5%)
Age (years)	Mean (SD)	46.7 (10.5)	53.1 (12.0)	51.4 (12.2)	46.9 (10.6)	54.6 (11.6)	53.4 (11.9)
DCI	Mean (SD)	2.0 (2.8)	2.0 (3.1)	1.7 (2.8)	2.0 (2.8)	2.4 (3.3)	2.0 (3.0)
Clinical and co-morbidity characteristics	Abdominal Pain	99,797 (19.1%)	80,535 (14.3%)	55,554 (14.7%)	436,472 (21.4%)	179,919 (18.4%)	120,612 (18.4%)
	Chronic pain	104,311 (20.0%)	65,463 (11.7%)	63,456 (16.8%)	427,644 (21.0%)	143,661 (14.7%)	138,170 (21.1%)
	Neuropathic pain	16,857 (3.2%)	14,164 (2.5%)	10,627 (2.8%)	70,734 (3.5%)	32,678 (3.4%)	26,043 (4.0%)
	COPD	102,942 (19.7%)	64,556 (11.5%)	49,926 (13.2%)	401,863 (19.7%)	129,161 (13.2%)	104,775 (16.0%)
	Major depression disorder	88,372 (16.9%)	62,556 (11.1%)	58,692 (15.5%)	378,331 (18.6%)	128,661 (13.2%)	119,470 (18.3%)
	History of overdose	2,657 (0.5%)	1,428 (0.3%)	1,110 (0.3%)	15,485 (0.8%)	3,801 (0.4%)	3,160 (0.5%)
	Opioid type dependence	30,472 (5.8%)	9,560 (1.7%)	11,343 (3.0%)	119,537 (5.9%)	18,777 (1.9%)	23,706 (3.6%)
	Non-opioid drug dependence	32,589 (6.2%)	7,963 (1.4%)	8,840 (2.3%)	119,625 (5.9%)	15,083 (1.5%)	19,215 (2.9%)
	Benzodiazepines	97,110 (18.6%)	86,631 (15.4%)	60,818 (16.1%)	368,051 (18.1%)	154,579 (15.8%)	109,074 (16.7%)

Frequency (percent) presented unless otherwise specified
*Any use of OxyContin excluding concomitant primary comparator opioid use.
^Any use of any of the primary comparators (ER morphine, TD fentanyl, or methadone) excluding concomitant OxyContin or other primary comparator use.
Abbreviations: DCI=Deyo-Charlson Index; HIRD=HealthCore Integrated Research Database; SD=standard deviation; COPD=Chronic Obstructive Pulmonary Disease.

(*Sponsor table taken from PMR 3051-4 study report*)

When comparing NDI-linkable patients to "un-linkable" patients in the commercial claims databases (see Appendix 8.4.2 and 8.4.3) among all patients dispensed opioid analgesics, the patients were largely similar with respect to the demographic and clinical characteristics.

Table 6 shows unadjusted opioid overdose incidence rate ratios (IRRs)[xxiii] for some relevant comorbidities using all patients dispensed any opioid analgesic. Across databases, IRRs comparing those with prior opioid overdose to those without prior overdose were very high, substantially higher than other comorbidities with elevated statistically significant IRRs. Of note, the sponsor only provided these IRR data (Table 6), so IRRs for other relevant comorbidities are unknown.

[xxiii] IRRs were calculated without regard to pre- or post-period, meaning all exposure time was combined for all opioid analgesics across the study period

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Table 6: Incidence rate ratios for select variables, by database

Preceding characteristics	HIRD			MarketScan			Medicaid		
	IRR	LCL	UCL	IRR	LCL	UCL	IRR	LCL	UCL
Large Risk Elevation									
Opioid overdose	29.27	20.39	42.02	19.02	14.76	24.53	14.64	13.19	16.24
Modest Risk Elevation									
Stroke	1.54	1.10	2.16	1.34	1.03	1.74	1.28	1.11	1.48
COPD	1.50	1.29	1.75	1.28	1.12	1.46	1.33	1.25	1.41
Impaired respiratory function	1.44	1.18	1.76	1.61	1.38	1.88	1.50	1.39	1.61
Chronic pain	1.48	1.28	1.70	1.48	1.31	1.66	1.37	1.30	1.44
Reduced Risk									
Malignancy	0.61	0.42	0.88	0.65	0.52	0.82	0.73	0.66	0.82

Abbreviations: HIRD=HealthCore Integrated Research Database; COPD=Chronic Obstructive Pulmonary Disease, LCL=lower confidence interval; UCL=upper confidence limit; IRR=incidence rate ratio.
All characteristics are as noted on claims diagnoses in the preceding 92 days.
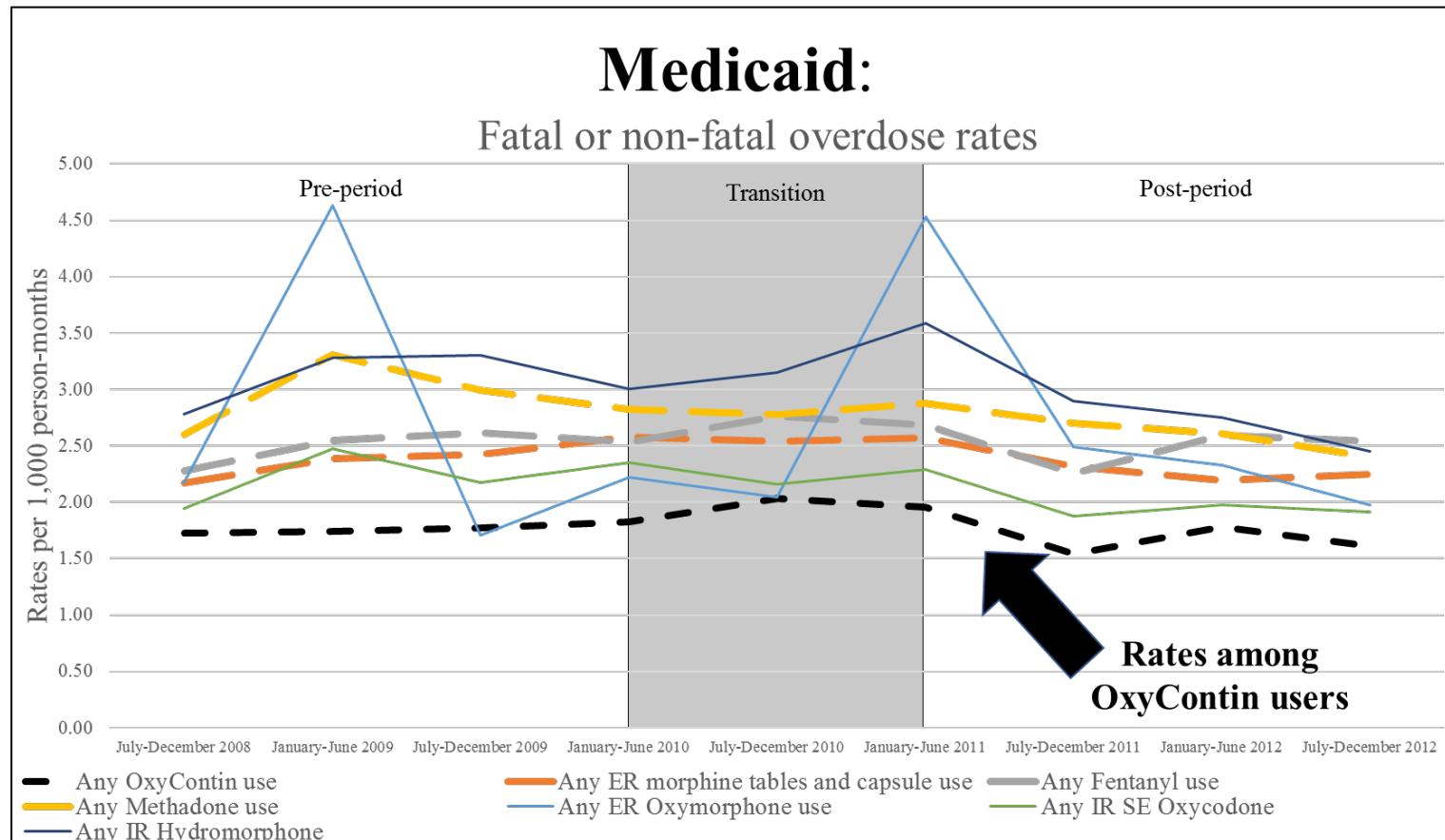
(*Sponsor table taken from PMR 3051-4 study report*)

Across all opioid analgesic exposure groups, ~10% of patients with an opioid overdose had multiple, distinct non-fatal overdoses during follow-up of the study, but no data were provided on whether this disproportionately involved one opioid analgesic exposure group or another.

4.1.2 Overdose Rate Trends Over Time

Figure 3 shows the bi-annual overdose rates (per 1,000 person-months) among patients dispensed OxyContin and other opioid analgesic comparators in the Medicaid data across the study period (note the shorter study period with these analyses: *July 2008 - December 2012*). Like all the other opioid analgesic comparators with the exception of ER oxymorphone, bi-annual overdose rates among patients dispensed OxyContin were relatively stable throughout the study period, with perhaps a slight decline immediately after the transition period. Overall, rates among patients dispensed OxyContin were lower than those for all of the other opioid analgesic comparator groups.

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Figure 3: Overdose rates over the study period in Medicaid data two years before versus two years after the reformulation (-2y/2y), by opioid analgesic exposure group
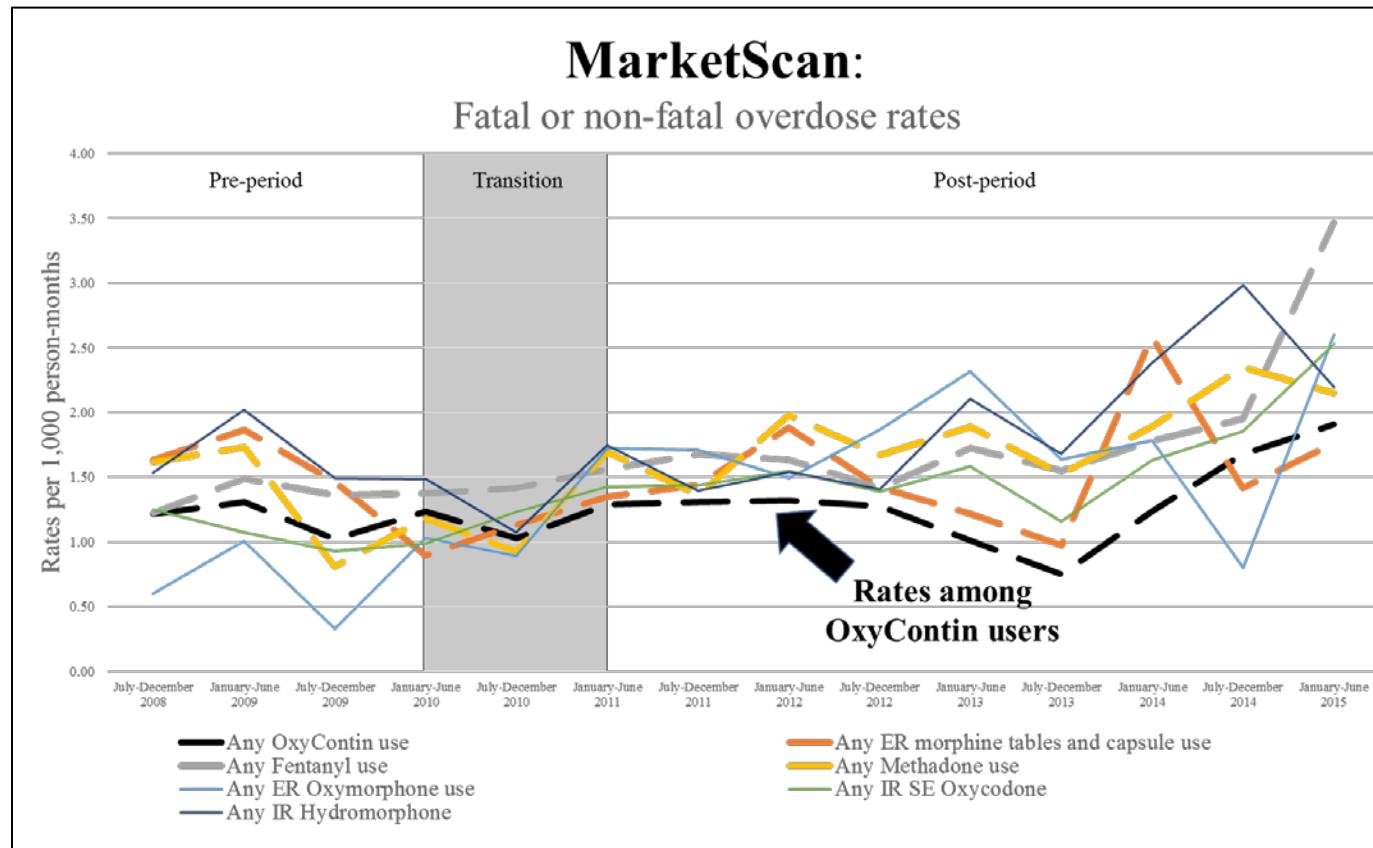
(*FDA generated figure using data from PMR 3051-4 study report*)

Key: immediate-release (IR); extended-release (ER); single-entity (SE); vertical line represents approximate date of reformulated OxyContin's initial marketing; the dashed (thicker) lines are for primary comparators; the solid (thinner) lines are for secondary comparators; grey box is the market transition period; **note:** Medicaid data were only analyzed through 2012

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Figure 4 shows the overdose rates (per 1,000 person-months) among patients dispensed OxyContin and other opioid analgesic comparators in the MarketScan data across the study period. Bi-annual overdose rates among patients dispensed OxyContin were also relatively stable around the time of reformulation, and similar to that of other opioid analgesic comparator groups. While there was no discernable decline in overdose rates among patients dispensed OxyContin immediately after the reformulation, there was an apparent decline in 2013, followed by a large increase in 2014. This increase at the end of the study period was seen for multiple opioid analgesic comparator groups

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Figure 4: Overdose rates over the study period in MarketScan data two years before versus five years after the reformulation (-2y/5y), by opioid analgesic exposure group
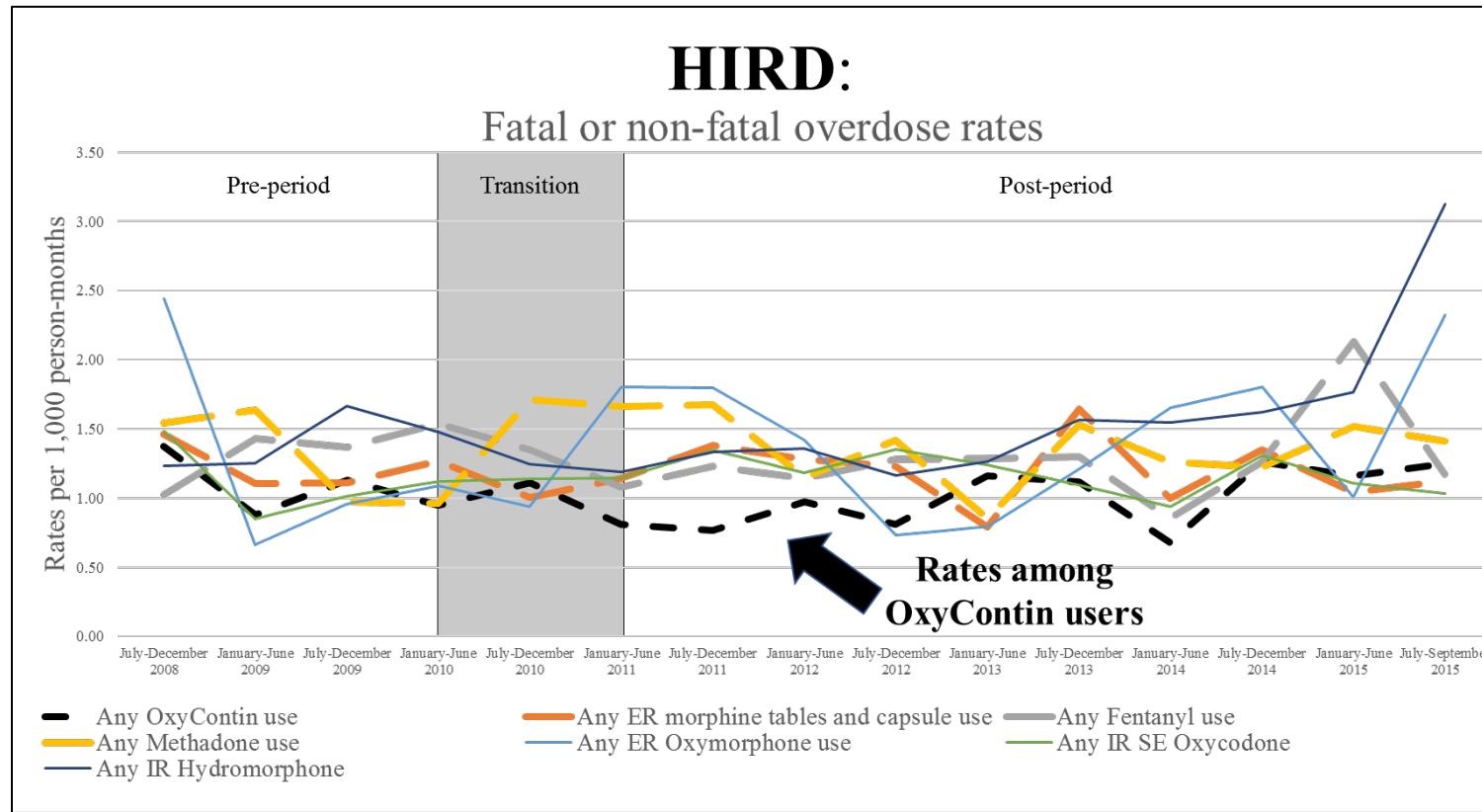
(*FDA generated figure using data from PMR 3051-4 study report*)

Key: immediate-release (IR); extended-release (ER); single-entity (SE); vertical line represents approximate date of reformulated OxyContin's initial marketing; the dashed (thicker) lines are for primary comparators; the solid (thinner) lines are for secondary comparators; grey box is the market transition period; **note**: the figure does not include data from 3Q2015 as these rates were based off of only a limited number of patients meeting criteria (must have had a opioid analgesic prescription before the beginning of 3Q2015)

Figure 5 shows the overdose rates (per 1,000 person-months) among patients dispensed OxyContin and other opioid analgesic comparators in the HIRD data across the study period. Bi-annual overdose rate trends among patients dispensed OxyContin were largely similar to those of the other opioid analgesic comparator groups in the pre-period. Rates in patients dispensed OxyContin appeared to decline following the transition period and then fluctuated throughout the post-period, returning to levels similar to those seen in the pre-period.

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Figure 5: Overdose rates over the study period in HIRD data, by opioid analgesic exposure group (-2y/5y)

(*FDA generated figure using data from PMR 3051-4 study report*)

Key: immediate-release (IR); extended-release (ER); single-entity (SE); vertical line represents approximate date of reformulated OxyContin's initial marketing; the dashed (thicker) lines are for primary comparators; the solid (thinner) lines are for secondary comparators; grey box is the market transition period; **note**: the figure does not include data from 3Q2015 as these rates were based off of only a limited number of patients meeting criteria (must have had a opioid analgesic prescription before the beginning of 3Q2015)

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4.2 OVERDOSE RATES COMPARING PRE- AND POST-REFORMULATION PERIODS

4.2.1 Overdose Rates Among Those Dispensed OxyContin[xxiv]

Table 7 shows the total number of overdoses, the total amount of person-time, the overdose rates (per 1,000 person-months) in the pre- and post-periods, and the rate ratios comparing periods among those dispensed any OxyContin[xxv] (with or without other opioid analgesics) in the Medicaid data. The information in the table is further stratified by time dispensed only OxyContin (without any other opioid analgesics concomitantly) and time dispensed OxyContin with any concomitant opioid analgesics.

The majority of exposure time among those dispensed OxyContin was time dispensed OxyContin with other opioid analgesics concomitantly, both in the pre- (65%) and post-periods (75%). Small reductions in adjusted overdose rates were observed across OxyContin exposure groups, but none were statistically significant.

Table 7: Medicaid data – overdose rates and rate ratios among those dispensed OxyContin, by concomitancy with other opioid analgesics (-2y/5y)

OxyContin dispensing	Pre-reformulation period (ref)			Post-reformulation period			Unadjusted rate ratio (CI)	Adjusted rate ratio (CI)
	Overdoses (fatal or non-fatal)	Person months of exposure time	Rate per 1,000 person months (CI)	Overdoses (fatal or non-fatal)	Person months of exposure time	Rate per 1,000 person months (CI)		
Any use	800	414,793	1.93 (1.79-2.08)	733	373,766	1.96 (1.80-2.13)	1.02 (0.91-1.14)	0.95 (0.84-1.08)
Only use	236	143,156	1.65 (1.44-1.89)	131	92,079	1.42 (1.19-1.71)	0.86 (0.69-1.08)	0.83 (0.64-1.08)
With concomitant opioid analgesics	564	271,637	2.08 (1.89-2.28)	602	281,687	2.14 (1.95-2.35)	1.03 (0.91-1.17)	0.95 (0.82-1.10)

(*FDA generated table using data from the April 1, 2020, information request response*)

Key: *= statistically significant (p<0.05); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5; "Any use" includes person-time among all patients dispensed OxyContin, including those with or without concomitant dispensing of other opioid analgesics; "Only use" includes person-time among patients dispensed OxyContin alone, without concomitant dispensing of other opioid analgesics; "With concomitant opioid analgesics" includes person-time among patients dispensed OxyContin with concomitant dispensing of other opioid analgesics; **note**: "any use" is the total, meaning it combines "only use" periods and "with concomitant opioid analgesics" periods

Table 8 shows the total number of overdoses, the total amount of person-time, and the overdose rates (per 1,000 person-months) in the pre- and post-periods, and the rate ratios comparing periods among those dispensed any OxyContin in the HIRD data.; table 8 also stratifies by time dispensed only OxyContin and time dispensed OxyContin with any concomitant opioid analgesics.

[xxiv] These analyses had only been conducted in the Medicaid and HIRD databases at the time of this FDA review. FDA expects MarketScan data to be provided at a later date.

[xxv] Because these were not comparative analyses, this group also includes concomitant use with primary or secondary comparators.

The majority of exposure time among those dispensed OxyContin was time dispensed OxyContin with other opioid analgesics concomitantly, both in the pre- (66%) and post-periods (73%). Like in Medicaid, reductions in overdose rates were observed across OxyContin exposure groups, but only when analyses were restricted to time dispensed OxyContin without other opioid analgesics were they of a large magnitude and statistically significant (adjusted rate ratio [aRR] = 0.51, 95% confidence interval [CI]: 0.32-0.81).

Table 8: HIRD data – overdose rates and rate ratios among those dispensed OxyContin, by concomitancy with other opioid analgesics (-2y/5y)

OxyContin dispensing	Pre-reformulation period (ref)			Post-reformulation period			Unadjusted rate ratio (CI)	Adjusted rate ratio (CI)
	Overdoses (fatal or non-fatal)	Person months of exposure time	Rate per 1,000 person months (CI)	Overdoses (fatal or non-fatal)	Person months of exposure time	Rate per 1,000 person months (CI)		
Any use	205	188,219	1.09 (0.91-1.30)	319	331,823	0.96 (0.79-1.17)	0.88 (0.68-1.15)	0.84 (0.66-1.08)
Only use	58	63,959	0.91 (0.62-1.32)	43	90,142	0.48 (0.34-0.67)	**0.53 (0.32-0.87)***	**0.51 (0.32-0.81)***
With concomitant opioid analgesics	147	124,260	1.18 (0.97-1.44)	276	241,681	1.14 (0.91-1.43)	0.97 (0.72-1.30)	0.92 (0.70-1.21)

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *= statistically significant (p<0.05); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5; "Any use" includes person-time among all patients dispensed OxyContin, including those with or without concomitant dispensing of other opioid analgesics; "Only use" includes person-time among patients dispensed OxyContin alone, without concomitant dispensing of other opioid analgesics; "With concomitant opioids analgesic" includes person-time among patients dispensed OxyContin with concomitant dispensing of other opioid analgesics; **note**: "any use" is the total, meaning it combines "only use" periods and "with concomitant opioid analgesics" periods

4.2.2 Overdose Rates Among Those Dispensed OxyContin and Primary Comparators

4.2.2.1 Medicaid data

Table 9 shows overdose rates and rate ratios among those dispensed OxyContin and primary comparators, stratified by concomitancy with other opioid analgesics in the Medicaid cohort. Ratio of rate ratios (RORRs) are also provided to compare pre- vs. post-period opioid overdose rate ratios for OxyContin to those of primary comparators (RORR = [comparator RR] / [OxyContin RR]). In the pre- and post-periods, overdose rates were highest among those dispensed methadone with or without other opioid analgesics concomitantly, and lowest among those dispensed OxyContin with or without other opioid analgesics concomitantly. This was the same when restricted to person-time dispensed the comparator opioid analgesic alone (without other opioid analgesics concomitantly).

Among those dispensed OxyContin with or without other opioid analgesics concomitantly, there was no change in overdose rates comparing periods. For those dispensed comparators, ER morphine (adjusted RR = 0.91, CI: 0.85-0.98) and methadone (adjusted RR=0.85, CI: 0.78-0.93) did have statistically significant reductions comparing periods after covariate adjustment. While the RORRs favored those two comparators over OxyContin (i.e., RORR < 1, representing a more favorable change in opioid overdose rates

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among those dispensed the comparator relative to those dispensed OxyContin), only the unadjusted and adjusted RORRs for methadone were statistically significant.

When restricted to person-time dispensed OxyContin alone, the reduction in overdose rates was not statistically significant. For this exposure group, although all RORRs were greater than one (favoring OxyContin), none were statistically significant.

Table 9: Medicaid data – overdose rates, rate ratios, and ratio of rate ratios among those dispensed OxyContin and primary comparators, by concomitancy with other opioid analgesics (-2y/2y)

Opioid analgesic	Exposure period category	Pre-reformulation period (ref)			Post-reformulation period			Unadjusted rate ratio (CI)	Adjusted rate ratio (CI)	Unadjusted ratio of rate ratio (CI)[ii]	Adjusted ratio of rate ratio (CI)[ii]
		Overdoses (fatal or non-fatal)	Person months of exposure time	Rate per 1,000 person months (CI)	Overdoses (fatal or non-fatal)	Person months of exposure time	Rate per 1,000 person months (CI)				
OxyContin	Any use[i] (**with or without** concomitant opioid analgesic use periods)	693	384,417	1.80 (1.66-1.95)	651	349,899	1.86 (1.70-2.03)	1.03 (0.92-1.16)	1.00 (0.89-1.12)	ref	ref
ER morphine		1,562	581,045	2.69 (2.53-2.85)	2,013	803,822	2.50 (2.38-2.63)	0.93 (0.86-1.01)	**0.91 (0.85-0.98)***	0.90 (0.79-1.04)	0.91 (0.80-1.04)
Fentanyl		862	337,179	2.56 (2.38-2.75)	987	359,083	2.75 (2.56-2.95)	1.08 (0.97-1.19)	1.05 (0.95-1.15)	1.04 (0.89-1.22)	1.05 (0.90-1.22)
Methadone		1,350	421,755	3.20 (2.99-3.42)	1,334	477,538	2.79 (2.62-2.98)	**0.87 (0.80-0.96)***	**0.85 (0.78-0.93)***	**0.85 (0.73-0.98)***	**0.85 (0.74-0.98)***
OxyContin	Use alone (**without** concomitant opioid analgesic use periods)	236	143,156	1.65 (1.44-1.89)	131	92,079	1.42 (1.19-1.71)	0.86 (0.69-1.08)	0.85 (0.68-1.06)	ref	ref
ER morphine		409	180,388	2.27 (2.04-2.52)	482	211,101	2.28 (2.07-2.52)	1.01 (0.87-1.16)	1.00 (0.87-1.15)	1.17 (0.89-1.53)	1.17 (0.90-1.52)
Fentanyl		245	111,001	2.21 (1.93-2.53)	254	105,633	2.40 (2.11-2.74)	1.09 (0.90-1.32)	1.08 (0.89-1.30)	1.26 (0.94-1.70)	1.27 (0.95-1.69)
Methadone		652	220,697	2.95 (2.67-3.27)	610	235,976	2.59 (2.36-2.83)	**0.88 (0.77-1.00)***	**0.88 (0.77-1.00)***	1.01 (078-1.32)	1.03 (0.79-1.33)

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *= statistically significant (p<0.05); [i]=excludes periods dispensed OxyContin or primary comparator concomitantly; [ii]= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); person-months (PMs); extended-release (ER); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

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FDA requested that the sponsor re-analyze adjusted analyses to also include baseline benzodiazepine dispensing as a covariate in the model, and the results were nearly identical to the primary adjusted analyses when baseline benzodiazepine dispensing was not included in the model (See Appendix 8.7). FDA also requested that the sponsor explore the role of baseline benzodiazepine dispensing as an effect modifier. In those analyses, the interactions were not statistically significant for any opioid analgesic exposure group (See Appendix 8.7). Stratified analyses based on the presence of baseline benzodiazepine dispensing were also similar to each other.

When using the opioid overdose algorithm that differentiates by intentionality in exploratory analyses (See Appendix 8.6), unintentional overdose adjusted RORR results were overall similar to those using the any overdose outcome.

4.2.2.2   MarketScan data

Table 10 shows overdose rates and rate ratios among those dispensed OxyContin and primary comparators, stratified by concomitancy with other opioid analgesics in the MarketScan cohort; RORRs are also provided. In the pre- and post-periods, overdose rates among those dispensed OxyContin with or without other opioid analgesics concomitantly, and when restricted to person-time dispensed OxyContin alone, were the lowest but still relatively similar to the other opioid analgesics.

Among those dispensed OxyContin with or without other opioid analgesics concomitantly, reductions in overdose rates comparing periods were not statistically significant. Unadjusted overdose rates for those dispensed fentanyl (RR = 1.23, CI: 1.02-1.47) and methadone (RR = 1.31, CI: 1.01-1.70) had statistically significant increases comparing the periods, but not after adjusting for covariates. The RORRs all favored OxyContin, but none were statistically significant.

When restricted to person-time dispensed OxyContin alone, reductions in overdose rates were observed but were also not statistically significant. Unadjusted and adjusted RORRs all favored OxyContin, and all were statistically significant with the exception of the adjusted RORR for ER morphine.

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Table 10: MarketScan data – overdose rates, rate ratios, and ratio of rate ratios among those dispensed OxyContin and primary comparators, by concomitancy with other opioid analgesics (-2y/5y)

Opioid analgesic	Exposure period category	Pre-reformulation period (ref)			Post-reformulation period			Unadjusted rate ratio (CI)	Adjusted rate ratio (CI)	Unadjusted ratio of rate ratio (CI)[ii]	Adjusted ratio of rate ratio (CI)[ii]
		Overdoses (fatal or non-fatal)	Person months of exposure time	Rate per 1,000 person months (CI)	Overdoses (fatal or non-fatal)	Person months of exposure time	Rate per 1,000 person months (CI)				
OxyContin	Any use[i] **(with or without** concomitant opioid analgesic use periods)	220	268,476	0.82 (0.70-0.96)	367	459,907	0.80 (0.71-0.89)	0.97 (0.81-1.18)	0.90 (0.75-1.08)	ref	ref
ER morphine		194	190,891	1.02 (0.86-1.20)	430	378,948	1.13 (1.01-1.28)	1.12 (0.91-1.37)	1.01 (0.83-1.23)	1.15 (0.87-1.51)	1.12 (0.86-1.46)
Fentanyl		206	216,440	0.95 (0.82-1.11)	436	373,612	1.17 (1.06-1.29)	**1.23 (1.02-1.47)***	1.07 (0.90-1.27)	1.26 (0.97-1.64)	1.19 (0.93-1.53)
Methadone		101	102,965	0.98 (0.80-1.21)	229	177,857	1.29 (1.10-1.51)	**1.31 (1.01-1.70)***	1.19 (0.93-1.52)	1.35 (0.98-1.86)	1.32 (0.97-1.79)
OxyContin	Use alone **(without** concomitant opioid analgesic use periods)	58	97,454	0.60 (0.46-0.78)	62	140,826	0.44 (0.34-0.57)	0.74 (0.51-1.08)	0.72 (0.50-1.04)	ref	ref
ER morphine		41	64,175	0.64 (0.47-0.87)	93	115,790	0.80 (0.64-1.00)	1.26 (0.86-1.83)	1.16 (0.81-1.68)	**1.70 (1.00-2.89)***	1.62 (0.97-2.72)
Fentanyl		50	77,764	0.64 (0.48-0.86)	108	124,640	0.87 (0.71-1.05)	1.35 (0.95-1.91)	1.21 (0.85-1.70)	**1.82 (1.09-3.04)***	**1.68 (1.02-2.78)***
Methadone		40	53,956	0.74 (0.54-1.03)	101	88,928	1.14 (0.91-1.41)	1.53 (1.04-2.26)	1.39 (0.95-2.02)	**2.07 (1.21-3.56)***	**1.94 (1.14-3.29)***

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *= statistically significant (p<0.05); [i]=excludes periods dispensed OxyContin or primary comparator concomitantly; [ii]= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); person-months (PMs); extended-release (ER); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

When using the opioid overdose algorithm that differentiates by intentionality in exploratory analyses (See Appendix 8.6), RORR results for unintentional overdose were overall similar to those using the any overdose outcome.

4.2.2.3 HIRD data

Table 11 shows overdose rates and rate ratios among those dispensed OxyContin and primary comparators, stratified by concomitancy with other opioid analgesics in the HIRD cohort; RORRs are also provided. As in MarketScan, in the pre- and post-periods, overdose rates among those dispensed OxyContin with or without other opioid analgesics concomitantly, and when restricted to person-time dispensed OxyContin alone, were generally lower but still similar to rates among those dispensed other opioid analgesics.

Among those dispensed OxyContin with or without other opioid analgesics concomitantly, reductions were not statistically significant. This was also true for the primary opioid analgesic comparators. The RORRs all favored OxyContin but were not statistically significant.

When restricted to person-time dispensed OxyContin alone, there was a statistically significant reduction (adjusted RR = 0.52, CI: 0.32-0.83) in overdose rates comparing periods; however, while all RORRs favored OxyContin, RORRs were only statistically significant for ER morphine.

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Table 11: HIRD data – overdose rates, rate ratios, and ratio of rate ratios among those dispensed OxyContin and primary comparators, by concomitancy with other opioid analgesics (-2y/5y)

Opioid analgesic	Exposure period category	Pre-reformulation period (ref)			Post-reformulation period			Unadjusted rate ratio (CI)	Adjusted rate ratio (CI)	Unadjusted ratio of rate ratio (CI)[ii]	Adjusted ratio of rate ratio (CI)[ii]
		Overdoses (fatal or non-fatal)	Person months of exposure time	Rate per 1,000 person months (CI)	Overdoses (fatal or non-fatal)	Person months of exposure time	Rate per 1,000 person months (CI)				
OxyContin	Any use[i] (with or without concomitant opioid analgesic use periods)	164	176,145	0.93 (0.77-1.13)	268	314,899	0.85 (0.69-1.04)	0.91 (0.69-1.21)	0.84 (0.65-1.09)	ref	ref
ER morphine		133	121,089	1.10 (0.91-1.32)	328	293,756	1.12 (0.96-1.30)	1.02 (0.80-1.29)	0.91 (0.73-1.14)	1.11 (0.77-1.60)	1.09 (0.78-1.53)
Fentanyl		160	132,254	1.21 (0.97-1.51)	293	250,060	1.17 (1.02-1.35)	0.97 (0.75-1.25)	0.88 (0.69-1.12)	1.06 (0.72-1.55)	1.04 (0.73-1.49)
Methadone		100	86,429	1.16 (0.93-1.45)	224	169,022	1.33 (1.08-1.63)	1.15 (0.86-1.53)	1.01 (0.77-1.32)	1.25 (0.84-1.87)	1.20 (0.83-1.74)
OxyContin	Use alone (without concomitant opioid analgesic use periods)	58	63,959	0.91 (0.62-1.32)	43	90,142	0.48 (0.34-0.67)	**0.53 (0.32-0.87)***	**0.52 (0.32-0.83)***	ref	ref
ER morphine		33	40,538	0.81 (0.57-1.16)	81	82,527	0.98 (0.76-1.27)	1.21 (0.78-1.87)	1.13 (0.74-1.73)	**2.29 (1.18-4.45)***	**2.20 (1.18-4.10)***
Fentanyl		47	45,981	1.02 (0.71-1.47)	62	79,376	0.78 (0.60-1.02)	0.76 (0.49-1.20)	0.72 (0.47-1.11)	1.45 (0.73-2.89)	1.40 (0.73-2.70)
Methadone		58	46,873	1.24 (0.93-1.65)	107	83,859	1.28 (0.92-1.76)	1.03 (0.70-1.52)	0.91 (0.63-1.31)	1.96 (1.04-3.71)	1.76 (0.98-3.17)

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *= statistically significant (p<0.05); [i]=excludes periods dispensed OxyContin or primary comparator concomitantly; [ii]= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); person-months (PMs); extended-release (ER); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5
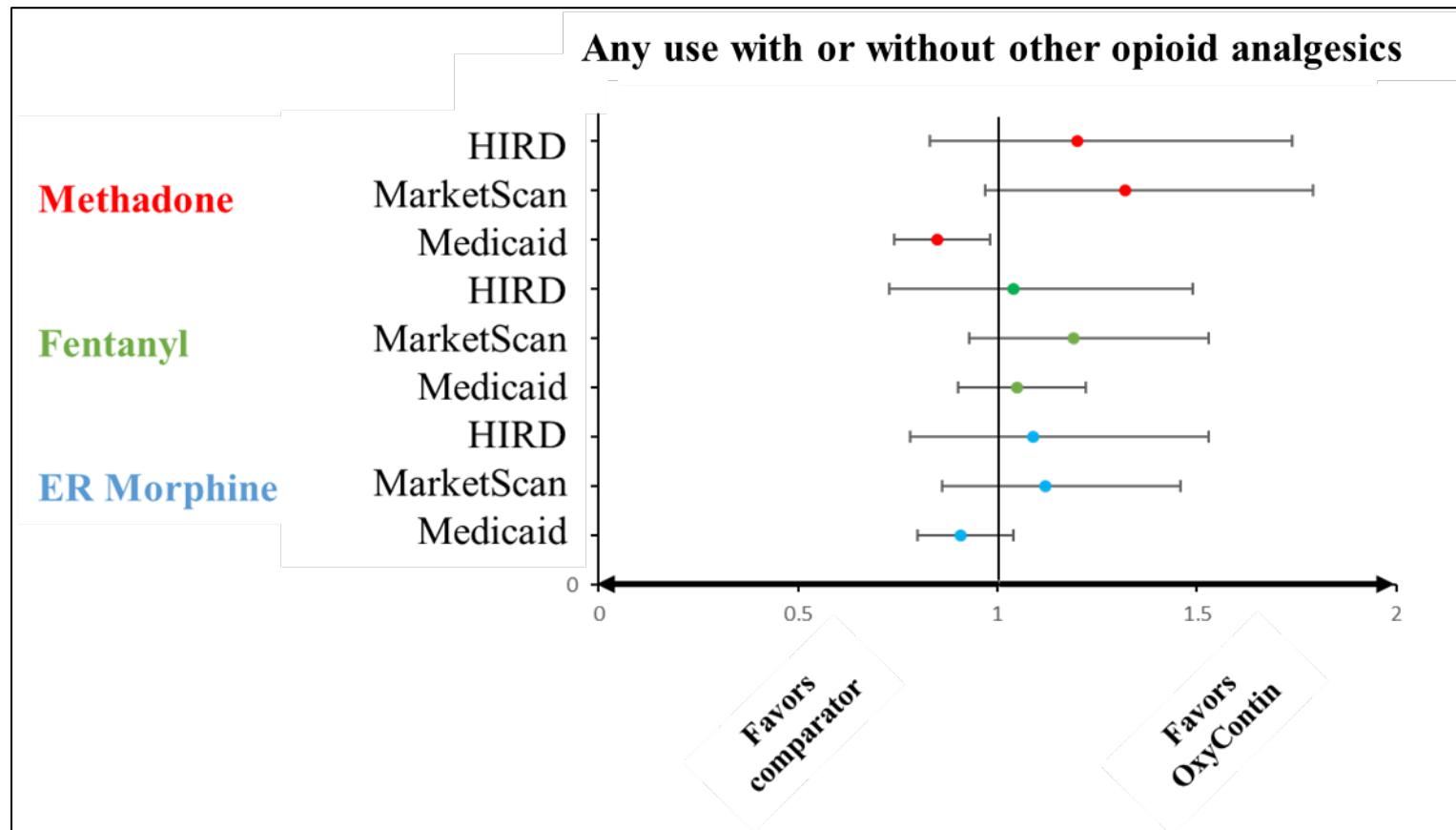
When baseline benzodiazepine dispensing was included as a covariate in the adjusted model the results were also nearly identical to the primary adjusted analyses when baseline benzodiazepine dispensing was not included in the model (See Appendix 8.7). Like in the Medicaid cohort, baseline benzodiazepine dispensing did not appear to be an effect modifier, with no statistically significant interactions for any opioid analgesic exposure group, both in analyses with other opioid analgesics concomitantly, and those without other opioid analgesics concomitantly (See Appendix 8.7).

When using the opioid overdose algorithm that differentiates by intentionality in exploratory analyses (See Appendix 8.6), unintentional overdose adjusted RORR results were overall similar to those using the any overdose outcome.

Figures 6.A and 6.B visually depict only the adjusted RORRs from Tables 8-10 (above), by database and concomitancy with other opioid analgesics. Overall, the RORRs are more favorable to OxyContin when analyses are restricted to exposure time in which a patient was dispensed a single opioid analgesic alone (Figure 6.B) compared to when analyses include exposure time with and without other opioid analgesics (i.e., among all patients using OxyContin) dispensed concomitantly (Figure 6.A).

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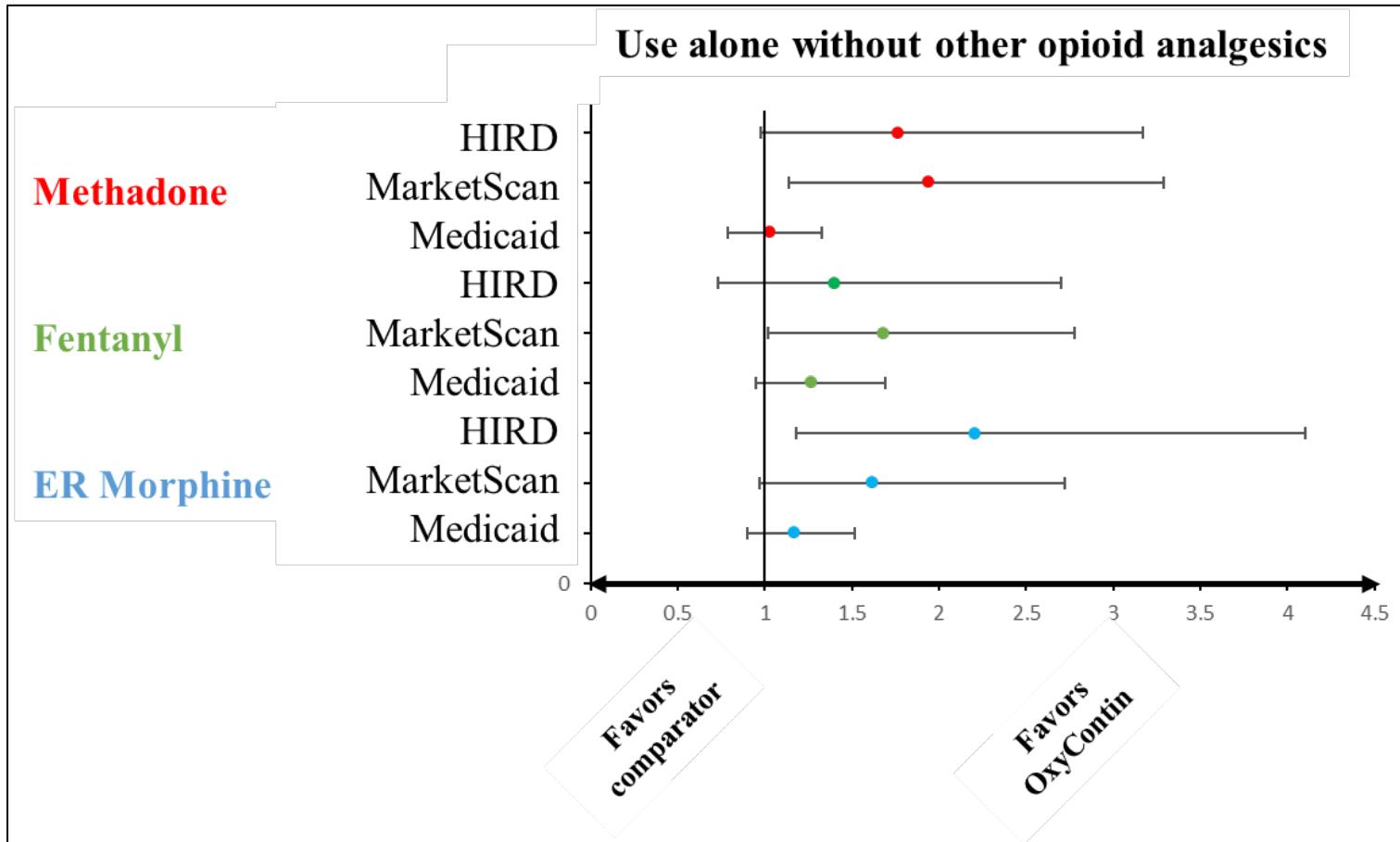
Figure 6.A and 6.B: Adjusted ratios of rate ratios – pre- versus post-period change in opioid overdose rates in patients dispensed primary comparator opioid analgesics compared to the change in patients dispensed OxyContin: with or without concomitant opioid analgesics (A) and without concomitant opioid analgesics (B)

6A:

(*FDA generated figure using data from PMR 3051-4 study report*)

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6B:

Use alone without other opioid analgesics

(*FDA generated figure using data from PMR 3051-4 study report*)

Key: extended-release (ER); X-axis is adjusted ratios of rate ratios (RORR); null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); horizontal lines are 95% confidence interval

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4.2.2.4 Meta-analyzed commercial claims data

Table 12 shows RORRs for primary comparators, by concomitancy with other opioid analgesics, using meta-analytic methods to generate "combined" RORR results for the commercial claims databases (MarketScan and HIRD). Overall the results were generally consistent with those from analyses conducted in the commercial claims databases separately. Among those dispensed OxyContin with or without other opioid analgesics concomitantly, RORRs for all comparators favored OxyContin, but only the RORRs for methadone were statistically significantly. When restricted to person-time dispensed OxyContin alone, RORRs for all primary comparators were statistically significantly, favoring OxyContin.

Table 12: Meta-analyzed data – Commercial claims *combined* overdose ratio of rate ratios among those dispensed OxyContin and primary comparators, by concomitancy with other opioid analgesics (-2y/5y)

Opioid analgesic	Exposure period category	Meta-analysis: Commercial claims databases^	
		Unadjusted ratio of rate ratio (CI)[ii]	Adjusted ratio of rate ratio (CI)[ii]
		Any OxyContin[i] (reference)	
ER morphine	Any use[i] (**with or without** concomitant opioid analgesic use periods)	1.13 (0.91-1.41)	1.11 (0.90-1.37)
Fentanyl		1.19 (0.96-1.48)	1.14 (0.93-1.40)
Methadone		**1.31 (1.02-1.68)***	**1.27 (1.00-1.61)***
		OxyContin alone (reference)	
ER morphine	Use alone (**without** concomitant opioid analgesic use periods)	**1.91 (1.26-2.89)***	**1.84 (1.24-2.74)***
Fentanyl		**1.68 (1.12-2.53)***	**1.57 (1.06-2.34)***
Methadone		**2.02 (1.34-3.06)***	**1.86 (1.25-2.75)***

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *=statistically significant (p<0.05); ^=MarketScan and HIRD only; [i]=excludes periods dispensed OxyContin or primary comparator concomitantly; [ii]= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); extended-release (ER); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

4.2.2.5 OxyContin or comparators dispensed concomitantly with an immediate-release opioid analgesic only

Table 13 and Figure 7 shows RORRs comparing overdose rate changes among those dispensed comparator opioid analgesics with any IR opioid analgesic concomitantly to those dispensed OxyContin with any IR opioid analgesic concomitantly across databases. In Medicaid, all RORRs favored comparators, but only RORRs for ER morphine and methadone were statistically significant. The results from the commercial claims databases

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were entirely different, with nearly all RORRs favoring OxyContin, but none statistically significant.
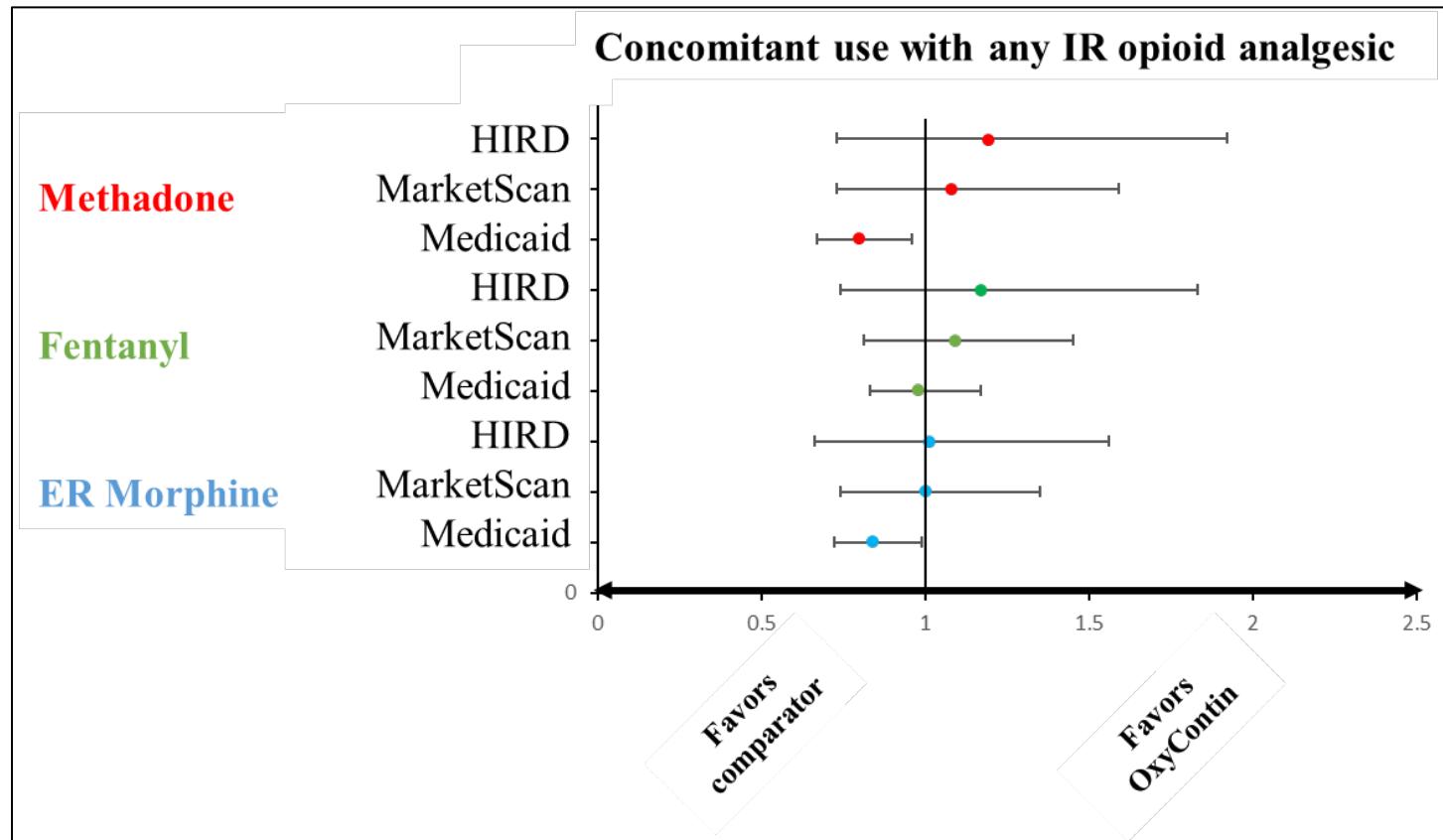
Table 13: Unadjusted and adjusted overdose rate ratios and ratios of rate ratios among those dispensed primary comparators concomitantly with any IR opioid analgesic compared to those dispensed OxyContin concomitantly with any IR opioid analgesic, by database

Opioid analgesic[i]	Medicaid		MarketScan		HIRD	
	Unadjusted ratio of rate ratio (CI)[ii]	Adjusted ratio of rate ratio (CI)[ii]	Unadjusted ratio of rate ratio (CI)[ii]	Adjusted ratio of rate ratio (CI)[ii]	Unadjusted ratio of rate ratio (CI)[ii]	Adjusted ratio of rate ratio (CI)[ii]
OxyContin with concomitant IR opioid analgesic	ref					
ER morphine with concomitant IR opioid analgesic	**0.84 (0.71-0.99)***	**0.84 (0.72-0.99)***	1.02 (0.74-1.41)	1.00 (0.74-1.35)	1.03 (0.65-1.62)	1.01 (0.66-1.56)
Fentanyl with concomitant IR opioid analgesic	0.98 (0.82-1.18)	0.98 (0.83-1.17)	1.16 (0.86-1.57)	1.09 (0.81-1.45)	1.19 (0.74-1.90)	1.17 (0.74-1.83)
Methadone with concomitant IR opioid analgesic	**0.81 (0.67-0.97)***	**0.80 (0.67-0.96)***	1.10 (0.73-1.66)	1.08 (0.73-1.59)	1.21 (0.72-2.03)	1.19 (0.73-1.92)

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *= statistically significant (p<0.05); [i]=excludes periods dispensed OxyContin or primary comparator concomitantly; [ii]= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); person-months (PMs); extended-release (ER); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

Figure 7: Adjusted ratios of rate ratios – pre- versus post-period change in opioid overdose rates in patients dispensed primary comparators concomitantly with any IR opioid analgesic compared to those dispensed OxyContin concomitantly with any IR opioid analgesic, by database

(*FDA generated figure using data from PMR 3051-4 study report*)

Key: X-axis is adjusted ratios of rate ratios (RORR); null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); horizontal lines are 95% confidence interval; extended-release (ER)

4.2.2.6 Overdose death in the pre- and post-periods

Table 14 shows the total number of overdose deaths, and the proportion of fatal overdoses among the total number of overdoses in the pre and post-periods, by database and opioid analgesic comparator. Of note, counts less than or equal to 10 were suppressed in the PMR 3051-4 study report, therefore, proportions of fatal overdose could not be calculated for these periods. Overall, the number of fatal overdoses was considerably lower than non-fatal overdoses for OxyContin and the comparators, but there do not appear to be meaningful changes comparing periods in the proportion of fatal overdose among all overdose for OxyContin and the comparators.

Table 14: Fatal overdose cases by period and opioid analgesic comparators

Opioid analgesic	Exposure period category	Medicaid		MarketScan		HIRD	
		Pre-reformulation period	Post-reformulation period	Pre-reformulation period	Post-reformulation period	Pre-reformulation period	Post-reformulation period
		Fatal overdoses (Proportion of total overdoses)	Fatal overdoses (Proportion of total overdoses)	Fatal overdoses (Proportion of total overdoses)	Fatal overdoses (Proportion of total overdoses)	Fatal overdoses (Proportion of total overdoses)	Fatal overdoses (Proportion of total overdoses)
OxyContin	Any use[i] (with or without concomitant opioid analgesic use periods)	124 (18%)	94 (14%)	24 (11%)	56 (15%)	≤10	≤10
ER morphine		184 (12%)	274 (14%)	30 (15%)	67 (16%)	≤10	11 (3%)
Fentanyl		135 (16%)	144 (15%)	25 (12%)	75 (17%)	≤10	≤10
Methadone		191 (14%)	218 (16%)	15 (15%)	58 (25%)	≤10	15 (7%)
OxyContin	Use alone (without concomitant opioid analgesic use periods)	41 (17%)	16 (12%)	≤10	≤10	≤10	≤10
ER morphine		61 (15%)	66 (14%)	≤10	15 (16%)	≤10	≤10
Fentanyl		41 (17%)	32 (13%)	≤10	18 (17%)	≤10	≤10
Methadone		89 (14%)	95 (16%)	≤10	33 (33%)	≤10	≤10

(*FDA generated table using data from PMR 3051-4 study report*)

Key: [i]=excludes periods dispensed OxyContin or primary/secondary comparator concomitantly; extended-release (ER); When counts were less than or equal 10 (denoted in table as ≤10), the number of fatal overdoses was suppressed in the study report, so the proportion of fatal overdoses among all overdoses could not be calculated

4.2.3 Overdose Rates Among Those Dispensed OxyContin and Other Secondary Comparators

Table 15 shows overdose rate ratios and RORRs for secondary comparators, stratified by concomitancy with other opioid analgesics and database. Of note, MarketScan analyses were only conducted using the unintentional overdose algorithm to ascertain overdose outcomes, therefore, these analyses are considered exploratory (See Appendix 8.4.2).

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In Medicaid, overdose rate reductions were observed among those dispensed SE IR oxycodone with or without other opioid analgesics concomitantly, and alone, but this was not seen in the HIRD database. Results for the other secondary comparators were more consistent across databases, and overdose rate ratios were mostly not statistically significant. All the RORRs generally favored OxyContin when it was compared to the secondary comparators, but the RORRs were only statistically significant for SE IR oxycodone in HIRD.

Table 15: Unadjusted and adjusted overdose rate ratio and ratio of rate ratios among those dispensed OxyContin and other secondary comparators, by database and concomitancy with other opioid analgesics[xxvi]

Opioid analgesic	Exposure period category	Medicaid				HIRD			
		Unadjusted rate ratio (CI)	Adjusted rate ratio (CI)	Unadjusted ratio of rate ratio (CI)[ii]	Adjusted ratio of rate ratio (CI)[ii]	Unadjusted rate ratio (CI)	Adjusted rate ratio (CI)	Unadjusted ratio of rate ratio (CI)[ii]	Adjusted ratio of rate ratio (CI)[ii]
OxyContin	Any use[i] (with or without concomitant opioid analgesic use periods)	0.92 (0.80-1.06)	0.88 (0.76-1.01)	ref		**0.66 (0.49-0.90)***	**0.61 (0.46-0.82)***	ref	
ER Oxymorphone		0.98 (0.74-1.30)	1.01 (0.77-1.32)	1.06 (0.77-1.45)	1.15 (0.85-1.55)	0.99 (0.54-1.82)	0.81 (0.47-1.40)	1.50 (0.77-2.95)	1.32 (0.71-2.44)
SE IR Oxycodone		**0.89 (0.81-0.98)***	**0.88 (0.81-0.97)***	0.97 (0.82-1.15)	1.01 (0.85-1.19)	1.12 (0.82-1.54)	0.99 (0.73-1.35)	**1.70 (1.09-2.63)***	**1.62 (1.07-2.44)***
IR Hydromorphone		0.90 (0.76-1.06)	0.89 (0.76-1.04)	0.98 (0.78-1.22)	1.02 (0.82-1.25)	0.92 (0.61-1.39)	0.81 (0.55-1.19)	1.39 (0.83-2.32)	1.32 (0.82-2.11)
OxyContin	Use alone (without concomitant opioid analgesic use periods)	0.86 (0.69-1.08)	0.84 (0.67-1.04)	ref		**0.53 (0.32-0.87)***	**0.51 (0.32-0.81)***	ref	
ER Oxymorphone		1.03 (0.67-1.57)	1.09 (0.72-1.63)	1.19 (0.74-1.93)	1.30 (0.82-2.06)	1.13 (0.37-3.44)	1.13 (0.41-3.13)	2.15 (0.63-7.28)	2.24 (0.73-6.86)
SE IR Oxycodone		**0.90 (0.80-1.00)***	0.90 (0.81-1.01)	1.04 (0.81-1.34)	1.08 (0.85-1.38)	1.14 (0.78-1.66)	1.02 (0.71-1.48)	**2.16 (1.15-4.05)***	**2.02 (1.12-3.64)***
IR Hydromorphone		0.98 (0.80-1.21)	0.96 (0.79-1.18)	1.14 (0.84-1.55)	1.15 (0.86-1.55)	0.94 (0.57-1.55)	0.80 (0.50-1.27)	1.79 (0.89-3.64)	1.58 (0.84-2.97)

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *= statistically significant (p<0.05); [i]=excludes periods dispensed OxyContin or primary/secondary comparator concomitantly; [ii]= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); person-months (PMs); extended-release (ER); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

Of note, the exposure time was much lower for secondary comparators ER oxymorphone and IR hydromorphone compared to OxyContin in both the pre- and post-periods and across databases (See Appendix 8.5), particularly when further restricted to use without other opioid analgesics concomitantly.

4.2.4 Sensitivity and Exploratory Analyses

4.2.4.1 Results comparing incident user cohort to the combined (incident and prevalent)

[xxvi] FDA is waiting for sponsor submission of MarketScan results using the any overdose outcome (intentional and unintentional)

user cohorts

Table 16 shows the total number of overdoses, the total amount of person-time, and the overdose rates in the pre- and post-periods among those dispensed OxyContin in the Medicaid database, stratified by combined (incident and prevalent patients) and incident[xxvii] only patient cohorts, and opioid analgesic concomitancy. Unadjusted and adjusted rate ratios are also provided.

The exposure time was ~70% lower in the pre-period and ~75% lower in the post-period among those dispensed OxyContin with or without other opioid analgesics in the incident only cohort compared to the combined cohort; unadjusted and adjusted rate ratios were similar comparing the incident cohort and combined cohort, and neither statistically significant.

When restricted to person-time dispensed OxyContin alone in the incident only cohort compared to the combined cohort, the exposure time was ~64% lower in the pre-period and ~68% lower in the post-period. Also, unadjusted and adjusted rate ratio were qualitatively different comparing the incident cohort and combined cohort, but neither were statistically significant.

Table 16: Medicaid data - overdose rates (and exposure time) and overdose rate ratios among those dispensed OxyContin in the combined (incident and prevalent) and incident only cohorts by concomitancy with other opioid analgesics (-2y/2y)

OxyContin cohort	Cohort	Pre-reformulation period (ref)			Post-reformulation period			Unadjusted rate ratio (CI)	Adjusted rate ratio (CI)
		Overdoses (fatal or non-fatal)	Person months of exposure time	Rate per 1,000 person months (CI)	Overdoses (fatal or non-fatal)	Person months of exposure time	Rate per 1,000 person months (CI)		
Any OxyContin[i]	Combined (Incident and prevalent)	693	384,417	1.80 (1.66-1.95)	651	349,899	1.86 (1.70-2.03)	1.03 (0.92-1.16)	1.00 (0.89-1.12)
	Incident only	198	113,884	1.74 (1.51-2.01)	153	87,758	1.74 (1.47-2.06)	1.00 (0.81-1.25)	0.98 (0.79-1.22)
OxyContin use alone[ii]	Combined (Incident and prevalent)	236	143,156	1.65 (1.44-1.89)	131	92,079	1.42 (1.19-1.71)	0.86 (0.69-1.08)	0.85 (0.68-1.06)
	Incident only	69	51,166	1.35 (1.06-1.72)	42	29,192	1.44 (1.05-1.98)	1.07 (0.72-1.59)	1.08 (0.73-1.61)

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *= statistically significant (p<0.05); [i]=Any OxyContin use (with or without concomitant opioid analgesics) excluding periods dispensed OxyContin or primary comparator concomitantly; [ii]= when restricted to person-time dispensed OxyContin alone (without concomitant opioid analgesics); Confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

Table 17 shows the total number of overdoses, the total amount of person-time, the overdose rates and rate ratios among those dispensed OxyContin in the MarketScan database, stratified by combined and incident only patient cohorts, and opioid analgesic concomitancy. Among those dispensed OxyContin with or without other opioid analgesics, the exposure time in the incident only cohort was ~72% lower in the pre-period and ~81%

[xxvii] No use of any opioid comparator in the prior 3 months, but patients could have been dispensed non-comparator opioids during that period and patients could be included as incident multiple times throughout the study period

lower in the post-period, compared to the combined cohort; however unadjusted and adjusted rate ratios were similar comparing the incident cohort and combined cohort, and neither was statistically significant.

When restricted to person-time dispensed OxyContin alone, the incident only cohort had ~68% lower exposure time in the pre-period and ~78% lower in the post-period, compared to the combined cohort. Again, unadjusted and adjusted rate ratios were similar comparing the incident only and combined cohorts, and neither was statistically significant.

Table 17: MarketScan data - overdose rates (and exposure time) and overdose rate ratios among those dispensed OxyContin in the combined (incident and prevalent) and incident only cohorts by concomitancy with other opioid analgesics (-2y/5y)

OxyContin cohort	Cohort	Pre-reformulation period (ref)			Post-reformulation period			Unadjusted rate ratio (CI)	Adjusted rate ratio (CI)
		Overdoses (fatal or non-fatal)	Person months of exposure time	Rate per 1,000 person months (CI)	Overdoses (fatal or non-fatal)	Person months of exposure time	Rate per 1,000 person months (CI)		
Any OxyContin[i]	Combined (Incident and prevalent)	220	268,476	0.82 (0.70-0.96)	367	459,907	0.80 (0.71-0.89)	0.97 (0.81-1.18)	0.90 (0.75-1.08)
	Incident only	57	75,220	0.76 (0.53-1.08)	52	88,378	0.59 (0.44-0.78)	0.78 (0.49-1.22)	0.71 (0.45-1.12)
OxyContin use alone[ii]	Combined (Incident and prevalent)	58	97,454	0.60 (0.46-0.78)	62	140,826	0.44 (0.34-0.57)	0.74 (0.51-1.08)	0.72 (0.50-1.04)
	Incident only	18	31,262	0.58 (0.35-0.94)	≤10	30,769	0.26 (0.11-0.61)	0.45 (0.17-1.20)	0.44 (0.17-1.17)

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *= statistically significant (p<0.05); [i]=Any OxyContin use (with or without concomitant opioid analgesics) excluding periods dispensed OxyContin or primary comparator concomitantly; [ii]= when restricted to time OxyContin alone (without concomitant opioid analgesics); Confidence interval (CI); adjusted for variables in section 3.4.5

Table 18 shows the total number of overdoses, the total amount of person-time, the overdose rates and rate ratios among those dispensed OxyContin in the HIRD database, stratified by combined and incident only patient cohorts, and opioid analgesic concomitancy. Among those dispensed OxyContin with or without other opioid analgesics, the exposure time was ~46% lower in the pre-period and ~73% lower in the post-period in the incident only cohort compared to the combined cohort; unadjusted and adjusted rate ratios were similar comparing the incident cohort and combined cohort, and neither was statistically significant.

When restricted to person-time dispensed OxyContin alone in the incident only cohort compared to the combined cohort, the exposure time was ~35% lower in the pre-period and ~67% lower in the post-period. Also, unadjusted and adjusted rate ratios were similar comparing the incident cohort and combined cohort, but only statistically significant when using the combined cohort.

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Table 18: HIRD data - overdose rates (and exposure time) and overdose rate ratios among those dispensed OxyContin in the combined (incident and prevalent) and incident only cohorts by concomitancy with other opioid analgesics (-2y/5y)

OxyContin cohort	Cohort	Pre-reformulation period (ref)			Post-reformulation period			Unadjusted rate ratio (CI)	Adjusted rate ratio (CI)
		Overdoses (fatal or non-fatal)	Person months of exposure time	Rate per 1,000 person months (CI)	Overdoses (fatal or non-fatal)	Person months of exposure time	Rate per 1,000 person months (CI)		
Any OxyContin[i]	Combined (Incident and prevalent)	164	176,145	0.92 (0.77-1.13)	268	314,899	0.85 (0.69-1.04)	0.91 (0.69-1.21)	0.84 (0.65-1.09)
	Incident only	85	95,484	0.89 (0.67-1.18)	61	86,036	0.71 (0.54-0.93)	0.80 (0.54-1.18)	0.76 (0.51-1.12)
OxyContin use alone[ii]	Combined (Incident and prevalent)	58	63,959	0.91 (0.62-1.32)	43	90,142	0.48 (0.34-0.67)	**0.53 (0.32-0.87)***	**0.52 (0.32-0.83)***
	Incident only	37	41,461	0.89 (0.53-1.50)	17	29,741	0.57 (0.34-0.97)	0.64 (0.31-1.34)	0.60 (0.28-1.28)

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *= statistically significant (p<0.05); [i]=Any OxyContin use (with or without concomitant opioid analgesics) excluding periods dispensed OxyContin or primary comparator concomitantly; [ii]= when restricted to person-time dispensed OxyContin alone (without concomitant opioid analgesics); Confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

Table 19 shows adjusted RORRs for primary comparators using the combined (incident and prevalent patients) and incident only cohorts, stratified by concomitancy with other opioids analgesics and database.

The adjusted RORRs were similar and not statistically significant for analyses using the combined cohort and the incident only cohort for ER morphine with or without other opioid analgesics concomitantly, and fentanyl with or without other opioid analgesics concomitantly. For methadone with or without other opioid analgesics concomitantly, the RORR using the incident only cohort in MarketScan was considerably larger than when using the combined cohort, but results were generally similar in the other databases.

When restricted to person-time dispensed OxyContin alone, the adjusted RORRs were qualitatively different comparing cohorts in Medicaid for ER morphine and methadone, but results were rather similar between cohorts in the other databases for all primary comparators.

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Table 19: Adjusted ratio of rate ratios among those dispensed primary comparators using the combined cohort (incident and prevalent users) and incident user only cohort, by database and concomitancy with other opioid analgesics

Opioid analgesic[i]	Exposure period category	Medicaid		MarketScan		HIRD	
		Combined cohort: Adjusted ratio of rate ratio (CI)[ii]	Incident only: Adjusted ratio of rate ratio (CI)[ii]	Combined cohort: Adjusted ratio of rate ratio (CI)[ii]	Incident only: Adjusted ratio of rate ratio (CI)[ii]	Combined cohort: Adjusted ratio of rate ratio (CI)[ii]	Incident only: Adjusted ratio of rate ratio (CI)[ii]
		Any OxyContin[i] (reference)					
ER morphine	Any use[i] (with or without concomitant opioid analgesic use periods)	0.91 (0.80-1.04)	0.89 (0.70-1.13)	1.12 (0.86-1.46)	1.27 (0.74-2.17)	1.09 (0.78-1.53)	1.45 (0.88-2.39)
Fentanyl		1.05 (0.90-1.22)	1.13 (0.86-1.48)	1.19 (0.93-1.53)	1.36 (0.79-2.34)	1.04 (0.73-1.49)	1.10 (0.66-1.84)
Methadone		**0.85 (0.74-0.98)***	0.83 (0.64-1.07)	1.32 (0.97-1.79)	**2.17 (1.11-4.26)***	1.20 (0.83-1.74)	1.40 (0.84-2.35)
		OxyContin alone (reference)					
ER morphine	Use alone (without concomitant opioid analgesic use periods)	1.17 (0.90-1.52)	0.77 (0.50-1.21)	1.62 (0.97-2.72)	2.24 (0.72-6.96)	**2.20 (1.18-4.10)***	1.99 (0.83-4.76)
Fentanyl		1.27 (0.95-1.77)	1.16 (0.71-1.89)	**1.68 (1.02-2.78)***	1.58 (0.53-4.75)	1.40 (0.73-2.70)	1.34 (0.53-3.43)
Methadone		1.06 (0.81-1.40	0.76 (0.49-1.18)	**1.94 (1.14-3.29)***	3.43 (0.97-12.10)	1.76 (0.98-3.17)	1.56 (0.67-3.61)

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *= statistically significant (p<0.05); [i]=excludes periods dispensed OxyContin or primary comparator concomitantly; [ii]= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); confidence interval (CI); combined cohort includes incident and prevalent patients; adjusted for variables in section 3.4.5

Of note, similar to what was observed among those dispensed OxyContin (Tables 15-17, above), exposure time was much lower among primary comparators when analyses were restricted to the incident only cohort (See Appendix 8.5), particularly when further restricted to time dispensed alone (without other opioid analgesics concomitantly).

4.2.4.2 Medicaid data: fee-for-service versus managed care plans

Table 20 shows adjusted overdose rate ratios among those dispensed OxyContin and primary comparators, and RORRs, in the Medicaid database stratified by Medicaid plan type and by concomitancy with other opioid analgesics. Of note, these Medicaid analyses were only conducted using the unintentional overdose algorithm to ascertain overdose outcomes, therefore, these analyses are considered exploratory.

Comparing the results from those with fee-for-service (FFS) plans to those with managed care plans, some differences were observed. Among those dispensed OxyContin with or without other opioid analgesics concomitantly, all adjusted RORRs for primary comparators favored OxyContin in the FFS cohort, while in the managed care cohort, all RORRs for primary comparators favored the comparators, with varying statistical significance. When restricted to person-time dispensed OxyContin alone, the adjusted

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RORRs for ER morphine were similar comparing cohorts, but this was not true for fentanyl and methadone.

Table 20: Unintentional overdose rate ratio and adjusted ratio of rate ratios among those dispensed OxyContin and primary comparators in the Medicaid data, by plan type and concomitancy with other opioid analgesics

Opioid analgesic	Exposure period category	Fee-For-Service		Managed Care	
		Adjusted rate ratio (CI)	Adjusted ratio of rate ratio (CI)[ii]	Adjusted rate ratio (CI)	Adjusted ratio of rate ratio (CI)[ii]
OxyContin	Any use[i] **(with or without** concomitant opioid analgesic use periods)	**0.81 (0.68-0.95)***	ref	1.18 (0.98-1.42)	ref
ER morphine		0.90 (0.80-1.01)	1.11 (0.91-1.37)	0.99 (0.89-1.09)	0.84 (0.68-1.03)
Fentanyl		1.03 (0.90-1.18)	**1.28 (1.03-1.59)***	0.99 (0.84-1.16)	0.84 (0.66-1.07)
Methadone		**0.81 (0.70-0.94)***	1.01 (0.81-1.26)	0.91 (0.81-1.03)	**0.77 (0.62-0.96)***
OxyContin	Use alone **(without** concomitant opioid analgesic use periods)	0.80 (0.59-1.09)	ref	0.91 (0.61-1.34)	ref
ER morphine		0.91 (0.73-1.13)	1.13 (0.78-1.64)	1.04 (0.84-1.29)	1.15 (0.73-1.79)
Fentanyl		1.21 (0.95-1.54)	**1.51 (1.02-2.22)***	0.78 (0.55-1.12)	0.86 (0.51-1.46)
Methadone		**0.78 (0.64-0.95)***	0.97 (0.68-1.40)	0.97 (0.80-1.18)	1.07 (0.69-1.65)

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *= statistically significant (p<0.05); [i]=excludes periods dispensed OxyContin or primary comparator concomitantly; [ii]= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

4.2.4.3 Propensity score analyses

Table 21 shows adjusted unintentional overdose rate ratios among those dispensed OxyContin and primary comparators, and RORRs, from the propensity-score (PS)-weighted analyses, across databases. Of note, these analyses were only conducted using the unintentional overdose algorithm to ascertain overdose outcomes; therefore, these analyses are considered exploratory.

The results of the PS-weighted analyses among patients dispensed OxyContin with or without other opioid analgesics concomitantly were generally consistent with the main results based on multivariable modeling, except that no RORR was statistically significant in the PS-weighted analyses.

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Table 21: PS-weighted unintentional overdose rate ratio and adjusted ratio of rate ratios (RORRs) among those dispensed OxyContin and primary comparators, by database

Opioid analgesic[i]	Medicaid		MarketScan		HIRD	
	Adjusted rate ratio (CI)	Adjusted ratio of rate ratio (CI)[ii]	Adjusted rate ratio (CI)	Adjusted ratio of rate ratio (CI)[ii]	Adjusted rate ratio (CI)	Adjusted ratio of rate ratio (CI)[ii]
Any OxyContin	0.90 (0.69-1.17)	ref	0.73 (0.44-1.20)	ref	**0.64 (0.41-0.99)***	ref
Any ER morphine	0.89 (0.78-1.02)	0.99 (0.74-1.33)	0.89 (0.65-1.22)	1.22 (0.67-2.22)	1.03 (0.72-1.49)	1.61 (0.92-2.82)
Any fentanyl	1.09 (0.90-1.33)	1.22 (0.88-1.69)	0.91 (0.65-1.28)	1.25 (0.68-2.29)	0.75 (0.50-1.11)	1.16 (0.64-2.11)
Any methadone	0.88 (0.74-1.04)	0.98 (0.72-1.33)	1.49 (0.86-2.58)	2.05 (0.98-4.27)	0.93 (0.64-1.35)	1.45 (0.82-2.57)

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *= statistically significant (p<0.05); [i]=including use with or without other opioid analgesics concomitantly, but excluding periods dispensed OxyContin or primary comparator concomitantly; [ii]= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); propensity score (PS); confidence interval (CI); reference (ref); variables used in the PS-weighting are noted in in section 3.4.5

4.2.4.4 Analyses among those dispensed OxyContin or comparators continuously from pre- to post-periods

Table 22 shows the *unintentional*[xxviii] overdose rate ratios among patients dispensed OxyContin or primary comparators with or without other opioid analgesics concomitantly who had continuous dispensings from the pre-period continuing into the post-period. Across all databases, reductions in unintentional overdose were observed among those dispensed OxyContin, but in adjusted analyses rate ratios were not statistically significant. Reductions in unintentional overdose were also observed across all comparators and databases, with statistically significant rate ratios among those dispensed ER morphine in Medicaid and HIRD, and statistically significant rate ratios among those dispensed fentanyl and methadone in Medicaid.

[xxviii] Of note, these analyses were only conducted using the unintentional overdose algorithm therefore they are considered exploratory (see Section 3.4.6)

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Table 22: Unadjusted and adjusted unintentional overdose rate ratio among those dispensed OxyContin and primary comparators with or without other opioid analgesics concomitantly and with "continuous use" from the pre- to post-reformulation periods, by database

Opioid analgesic[i]	Medicaid		MarketScan		HIRD	
	Unadjusted rate ratio (CI)	Adjusted rate ratio (CI)	Unadjusted rate ratio (CI)	Adjusted rate ratio (CI)	Unadjusted rate ratio (CI)	Adjusted rate ratio (CI)
Any OxyContin	**0.76 (0.60-0.97)***	0.86 (0.68-1.10)	0.72 (0.38-1.37)	0.75 (0.41-1.37)	0.68 (0.38-1.24)	0.79 (0.45-1.39)
Any ER morphine	**0.62 (0.53-0.74)***	**0.73 (0.62-0.87)***	0.56 (0.25-1.22)	0.61 (0.29-1.31)	**0.33 (0.17-0.63)***	**0.33 (0.17-0.65)***
Any fentanyl	**0.63 (0.50-0.79)***	**0.76 (0.60-0.97)***	0.74 (0.37-1.50)	0.81 (0.41-1.61)	**0.59 (0.36-0.97)***	0.71 (0.45-1.13)
Any methadone	**0.48 (0.39-0.59)***	**0.55 (0.45-0.67)***	0.68 (0.32-1.47)	0.68 (0.34-1.34)	**0.51 (0.29-0.88)***	0.56 (0.32-0.98)

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *= statistically significant (p<0.05); [i]=excludes periods dispensed OxyContin or primary comparator concomitantly; person-months (PMs); extended-release (ER); confidence interval (CI); reference (ref); adjusted for variables in section 3.4.5

4.3 SPONSOR'S INTERPRETATION OF PMR 3051-4 RESULTS

 "*The 2010 reformulation of OxyContin to a product with physicochemical barriers to deter injection or insufflation was not associated with a substantial decline in the overall incidence of unintentional opioid overdose in OxyContin users, beyond what might have been expected from secular trends seen in comparator opioids. However, when attention was restricted to person-time during which there was no use of concomitant opioids, the OxyContin reformulation was associated with an unequivocal decline in overdose rates during only OxyContin use as compared to during the use of only comparators, particularly in the commercially insured databases. There was a more modest decline among the Medicaid population*.*"*

Note: The sponsor's interpretation in the PMR 3051-4 study report was based on the unintentional overdose outcome findings, which FDA considers to be exploratory due to its inferior performance in algorithm validation studies relative to the "any" opioid overdose algorithm.

5 DISCUSSION

5.1 FDA SUMMARY OF PMR STUDY 3051-4 FINDINGS

Changes in opioid overdose rates among patients dispensed OxyContin

In the commercial claims combined incident and prevalent user cohorts (see Table 23), there were modest reductions in opioid overdose rates among patients dispensed OxyContin with or without other opioid analgesics concomitantly, and when restricted to person-time dispensed OxyContin with any immediate-release (IR) opioid analgesic

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concomitantly. These reductions were not seen in the Medicaid cohort. None of the adjusted overdose rate ratios for these cohorts were statistically significant. When restricted to person-time dispensed OxyContin alone (with no other opioid analgesics), there were larger reductions in opioid overdose rates among OxyContin recipients across all databases, but the changes were only statistically significant in one database (HIRD).

Table 23: Adjusted overdose rate ratios among those dispensed OxyContin across databases, by concomitancy with other opioid analgesics

OxyContin exposure group	Medicaid			MarketScan			HIRD		
	Pre-period rate per 1,000 PMs (ref)	Post-period rate per 1,000 PMs	Adjusted rate ratio (CI)	Pre-period rate per 1,000 PMs (ref)	Post-period rate per 1,000 PMs	Adjusted rate ratio (CI)	Pre-period rate per 1,000 PMs (ref)	Post-period rate per 1,000 PMs	Adjusted rate ratio (CI)
Any OxyContin use[i]	1.80	1.86	1.00 (0.89-1.12)	0.82	0.80	0.90 (0.75-1.08)	0.93	0.85	0.84 (0.65-1.09)
Concomitant use[ii] with any IR opioid analgesic	1.89	2.02	1.04 (0.91-1.19)	0.93	0.96	0.95 (0.77-1.17)	0.93	0.75	0.74 (0.54-1.02)
OxyContin use alone	1.65	1.42	0.85 (0.68-1.06)	0.60	0.44	0.72 (0.50-1.04)	0.91	0.48	**0.52 (0.32-0.83)***

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *= statistically significant (p<0.05); [i]=excludes periods dispensed OxyContin or primary comparator concomitantly; [ii]=includes only periods dispensed an IR opioid analgesic concomitantly, excluding periods dispensed OxyContin or primary comparator use concomitantly; person-months (PMs); confidence interval (CI); adjusted for variables in section 3.4.5; For all databases, the pre-period is two years before the reformulation, but the post-period for Medicaid analyses is two years after the reformulation and the post-period for MarketScan/HIRD analyses is five years after the reformulation

Overall, the incident only cohorts were smaller samples with substantially reduced aggregate exposure time across databases compared to analyses from combined cohorts. Overdose rate ratios using incident only cohorts were generally similar to those of the combined cohort, but not statistically significant for any of the OxyContin exposure groups.

Overdose rate changes for OxyContin compared to changes for primary comparators

In Medicaid analyses, with the exception of fentanyl, the adjusted ratio of rate ratios (RORR) favored the comparators (i.e., RORR < 1) over OxyContin among patients with or without other opioid analgesics dispensed concomitantly, but the RORR was only statistically significant for methadone (see Table 24). Adjusted RORRs also favored comparators when restricted to person-time dispensed any IR opioid analgesic concomitantly, with statistically significant RORRs for ER morphine and methadone. In the commercial claims analyses (MarketScan and HIRD), the adjusted RORRs all generally favored OxyContin when looking at those dispensed the comparators with or

without other opioid analgesics concomitantly, or when restricted to person-time dispensed with an IR opioid analgesic concomitantly, but no RORR was statistically significant for any comparator. Meta-analyzed comparative results from the commercial claims databases were generally consistent with results of the commercial claims analyzed separately, except that the RORRs were statistically significant for methadone (favoring OxyContin) when analyzed separately.

When restricted to person-time dispensed OxyContin or comparators alone, all adjusted RORRs favored OxyContin, but only in the commercial claims databases were some adjusted RORRs statistically significant: ER morphine in the HIRD data, and fentanyl and methadone in the MarketScan data. Meta-analyzed results from the commercial claims databases were also generally consistent with results when analyzed separately, except that all RORRs were statistically significant (favoring OxyContin) when meta-analyzed.

Table 24: Adjusted ratio of rate ratios among those dispensed primary comparators compared to those dispensed OxyContin, by database and concomitancy with other opioid analgesics

Opioid analgesic exposure group	Exposure period category	Medicaid	MarketScan	HIRD
		Adjusted ratio of rate ratio (CI)[iii]	Adjusted ratio of rate ratio (CI)[iii]	Adjusted ratio of rate ratio (CI)[iii]
ER morphine	Any use[i] (**with or without** concomitant opioid analgesic use periods)	0.91 (0.80-1.04)	1.12 (0.86-1.46)	1.09 (0.78-1.53)
Fentanyl		1.05 (0.90-1.22)	1.19 (0.93-1.53)	1.04 (0.73-1.49)
Methadone		**0.85 (0.74-0.98)***	1.32 (0.97-1.79)	1.20 (0.83-1.74)
ER morphine	Concomitant IR opioid analgesic use[ii] (**with** concomitant IR opioid analgesic use periods)	**0.84 (0.72-0.99)***	1.00 (0.74-1.35)	1.01 (0.66-1.56)
Fentanyl		0.98 (0.83-1.17)	1.09 (0.81-1.45)	1.17 (0.74-1.83)
Methadone		**0.80 (0.67-0.96)***	1.08 (0.73-1.59)	1.19 (0.73-1.92)
ER morphine	Use alone (**without** concomitant opioid analgesic use periods)	1.17 (0.90-1.52)	1.62 (0.97-2.72)	**2.20 (1.18-4.10)***
Fentanyl		1.27 (0.95-1.69)	**1.68 (1.02-2.78)***	1.40 (0.73-2.70)
Methadone		1.03 (0.79-1.33)	**1.94 (1.14-3.29)***	1.76 (0.98-3.17)

(*FDA generated table using data from PMR 3051-4 study report*)

Key: *= statistically significant (p<0.05); [i]=excludes periods dispensed OxyContin or primary comparator concomitantly; [ii]=includes only periods dispensed an IR opioid analgesic concomitantly, excluding periods dispensed OxyContin or primary comparator opioid analgesic concomitantly; [iii]= null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group); person-months (PMs); confidence interval (CI); adjusted for variables in section 3.4.5; reference for this table is OxyContin adjusted rate ratio (see Table 1); adjusted for variables in section 3.4.5; for all databases, the pre-period is two years before the reformulation, but the post-period for Medicaid analyses is two years after the reformulation and the post-period for MarketScan/HIRD analyses is five years after the reformulation

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The adjusted RORR point estimates using the incident user only cohort were generally similar to those using the combined cohort, but the RORRs were not statistically significant, with the exception of methadone which was statistically significant (favoring OxyContin) among patients with or without other opioid analgesics dispensed concomitantly. When the Medicaid analyses were stratified by plan type (FFS or managed care),[xxix] some adjusted RORR estimates were qualitatively different from each other, notably for fentanyl, but RORRs in both cohorts were mostly not significant.

The RORR estimates using the unintentional opioid overdose algorithm were similar to the RORR estimates using the primary any opioid overdose algorithm. Overall, the number of fatal overdoses was much lower than non-fatal overdose, and the proportion of overdoses that were fatal did not change across time periods, either for OxyContin or any comparator group.

5.2   PUBLISHED LITERATURE

DEPI identified two relevant publications in the scientific literature that used electronic healthcare databases to evaluate changes in overdose rates after the OxyContin reformulation (See Appendix 8.8 for summary table); one publication (Coplan et al., 2016)[1] was authored by the sponsor. Coplan et al. describes the results for the original 10 studies/analyses conducted by the sponsor to support potential postmarket labeling claims for OxyContin. One of the analyses assessed the overdose rates among those dispensed OxyContin one year before versus three years after the reformulation using MarketScan claims data, and similar methods to PMR study 3051-4. Opioid overdose rates (based on diagnosis codes) among those dispensed OxyContin decreased 34% (95% CI: 7 to 53%) comparing the pre- and post-periods, from 0.42 to 0.28 per 100 person-years, and that change was statistically significantly different (p<0.027) to that of ER morphine (+17%, CI: -19 to 69%). The RRs in Coplan et al. are relatively consistent with what was observed in MarketScan for PMR study 3051-4, but the percent reductions for OxyContin in PMR study 3051-4 were not statistically significant comparing pre- and post-periods, nor were the RORRs for ER morphine. Different from PMR study 3051-4, Coplan et al. used only overdoses captured in the administrative claims (without mortality linkage) and shorter pre- and post-periods, and analyses did not adjust for differences in patient characteristics between periods. It is unclear whether Coplan's analyses included or excluded person-time in which other opioid analgesics were used concomitantly with OxyContin. Given the more rigorous methods used in PMR study 3051-4, with a longer time period and more complete capture of overdose events (including both fatal or nonfatal), it is not unexpected that the percent changes observed for OxyContin in PMR study 3051-4 would be more attenuated than what was observed in Coplan et al.

The other relevant published study, Larochelle et al. (2015), aimed to evaluate how opioid analgesic dispensing and overdose rates were impacted by two changes in the opioid analgesic market: the withdrawal of propoxyphene (11/2010), and the introduction of reformulated OxyContin (8/2010). Larochelle et al. used Optum commercial claims data to assess rates of opioid analgesic dispensing and prescription opioid overdose (based on

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[xxix] This was only conducted using the unintentional opioid overdose algorithm

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diagnosis codes) before and after the interventions using an interrupted time series design. Analyses did not differentiate between opioid analgesics, and all eligible patients in the data were included regardless of whether they had been dispensed opioid analgesics. In the two years after both opioid analgesic market changes, the total opioid analgesic dispensing rate in milligrams of morphine-equivalent dose (MED) per member per quarter decreased by 19% from the expected rate; ER oxycodone decreased by 39% from the expected rate (absolute change: -11.3 mg MED per member per quarter [95% CI, −12.4 to −10.1]). For overdose, the estimated rate (per 100,000 members per quarter) attributed to prescription opioid analgesics decreased by 20% (absolute change: -1.10 per 100,000 members per quarter [95% CI, -1.47 to -0.74]), and heroin overdose increased by 23% (absolute change: 0.26 per 100,000 members per quarter [95% CI: −0.01 to 0.53]). Like Coplan et al., only overdoses treated in emergency departments and hospitals that would generate claims were captured, thus excluding most overdose fatalities. Larochelle et al. contend that the overall reduction in rates of opioid analgesic dispensing and prescription opioid overdose was associated with both market changes, and also notes the need to address increasing heroin overdose. With no differentiation between type of opioid analgesic dispensed in overdose rates in Larochelle et al., it was not possible to directly compare their results to those of PMR study 3051-4.

5.3 METHODOLOGICAL CONSIDERATIONS FOR CAUSAL INTERPRETATIONS

5.3.1 Patient Characteristics and Sample Selection

PMR study 3051-4 assessed opioid overdose rates among patients directly dispensed opioid analgesics through traditional channels of distribution and reimbursed by Medicaid or commercial insurance. While important to study with respect to the impact of the reformulation, patients who receive an insurance-reimbursed prescription for opioid analgesics may not be representative of the populations where non-oral abuse and overdose are most common. This type of patient-based study population receiving prescription opioid analgesics paid for by health insurance may be at an inherently lower risk for opioid abuse and overdose than individuals who obtain prescription opioid analgesics using cash or through diversion (i.e., from other sources like friends or illicit channels). Those who obtain opioid analgesics from sources other than their own prescription may be particularly at risk for abuse and overdose via non-oral routes, which are *a priori* expected to be impacted the most by OxyContin's reformulation based on the pre-market data suggesting that crushing tablets for non-oral use was made more difficult. MarketScan and HIRD data also include patients with primarily employer-based health insurance, potentially selecting for those with lower overdose risk. Medicaid data, on the other hand, include patients with a higher prevalence of important comorbidities, such as opioid use disorder (OUD) and respiratory impairment (see Table 4), with perhaps challenging socioeconomic circumstances. However, as active patients with regular healthcare encounters, it is likely their overdose risk is still lower than what would be expected in an enriched population sample selected because of having OUD or the use of opioids via non-oral routes.

Many otherwise eligible patients could not be included in PMR study 3051-4 due to lack of data linkage capability and other data quality issues, but these exclusions likely did not bias the comparative analyses. The generalizability of study findings was also likely not

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impacted by these exclusions as the sample of patients dispensed opioid analgesics and person-time of exposure were large in all three databases. In MarketScan, ~60% of the eligible opioid-analgesic-using patients could not be linked to the NDI (~40% in HIRD) for full outcome ascertainment, which did dramatically reduce available exposure time and statistical power to compare rates of opioid overdose, particularly in comparative analyses of opioid analgesics with lower utilization rates. Importantly, demographic characteristics and comorbidities were similar when comparing those who were linkable to those who were not. In Medicaid, only ~25% of all beneficiaries had data deemed usable (i.e., "complete") for this study, with both fee-for-service (FFS) and, to a greater extent, comprehensive managed care members being affected. Nevertheless, there did not appear to be differential inclusion by patient characteristics in the commercial claims databases with respect to linkage to NDI (see Appendix 8.4.2 and 8.4.3), nor did there appear to be meaningful differences in the results of stratified analyses by Medicaid coverage type (see Table 19)[xxx]. Also, since Medicaid data were excluded at that state/year-level and not patient-level, patients were not differentially excluded based on opioid analgesic exposure or clinical characteristics.

Sensitivity analyses were conducted using an incident user cohort to help minimize potential selection biases resulting from including prevalent (ongoing) users; however, despite the substantially reduced exposure time in the incident user only analyses (see Tables 15-17 and Appendix 8.5), the results using the combined user cohort (incident and prevalent) and incident user only cohort were very similar. PMR study 3051-4 did not use a traditional definition of incident use. In this study, incident users of a particular drug could not have had prior dispensing of any study opioid analgesics within the previous three months, but patients could have had recent dispensing of non-study opioid analgesics, including commonly used opioid analgesics like IR hydrocodone, and patients could contribute "incident" time in subsequent treatment episodes over the study period if they met the criteria again. Prevalent users with experience with the study drug had to survive long enough to be included in the study, and thus may be at a potentially lower risk for the outcome (otherwise known as the "depletion of susceptibles" bias). Therefore, inclusion of prevalent users in PMR study 3051-4 can introduce selection bias, but with an effect that is difficult to predict since it is also possible that the likelihood of the outcome *increases* with greater exposure time. Selection biases can also be introduced by adjusting for variables that are impacted by treatment selection after initiation. This is of particular concern in analyses that include prevalent users, as baseline characteristics are measured after initiation of the opioid analgesic for that exposure period. Nevertheless, because of the way "incident" use was defined in PMR study 3051-4, incident and prevalent users were more or the less comparable, as both can have prior experience with non-study opioid analgesics, and both can contribute multiple treatment episodes during the study period. Overall, patient characteristics associated with incident only versus prevalent only treatment episodes were very similar to each other, which also helps mitigate some concerns with using a combined cohort.

[xxx] Note this was only using the unintentional overdose outcome

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5.3.2 Challenges with Exposure and Outcome Measurement in Administrative Claims Data

Drug exposure is difficult to measure and characterize in claims-based observational studies, particularly for opioid analgesics. While opioid analgesic drugs can be taken routinely like antihypertensives, they are also taken as needed or sporadically for acute conditions, acute exacerbations of chronic conditions, or for intermittent chronic pain. Opioid analgesics can be taken alone, or in combination with other opioid analgesics, for example where a long-acting product is used for sustained pain management and a short-acting product used for breakthrough pain. The variability in use patterns creates uncertainty with respect to measuring exposure time and defining time at risk for the outcome. Unlike many drugs for chronic conditions, opioid analgesic prescriptions are not used in uniform, regular, or predictable ways, and therefore, many assumptions made to generate exposure time may be inaccurate. For instance, PMR study 3051-4 calculated exposed days by using prescription dispensing date, days' supply, and tablets dispensed. However, the treatment instructions from the prescriber or the actual use patterns by the patient may not be well represented by the days' supply which is a variable input by the pharmacist based on a combination of factors. Similarly, while tablet strength is typically available, daily morphine equivalent dose (MED) can be challenging to define based on the prescription data, particularly when multiple opioid analgesics are prescribed concomitantly but taken in different ways. Any differential change in mean MED and/or dispensed tablet strengths by study opioid analgesic and period could bias overdose rate comparative analyses with respect to overdose risk. Data were not provided on MED or tablet strength dispensing rates among those dispensed OxyContin or comparators comparing the pre- versus post-periods; these data would be useful in assessing the potential for changes in the user cohorts, particularly the proportion of patients receiving the highest dosage strengths, which may be more likely to be diverted and abused.[xxxi]

Carefully defining exposed periods and measuring exposure time is critical, as outcomes occurring outside of those periods would not be captured despite their being potentially associated with a recent opioid analgesic dispensing. The sponsor assumed no indefinite "stockpiling," meaning leftover opioid analgesic tablets from the previous dispensing were ignored in exposure time calculations, excluding what could have been additional "at risk" exposure time. Because of the potential for lagged outcomes in this study, where events occur outside of the exposure time window but may still be related to prior opioid analgesic exposures (i.e., leftover drug), relevant outcomes may be systematically missed using a narrower exposure definition, under-ascertaining the "true" overdose rates associated with these drugs. The exposure time definition in this PMR study 3051-4 included an extension period of half of the days' supply of the last prescription in which an outcome could still be captured. However, if "stockpiling" differed by opioid analgesic or across time periods, this could bias relative changes in overdose rates by differentially shortening exposed time, but more granular opioid-analgesic-specific data were not provided to explore these potential differences. When comparing OxyContin to primary comparators (in aggregate) combining the pre- and post-periods (see Appendix 8.4.1-8.4.3), mean exposure time per

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[xxxi] Rigg KK, Kurtz SP, Surratt HL (2012) Patterns of prescription medication diversion among drug dealers. Drugs (Abingdon Engl); 19(2): 144–155

individual treatment episode was roughly equivalent suggesting relative parity in measured exposure time and comparative analyses not meaningfully impacted by disproportionate amounts of exposure time per episode. Also of concern but difficult to address, claims-based pharmacy dispensing data do not include prescriptions paid for with cash, and therefore, these prescriptions would not be included in exposure time calculations. In another commercial insurance population, approximately 8% of opioid analgesics were paid for with cash.[xxxii]

In general, because of the potential for unattributed outcomes and missing cash payments, a less restrictive definition of when an episode ends (i.e., accounting for "stockpiling") may be preferred over the narrower definition. At the same time, there are also trade-offs with using a less restrictive definition in accurately allocating exposure time when comparing drugs that are often substituted for one another (as is the case for PMR study 3051-4), and with respect to causal inference in that more distal prescription dispensing may be inaccurately associated with more recent outcomes. Regardless of the assumptions made on exposure time calculations, there are factors motivating prescribing decisions that are unobservable in these data but that can have meaningful impact on comparative results. One particular issue in this study stems from prescribers potentially discontinuing an opioid analgesic prescription over concerns about aberrant behaviors and risk of overdose. This would effectively censor exposure time in the higher risk patients and may mitigate overdose rates differentially by opioid analgesic product; this type of informative censoring can also bias relative comparisons between opioid analgesic and periods.

Without reliable ascertainment of intentionality, route-specific information, or any information on the opioid(s) involved, PMR study 3051-4 was unable to examine specific subsets of overdose cases likely most relevant to understanding the overall impact of the reformulation (i.e., unintentional overdose involving non-oral abuse of OxyContin). This study used a validated algorithm to ascertain any opioid overdose events in administrative claims and mortality data; however, these databases do not have information on either the route (i.e., oral, inhalation, injection) or specific opioid(s) involved in the overdose event, making evaluating the impact of the reformulation even more challenging. The greatest impact of the reformulation would be expected in overdoses involving product manipulation (i.e., crushing, dissolving) and non-oral routes, the specific routes it was designed to deter, but these data are not available in claims or mortality database linkages. Additionally, while it is unknown what opioid(s) specifically precipitated the overdose in this study, the overdose event is attributed to the last opioid analgesic(s) the patient was dispensed, and therefore, some inaccurate attribution of overdoses to specific opioid analgesic groups is likely (e.g., a patient overdoses on heroin when they are prescribed ER morphine). Because opioids obtained through other means, including those outside of traditional prescribing channels (e.g., bought illegally on the black market), heroin, or other non-opioid prescription or illicit drugs that may have contributed to the overdose are unknown, it is not clear whether there was differential use of these substances across time periods and across patients receiving different opioid analgesics that could have impacted comparative analyses. The specificity of the primary outcome was also limited because the

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[xxxii] Walker AM et al. (2017) Possible Opioid Shopping and its Correlates. The Clinical Journal of Pain; 33 (11): 976-982.

opioid overdose algorithm that differentiated intentionality did not perform reliably across other claims databases, most notably in the TennCare (Tennessee's Medicaid data). While the "any opioid overdose" outcome may indeed be the most appropriate outcome in this study given that opioid overdose is a rare outcome where intent is not always easily determined, unintentional opioid overdose analyses were originally planned as primary objectives. However, in light of the portability data from Green et al.[xxxiii], FDA views the unintentional opioid overdose analyses in PMR study 3051-4 to be exploratory.

5.3.3   Adjusting for potential confounders

5.3.3.1   Risk factors for overdose

Without sufficient adjustment for *all* important confounders it is difficult to say whether observed changes in overdose rates were due to the effect of the reformulation on overdose risk in patients receiving the drug or simply a shift in the risk profile of patients receiving the drug. Preliminary data suggested that there were indeed differences in the patients dispensed OxyContin comparing the pre- and post-periods, including potentially relevant comorbidities. It is unclear, however, whether confounding was adequately addressed in this study.

Risk factors like opioid use disorder (OUD) and prior overdose were considered for adjustment in the models, but doing so comes with challenges, particularly when using administrative claims data. The sponsor contends (in their December 2019 information request response) that OUD is actually better operationalized as a mediator in the causal pathway between opioid analgesic dispensing and overdose, where model adjustment would thus not be appropriate. While the proportion of patients with OUD diagnosis codes when the pre- and post-periods were combined was similar when comparing those dispensed OxyContin to the primary comparators (in aggregate), it is not clear whether there was actually differential prescribing of specific opioid analgesic to patients with OUD diagnosis codes in the pre- versus post-periods as those data were not provided. Any systematic differential opioid analgesic prescribing by OUD diagnosis and study period could bias results considerably. Including prevalent users further complicates adjusting for baseline OUD, as these may be measured after opioid analgesic initiation. Furthermore, because patients can be "incident users" multiple times in this study, an incident user only analysis still cannot fully address its potential role as a confounder. At the same time, the sensitivity and positive predictive value of OUD diagnosis codes in claims data are inadequate,[xxxiv] which limits their utility in claims-based analyses, including their use as a covariate in statistical models. Therefore, while the data provided by the sponsor do not support their position that OUD is a mediator, it is reasonable to not adjust for an OUD variable based solely on the presence of diagnosis codes, as it is not a reliable indicator of true OUD. Including OUD defined by codes in the model would not adequately address

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[xxxiii] Green CA, et al. (2019) Identifying and classifying opioid-related overdoses: A validation study. Pharmacoepidemiol Drug Saf; 28: 1127–1137. https://doi.org/10.1002/pds.4772

[xxxiv] Carrell DS, et al. (2020) Measuring problem prescription opioid use among patients receiving long-term opioid analgesic treatment: development and evaluation of an algorithm for use in EHR and claims data, Journal of Drug Assessment, 9:1, 97-105, DOI: 10.1080/21556660.2020.1750419

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confounding by OUD and may consequently introduce additional unforeseen biases of relative comparisons.

As for prior opioid overdose, the prevalence was relatively balanced when comparing those dispensed OxyContin to the primary comparators (in aggregate across entire study period), but it was included in all adjusted models as a time-varying covariate to account for its strong association with the outcome of interest (see Table 5). Time-varying covariates can introduce time-varying confounding and bias associations, but from the sponsor's perspective it was important to account for the within-person correlation from patients' contributing multiple overdose events (~10% of patients across all three databases) over the study period. FDA concurs that including a time-varying prior overdose variable is appropriate given the definition/algorithm's validity in administrative claims data, but also given that it is highly predictive of future overdose and that the PMR 3051-4 study design includes multiple treatment episodes per patient where the outcome can occur.

The sponsor argued that other potentially important risk factors like major depressive disorder, alcohol use disorder, or other substance use disorders are also better operationalized as mediators in the causal pathway, but again, the sponsor did not submit any data to support this position. To be mediators these conditions would have to occur as a result of starting a specific opioid analgesic therapy, but many of the conditions are common and likely to be present before treatment initiation in many patients. In other words, these types of variables may be confounders, or effect modifiers, of the association between OxyContin reformulation and overdose.

Concomitant benzodiazepine use is a known risk factor for opioid overdose, but it was not adjusted for in any primary analyses as the sponsor again viewed this as a potential mediator. Overall, benzodiazepine use was relatively rare and comparable across study opioid analgesics in all three databases (see Table 4 and Appendix 8.4.1-8.4.3), with the prevalence of any benzodiazepine dispensing similar across study opioid analgesics when combining the pre- and post-periods, but slightly higher in Medicaid compared to the commercial claims databases. In both the HIRD and Medicaid databases (see Appendix 8.4.2 and 8.4.3), the majority of patients dispensed opioid analgesics were not dispensed benzodiazepines; rates of benzodiazepine dispensing across study opioid analgesics were largely the same comparing the pre- and post-periods in Medicaid, while rates across nearly all study opioid analgesics decreased from the pre- to post-periods in HIRD. These data suggest that any benzodiazepine dispensing changes from the pre- to post-periods were likely nondifferential by opioid analgesic. To better understand the potential impact of benzodiazepine use on study results, FDA recommended that the sponsor explore the effect of benzodiazepine dispensing as a confounder, and separately as an effect modifier. In their subsequent re-analysis of the data, the sponsor found that additionally adjusting for baseline benzodiazepine use (as a covariate in the model) did not meaningfully impact results in HIRD and Medicaid, and that benzodiazepine use was not a statistically significant effect modifier (interaction $p>0.05$) (see Appendix 8.7). Given these results, and the relative balance in benzodiazepine dispensing rates across opioid analgesic exposure groups overall, and across time periods, relative comparisons between opioid analgesics are likely not substantially biased by any changes in concomitant benzodiazepine use. Nonetheless, because benzodiazepines and opioid analgesics are often obtained through means other than one's own (insurance reimbursed) prescription, it is

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unknown whether there was actual differential use of other substances across time periods or comparators.

5.3.3.2   Adequacy of adjusted models in controlling for confounding

To account for differences in the patient populations before and after the reformulation and mitigate the impact of confounding, some Poisson models were adjusted by demographic and clinical characteristics, while others were weighted by the propensity score (PS),[xxxv] but the results were not substantively different from unadjusted results. Adjusting for pre- versus post-period changes in the composition of the patient populations can help minimize bias with respect to relative comparisons within and between opioid analgesics if the propensity for exposure, or risk of outcome shifts based on the patient characteristics. However, the results of adjusted analyses in PMR study 3051-4 were similar and only minimally attenuated, if at all, compared to the crude, unadjusted results. This may be due, in part, to limited and incomplete adjustment for some important potential confounders, as discussed above. Adequately adjusting for confounders in these types of claims-based analyses is often challenged by incomplete data (e.g., smoking status, current alcohol and illicit substance use, socioeconomic status), and a lack of validated diagnosis codes known to accurately reflect important medical conditions (e.g., OUD). Including time-varying covariates in the model (e.g., prior overdose) can help with time-varying confounding, but it can also introduce additional time-varying confounding if other important time-varying exposures are not adequately controlled for. This may not be the case in PMR study 3051-4, but only one variable was ultimately incorporated as a time-varying exposure. Nonetheless, adjusted analyses that control for patient characteristics, including demographic information and certain conditions that are more reliably captured using claims-based diagnosis codes, are still preferable to unadjusted analyses, however limited. Unadjusted analyses can be fraught as they inherently assume complete exchangeability in patient populations over the study period across opioid analgesics.

Still, even after adjusting for measurable potential confounders in PMR study 3051-4, it is likely that channeling bias (a type of selection bias), is still relevant. Because the reformulation was specifically designed to deter tablet manipulation for the purposes of abuse, it is possible that prescribers differentially prescribed ("channeled") reformulated OxyContin to patients they perceived to have a higher risk of misusing the drug. This channeling of patients to one opioid analgesic over another would introduce imbalances in the overdose risk profile of patients comparing the two periods, potentially attenuating any true benefit of the reformulation. This type of bias is prevalent in pharmacoepidemiology studies in general, and it can be particularly challenging to address using administrative claims data alone. In some respects, the sponsor had already been marketing original OxyContin as the "safer" alternative to other opioid analgesics with respect to abuse due to its ER properties for many years prior to its reformulation.[xxxvi] Therefore, the true extent

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[xxxv] Unintentional overdose algorithm only (exploratory outcome)

[xxxvi] New York Times, published May 10th, 2007, "In guilty plea, OxyContin maker to pay $600 million": https://www.nytimes.com/2007/05/10/business/11drug-web.html?auth=login-email&login=email ; The United States Attorney's Office, Western District of Virginia, John L. Brownlee, News release May 10th, 2007: https://media.defense.gov/2007/May/10/2001711223/-1/-1/1/purdue_frederick_1.pdf

of this type of differential channeling by study period is unclear, and it is possible its effect when comparing study periods is ultimately negligible.

An alternative scenario must also be considered, however, wherein patients seeking to abuse OxyContin "self-selected" *not* to receive the abuse-deterrent product, requesting and receiving different opioid analgesics without abuse-deterrent properties, or transitioning to non-prescribed opioids (e.g., heroin), thus creating a *lower* risk cohort of OxyContin users following reformulation. In this scenario, results would show a more favorable impact of the reformulation on overdose risk. The overall decline in dispensing, and particularly of the 80 milligram tablets ([See Appendix 8, and background document: OSE Drug Utilization Review](#)), may in part reflect such a migration away from OxyContin by people wishing to divert and/or abuse it. Although it is unclear to what extent that ultimately explains the decreased dispensing, it does at least suggest some significant changes in prescribing patterns for OxyContin. Changes in prescribing patterns may also be due to multiple factors, including changes in insurance coverage or formularies (i.e., reimbursement) that would not necessarily bias relative comparisons, but this information was not available in PMR study 3051-4.

5.4   OVERALL INTERPRETATION OF PMR STUDY 3051-4 FINDINGS

When interpreting PMR study 3051-4 results, one overarching concern is the potential for inappropriately attributing observed changes in overdose rates to the reformulation when the changes were, in fact, caused by other factors. The use of comparators, adjustment for confounders, and various sensitivity analyses to assess bias can help to determine whether causal inference is warranted and to better understand the uncertainty surrounding any observed overdose rate changes; however, with respect to PMR study 3051-4, any assertions of a direct effect of the reformulation must be appropriately qualified. A *quantitative* interpretation of a direct effect on overdose rates is not appropriate given the study design and described data limitations, but *qualitatively* attributing some unknown, but "non-zero," effect of the reformulation could be, if supported by the totality of findings. Importantly, this study was not designed to evaluate overdose rates in those who may obtain OxyContin through cash payments or channels other than their own prescription, nor was it able to specifically evaluate overdose involving product manipulation or non-oral routes.

Effect of OxyContin's reformulation on <u>overdose rates among those dispensed any OxyContin</u> (i.e., with or without other opioid analgesics concomitantly):

The results of PMR 3051-4 do not demonstrate that the reformulation reduced the risk of opioid overdose in patients dispensed OxyContin, overall (i.e., including exposure with or without other opioid analgesics). Our interpretation is based on results using the "any opioid overdose" (fatal and non-fatal; intentional and unintentional) outcome algorithm, although these results were similar, overall, to those using the unintentional overdose outcome algorithm, which showed inferior performance in validation studies.

A conclusion that OxyContin's reformulation actually reduced opioid overdose risk in these patients would be supported by robust and statistically significant reductions in overdose rates that were temporally associated with the intervention, largely consistent across databases, and unlikely to be explained by either systematic (i.e., bias and

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confounding) or random (i.e., chance) error. In HIRD, the overdose rates among OxyContin recipients appeared to decrease modestly immediately after the reformulation (transition period) but the decline was not sustained, and there was no discernable decline in overdose rates among those dispensed OxyContin in either the Medicaid or MarketScan databases. Observed pre-post changes in the overdose rates among those dispensed OxyContin were of relatively small magnitude, and small changes are more likely to be completely explained by residual confounding, particularly when we are not confident that confounding was adequately controlled for, given the limited adjustment for some potentially important covariates and limited ability to measure others. Furthermore, most changes across time periods were not statistically significant, indicating that random chance cannot be ruled out as an explanation either.

To account for potential confounding by calendar time (i.e., secular trends), changes in opioid overdose rates among those dispensed OxyContin should *also* differ meaningfully from any changes observed in those dispensed comparator opioid analgesics. In the commercial claims populations, changes in opioid overdose rates among patients dispensed OxyContin compared to the changes among patients dispensed primary comparators modestly favored OxyContin, but they were not significantly different from each other. In fact, the results of Medicaid analyses among patients dispensed any OxyContin or OxyContin with IR opioid analgesics concomitantly were actually *unfavorable* to OxyContin with respect to changes in overdose rates after the reformulation, in that reductions in overdose rates among those dispensed ER morphine and methadone were observed but there was no change among those dispensed OxyContin.

Concomitant dispensing and switching from one opioid analgesic to another creates challenges in disentangling the marginal effect of one opioid analgesic on overdose risk in the context of multiple concurrent opioid analgesic exposures, but the use of multiple opioid analgesics concurrently was more the rule than the exception in these populations. Although it complicates causal inference, studying the effect of the reformulation in settings in which the drug is most commonly used (i.e., with other opioid analgesics) is still important. One possible explanation for the lack of an observed effect in this cohort is that the reformulation actually had little or no effect on overall opioid overdose, in part because opioid analgesic use and abuse patterns are complex and dynamic, in some cases including both prescription and illicit opioids. Opioid analgesic concomitancy patterns in patients dispensed OxyContin also changed over the study period, with increased concomitant prescribing overall and changes in the types of opioid analgesics used with OxyContin (see Appendix 8.1). It is therefore perhaps not unexpected that changing a single product's formulation did not appear to result in an overall reduction in opioid overdose.

Although PMR study 3051-4 does not convincingly show that the reformulation reduced overdose risk in insured patients receiving OxyContin, the findings also do not prove that the reformulated had no effect on overdose risk or preclude this possibility. While certainly important to study, this study cohort may not reflect the population most likely to abuse or experience an overdose involving OxyContin. The effects of the reformulation might be more easily detected in higher risk groups where its impact may be greatest, including those obtaining OxyContin from sources other than their own prescription or using cash to purchase prescription opioids, and those abusing opioids by non-oral routes. However, these groups are generally not distinguishable in data sources capable of linking a specific

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drug exposure to overdose outcomes, while controlling for other confounding factors. It is possible that studying lower risk patient populations, coupled with the lack of information on route of administration and the opioid(s) involved in the overdose, limited the ability to detect some true effect of the reformulation on overdose risk in individuals exposed to the product.[xxxvii]

__Effect of OxyContin's reformulation on overdose rates among those dispensed OxyContin alone__ (i.e., without other opioid analgesics concomitantly):

When restricting analyses to patients dispensed OxyContin or comparators alone, results were somewhat more favorable with respect to the impact of the reformulation on opioid overdose risk, although this was true only in the commercial claims populations (not Medicaid), and the implications and generalizability of this finding are not entirely clear. Analyses that only include patients using one opioid analgesic product at a time are simpler from a causal inference perspective, as noted above, but OxyContin use without the concomitant dispensing of any other opioid analgesics—primarily IR opioid analgesics— is much less common than dispensing of OxyContin with at least intermittent use of other opioid analgesics (see Appendix 8.1) and represents a relatively small subset of OxyContin use in real-world settings.

While the results were more favorable with respect to the impact of the reformulation, they were not entirely consistent across databases, or across comparators, and there was greater uncertainty in the estimates due to the reduced exposure time. When restricted to person-time dispensed OxyContin alone, observed reductions in opioid overdose rates were modest and only statistically significant in one commercial claims database (HIRD). Overall, changes in opioid overdose rates when restricted to person-time dispensed OxyContin alone differed favorably from changes in comparators, to varying degrees. None of the differences were statistically significantly in Medicaid, however, and statistical significance varied across comparators in the two commercial claims databases where the differences were larger. When the results of the commercial claims databases were combined using meta-analytic methods, the associations were generally consistent with the results of analyses conducted separately in each database, but the comparative results were all statistically significant using meta-analysis. At the same time, these results must be interpreted with caution as only two databases (effectively two separate "studies") were combined, and between-study heterogeneity could not be properly evaluated (See background document: OB Statistical Review Memo).

Given the potential for residual confounding in these analyses, it is also important to consider alternative explanations for these findings. It is possible that OxyContin's reformulation reduced the risk of overdose in patients who received this product without any other opioid analgesics, at least among patients with commercial insurance. It is also possible, however, that patients receiving reformulated OxyContin were inherently at lower risk of overdose than those who received original OxyContin. This "non-exchangeability" of the cohorts would remain if there were important unmeasured differences between these groups. Such differences could be due to increased prescriber

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[xxxvii] PMR study 3051-1 and study 3051-3 targeted higher risk groups like those being specifically assessed for opioid treatment, but overdose outcomes were not assessed in those studies

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awareness of risk of OxyContin abuse in general (e.g., due to the 2010 OxyContin REMS provider communications), or changes in patient selection related specifically to OxyContin's abuse-deterrent properties.

Differences could also be related to patient "self-selection;" for example, if individuals seeking to abuse OxyContin non-orally stopped abusing OxyContin, perhaps instead seeking out other opioids, either prescription or illicit, when OxyContin was reformulated. If this was the case, then post-period OxyContin user cohort might have had a lower risk of overdose. Although this latter explanation would be consistent with reformulated OxyContin having an abuse-deterrent effect, it does not necessarily show that the abuse-deterrent properties conferred a reduced risk of overdose among those exposed to the product, or that those who stopped using OxyContin because of its reformulation (and were therefore not included in the reformulated OxyContin exposure group) were less likely to experience an overdose. In addition, the distribution of dispensed OxyContin tablet strengths skewed lower in the post-period (See Appendix 8.1, and background document: OSE Drug Utilization Review), which could have contributed to the observed declines in overdose rates when restricted to person-time dispensed OxyContin alone relative to comparators, independent of any risks associated with non-oral abuse specifically or the direct ability of the abuse-deterrent properties to reduce these risks. Again, the changes in OxyContin dosage strengths dispensed could reflect some abuse-deterrent effect of the reformulation, with individuals who seek high-strength tablets to manipulate for the purposes of abuse migrating away from OxyContin after its reformulation, but it is unclear whether subsequent decreases in overdose rates in a cohort receiving lower doses of OxyContin can reasonably be interpreted as the "abuse-deterrent" properties reducing the risk of overdose.

6 CONCLUSION

The results of PMR 3051-4 do not demonstrate that the reformulation reduced the risk of opioid overdose in patients dispensed OxyContin, overall. When restricted to person-time dispensed OxyContin or comparators *alone* (i.e., without other opioid analgesics), results were somewhat more favorable with respect to the reformulation reducing opioid overdose risk, although this was true only in the commercial claims populations and not the Medicaid cohort. The implications and generalizability of this specific finding are not entirely clear, however, in part because OxyContin use without concomitant dispensing of any other opioid analgesics was relatively uncommon. The interpretation of this finding is further complicated by the potential for unmeasured differences between the prescribed patient populations in the pre- and post-reformulation periods. It is possible that OxyContin's abuse-deterrent properties did confer a reduced risk of overdose among patients using the product without any other opioid analgesics. However, it is also plausible that patients receiving OxyContin alone in the post-reformulation period were inherently at a lower risk of overdose than those who received OxyContin alone during the pre-period, either through changes in OxyContin prescribing practices, or through "self-selection" away from reformulated OxyContin among patients seeking to abuse it via non-oral routes. While the latter explanation may be consistent with reformulated OxyContin having an abuse-deterrent effect, it does not necessarily follow that the abuse-deterrent properties conferred

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a reduced risk of overdose among those exposed to the product or that those who migrated away from OxyContin because of its reformulation actually had a lower risk of overdose.

7   REFERENCES

1. Coplan PM, Chilcoat HD, Butler SF, et al. (2016) The Effect of an Abuse-Deterrent Opioid Formulation (OxyContin) on Opioid Abuse- Related Outcomes in the Postmarketing Setting. Clinical Pharmacology & Therapeutics; 100 (3): 275-286.

2. Larochelle MR, Zhang F, Ross-Degnan D, et al. (2015) Rates of Opioid Dispensing and Overdose After Introduction of Abuse-Deterrent Extended-Release Oxycodone and Withdrawal of Propoxyphene. JAMA Intern Med; 175 (6): 978-987.

8   APPENDICES

8.1   SPONSOR RESPONSE'S TO FDA INFORMATION REQUESTS FROM 2016

Sponsor response from March 3rd, 2017:

"Responses to FDA Information Request email dated November 23, 2016 on the protocol for OxyContin® NDA 022272 PMR 3051-4 (Fatal and Non-Fatal Overdose – A Healthcare Database Analysis with Linkage to the National Death Index): Question #3 Responses on Switching Patterns Around the Time of OxyContin's Reformulation"

Figure 1: MarketScan data - Switching to reformulated OxyContin or other opioids among patients with a dispensing for OxyContin that covered the date reformulated OxyContin was introduced to the market (*opioid dispensing within 3 months after 8/10/2010) (MarketScan, N=22,153)
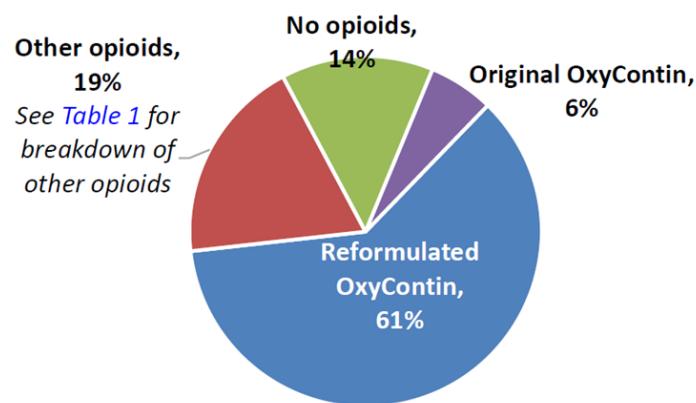
Figure 2: Medicaid data - Switching to reformulated OxyContin or other opioids among patients with a dispensing for OxyContin that covered the date reformulated OxyContin was introduced to the market (*opioid dispensing within 3 months after 8/10/2010) (Medicaid, N=3,020)

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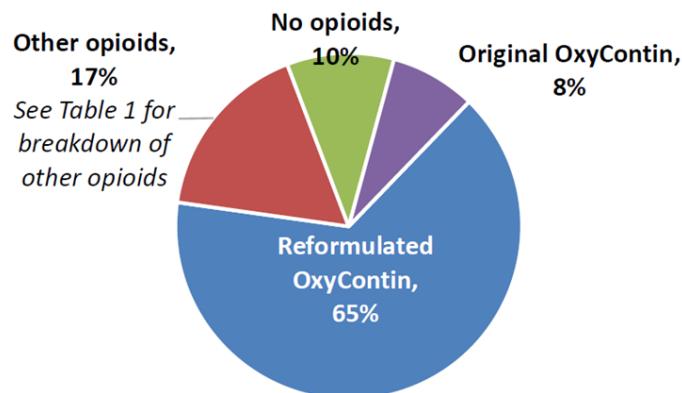
Table 1: Type of opioid switched to among patients dispensed other (Non-OxyContin) opioids

	Commercial N=4,276	Medicaid N=515
	N (%)	N (%)
Generic ER/LA	1,448 (34%)	163 (32%)
Generic IR	3,467 (81%)	442 (86%)
Brand ER/LA	480 (11%)	55 (11%)
Brand IR	360 (8%)	50 (10%)

Note: total exceeds 100% because patients could have more than one opioid type

Table 2: Most common opioids switched to by tablet strength

Commercial N=4,276 N (%)			Medicaid N=515 N (%)		
Opioid and Tablet Strength	N	%	Opioid and Tablet Strength	N	%
IR oxycodone 30mg	731	17%	IR Oxycodone Hydrochloride 30 MG	65	13%
IR hydrocodone APAP 325mg-10mg	516	12%	IR Acetaminophen/oxycodone Hydrochloride 325 MG-10 MG	56	11%
ER oxycodone 80mg	457	11%	IR Tramadol Hydrochloride 50 MG	54	10%
IR oxycodone APAP 325mg-10mg	395	9%	IR Acetaminophen/oxycodone Hydrochloride 325 MG-5 MG	53	10%
IR oxycodone 15mg	345	8%	IR Acetaminophen/hydrocodone Bitartrate 325 MG-10 MG	45	9%
IR hydrocodone APAP 500mg-5mg	261	6%	IR Oxycodone Hydrochloride 5 MG	43	8%
IR oxycodone 5mg	246	6%	ER Oxycodone Hydrochloride 80 MG	42	8%
IR oxycodone APAP 325mg-5mg	243	6%	IR Acetaminophen/hydrocodone Bitartrate 500 MG-5 MG	42	8%
IR tramadol 50mg	223	5%	IR Oxycodone Hydrochloride 15 MG	36	7%
IR hydrocodone APAP 750mg-7.5mg	222	5%	ER Methadone Hydrochloride 10 MG	29	6%
IR hydrocodone APAP 500mg-10mg	194	5%	IR Acetaminophen/oxycodone Hydrochloride 325 MG-10 MG	25	5%
ER oxymorphone 40mg (brand)	182	4%	ER Morphine Sulfate 60 MG	25	5%
Methadone 10mg	176	4%	ER Oxycodone Hydrochloride 40 MG	21	4%
IR oxycodone APAP 325mg-10mg (brand)	148	3%	IR Acetaminophen/hydrocodone Bitartrate 325 MG-5 MG	20	4%
Buprenorphine/naloxone 8mg-2mg	146	3%	IR Acetaminophen/hydrocodone Bitartrate 325 MG-7.5 MG	19	4%
ER oxycodone 20mg	138	3%	IR Hydromorphone Hydrochloride 4 MG	19	4%
ER oxycodone 40mg	122	3%	IR Acetaminophen/hydrocodone Bitartrate 500 MG-10 MG	18	3%
ER morphine 30mg	106	2%	ER Morphine Sulfate 30 MG	18	3%
Fentanyl patch 100mcg/h	100	2%	IR Acetaminophen/oxycodone Hydrochloride 325 MG-7.5 MG	16	3%
IR hydrocodone APAP 750mg-7.5mg	99	2%	IR Acetaminophen/hydrocodone Bitartrate 500 MG-7.5 MG	16	3%
Fentanyl patch 50mcg/h	93	2%	IR Fentanyl Citrate 0.05 MG/1 ML	13	3%
IR hydromorphone 4mg	89	2%	ER Oxymorphone Hydrochloride 40 MG	13	3%
ER morphine 60mg	85	2%	ER Morphine Sulfate 15 MG	13	3%
ER oxymorphone 20mg (brand)	64	1%	ER Morphine Sulfate 100 MG	11	2%
Fentanyl patch 25mcg/h	62	1%	IR Acetaminophen/oxycodone Hydrochloride 650 MG-10 MG	10	2%

Note: total exceeds 100% because patients could have more than one opioid/dose
IR=immediate release; ER=extended release; APAP=acetaminophen; MG=milligrams

Table 3: Patterns of opioid use three and six months after an index generic ER oxycodone prescription between October 1, 2010 and March 31, 2011

	Commercial N=5,963		Medicaid N=452	
	3 months	6 months	3 months	6 months
OxyContin[1]	2,533 (42%)	2,792 (47%)	257 (57%)	286 (63%)
Other Opioids	1,238 (21%)	1,442 (24%)	92 (20%)	109 (24%)
No Opioids	1,391 (23%)	1,552 (26%)	43 (10%)	53 (12%)
Generic ER oxycodone	801 (13%)	177 (3%)	60 (13%)	4 (1%)

[1] represents all OxyContin, original or reformulated, but given the timing the large majority would have been reformulated OxyContin

Sponsor response from March 3rd, 2017:

"**Responses to FDA Information Request email dated November 23, 2016 on the protocol for OxyContin® NDA 022272 PMR 3051-4 (Fatal and Non-Fatal Overdose – A Healthcare Database Analysis with Linkage to the National Death Index): Question #1 Responses on Descriptive Information on Proposed Analytic Cohort**"

Table 4: Opioid analgesics analyzed

Opioid Group	Opioids Included
Comparator opioid analgesics	• Extended-release (ER) morphine • ER hydromorphone • ER oxymorphone • Immediate-release (IR) single-entity (SE) oxycodone • IR morphine[a] • IR hydrocodone acetaminophen • IR hydromorphone • Methadone
Other non-comparator opioid analgesics	• IR oxycodone acetaminophen • IR oxymorphone • Fentanyl (all formulations) • IR tapentadol • Codeine • Meperidine • Propoxyphene • ER hydrocodone • ER tapentadol • Levorphanol • Buprenorphine[b]

[a] IR morphine included as a comparator opioid analgesic in MarketScan commercial analysis but not in Medicaid analysis
[b] Excludes Suboxone, Subutex and associated generics.

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Table 5: Demographics of patients dispensed OxyContin (MarketScan data)

	2H2008-1H2009	2H2009-1H2010	2H2010	2011	2012	2013	2014	1Q2015-3Q2015
Number of patients [a]	70,808	71,796	44,436	67,708	64,753	51,584	51,929	29,028
Age, Years Mean (SD)	48.2 (10.9)	48.4 (11.1)	49 (10.6)	48.8 (11.2)	48.8 (11.3)	49 (11.3)	49.3 (11.2)	49.8 (10.9)
Age, Years Median (Range)	50 (16-64)	50 (16-64)	51 (16-64)	51 (16-64)	51 (16-64)	52 (16-64)	52 (16-64)	53 (16-64)
Age Categorized, n (%)								
16-24	2,616 (4%)	2,759 (4%)	1,362 (3%)	2,878 (4%)	2,856 (4%)	2,298 (4%)	2,153 (4%)	1,008 (3%)
25-34	6,585 (9%)	6,563 (9%)	3,701 (8%)	5,817 (9%)	5,677 (9%)	4,285 (8%)	4,211 (8%)	2,194 (8%)
35-44	13,112 (18.5%)	13,032 (18%)	7,744 (17%)	11,398 (17%)	10,902 (17%)	8,589 (17%)	8,553 (16%)	4,713 (16%)
45-54	24,988 (35%)	24,574 (34%)	15,590 (35%)	22,652 (33%)	20,910 (32%)	16,318 (32%)	16,100 (31%)	8,906 (31%)
55-64	23,507 (33%)	24,868 (35%)	16,039 (36%)	24,963 (37%)	24,408 (38%)	20,094 (39%)	20,912 (43%)	12,207 (42%)
Gender, n (%)								
Male	34,885 (49%)	35,466 (49%)	21,960 (49%)	33,304 (49%)	32,410 (50%)	25,607 (50%)	25,805 (50%)	14,218 (49%)
Female	35,923 (51%)	36,330 (51%)	22,476 (51%)	34,404 (51%)	32,343 (50%)	25,977 (50%)	26,124 (50%)	14,810 (51%)
Geographic region, n (%)								
Northeast	10,130 (14%)	10,935 (15%)	7,125 (16%)	12,001 (18%)	12,763 (20%)	9,899 (19%)	12,036 (23%)	6,125 (21%)
North Central	19,612 (28%)	19,268 (27%)	11,506 (26%)	17,110 (25%)	15,640 (24%)	11,632 (23%)	10,282 (20%)	5,458 (19%)
South	24,804 (35%)	25,325 (35%)	15,544 (35%)	22,008 (33%)	20,700 (32%)	15,730 (30%)	18,267 (35%)	12,152 (42%)
West	14,379 (20%)	14,919 (21%)	10,078 (23%)	14,797 (22%)	14,307 (22%)	12,731 (25%)	9,669 (19%)	5,232 (18%)
Unknown	1,883 (3%)	1,349 (2%)	183 (<1%)	1,792 (3%)	1,343 (2%)	1,592 (3%)	1,675 (3%)	61 (<1%)

[a] Total number of patients based on patients with an OxyContin dispensing in each calendar year with no carry-over of prescriptions spanning multiple years (ie, prescriptions truncated at the end of the time period)

Table 6: Prevalence of relevant diagnoses among patients dispensed OxyContin (MarketScan data)

	2H2008-1H2009 (n=70,808)	2H2009-1H2010 (n=71,796)	2H2010 (n=44,436)	2011 (n=67,708)	2012 (n=64,753)	2013 (n=51,584)	2014 (n=51,929)	1Q2015-3Q2015 (n=29,028)
Diagnosis, n (%)								
Abdominal pain	5,134 (7%)	5,181 (7%)	3,152 (7%)	5,067 (7%)	4,902 (8%)	3,883 (8%)	4,178 (8%)	2,383 (8%)
Amputation	593 (<1%)	622 (<1%)	393 (<1%)	704 (1%)	728 (1%)	588 (1%)	738 (1%)	506 (2%)
Arthritis [a]	25,802 (36%)	28,177 (39%)	16,939 (38%)	30,607 (45%)	30,588 (47%)	24,654 (48%)	25,987 (50%)	14,398 (50%)
Back pain	32,726 (46%)	33,854 (47%)	22,016 (50%)	30,736 (45%)	30,147 (47%)	24,086 (47%)	25,099 (48%)	15,671 (54%)
Chronic pain	5,135 (7%)	6,544 (9%)	4,963 (11%)	7,330 (11%)	8,273 (13%)	6,990 (14%)	8,747 (17%)	6,258 (22%)
Fibromyalgia	4,773 (7%)	5,397 (8%)	3,581 (8%)	5,001 (7%)	5,016 (8%)	4,044 (8%)	4,626 (9%)	3,022 (10%)
Headache	5,222 (7%)	5,556 (8%)	3,450 (8%)	5,228 (8%)	5,262 (8%)	4,071 (8%)	4,500 (9%)	2,675 (9%)
Malignancy	8,210 (12%)	8,159 (11%)	4,903 (11%)	8,455 (12%)	8,245 (13%)	6,539 (13%)	6,808 (13%)	3,911 (13%)
Multiple sclerosis	482 (<1%)	521 (<1%)	346 (<1%)	484 (<1%)	480 (<1%)	353 (<1%)	359 (<1%)	219 (<1%)
Neuropathic pain	7,869 (11%)	8,438 (12%)	5,471 (12%)	8,264 (12%)	8,255 (13%)	6,563 (13%)	7,442 (14%)	4,798 (17%)
Major depression	7,205 (10%)	7,767 (11%)	4,879 (11%)	7,705 (11%)	8,158 (13%)	6,162 (12%)	6,933 (13%)	4,163 (14%)
Generalized anxiety	3,706 (5%)	4,360 (6%)	2,897 (7%)	4,836 (7%)	5,622 (9%)	4,718 (9%)	6,226 (12%)	4,049 (14%)
Bipolar disorder	900 (1%)	928 (1%)	606 (1%)	860 (1%)	849 (1%)	664 (1%)	721 (1%)	428 (1%)
Substance use disorder [b]	857 (1%)	1,107 (2%)	720 (2%)	967 (1%)	985 (2%)	851 (2%)	972 (2%)	761 (3%)

[a] Arthritis, arthropathies, osteoarthritis and musculoskeletal pain
[b] Substance use disorder excludes opioid dependence/addiction

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Table 7: Opioid utilization patterns among patients dispensed OxyContin (MarketScan data)

	2H2008-1H2009 (n=70,808)	2H2009-1H2010 (n=71,796)	2H2010 (n=44,436)	2011 (n=67,708)	2012 (n=64,753)	2013 (n=51,584)	2014 (n=51,929)	1Q2015-3Q2015 (n=29,028)
# prescriptions dispensed, mean	4.71	4.66	3.40	4.40	4.35	4.37	4.31	4.02
# days dispensed, mean	133.91	131.35	95.47	121.55	118.81	119.2	116.92	109.8
# tablets dispensed, mean	389.23	373.39	267.13	332.84	328.23	407.19	325.05	328.26
Total # prescription dispensed	333,446	334,373	151,163	298,053	281,361	225,244	223,893	116,808
10 mg	59,896	58,905	25,929	60,056	59,533	49,164	52,142	26,671
15 mg	3,702	5,533	3,282	7,206	8,635	8,486	11,655	6,934
20 mg	95,597	86,297	39,488	82,336	76,002	58,705	58,338	30,315
30 mg	15,770	22,167	12,610	25,407	27,099	24,668	27,455	16,761
40 mg	81,825	80,029	33,703	60,352	54,065	40,429	36,054	17,540
60 mg	15,270	21,992	11,670	20,890	21,218	17,914	17,771	9,587
80 mg	61,377	59,450	24,481	41,806	34,809	25,878	20,478	9,000
160 mg	9	0	0	0	0	0	0	0
Total # tablets dispensed	27,560,455	26,808,087	11,870,202	22,536,212	21,254,167	21,004,270	16,879,726	9,528,628
10 mg	3,984,643	3,652,835	1,575,582	3,432,195	3,471,279	3,548,520	3,178,597	1,766,567
15 mg	242,918	365,434	213,852	474,041	590,843	742,707	832,420	600,340
20 mg	7,349,620	6,420,793	2,866,969	5,768,009	5,432,677	5,385,618	4,263,155	2,471,278
30 mg	1,118,953	1,581,340	906,956	1,801,877	2,016,251	2,373,664	2,204,643	1,453,792
40 mg	7,254,714	6,934,140	2,885,581	5,107,369	4,515,733	4,170,675	2,949,052	1,499,629
60 mg	1,200,231	1,753,143	918,396	1,667,344	1,709,289	1,824,256	1,460,956	830,276
80 mg	6,408,616	6,100,402	2,502,866	4,285,377	3,518,095	2,958,830	1,990,903	906,746
160 mg	760	0	0	0	0	0	0	0

Table 8: Number of patients dispensed OxyContin, by opioid concomitancy (MarketScan data)

	2H2008-1H2009	2H2009-1H2010	2H2010	2011	2012	2013	2014	1Q2015-3Q2015
Number (%)								
OxyContin alone for the duration of OxyContin dispensed prescriptions in that year [a]	9,990 (14%)	10,675 (14%)	7,346 (15%)	7,938 (11%)	7,142 (10%)	5,645 (10%)	5,294 (10%)	3,389 (11%)
OxyContin dispensed concurrently with comparator opioids in that year [b]	46,123 (65%)	49,131 (65%)	30,695 (64%)	49,365 (69%)	48,597 (70%)	38,559 (70%)	38,714 (70%)	21,309 (68%)
A mixture of OxyContin alone and OxyContin concurrent with comparator opioids [c]	39,253 (85%)	41,481 (84%)	24,115 (79%)	41,678 (84%)	40,886 (84%)	32,337 (84%)	32,545 (84%)	17,290 (81%)
OxyContin dispensed concurrently with comparator opioids only	6,870 (15%)	7650 (16%)	6,580 (21%)	7,687 (16%)	7,711 (16%)	6,222 (16%)	6,169 (16%)	4,019 (19%)
OxyContin dispensed concurrently with non-comparator opioids in that year	14,695 (21%)	15,591 (21%)	9,676 (21%)	14,758 (21%)	13,426 (19%)	11,031 (20%)	11,084 (20%)	6,698 (21%)
Total [d]	70,808	75,397	47,717	72,061	69,165	55,235	55,092	31,396
Mean Person time (Days)								
OxyContin alone for the duration of OxyContin use in that year [a]	127.0	117.4	86.2	110.2	101.5	102.9	99.5	93.0
OxyContin dispensed concurrently with comparator opioids in that year [b]	133.9	133.1	94.1	124.0	121.7	122.9	121.6	112.5
A mixture of OxyContin alone and OxyContin concurrent with comparator opioids [c]	141.8	140.3	98.5	130.9	127.6	129.0	127.1	117.7
OxyContin alone	50.3	48.5	33.3	43.7	41.5	39.8	38.4	32.9
OxyContin dispensed concurrently with comparator opioids	91.5	91.8	65.1	87.3	86.1	89.2	88.7	84.8
OxyContin dispensed concurrently with comparator opioids only	88.6	93.9	77.9	86.6	90.3	91.6	92.3	90.3
OxyContin dispensed concurrently with non-comparator opioids in that year	108.2	107.8	83.3	97.6	98.6	97.5	100.2	101.4
Total	127.6	125.7	90.7	117.1	115.1	115.8	115.2	108.0

[a] OxyContin alone indicates OxyContin dispensed without other opioids as defined in Table 2 above (ie, neither comparator nor non-comparator opioid analgesics).
[b] OxyContin and comparator opioids concurrently, with or without non-comparator opioids
[c] Reflects the number of patients/person-time for patients who did not exclusively use OxyContin alone, but had periods of use of OxyContin alone as well as periods of use of OxyContin concurrently with comparator opioids.
[d] Total reflects total number of patients contributing person-time in any calendar year based on episodes of treatment (ie, prescriptions are not truncated at the end of the calendar year)

Table 9: Most common opioids dispensed concurrently with OxyContin of those analyzed (MarketScan data)

Rank	2H2008-1H2009	2H2009-1H2010	2H2010	2011	2012	2013	2014	1Q2015-3Q2015
1	IR Hydrocodone acetaminophen 28,049 (61%)	IR hydrocodone acetaminophen 29,236 (60%)	IR hydrocodone acetaminophen 16,480 (54%)	IR hydrocodone acetaminophen 27,277 (55%)	IR hydrocodone acetaminophen 25,626 (53%)	IR oxycodone SE 21,973 (57%)	IR oxycodone SE 23,651 (61%)	IR oxycodone SE 13,532 (64%)
2	IR oxycodone SE 19,207 (42%)	IR oxycodone SE 21,449 (44%)	IR oxycodone SE 14,531 (47%)	IR oxycodone SE 24,379 (49%)	IR oxycodone SE 25,345 (52%)	IR hydrocodone acetaminophen 18,167 (47%)	IR hydrocodone acetaminophen 16,414 (42%)	IR hydrocodone acetaminophen 7,786 (37%)
3	IR hydromorphone 4,485 (10%)	IR hydromorphone 4,488 (9%)	IR hydromorphone 2,625 (9%)	IR hydromorphone 5,044 (10%)	IR hydromorphone 5,104 (11%)	IR hydromorphone 4,179 (11%)	IR hydromorphone 4,131 (11%)	IR hydromorphone 2,163 (10%)
4	ER morphine 3,398 (7%)	ER morphine 3,489 (7%)	ER morphine 2,117 (7%)	ER morphine 3,597 (7%)	ER morphine 3,240 (7%)	ER morphine 2,544 (7%)	ER morphine 2,547 (7%)	ER morphine 1,526 (7%)
5	Methadone 1,953 (4%)	Methadone 1,841 (4%)	Methadone 1,016 (3%)	ER oxymorphone 1,655 (3%)	ER oxymorphone 1,651 (3%)	IR morphine 1,049 (3%)	IR morphine 938 (2%)	IR morphine 528 (2%)

Figure 3: Most common opioids dispensed concurrently with OxyContin of those analyzed (MarketScan data)

Note that total does not equal 100% because individuals could be dispensed multiple comparator opioids. Denominator includes all patients dispensed OxyContin and comparator opioids concurrently.

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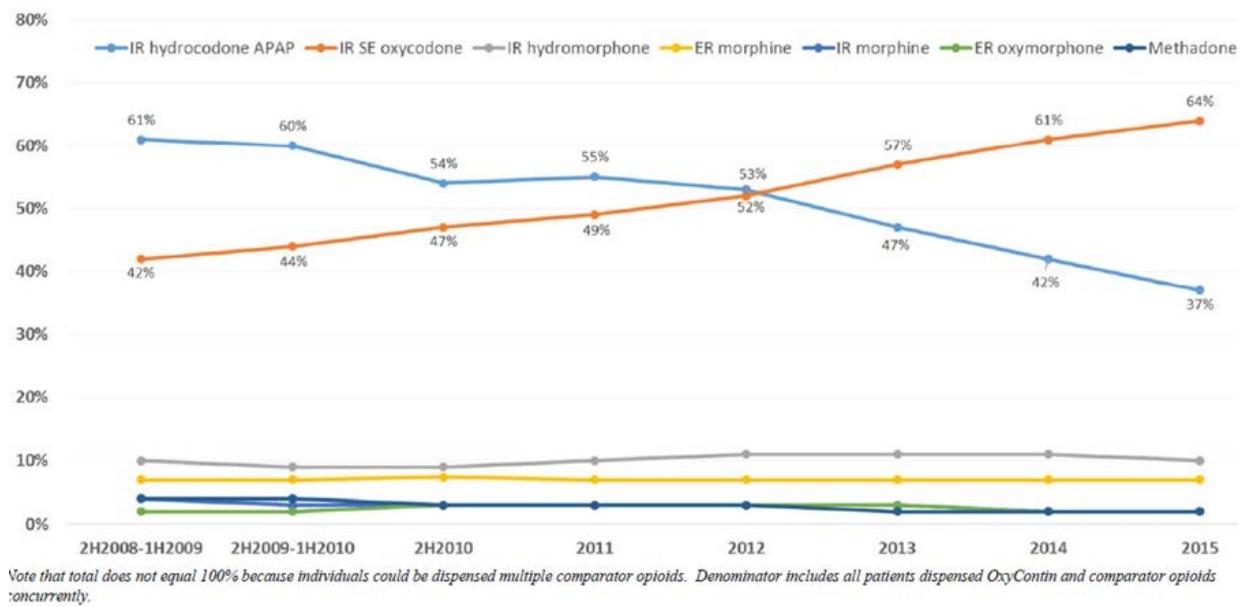
Table 10: Demographics of patients dispensed OxyContin (Medicaid data)

	2H2008-1H2009	2H2009-1H2010	2H2010	2011	2012
Number of patients	43,712	47,701	35,532	47,138	44,064
Geographic distribution, n (%)					
Northeast	13,302 (30%)	16,241 (34%)	12,663 (36%)	14,090 (30%)	12,798 (29%)
Midwest	9,898 (23%)	11,039 (23%)	8,493 (24%)	17,038 (36%)	14,954 (34%)
South	14,225 (33%)	14,569 (31%)	10,467 (29%)	12,194 (26%)	12,970 (29%)
West	6,287 (14%)	5,852 (12%)	3,909 (11%)	3,816 (8%)	3,342 (8%)
Age, Years, mean	47.04	46.65	47.06	47.10	47.33
Age, categorized, n (%)					
0-15 years	188 (<1%)	198 (0%)	117 (<1%)	223 (<1%)	221 (1%)
16-34 years	7,001 (16%)	8,259 (17%)	5,804 (16%)	7,979 (17%)	7,239 (16%)
35-64 years	33,980 (78%)	36,605 (77%)	27,763 (78%)	36,563 (78%)	34,288 (78%)
65-74 years	1,286 (3%)	1,402 (3%)	930 (3%)	1,330 (3%)	1,312 (3%)
75+ years	1,204 (3%)	1,175 (2%)	877 (2%)	999 (2%)	942 (2%)
Unknown	53 (<1%)	62 (<1%)	41 (<1%)	44 (<1%)	62 (<1%)
Gender, n (%)					
Female	25,096 (57%)	26,763 (56%)	19,912 (56%)	26,648 (57%)	25,077 (57%)
Male	18,563 (42%)	20,876 (44%)	15,579 (44%)	20,446 (43%)	18,925 (43%)
Gender Unknown	53 (<1%)	62 (<1%)	41 (<1%)	44 (<1%)	62 (<1%)
Race, n (%)					
White	30,028 (69%)	31,465 (66%)	23,158 (65%)	32,469 (69%)	30,297 (69%)
Black	8,094 (19%)	9,734 (20%)	7,416 (21%)	9,061 (19%)	8,309 (19%)
American Indian	722 (2%)	692 (1%)	518 (1%)	669 (1%)	717 (2%)
Asian	213 (<1%)	242 (1%)	186 (1%)	285 (1%)	251 (1%)
Hispanic	666 (2%)	710 (1%)	583 (2%)	705 (1%)	751 (2%)
Hawaiian	63 (<1%)	61 (<1%)	42 (<1%)	37 (<1%)	25 (<1%)
Other Race	2,141 (5%)	2,937 (6%)	2,305 (6%)	2,180 (5%)	1,936 (4%)
Race Unknown	1,785 (4%)	1,860 (4%)	1,324 (4%)	1,732 (4%)	1,778 (4%)

Table 11: Prevalence of relevant diagnoses among patients dispensed OxyContin (Medicaid data)

	2H2008-1H2009 (n=43,712)	2H2009-1H2010 (n=47,701)	2H2010 (n=35,532)	2011 (n=47,138)	2012 (n=44,064)
Diagnoses, n (%)					
Pain	38,831 (89%)	42,325 (89%)	29,722 (84%)	43,505 (92%)	40,880 (93%)
Psychiatric/ Substance Use Disorders	21,122 (48%)	22,475 (47%)	11,717 (33%)	21,737 (46%)	21,077 (48%)

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Table 12: Opioid utilization patterns among patients dispensed OxyContin (Medicaid data)

	2H2008-1H2009 (n=43,712)	2H2009-1H2010 (n=47,701)	2H2010 (n=35,532)	2011 (n=47,138)	2012 (n=44,064)
# Prescriptions dispensed, mean	6.06	6.35	4.41	5.96	6.06
# days dispensed, mean	136.31	143.03	94.50	135.87	138.50
# tablets dispensed, mean	439.01	457.93	304.27	377.11	376.54
# tablets dispensed, median	258	300	240	208	210
# tablets dispensed by tablet strength, Mean					
10mg	44.35	41.08	29.41	41.98	42.40
15mg	3.70	5.70	4.70	7.21	9.95
20mg	93.41	84.20	57.03	75.95	74.97
30mg	17.06	27.65	22.30	32.69	38.55
40mg	117.17	112.24	70.61	83.99	79.11
60mg	23.39	36.18	27.20	36.97	40.81
80mg	139.94	150.87	93.02	98.32	90.74
Total # Prescriptions Dispensed	264,900	302,898	156,839	281,167	266,888
Total # Tablets Dispensed	19,189,979	21,843,840	10,811,152	17,776,215	16,591,948

Table 13: Number of patients dispensed OxyContin, by opioid concomitancy (Medicaid data)

	2H2008-1H2009	2H2009-1H2010	2H2010	2011	2012
Number (%)					
OxyContin alone for the duration of OxyContin prescriptions in that year [a]	13,345 (31%)	15,312 (32%)	12,226 (34%)	14,263 (30%)	12,495 (28%)
OxyContin dispensed concurrently with comparator opioids in that year [b]	26,649 (61%)	29,008 (61%)	21,525 (61%)	31,538 (67%)	30,495 (69%)
A mixture of OxyContin alone and OxyContin concurrent with comparator opioids [c]	21,504 (81%)	22,919 (79%)	15,774 (73%)	24,759 (79%)	23,574 (77%)
OxyContin dispensed concurrently with comparator opioids only	5,145 (19%)	6,089 (21%)	5,751 (27%)	6,779 (21%)	6,921 (23%)
OxyContin dispensed concurrently with non-comparator opioids in that year	3,718 (9%)	3,381 (7%)	1,781 (5%)	1,337 (3%)	1,074 (2%)
Total	43,712	47,701	35,532	47,138	44,064
Mean Person Time (Days)					
OxyContin alone for the duration of OxyContin use in that year [a]	119.1	126.2	88.2	116.8	123.7
OxyContin dispensed concurrently with comparator opioids in that year [b]	144.3	150.6	98.5	144.4	145.0
A mixture of OxyContin alone and OxyContin concurrent with comparator opioids [c]	157.5	164.0	104.4	158.0	159.0
OxyContin used alone	68.9	70.3	44.1	65.4	63.0
OxyContin dispensed concurrently with comparator opioids in that year	88.6	93.7	60.3	92.5	96.0
OxyContin dispensed concurrently with comparator opioids only	89.1	100.1	82.2	94.7	97.2
OxyContin dispensed concurrently with non-comparator opioids in that year	140.7	154.0	90.0	138.1	126.3
Total	136.3	143.0	94.5	135.9	138.5
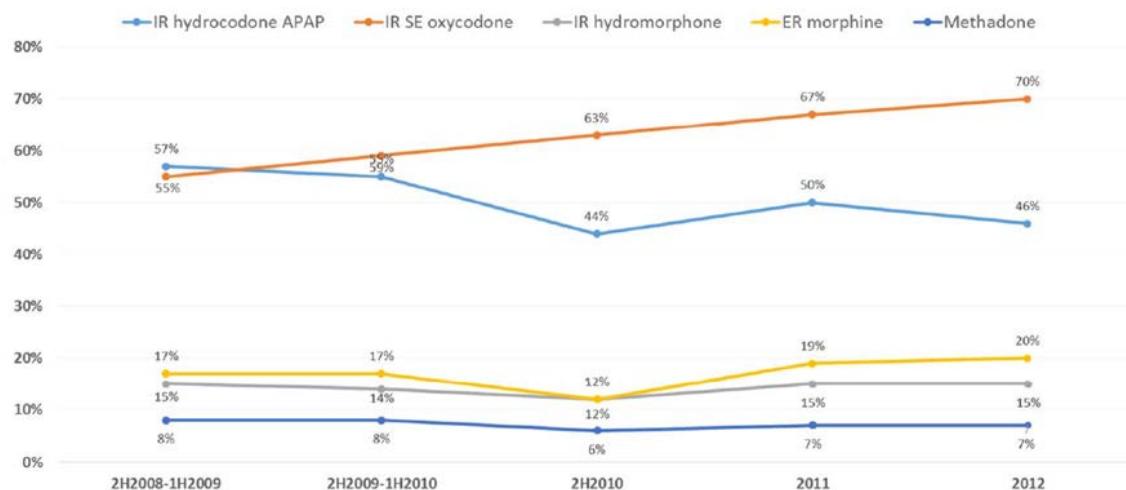
[a] OxyContin alone indicates OxyContin dispensed without other opioids as defined in Table 2 above (ie, neither comparator nor non-comparator opioid analgesics).
[b] OxyContin and comparator opioids concurrently, with or without non-comparator opioids
[c] Reflects the number of patients who did not exclusively use OxyContin alone, but had periods of use of OxyContin alone as well as periods of use of OxyContin concurrently with comparator opioids.

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Table 14: Most common opioids dispensed concurrently with OxyContin of those analyzed (Medicaid data)

Rank	2H2008-1H2009	2H2009-1H2010	2H2010	2011	2012
1	IR hydrocodone-acetaminophen 15,198 (57%)	IR SE oxycodone 17,151 (59%)	IR SE oxycodone 13,649 (63%)	IR SE oxycodone 20,992 (67%)	IR SE oxycodone 21,436 (70%)
2	IR SE oxycodone 14,788 (55%)	IR hydrocodone-acetaminophen 15,879 (55%)	IR hydrocodone-acetaminophen 9,378 (44%)	IR hydrocodone-acetaminophen 15,619 (50%)	IR hydrocodone-acetaminophen 14,103 (46%)
3	ER morphine 4,596 (17%)	ER morphine 4,830 (17%)	ER morphine 2,591 (12%)	ER morphine 5,839 (19%)	ER morphine 6,004 (20%)
4	IR hydromorphone 4,033 (15%)	IR hydromorphone 4,113 (14%)	IR hydromorphone 2,587 (12%)	IR hydromorphone 4,623 (15%)	IR hydromorphone 4,547 (15%)
5	Methadone 2,194 (8%)	Methadone 2,371 (8%)	Methadone 1,193 (6%)	Methadone 2,278 (7%)	ER oxymorphone 2,395 (8%)

Figure 4: Most common comparator opioids dispensed concurrently with OxyContin (Medicaid data)

Note that total does not equal 100% because individuals could be dispensed multiple comparator opioids. Denominator includes all patients dispensed OxyContin and comparator opioids concurrently. Though not shown in figure, in 2012, methadone was replaced by ER oxymorphone as the fifth most common comparator opioid dispensed concurrently with OxyContin as shown in Table 12; methadone shown in figure for completeness (n=2,006 patients [7%] were prescribed methadone in 2012).
APAP: acetaminophen; ER: extended-release; IR: immediate-release; SE: single-entity

8.2 OUTCOME VALIDATION SUB-STUDY

NOTE: Sponsor description of outcome validation sub-study results (HIRD data only)
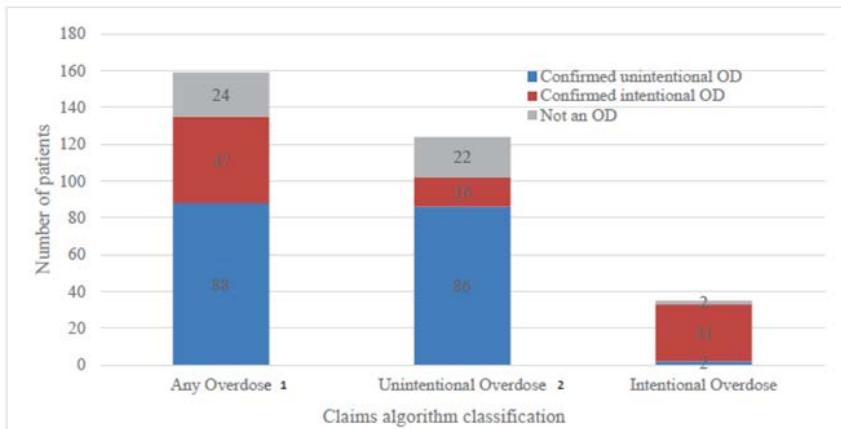
For this sub-study, medical records were requested for 300 randomly selected individuals with claims diagnoses of opioid overdose during the study period of 2008 to 2015 in HIRD, and 159 medical records were reviewed.

Of the 159 cases identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) overdose codes and for which medical records were obtained, 135 (85%; 95% CI = 78-90%) were confirmed overdoses (47 intentional and 88 unintentional; Figure 5 below). The false positive cases consisted of 12 patients (8%) with opioid adverse events or with anesthesia or surgery related events, and 12 (8%) with no relevant event (miscoded or undeterminable). Results were similar by place of setting, and

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when excluding the 12 individuals with heroin codes (965.01, E850.0), the PPV among remaining patients was 84% (123/147).

The algorithm to detect unintentional overdose had lower accuracy than the overall overdose algorithm (PPV=69.4%), but a high sensitivity (97.7%) (Figure 5 and Figure 6 below). The lower PPV was due to 16 intentional overdoses being misclassified as unintentional overdoses with the intentionality algorithm (Figure 6).

Figure 5: Chart classifications of events identified as possible opioid-related overdoses using claims-based opioid-related poisoning codes in HIRD
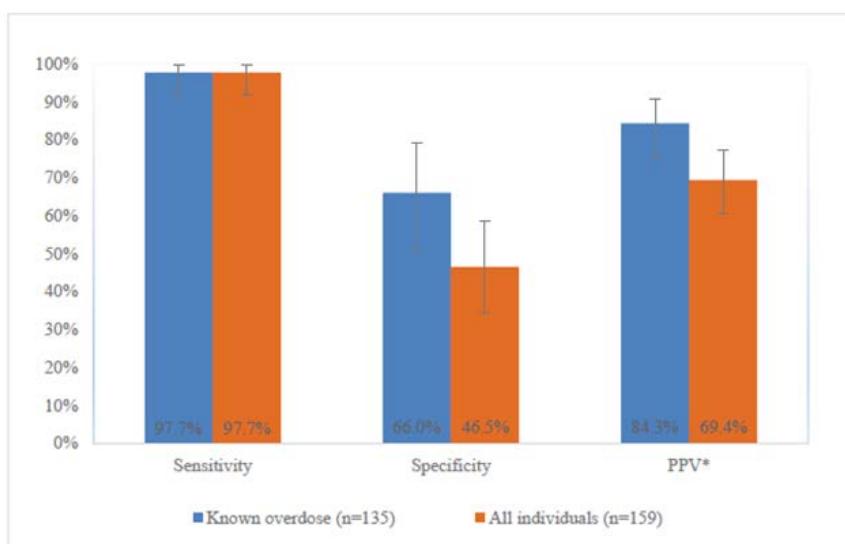
[1] Any type of overdose included intentional overdoses, unintentional overdoses, and overdoses of unknown intent. The PPV for any overdose=85%, 95% confidence interval=78%-90% (calculated as a binomial exact confidence interval).
[2] Among the 159 patients in this validation study, 124 met the claims algorithm for unintentional overdose further defined in Section 6.5.2. Of the 124 classified as unintentional overdose 86 were found on medical record review to have had an unintentional overdose, while 16 had intentional overdose and 22. This represents a PPV of 69.4% (86/124) for unintentional overdose, with a 95%CI of 60.4%-77.3%.
Abbreviations: HIRD=HealthCore Integrated Research Database®; OD=opioid overdose; PPV=positive predictive value.

Figure 6: Performance of unintentional overdose definition among patients with a known overdose and all patients with an overdose code in the validation study in HIRD

Abbreviations: n=number; PPV=positive predictive value.
[a] Defined as either unintentional or unknown intentionality by medical record.
[b] The PPV for an unintentional overdose among all 159 individuals=86/124 (69.4%).

8.3 MEDICAID DATA USABILITY SUB-ANALYSES

NOTE: Sponsor description of Medicaid MAX data usability sub-study (See Li et al for complete description of study methods)

Background:

The Medicaid MAX data for use in this study has been the subject of extended discussion between Purdue and the US Food and Drug Administration (FDA), primarily focusing on which states and years could be used in a comprehensive review that combines fee-for-service (FFS) and comprehensive managed care (CMC) files. The FDA suggested that Purdue apply recently published screening criteria for Medicaid (Li et al. 2017[xxxviii]) to select states and years for the 3051-4 common-protocol analyses with Medicaid MAX data.

Specifications of study measures from Li et al. (2017):

Connectivity:

"[T]o test measures of connectivity criteria, we first defined minimum continuous enrollment periods, during which beneficiaries were enrolled exclusively in FFS or CMC plans. We then constructed cohorts in which enrollees met the denominator definitions (i.e., received the first element in the service pair, such as having diabetes diagnosis) for each calendar year. Finally, we identified enrollees with complete service pairs as the numerators (i.e., with the second element, such as having antidiabetic fill) and compared the resulting proportions of enrollees in CMC and FFS plans."

Continuity:

"[T]o test measures of continuity criteria, we first identified beneficiaries who switched enrollment from FFS to CMC plans with defined minimum lengths of continuous enrollment (4 months before and after enrollment for antidiabetic and antihypertensive refill measures and 4 months before and 3 months after enrollment for the evaluation and management services measures) for each calendar year. We then selected patients meeting the definition of chronic service/treatment use during the FFS period prior to enrollment switch. Lastly, we checked the recurrence of service/ treatment use during the CMC period after enrollment switch and calculated the proportion of continuous use to determine whether a measure was satisfied."

Evaluation:

"We considered a connectivity measure to be satisfied if a state had at least 50 CMC enrollees in a given study year and the calculated proportion for CMC plans was no more than 10% below the average proportion for FFS plans of the same states from 2006 to 2010."

[xxxviii] Li et al. (2017) Internal validation of Medicaid Analytic eXtract (MAX) data capture for comprehensive managed care plan enrollees from 2007 to 2010. Pharmacoepidemiology and Drug Safety: 1-10; https://doi.org/10.1002/pds.4365

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NOTE: The connectivity criteria used for PMR 3051-4 differs slightly, as a more lenient difference of 15% was allowed between the CMC and FFS proportions.

"A continuity measure was considered as satisfied if a state had at least 50 enrollees in a given study year and the calculated proportion was greater than 60%."

NOTE: The continuity criteria used for PMR 3051-4 also differed as a calculated proportion of 50% or more was considered acceptable.

Table 16: Specifications of study measures noted in Li et al.

Measures	Enrollment	Numerator	Denominator
Connectivity measures			
Diabetic patients filling antidiabetic	3 months after the eligible diagnosis	1 antidiabetic pharmacy claim record within 3 months after the eligible diagnosis	1 IP or 2 OT encounter/claims records within 6 months with diagnosis of diabetes (ICD 9 codes 250.x)
Hypothyroid patients filling thyroid agents	3 months after the eligible diagnosis	1 hypothyroid pharmacy claim record within 3 months after the eligible diagnosis	1 IP or 2 OT encounter/claims records within 6 months with diagnosis of hypothyroidism (ICD 9 codes 243.x, 244.x)
Antibiotic fills following health care visits[a]	1 month before the prescription fill	1 IP or OT encounter/claims record within the 1 month preceding the antibiotic fill	1 pharmacy claim record for oral antibiotics
Fracture hospitalizations having follow-up visits	3 months after the eligible diagnosis	1 OT encounter/claim record within 3 months after the eligible diagnosis	1 IP encounter/claim record with fracture (ICD 9 codes 805.xx-829.xx) as primary or secondary diagnosis
Continuity measures			
Antidiabetic refills	4 months before and 4 months after enrollment switch	Recurrent antidiabetic pharmacy claim record within 4 months after enrollment switch	2 separate pharmacy claims records for antidiabetics (≥30 days apart but within 6 months) and 1 OT or IP claim record with diagnosis of diabetes before enrollment switch
Antihypertensive refills	4 months before and 4 months after enrollment switch	Recurrent antihypertensive pharmacy claim record within 4 months after enrollment switch	2 separate pharmacy claims records for antihypertensive (≥30 days apart but within 6 months) and 1 OT or IP claim with diagnosis of hypertension before enrollment switch
E&M services use	4 months before and 3 months after enrollment switch	Recurrent OT E&S service claim records within 3 months after enrollment switch	3 OT E&S services claim records (≥4 weeks apart but within 2 months) before enrollment switch

Abbreviations: E&M, evaluation and management; ICD, International Classification of Diseases; IP, inpatient; OT, other therapy.

[a]Considering the large sample size of the antibiotic cohort, our analysis used a 5% random sample of eligible patients for this specific measure.

Final criteria:

"To consider the CMC data as usable in research and policy analyses, states with CMC enrollment of more than 5% (among full-benefit enrollees) had to satisfy at least 3 out of 4 connectivity measures (to accommodate small sample size issues that did not allow stable estimates for some measures in some states) and all 3 continuity measures."

Sponsor description of results for FFS and CMC usability by state*year*basis of eligibility (BOE) group

Summary of FFS usability:

Not all FFS beneficiaries were retained for the PMR 3051-4 study even if they had a high FFS penetration in the state*year*BOE group. While Li et al. considered FFS as the gold standard to evaluate the completeness of CMC data, during the analysis of the connectivity measures, we came across results that questioned the completeness of FFS in a subset of states. Thus, FFS beneficiaries were only retained among those states, years, and BOE groups in which there were at least 3 connectivity measure percentages that are consistently greater than 40%. For example, within the adult population, FFS beneficiaries in Arkansas had 3 out of 4 connectivity measure percentages greater than 40% in 2010 and 2011. Thus,

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the FFS plans in Arkansas for those with BOE adult from 2010 to 2011 were deemed usable. However, the FFS data were excluded for Arkansas*adult in 2008, 2009, and 2012 since those combinations had less than 3 connectivity measures available.

Similarly, within the disabled group, FFS beneficiaries in Arkansas were both retained as usable for all study years (2008-2012), as there were at least 3 connectivity measures at greater than 40%. There were 20 states that had all their years in both the adult and disabled populations included (i.e. 2008-2012).

In some states, only a subset of years was included. For example, in Arkansas, FFS data were retained as usable among the disabled population for all study years (2008-2012); however, only 2010 and 2011 were considered as usable in the adult population. Oregon, on the other hand, had usable FFS plans for study years (2008-2012) in the adult group and only 2008 and 2010 were usable in the disabled group. Some states only had usable FFS plans in one BOE category. For example, Georgia was not usable for any study years (2008-2012) in the adult group and was usable in 2008, 2009, and 2010 for the disabled population. Overall, 6 states didn't have usable FFS plans for the adult population while FFS plans in Delaware and Iowa were not considered as usable within the disabled population.

Summary of CMC usability:

Li et al. used a set of pre-defined cut off values as a standard to make recommendations for the CMC usability. For the PMR 3051-4 study, a connectivity measure was considered to be satisfied if the calculated proportion for CMC plans was no more than 15% below the average proportion for FFS plans of the same states from 2006 to 2010. A continuity measure was considered as satisfied if the calculated proportion was greater than 50% for this study. As mentioned above in the methods, this is a more lenient scenario in comparison to Li et. al, however, other selection criteria were the same.

To evaluate the usability of CMC data, we first checked the FFS proportion in each year*state*BOE group. For example, California*adult had a 24% FFS penetration in 2008 which meant that the CMC data were more than 5% in this combination. Thus, we checked the connectivity and continuity measures for California*adult*2008.

Among the adult population in California*2008, the connectivity measure of diabetic patients with antidiabetic claims in CMC data was 80.40% which was higher than the average proportion of FFS plans, 76.70%. It thus satisfied the selection criteria that CMC plans were no more than 15% below the average proportion of FFS plans of the same state and BOE group. Additionally, California had more than 50 total CMC enrollees (1,020,932) in 2008. Therefore, we considered the connectivity measure of diabetic patients filling antidiabetic claims to be satisfied for the CMC data. Similarly, all other 3 connectivity measures were satisfied for California in 2008.

As for the 3 continuity measures in California*2008, antidiabetic refills, antihypertensive refills, and E&M services use had the proportions of 81%, 77.1%, 52.4%, respectively, for the CMC data. This indicated that all the 3 continuity measures were satisfied as their proportions were greater than 50%. To summarize, we had 4 connectivity measures and 3 continuity measures which were all satisfied for California*adult*2008. Therefore, CMC data were usable in the California*2008*adult category based on the above evaluation

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criteria. However, CMC data in California was not considered as usable in 2011 because it had one continuity measure proportion (34.10%) less than 50% even though other inclusion criteria were satisfied.

The continuity measures were not considered if they had less than 50 beneficiaries who switched from FFS to CMC. For example, in Virginia*adult, the 3 continuity measures (71.8%, 85.7%, 62.2%) were all larger than 50% in 2011, however the continuity measure of antidiabetic refills had less than 50 enrollees who switched thus this measure was not evaluated while other measures were.

There were 12 states that had CMC claims deemed usable for all years in both the adult and disabled groups. However, there were 19 states in which the CMC population were deemed unusable for all years in both the adult and disable groups. In the other 19 states (and DC), a subset of year*BOE groups met the criteria for CMC inclusion. For example, in Colorado, CMC data were usable only in 2010 for the adult population.

Comparison with Li et al. results:

Among the 7 of the 29 states (Alabama, Arkansas, Idaho, Iowa, Louisiana, Mississippi, and North Carolina) that Li et al. did not assess, all 7 states did not qualify in our analysis for CMC usability. Among the remaining 22 states assessed in Li et al., for the same years 2007-2010, 6 states differed in the CMC usability conclusion (Kansas, Massachusetts, Missouri, Tennessee, Washington and Wisconsin). Some differed in adult population, some in disabled and some in both.

The results could have differed due to our stratification of BOE categories. Li et al. assumed that selected measures would be expected to reflect essential and consistently covered services regardless of the basis for Medicaid eligibility, however, our data showed a difference between the adult and disabled category in a number of states. For example, we gained Massachusetts in 2010 as compared to Li et al. However, we lost Kansas (2008-2010), Missouri (2008-2010; disabled), Tennessee (2009-2010; adult), Washington (2008-2010, adult) and Wisconsin (2008-2010). For the remaining 22 states that Li et al. did not assess, the additional gain for CMC usability included 5 states from 2008, 7 from 2009 and 2010 for adult population; as well as 3 from 2008, and 4 from 2009 and 2010 for disabled. In 2011-2012, the years that were not available in Li et al. analysis, we have 23 states from 2011 and 22 states from 2012 in the adult population and 22 from 2011 and 25 states in 2012 in the disabled population.

FDA's review of the Medicaid MAX data usability findings

DEPI compared tables in the Medicaid MAX data usability appendix of the PMR 3051-4 study report. Specifically, DEPI compared what the sponsor deemed as usable state*year*BOE groups (Table 11 and 12 in that appendix) to other tables in the Appendix that describe the process for evaluating data usability. Upon review, DEPI found that one state*year*BOE category (Idaho*2010*Disabled) may have been included despite not meeting criteria for FFS claims as detailed above. Other state*year*BOE categories were included despite tables in the PMR 3051-4 study report appendix indicating very low FFS penetration in those specified years (Table 17). A few state*year*BOE groups (Connecticut*2008*Adult, Michigan*2008*Disabled, Nebraska*2009*Adult) may have

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been excluded from analysis despite meeting the Li et al. continuity criteria for FFS claims (Table 17).

DEPI also found that many CMC claims were retained, yet there was not enough information to determine whether continuity criteria were met (i.e., <50 beneficiaries in those BOE*state*year categories). This was a significant limitation as 75% of the 12 states that had CMC claims deemed usable for all years in both the adult and disabled groups had one or more BOE*state*year groups where connectivity was unable to be assessed due to the low number of beneficiaries. Additionally, 12 of the 19 states that had subsets of year*BOE groups which met the criteria for CMC inclusion were unable to be assessed for one or more measures of continuity for this same reason (Table 17). As a result, the data from several states may have been included erroneously.

Table 17: FFS data and CMC data usable by state, year and BOE category

States	Adult-FFS	Disabled-FFS	Adult- CMC	Disabled-CMC
AK	2008-2012	2008-2012	None	None
AL	2008-2012	2011-2012	None	None
AR	2010-2011	2008-2012	None	None
AZ	2011-2012	2011-2012	2008-2010*, 2011, 2012*	2008-2010*, 2011, 2012*
CA	2008-2012	2008-2012	2008-2010, 2012	2008-2012
CO	2010	2008-2010	2010*	None
CT	2008†, 2009-2012	2008-2012	2010, 2011	None
DC	2008-2011	2009-2012	2011*	2011*
DE	Excluded	Excluded	None	None
FL	2008-2012	2008-2012	2009-2010	2009-2012
GA	Excluded	2008-2009¥,2010	2008-2012*	2008-2012*
HI	2009-2012	2008	2012*	2012*
IA	2009	Excluded	None	None
ID	2008-2009	2008-2009, 2010‡	None	None
IL	2008-2012	2008-2012	2009-2012	2012
IN	2011-2012	2008-2012	2008-2012	2008-2012
KS	2009-2011	2008-2009, 2011	None	None
KY	2008-2009	2012	2008-2012*, 2009	2008-2012*
LA	2008-2011	2008-2012	2012	2012
MA	2009-2012	2008-2012	2010-2012*	2012*
MD	2008-2012	2008-2012	2008-2009*	2011-2012*
ME	2011-2012	2011-2012	None	None
MI	Excluded	2008†, 2009,2012	2008-2012*	2008-2012*

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MN	2008-2012	2008-2012	2008-2009*, 2010-2012	2008-2012*
MO	2008-2012	2008-2012	2008-2012*	None
MS	Excluded	2008¥,2010, 2011-2012¥	None	2011-2012*
MT	2008-2012	2008-2012	None	None
NC	2008-2012	2008-2012	None	None
ND	2008-2012	2008-2012	None	None
NE	2008, 2009†, 2010-2012	2008-2012	2008-2012	2008-2012
NH	2008-2012	2008-2012	None	None
NJ	2008-2010	2008-2010, 2012	2008-2012*	2008-2012*
NM	2008-2012	2008-2012	2008-2012*	2008-2012*
NV	Excluded	2008-2011	None	None
NY	2008-2012	2008-2012	2008-2012	2008-2012*
OH	2008-2011	2008-2012	2011-2012	2011-2012
OK	2008-2012	2008-2010, 2012	None	None
OR	2008-2012	2008-2010	2009-2012*	2009-2012*
PA	2008-2012	2008-2012	2008-2009,2011	None
RI	2010	2008-2011	2008-2011*	2008-2011*
SC	2008¥ (should have been excluded, discrepant information in percent of FFS enrollment)	2008-2009, 2010-2012¥ (should have been excluded, discrepant information in percent of FFS enrollment in 2010-2012)	2012*	2011-2012*
SD	2008-2012	2008-2012	None	None
TN	2010, 2011-2012¥ (2011-2012 should have been excluded, discrepant information in percent of FFS enrollment)	2008, 2011-2012¥ (2011-2012 should have been excluded, discrepant information in percent of FFS enrollment)	2008,2011-2012*	2008-2012*
TX	2008-2012	2008-2012	2008-2009*, 2010-2012	2008-2009*, 2010, 2011-2012*
UT	2010	2008,2011-2012	2009-2012*	None

			2008-2009*, 2010, 2011*, 2012	
VA	2008-2012	2008-2012	2008-2009*, 2010, 2011*, 2012	2008-2012
VT	2008-2012	2008-2012	None	None
WA	Exclude	2008¥, 2010-2012 (2008 should have been excluded, discrepant information in percent of FFS enrollment)	None	2008-2010, 2012*
WI	2008-2012	2008-2012	None	None
WV	2008-2012	2008-2012	None	None

(FDA generated table using data from the study report)

"Excluded" means that group did not meet FFS connectivity criteria

*Years where continuity was unable to be assessed due to <50 beneficiaries in state*year*BOE category

†Connectivity criteria met but FFS enrollees potentially excluded (based on data provided in tables 11 and 12 of the PMR 3051-4 study report appendices covering Medicaid MAX data usability)

¥ Discrepant information in percent of FFS enrollment provided in PMR 3051-4 study report appendix tables

‡Connectivity criteria not met but FFS enrollees potentially included (based on data provided in tables 11 and 12 of the PMR 3051-4 study report appendices covering Medicaid MAX data usability)

Overall, CMC treatment episodes were comprised of approximately 60% disabled beneficiaries and 40% adult beneficiaries. There were similar proportions of disabled and adult CMC beneficiaries when comparing treatment episodes involving OxyContin and other opioid analgesics. FFS treatment episodes were comprised of approximately 85% disabled beneficiaries, with OxyContin treatment episodes involving slightly higher percentages of disabled beneficiaries compared to other opioid analgesic episodes. For FFS claims, 23% and 77% of episodes involved any use of OxyContin and primary comparator opioid analgesics, respectively. For CMC claims, 18% and 83% of episodes involved any use of OxyContin and primary comparator opioid analgesics, respectively.

It is important to consider the suitability of the Li et al. criteria for evaluating data for use in PMR 3051-4, as these criteria were not developed specifically to evaluate the usability of Medicaid claims in relation to prescription opioid abuse. At the same time, we do not believe that it is a severe limitation as the continuity and connectivity criteria essentially evaluate the completeness of claims across years and states with changing adoption of CMC insurance coverage.

While there were some minor discrepancies between what data were deemed usable (i.e., Table 11 and 12 in the sponsor's appendix) and other tables in the sponsor's Medicaid MAX appendix, the sponsor appropriately implemented the methods for assessing Medicaid data usability proposed by Li et. al, and therefore from the perspective of FDA, the sponsor adequately evaluated the completeness of Medicaid data for use in this study. These minor discrepancies require further clarification by the sponsor, but we do not believe that resolving the noted discrepancies would have meaningfully impacted our interpretation of the primary Medicaid results. The most

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notable issues were primarily due to an inability to assess continuity in CMC claims due to the low number of beneficiaries, a limitation also noted by Li et al.

8.4 DESCRIPTIVE TABLES

8.4.1 Medicaid

Table 18: Demographic and clinical characteristics

	Any use of OxyContin based treatment episodes excluding primary comparators (2.1)		Any use of primary comparator opioids treatment episodes excluding OxyContin (2.1)		OxyContin alone treatment episodes (2.2)		Primary comparator alone opioid treatment episodes (2.2)	
Total treatment episodes, n (%)	522,775	20.40%	2,039,232	79.60%	196,455	7.67%	819,930	32.00%
Total patients, n (%)*	94,445	20.43%	367,814	79.57%	63,079	13.65%	256,839	55.56%
Mean person-time (months) per treatment episode, mean (sd)	2.04	2.99	2.06	2.90	1.43	2.58	1.48	2.53
Total person-time (months) per patient, mean (sd)	7.78	9.97	8.10	10.33	3.73	6.54	4.15	7.19
Demographic characteristics (treatment episode measures)								
Age (years)								
Mean, SD	46.67	10.46	46.94	10.55	47.10	10.51	47.28	10.62
Median	48		49		49		49	
Range (min, max)	16	64	16	64	16	64	16	64
Age category, n (%)								
16-34	81,700	15.63%	316,269	15.51%	29,427	14.98%	123,453	15.06%
35-64	441,075	84.37%	1,722,963	84.49%	167,028	85.02%	696,477	84.94%
Gender, n (%)								
Male	226,900	43.40%	797,712	39.12%	87,000	44.28%	323,947	39.51%
Female	295,875	56.60%	1,241,520	60.88%	109,455	55.72%	495,983	60.49%
Geographic region of patient residence (US), n (%)								
Midwest	192,353	36.79%	598,970	29.37%	71,750	36.52%	243,352	29.68%
Northeast	124,364	23.79%	310,186	15.21%	46,956	23.90%	124,721	15.21%
South	90,046	17.22%	517,380	25.37%	31,810	16.19%	200,656	24.47%
West	116,012	22.19%	612,696	30.05%	45,939	23.38%	251,201	30.64%
Year of index date, n (%)[#]								
2008	84,428	16.15%	269,802	13.23%	34,220	17.42%	113,324	13.82%
2009	132,713	25.39%	472,490	23.17%	52,139	26.54%	196,216	23.93%
2010	58,097	11.11%	215,590	10.57%	22,858	11.64%	87,893	10.72%

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2011	137,222	26.25%	536,537	26.31%	49,093	24.99%	211,594	25.81%
2012	110,315	21.10%	544,813	26.72%	38,145	19.42%	210,903	25.72%
Medicaid coverage type, n (%)								
CMC	227,414	43.50%	1,053,120	51.64%	80,451	40.95%	396,363	48.34%
FFS	295,361	56.50%	986,112	48.36%	116,004	59.05%	423,567	51.66%
Medicaid BOE group, n (%)								
Adult	131,253	25.11%	550,357	26.99%	45,971	23.40%	208,471	25.43%
Disabled	391,522	74.89%	1,488,875	73.01%	150,484	76.60%	611,459	74.57%
Pain diagnosis, n (%)								
Abdominal pain	99,797	19.09%	436,472	21.40%	35,412	18.03%	169,465	20.67%
Amputation	8,612	1.65%	29,062	1.43%	3,289	1.67%	11,761	1.43%
Arthritis, arthropathies, osteoarthritis and musculoskeletal pain	174,234	33.33%	654,673	32.10%	61,811	31.46%	250,189	30.51%
Back pain	238,737	45.67%	974,728	47.80%	82,754	42.12%	362,977	44.27%
Chronic pain	104,311	19.95%	427,644	20.97%	35,540	18.09%	161,434	19.69%
Fibromyalgia	33,511	6.41%	157,272	7.71%	11,001	5.60%	56,721	6.92%
Headache	50,025	9.57%	207,486	10.17%	17,193	8.75%	78,435	9.57%
Malignancy	76,684	14.67%	298,063	14.62%	29,178	14.85%	122,918	14.99%
Multiple sclerosis	5,195	0.99%	24,039	1.18%	1,983	1.01%	10,227	1.25%
Neuropathic pain	16,857	3.22%	70,734	3.47%	6,250	3.18%	28,067	3.42%
Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers	20,432	3.91%	85,372	4.19%	7,935	4.04%	34,887	4.25%
Stroke	8,288	1.59%	37,164	1.82%	3,099	1.58%	15,446	1.88%
Liver disease	36,038	6.89%	154,347	7.57%	13,833	7.04%	63,695	7.77%
Renal disease	19,594	3.75%	79,836	3.92%	7,745	3.94%	33,719	4.11%
COPD	102,942	19.69%	401,863	19.71%	37,814	19.25%	157,067	19.16%
Impaired respiratory function	64,831	12.40%	270,254	13.25%	23,913	12.17%	109,579	13.36%
Deyo-Charlson comorbidity index								
Mean, SD	2.03	2.80	2.02	2.83	2.10	2.83	2.08	2.86
Median	1.00		1.00		1.00		1.00	
Range (min, max)	0	21.00	0	30.00	0	21.00	0	30.00
Psychiatric comorbidities, n (%)								
Attention deficit hyperactive disorder (ADHD)	2,353	0.45%	10,398	0.51%	747	0.38%	3,953	0.48%
Bipolar disorder	32,554	6.23%	147,251	7.22%	11,849	6.03%	58,424	7.13%
Borderline personality disorder	1,766	0.34%	8,560	0.42%	646	0.33%	3,418	0.42%
Generalized anxiety disorder	49,405	9.45%	212,176	10.40%	16,895	8.60%	80,971	9.88%
Major depression disorder	88,372	16.90%	378,331	18.55%	32,646	16.62%	152,368	18.58%
Alcoholism	16,739	3.20%	65,856	3.23%	6,365	3.24%	26,650	3.25%
History of attempted suicide	1,399	0.27%	6,084	0.30%	471	0.24%	2,297	0.28%
Post-traumatic stress disorder	10,575	2.02%	47,743	2.34%	3,560	1.81%	18,596	2.27%
Sleep disorder	36,549	6.99%	146,515	7.18%	12,967	6.60%	56,529	6.89%
Somatoform disorder	233	0.04%	1,601	0.08%	85	0.04%	645	0.08%
Drug dependence								

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Opioid type dependence	30,472	5.83%	119,537	5.86%	11,655	5.93%	51,155	6.24%
Non-opioid drug dependence	32,589	6.23%	119,625	5.87%	11,904	6.06%	47,299	5.77%
History of overdose/poisoning	2,657	0.51%	15,485	0.76%	914	0.47%	6,205	0.76%
Non-opioid medications of abuse potential, n (%)							
Depressants							
Benzodiazepines	97,110	18.58%	368,051	18.05%	23,623	12.02%	104,049	12.69%
Barbiturates	693	0.13%	3,570	0.18%	233	0.12%	1,463	0.18%
Sleep medications	53,245	10.19%	193,823	9.50%	15,304	7.79%	58,931	7.19%
Stimulants							
Amphetamines	5,551	1.06%	21,590	1.06%	1,349	0.69%	6,858	0.84%
Methylphenidate	2,127	0.41%	10,307	0.51%	524	0.27%	3,560	0.43%
Dextromethorphan	59	0.01%	248	0.01%	11	0.01%	73	0.01%
Muscle relaxants	73,079	13.98%	330,895	16.23%	18,085	9.21%	91,563	11.17%
Opioid maintenance therapy medication use during treatment episode, n (%)							
Suboxone	1,094	0.21%	3,618	0.18%	430	0.22%	1,769	0.22%
Subutex/sublingual buprenorphine tablets	73	0.01%	374	0.02%	24	0.01%	167	0.02%
Solution of methadone	3,127	0.60%	12,954	0.64%	1,369	0.70%	6,590	0.80%
Duration of treatment episode (months), mean (sd)	1.40	2.80	1.46	2.78	1.20	2.56	1.30	2.61
Healthcare utilization during six months prior to the index date, mean (sd)^							
All-cause office visits	31.82	34.16	30.52	30.80	31.94	34.95	30.60	31.50
All-cause ED visits	2.28	4.51	2.29	4.26	2.10	4.25	2.15	4.04
All-cause hospitalizations	0.74	1.54	0.73	1.48	0.72	1.53	0.72	1.47
Exposures							
OxyContin dose, n (%)							
10 mg	72,707	13.91%	0	0.00%	28,091	14.30%	0	0.00%
15 mg	10,997	2.10%	0	0.00%	4,004	2.04%	0	0.00%
20 mg	114,431	21.89%	0	0.00%	43,125	21.95%	0	0.00%
30 mg	39,576	7.57%	0	0.00%	13,645	6.95%	0	0.00%
40 mg	114,687	21.94%	0	0.00%	43,009	21.89%	0	0.00%
60 mg	39,059	7.47%	0	0.00%	13,534	6.89%	0	0.00%
80 mg	131,318	25.12%	0	0.00%	51,047	25.98%	0	0.00%
Usage, n (%)							
Existing (continuing) user	371,235	71.01%	1,250,822	61.34%	130,803	66.58%	474,891	57.92%
Incident (new) user	151,540	28.99%	788,410	38.66%	65,652	33.42%	345,039	42.08%
Comparator usage, any, n (%)							
ER morphine	0	0.00%	964,343	47.29%	0	0.00%	360,904	44.02%
TD Fentanyl	0	0.00%	564,161	27.67%	0	0.00%	223,515	27.26%
Methadone tabs/capsules	0	0.00%	510,728	25.05%	0	0.00%	235,511	28.72%
IR oxycodone single entity	133,497	25.54%	290,641	14.25%	0	0.00%	0	0.00%

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IR hydromorphone	29,378	5.62%	137,657	6.75%	0	0.00%	0	0.00%
ER oxymorphone	4,937	0.94%	14,035	0.69%	0	0.00%	0	0.00%
Other opioid use (non primary or secondary comparators)	210,501	40.27%	924,121	45.32%	0	0.00%	0	0.00%
Transdermal delivery system (fentanyl or buprenorphine), n (%)	181	0.03%	317,487	15.57%	2	0.00%	91,952	11.21%
Buprenorphine	177	0.03%	708	0.03%	0	0.00%	0	0.00%
Prior use of opioid analgesics, n (%)								
ER opioid analgesic only	32,438	6.20%	157,941	7.75%	16,489	8.39%	86,306	10.53%
IR opioid analgesic only	58,682	11.23%	270,977	13.29%	8,575	4.36%	45,149	5.51%
Both ER and IR opioid analgesic	413,007	79.00%	1,519,890	74.53%	158,976	80.92%	626,279	76.38%
No opioid analgesic	18,648	3.57%	90,424	4.43%	12,415	6.32%	62,196	7.59%
Prior use of tramadol	40,798	7.80%	197,624	9.69%	12,175	6.20%	67,491	8.23%
Time since the end of the last opioid analgesic (months), mean (SD)	0.35	1.98	0.47	2.45	0.29	1.64	0.39	2.09
Number of different opioid analgesic agents (study drugs) used, mean (SD)	1.73	0.64	1.67	0.61	1.00	0	1.00	0
Number of prescribers of IR or ER opioid analgesics, mean (SD)	0.95	0.86	0.93	0.86	0.75	0.65	0.74	0.66
Number of pharmacies where patient obtained IR or ER opioid analgesics, mean (SD)	1.00	0.91	1.00	0.86	0.77	0.63	0.82	0.63

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Table 19: Benzodiazepine use for OxyContin and comparators, overall and by period

		Prevalence of Benzodiazepine use at baseline										
		All				Two years before reformulation				Two years after reformulation			
		No		Yes		No		Yes		No		Yes	
		N	%	N	%	N	%	N	%	N	%	N	%
Incident + Prevalent	Any OxyContin	332,116	63.5%	190,659	36.5%	175,253	63.7%	99,985	36.3%	156,863	63.4%	90,674	36.6%
	Any ER morphine	662,223	68.7%	302,120	31.3%	288,859	68.3%	133,785	31.7%	373,364	68.9%	168,335	31.1%
	Any TD Fentanyl	347,990	61.7%	216,171	38.3%	176,066	61.8%	108,887	38.2%	171,924	61.6%	107,284	38.4%
	Any Methadone	335,376	65.7%	175,352	34.3%	164,870	65.9%	85,415	34.1%	170,506	65.5%	89,937	34.5%
	Any ER oxymorphone	49,191	75.6%	15,857	24.4%	13,445	72.1%	5,202	27.9%	35,746	77.0%	10,655	23.0%
	Any IR oxycodone single-entity	769,885	68.7%	351,301	31.3%	222,174	65.4%	117,400	34.6%	547,711	70.1%	233,901	29.9%
	Any IR hydromorphone	233,124	67.9%	110,136	32.1%	100,689	68.1%	47,205	31.9%	132,435	67.8%	62,931	32.2%
Prevalent	Any OxyContin	230,602	62.1%	140,633	37.9%	116,994	61.9%	72,034	38.1%	113,608	62.4%	68,599	37.6%
	Any ER morphine	379,188	66.3%	192,473	33.7%	163,875	66.4%	82,767	33.6%	215,313	66.2%	109,706	33.8%
	Any TD Fentanyl	210,383	60.1%	139,628	39.9%	106,800	60.4%	70,145	39.6%	103,583	59.9%	69,483	40.1%
	Any Methadone	210,767	64.0%	118,383	36.0%	102,577	64.3%	56,831	35.7%	108,190	63.7%	61,552	36.3%
	Any ER oxymorphone	28,431	74.6%	9,657	25.4%	6,555	68.8%	2,973	31.2%	21,876	76.6%	6,684	23.4%
	Any IR oxycodone single-entity	241,778	62.8%	143,073	37.2%	68,328	59.5%	46,592	40.5%	173,450	64.3%	96,481	35.7%
	Any IR hydromorphone	79,687	61.0%	50,921	39.0%	34,934	61.8%	21,556	38.2%	44,753	60.4%	29,365	39.6%
Incident	Any OxyContin	101,514	67.0%	50,026	33.0%	58,259	67.6%	27,951	32.4%	43,255	66.2%	22,075	33.8%
	Any ER morphine	283,035	72.1%	109,647	27.9%	124,984	71.0%	51,018	29.0%	158,051	72.9%	58,629	27.1%
	Any TD Fentanyl	137,607	64.3%	76,543	35.7%	69,266	64.1%	38,742	35.9%	68,341	64.4%	37,801	35.6%
	Any Methadone	124,609	68.6%	56,969	31.4%	62,293	68.5%	28,584	31.5%	62,316	68.7%	28,385	31.3%
	Any ER oxymorphone	20,760	77.0%	6,200	23.0%	6,890	75.6%	2,229	24.4%	13,870	77.7%	3,971	22.3%
	Any IR oxycodone single-entity	528,107	71.7%	208,228	28.3%	153,846	68.5%	70,808	31.5%	374,261	73.1%	137,420	26.9%
	Any IR hydromorphone	153,437	72.2%	59,215	27.8%	65,755	71.9%	25,649	28.1%	87,682	72.3%	33,566	27.7%

Abbreviations: ER = extended release; IR = immediate release; N = number; PC = primary comparator; SC = secondary comparator; TD = transdermal; w = with.

^All OxyContin categories in this table exclude period w/ concomitant use of any PC or SC, and all comparator categories in this table exclude period w/ concomitant use with Oxy or PC or any other SC

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Table 20: Bi-annual rates of opioid overdose, by opioid

	Any OxyContin, Primary or Secondary Comparator use*				Any OxyContin use*				Any ER morphine tables and capsule use				Any Fentanyl use			
	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months
All users																
July-December 2008	152734	1074	519838.8	2.07	29037	182	105320.2	1.73	43130	312	143547.2	2.17	29480	228	100010.9	2.28
January-June 2009	170248	1332	537358.2	2.48	27225	169	96901.7	1.74	47890	360	151109.5	2.38	30015	248	97274.7	2.55
July-December 2009	188803	1421	615629.0	2.31	30261	196	110686.5	1.77	49448	402	165857.5	2.42	28572	249	95168.4	2.62
January-June 2010	184986	1379	597690.2	2.31	27800	186	101885.0	1.83	47140	405	157317.7	2.57	26124	218	86051.9	2.53
July-December 2010	201509	1563	666493.3	2.35	29137	218	107364.3	2.03	49937	434	171043.1	2.54	26495	250	90398.5	2.77
January-June 2011	230162	1657	686124.1	2.42	28087	181	92585.5	1.95	54984	450	175090.9	2.57	28297	239	88929.0	2.69
July-December 2011	252283	1701	810384.0	2.10	27230	151	98033.7	1.54	59813	470	203083.0	2.31	29855	226	100150.0	2.26
January-June 2012	277042	1795	850313.0	2.11	25776	160	90007.9	1.78	68421	483	220475.9	2.19	31280	263	101304.0	2.60
July-December 2012	286114	1787	899969.0	1.99	25173	150	93138.7	1.61	70287	539	239618.6	2.25	30793	264	103917.8	2.54

	Any Methadone use				Any ER Oxymorphone use				Any IR SE Oxycodone				Any IR Hydromorphone			
	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months
All users																
July-December 2008	27025	272	104559.2	2.60	2087	12	5526.9	2.17	44777	211	108324.8	1.95	24125	110	39510.6	2.78
January-June 2009	30707	366	110716.2	3.31	3096	38	8203.4	4.63	51419	287	115886.0	2.48	28448	145	44191.7	3.28
July-December 2009	32412	371	124046.0	2.99	3912	20	11699.1	1.71	68122	361	165720.1	2.18	29077	156	47272.6	3.30
January-June 2010	30439	329	116455.9	2.83	4255	29	13079.2	2.22	72049	428	181906.3	2.35	28004	138	45951.5	3.00
July-December 2010	31058	340	122451.4	2.78	5816	38	18581.9	2.04	86938	487	225565.7	2.16	31662	164	52012.9	3.15
January-June 2011	31852	333	115756.5	2.88	8672	126	27811.8	4.53	107977	592	258437.5	2.29	32814	187	52179.9	3.58
July-December 2011	32931	349	129168.6	2.70	11098	102	41016.0	2.49	126232	617	328865.0	1.88	36191	170	58694.2	2.90
January-June 2012	35005	340	130206.0	2.61	10249	82	35165.3	2.33	145300	731	370468.4	1.97	39205	175	63681.4	2.75
July-December 2012	34329	317	132215.1	2.40	6923	47	23752.6	1.98	155713	780	408339.7	1.91	40516	168	68591.8	2.45

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8.4.2 MarketScan

Table 21: Demographic and clinical characteristics

	Any use of OxyContin based treatment episodes excluding primary comparators (2.1)		Any use of primary comparator opioids treatment episodes excluding OxyContin and other primary comparators (2.1)		OxyContin alone treatment episodes (2.2)		Primary comparator alone opioid treatment episodes (2.2)	
Total treatment episodes, n (%)	561,703	36.5	975,389	63.5	209,536	13.6	395,916	25.8
Total patients, n (%)*	122,254	40.3	181,240	59.7	80,954	26.7	129,034	42.5
Mean person-time per treatment episode in months, mean (sd)	1.43	2.56	1.81	2.88	1.06	2.12	1.34	2.36
Total person-time per treatment episode in months, mean (sd)	5.96	10.28	7.95	11.86	2.94	6.62	4.07	7.93
Demographic characteristics (treatment episode measures)								
Age (years)								
Mean, SD	53.11	12.02	54.64	11.64	54.10	11.89	55.49	11.48
Median	55.00		56.00		56.00		57.00	
Range (min, max)	16.00	74.00	16.00	74.00	16.00	74.00	16.00	74.00
Age category, n (%)								
16-34	51,268	9.1%	66,844	7%	16,818	8.0%	24,024	6.1%
35-64	426,919	76.0%	726,312	75%	157,443	75.1%	290,192	73.3%
65-74	83,516	14.9%	182,233	19%	35,275	16.8%	81,700	20.6%
Gender, n (%)								
Male	276,337	49.2%	415,338	43%	102,715	49.0%	167,922	42.4%
Female	285,366	50.8%	560,051	57%	106,821	51.0%	227,994	57.6%
Geographic region of patient residence (US), n (%)								
Midwest	116,581	20.8%	211,161	22%	46,033	22.0%	88,523	22.4%
Northeast	111,153	19.8%	142,647	15%	42,414	20.2%	59,460	15.0%
South	209,476	37.3%	383,717	39%	74,769	35.7%	149,995	37.9%
West	123,772	22.0%	236,376	24%	46,039	22.0%	97,305	24.6%
Missing/Unknown	721	0.1%	1,488	0%	281	0.1%	633	0.2%
Health plan type, n (%)								
HMO	66,436	11.8%	158,327	16%	25,027	11.9%	66,929	16.9%
PPO	314,282	56.0%	499,367	51%	115,547	55.1%	198,799	50.2%
CDHP/HDHP	23,843	4.2%	41,671	4%	8,579	4.1%	16,338	4.1%
Other	110,481	19.7%	204,181	21%	42,880	20.5%	84,355	21.3%
Unknown	46,661	8.3%	71,843	7%	17,503	8.4%	29,495	7.4%
Year of index date, n (%)[#]								

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2008	56,637	10.1%	103,743	11%	22,380	10.7%	43,470	11.0%
2009	101,591	18.1%	164,693	17%	39,240	18.7%	68,584	17.3%
2010	51,073	9.1%	83,329	9%	19,656	9.4%	34,498	8.7%
2011	124,306	22.1%	208,544	21%	45,816	21.9%	84,483	21.3%
2012	98,785	17.6%	175,547	18%	35,950	17.2%	70,261	17.7%
2013	71,271	12.7%	133,335	14%	25,995	12.4%	53,476	13.5%
2014	51,198	9.1%	92,137	9%	18,027	8.6%	35,496	9.0%
2015	6,842	1.2%	14,061	1%	2,472	1.2%	5,648	1.4%
Pain diagnosis, n (%)								
Abdominal pain	80,535	14.3%	179,919	18%	29,483	14.1%	71,735	18.1%
Amputation	3,629	0.6%	5,950	1%	1,400	0.7%	2,472	0.6%
Arthritis, arthropathies, osteoarthritis and musculoskeletal pain	211,401	37.6%	299,111	31%	74,537	35.6%	114,533	28.9%
Back pain	253,930	45.2%	471,567	48%	86,043	41.1%	174,454	44.1%
Chronic pain	65,463	11.7%	143,661	15%	21,398	10.2%	52,674	13.3%
Fibromyalgia	36,288	6.5%	79,889	8%	12,052	5.8%	29,707	7.5%
Headache	40,416	7.2%	82,333	8%	14,018	6.7%	31,696	8.0%
Malignancy	125,792	22.4%	255,357	26%	52,040	24.8%	110,659	28.0%
Multiple sclerosis	3,973	0.7%	8,746	1%	1,521	0.7%	3,599	0.9%
Neuropathic pain	14,164	2.5%	32,678	3%	5,472	2.6%	13,650	3.4%
Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers	19,177	3.4%	38,666	4%	7,354	3.5%	15,720	4.0%
Stroke	8,341	1.5%	18,263	2%	3,269	1.6%	7,690	1.9%
Liver disease	26,527	4.7%	52,744	5%	10,089	4.8%	21,480	5.4%
Renal disease	18,590	3.3%	39,458	4%	7,505	3.6%	16,967	4.3%
COPD	64,556	11.5%	129,161	13%	23,929	11.4%	51,942	13.1%
Impaired respiratory function	62,946	11.2%	128,888	13%	24,477	0.117	54,017	13.6%
Deyo-Charlson comorbidity index								
Mean, SD	2.03	3.06	2.42	329%	2.21	3.17	2.56	3.36
Median	1.00		1.00		1.00		1.00	
Range (min, max)	0.00	20.00	0.00	2400%	0.00	20.00	0.00	24.00
Psychiatric comorbidities, n (%)								
Attention deficit hyperactive disorder (ADHD)	2,433	0.4%	3,399	0%	702	0.3%	1,166	0.3%
Bipolar disorder	12,755	2.3%	26,646	3%	4,512	2.2%	10,540	2.7%
Borderline personality disorder	263	0.0%	756	0%	102	0.0%	299	0.1%
Generalized anxiety disorder	37,346	6.6%	69,000	7%	12,391	5.9%	26,053	6.6%
Major depression disorder	62,556	11.1%	128,661	13%	22,024	10.5%	50,846	12.8%
Substance use disorder	16,038	2.9%	30,911	3%	4,838	2.3%	10,953	2.8%
Alcoholism	4,981	0.9%	8,617	1%	1,658	0.8%	3,302	0.8%
History of attempted suicide	761	0.1%	1,138	0%	241	0.1%	414	0.1%
Post-traumatic stress disorder	3,286	0.6%	7,346	1%	1,106	0.5%	2,891	0.7%
Sleep disorder	48,693	8.7%	90,282	9%	17,618	8.4%	36,005	9.1%
Somatoform disorder	110	0.0%	475	0%	32	0.0%	193	0.0%

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Drug dependence								
Opioid type dependence	9,560	1.7%	18,777	2%	2,952	1.4%	6,916	1.7%
Non-opioid drug dependence	7,963	1.4%	15,083	2%	2,374	1.1%	5,184	1.3%
History of overdose/poisoning	1,428	0.3%	3,801	0%	423	0.2%	1,355	0.3%
Non-opioid medications of abuse potential during treatment episode, n (%)^								
Depressants								
Benzodiazepines	86,631	15.4%	154,579	16%	21,350	10.2%	44,308	11.2%
Barbiturates	331	0.1%	637	0%	126	0.1%	192	0.0%
Sleep medications	51,642	9.2%	94,496	10%	14,691	7.0%	28,497	7.2%
Stimulants								
Amphetamines	6,895	1.2%	12,532	1%	1,583	0.8%	3,634	0.9%
Methylphenidate	3,336	0.6%	7,331	1%	906	0.4%	2,554	0.6%
Dextromethorphan	14	0.0%	14	0%	7	0.0%	1	0.0%
Muscle relaxants	68,062	12.1%	130,608	13%	14,877	7.1%	32,326	8.2%
Opioid maintenance therapy medication use during treatment episode, n (%)								
Suboxone	1,814	0.3%	1,999	0%	584	0.3%	762	0.2%
Subutex/sublingual buprenorphine tablets	346	0.1%	351	0%	96	0.0%	137	0.0%
Solution of methadone	50	0.0%	338	0%	17	0.0%	181	0.0%
Duration of treatment episode (months), mean (sd)	1.30	2.76	1.48	2.89	1.14	2.51	1.33	2.64
Healthcare utilization during six months prior to the index date, mean (sd)^								
All-cause office visits	8.63	7.00	9.16	7.16	8.48	7.17	9.00	7.26
All-cause ED visits	0.67	1.62	0.79	1.82	0.62	1.48	0.76	1.75
All-cause hospitalizations	0.53	0.93	0.54	1.03	0.52	0.94	0.54	1.04
Distinct medication classes (defined by the four-digit level of the GPI code) dispensed	9.25	5.03	10.13	5.10	9.27	4.98	10.07	5.08
Exposures								
OxyContin dose, n (%)								
10 mg	184,071	32.8%			71,193	34.0%		
15 mg	18,435	3.3%			6,504	3.1%		
20 mg	192,733	34.3%			71,276	34.0%		
30 mg	49,120	8.7%			15,887	7.6%		
40 mg	107,831	19.2%			38,289	18.3%		
60 mg	34,789	6.2%			10,956	5.2%		
80 mg	59,351	10.6%			21,100	10.1%		
Usage, n (%)								
Existing (continuing) user	395,420	70.4%	676,600	69.4%	142,230	67.9%	269,650	68.1%
Incident (new) user	166,283	29.6%	298,789	30.6%	67,306	32.1%	126,266	31.9%
Comparator usage, any, n (%)								
ER morphine			383,442	39.3%			147,513	37.3%

TD Fentanyl			441,383	45.3%			178,085	45.0%
Methadone tabs/capsules			150,564	15.4%			70,318	17.8%
IR oxycodone single entity	148,267	26.4%	122,702	12.6%				
IR hydromorphone	24,217	4.3%	67,264	6.9%				
ER oxymorphone	5,769	1.0%	10,630	1.1%				
Other opioid use (non primary or secondary comparators)	229,127	40.8%	451,161	46.3%				
Transdermal delivery system (fentanyl or buprenorphine), n (%)	551	0.1%	441,995	45.3%			178,085	45.0%
Buprenorphine	551	0.1%	1,074	0.1%				
Prior use of opioid analgesics, n (%)								
ER opioid analgesic only	35,112	6.3%	89,298	9.2%	17,346	8.3%	48,188	12.2%
IR opioid analgesic only	73,231	13.0%	114,103	11.7%	8,739	4.2%	18,465	4.7%
Both ER and IR opioid analgesic	420,080	74.8%	734,587	75.3%	172,133	82.1%	307,137	77.6%
No opioid analgesic	33,280	5.9%	37,401	3.8%	11,318	5.4%	22,126	5.6%
Prior use of tramadol	41,886	7.5%	79,506	8.2%	11,844	5.7%	26,765	6.8%
Time since the end of the last opioid analgesic (months), mean (sd)	0.49	2.79	0.49	2.78	0.33	2.00	0.39	2.29
Number of different opioid analgesic agents (study drugs) used, mean (sd)	1.73	0.64	1.67	0.62	1.00	0.00	1.00	0.00

Table 22: NDI-linkable versus non-linkable populations

	Any use of OxyContin based treatment episodes excluding primary comparators (2.1)				Any use of primary comparator opioids treatment episodes excluding OxyContin (2.1)			
	NDI linkable		Non-NDI linkable		NDI linkable		Non-NDI linkable	
Total treatment episodes, n (%)	561,703	12.01	1,179,442	25.22	975,389	20.86	1,959,309	41.90
Total patients, n (%)*	122,254	13.70	255,600	28.64	181,240	20.31	333,487	37.36
Mean person-time per treatment episode in months, mean (sd)	1.43	2.56	1.47	2.69	1.81	2.88	2.10	3.20
Total person-time per treatment episode in months, mean (sd)	5.96	10.28	6.47	12.38	7.95	11.86	9.96	15.18
Demographic characteristics (treatment episode measures)								
Age (years)								
Mean, SD	53.11	12.02	51.21	11.45	54.64	11.64	52.22	11.17
Median	55.00		53.00		56.00		53.00	
Range (min, max)	16.00	74.00	16.00	74.00	16.00	74.00	16.00	74.00
Age category, n (%)								
16-34	51,268	9.1%	111,136	9.4%	66,844	6.9%	146,589	7.5%
35-64	426,919	76.0%	959,809	81.4%	726,312	74.5%	1,586,780	81.0%
65-74	83,516	14.9%	108,497	9.2%	182,233	18.7%	225,940	11.5%
Gender, n (%)								
Male	276,337	49.2%	556,721	47.2%	415,338	42.6%	785,172	40.1%
Female	285,366	50.8%	622,721	52.8%	560,051	57.4%	1,174,137	59.9%

Geographic region of patient residence (US), n (%)								
Midwest	116,581	20.8%	288,945	24.5%	211,161	21.6%	518,873	26.5%
Northeast	111,153	19.8%	239,872	20.3%	142,647	14.6%	280,367	14.3%
South	209,476	37.3%	359,278	30.5%	383,717	39.3%	660,855	33.7%
West	123,772	22.0%	258,844	21.9%	236,376	24.2%	452,109	23.1%
Missing/Unknown	721	0.1%	32,503	2.8%	1,488	0.2%	47,105	2.4%
Health plan type, n (%)								
HMO	66,436	11.8%	148,502	12.6%	158,327	16.2%	294,914	15.1%
PPO	314,282	56.0%	719,186	61.0%	499,367	51.2%	1,141,147	58.2%
CDHP/HDHP	23,843	4.2%	82,238	7.0%	41,671	4.3%	125,754	6.4%
Other	110,481	19.7%	178,340	15.1%	204,181	20.9%	317,879	16.2%
Unknown	46,661	8.3%	51,176	4.3%	71,843	7.4%	79,615	4.1%
Year of index date, n (%)								
2008	56,637	10.1%	102,581	8.7%	103,743	10.6%	182,941	9.3%
2009	101,591	18.1%	189,328	16.1%	164,693	16.9%	296,037	15.1%
2010	51,073	9.1%	79,550	6.7%	83,329	8.5%	127,728	6.5%
2011	124,306	22.1%	208,294	17.7%	208,544	21.4%	343,127	17.5%
2012	98,785	17.6%	181,359	15.4%	175,547	18.0%	302,417	15.4%
2013	71,271	12.7%	147,257	12.5%	133,335	13.7%	247,531	12.6%
2014	51,198	9.1%	176,393	15.0%	92,137	9.4%	290,502	14.8%
2015	6,842	1.2%	94,680	8.0%	14,061	1.4%	169,026	8.6%
Pain diagnosis, n (%)								
Abdominal pain	80,535	14.3%	144,629	12.3%	179,919	18.4%	307,386	15.7%
Amputation	3,629	0.6%	7,230	0.6%	5,950	0.6%	10,675	0.5%
Arthritis, arthropathies, osteoarthritis and musculoskeletal pain	211,401	37.6%	484,765	41.1%	299,111	30.7%	657,231	33.5%
Back pain	253,930	45.2%	571,531	48.5%	471,567	48.3%	1,054,457	53.8%
Chronic pain	65,463	11.7%	170,470	14.5%	143,661	14.7%	358,647	18.3%
Fibromyalgia	36,288	6.5%	97,189	8.2%	79,889	8.2%	213,211	10.9%
Headache	40,416	7.2%	97,054	8.2%	82,333	8.4%	195,368	10.0%
Malignancy	125,792	22.4%	154,732	13.1%	255,357	26.2%	290,491	14.8%
Multiple sclerosis	3,973	0.7%	10,171	0.9%	8,746	0.9%	22,059	1.1%
Neuropathic pain	14,164	2.5%	30,312	2.6%	32,678	3.4%	65,949	3.4%
Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers	19,177	3.4%	34,858	3.0%	38,666	4.0%	64,975	3.3%
Stroke	8,341	1.5%	14,758	1.3%	18,263	1.9%	30,242	1.5%
Liver disease	26,527	4.7%	44,631	3.8%	52,744	5.4%	81,378	4.2%
Renal disease	18,590	3.3%	29,937	2.5%	39,458	4.0%	59,347	3.0%
COPD	64,556	11.5%	122,430	10.4%	129,161	13.2%	227,343	11.6%
Imparied respiratory function	62,946	11.2%	95,607	8.1%	128,888	13.2%	173,483	8.9%
Deyo-Charlson comorbidity index								
Mean, SD	2.03	3.06	1.32	2.36	2.42	3.29	1.56	2.58
Median	1.00		0.00		1.00		0.00	
Range (min, max)	0.00	20.00	0.00	22.00	0.00	24.00	0.00	25.00

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Psychiatric comorbidities, n (%)								
Attention deficit hyperactive disorder (ADHD)	2,433	0.4%	6,314	0.5%	3,399	0.3%	10,086	0.5%
Bipolar disorder	12,755	2.3%	27,766	2.4%	26,646	2.7%	58,649	3.0%
Borderline personality disorder	263	0.0%	615	0.1%	756	0.1%	1,663	0.1%
Generalized anxiety disorder	37,346	6.6%	96,071	8.1%	69,000	7.1%	172,621	8.8%
Major depression disorder	62,556	11.1%	149,437	12.7%	128,661	13.2%	294,988	15.1%
Substance use disorder	16,038	2.9%	43,811	3.7%	30,911	3.2%	86,518	4.4%
Alcoholism	4,981	0.9%	11,748	1.0%	8,617	0.9%	18,397	0.9%
History of attempted suicide	761	0.1%	1,943	0.2%	1,138	0.1%	3,307	0.2%
Post-traumatic stress disorder	3,286	0.6%	9,340	0.8%	7,346	0.8%	18,806	1.0%
Sleep disorder	48,693	8.7%	117,529	10.0%	90,282	9.3%	207,849	10.6%
Somatoform disorder	110	0.0%	488	0.0%	475	0.0%	1,144	0.1%
Drug dependence								
Opioid type dependence	9,560	1.7%	28,241	2.4%	18,777	1.9%	56,188	2.9%
Non-opioid drug dependence	7,963	1.4%	19,815	1.7%	15,083	1.5%	38,927	2.0%
History of overdose/poisoning	1,428	0.3%	2,802	0.2%	3,801	0.4%	7,406	0.4%
Non-opioid medications of abuse potential during treatment episode, n (%)								
Depressants								
Benzodiazepines	86,631	15.4%	180,770	15.3%	154,579	15.8%	321,250	16.4%
Barbiturates	331	0.1%	576	0.0%	637	0.1%	1,305	0.1%
Sleep medications	51,642	9.2%	110,466	9.4%	94,496	9.7%	207,110	10.6%
Stimulants								
Amphetamines	6,895	1.2%	18,330	1.6%	12,532	1.3%	34,653	1.8%
Methylphenidate	3,336	0.6%	7,343	0.6%	7,331	0.8%	16,677	0.9%
Dextromethorphan	14	0.0%	3	0.0%	14	0.0%	50	0.0%
Muscle relaxants	68,062	12.1%	161,487	13.7%	130,608	13.4%	321,082	16.4%
Opioid maintenance therapy medication use during treatment episode, n (%)								
Suboxone	1,814	0.3%	4,201	0.4%	1,999	0.2%	4,694	0.2%
Subutex/sublingual buprenorphine tablets	346	0.1%	711	0.1%	351	0.0%	940	0.0%
Solution of methadone	50	0.0%	141	0.0%	338	0.0%	670	0.0%
Duration of treatment episode (months), mean (sd)	1.30	2.76	1.40	3.08	1.48	2.89	1.69	3.33
Healthcare utilization during six months prior to index date, mean (sd)^								
All-cause office visits	8.63	7.00	7.77	6.19	9.16	7.16	8.26	6.57
All-cause ED visits	0.67	1.62	0.60	1.67	0.79	1.82	0.69	1.82
All-cause hospitalizations	0.53	0.93	0.46	0.89	0.54	1.03	0.42	0.95
Distinct medication classes (defined by the four-digit level of the GPI code) dispensed	9.25	5.03	8.83	4.96	10.13	5.10	9.65	5.02
Exposures								
OxyContin dose, n (%)								
10 mg	184,071	32.8%	390,155	33.1%				
15 mg	18,435	3.3%	41,595	3.5%				

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20 mg	192,733	34.3%	381,380	32.3%				
30 mg	49,120	8.7%	109,031	9.2%				
40 mg	107,831	19.2%	218,931	18.6%				
60 mg	34,789	6.2%	76,512	6.5%				
80 mg	59,351	10.6%	126,183	10.7%				
Usage, n (%)								
Existing (continuing) user	395,420	70.4%	829,329	70.3%	676,600	69.4%	1,418,769	72.4%
Incident (new) user	166,283	29.6%	350,113	29.7%	298,789	30.6%	540,540	27.6%
Comparator usage, any, n (%)								
ER morphine					383,442	39.3%	787,319	40.2%
TD Fentanyl					441,383	45.3%	837,133	42.7%
Methadone tabs/capsules					150,564	15.4%	334,857	17.1%
IR oxycodone single entity	148,267	26.4%	308,329	26.1%	122,702	12.6%	257,806	13.2%
IR hydromorphone	24,217	4.3%	51,493	4.4%	67,264	6.9%	130,023	6.6%
ER oxymorphone	5,769	1.0%	12,570	1.1%	10,630	1.1%	22,980	1.2%
Other opioid use (non primary or secondary comparators)	229,127	40.8%	498,083	42.2%	451,161	46.3%	924,896	47.2%
Transdermal delivery system (fentanyl or buprenorphine), n (%)	551	0.1%	1,561	0.1%	441,995	45.3%	838,758	42.8%
Buprenorphine	551	0.1%	1,561	0.1%	1,074	0.1%	2,937	0.1%
Prior use of opioid analgesics, n (%)								
ER opioid analgesic only	35,112	6.3%	71,483	6.1%	89,298	9.2%	189,497	9.7%
IR opioid analgesic only	73,231	13.0%	146,639	12.4%	114,103	11.7%	195,337	10.0%
Both ER and IR opioid analgesic	420,080	74.8%	882,167	74.8%	734,587	75.3%	1,503,113	76.7%
No opioid analgesic	33,280	5.9%	79,153	6.7%	37,401	3.8%	71,362	3.6%
Prior use of tramadol	41,886	7.5%	90,810	7.7%	79,506	8.2%	162,228	8.3%
Time since the end of the last opioid analgesic (months), mean (sd)	0.49	2.79	0.56	3.29	0.49	2.78	0.52	3.11
Number of different opioid analgesic agents (study drugs) used, mean (sd)	1.73	0.64	1.74	0.64	1.67	0.62	1.69	0.63

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Table 23: Bi-annual rates of opioid overdose, by opioid

	Any OxyContin, Primary or Secondary Comparator use				Any OxyContin use				Any ER morphine tables and capsule use				Any Fentanyl use			
	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months
All users																
July-December 2008	82,981	319	246,033	1.297	21,507	85	69,942	1.215	15,555	85	51,939	1.64	18,007	76	62,268	1.22
January-June 2009	80,317	325	223,330	1.455	21,233	80	61,096	1.309	15,255	90	48,161	1.87	17,411	84	56,375	1.49
July-December 2009	92,691	292	266,091	1.097	25,523	83	80,889	1.026	15,945	78	53,249	1.46	17,575	82	60,120	1.36
January-June 2010	97,044	266	257,581	1.033	24,364	91	73,638	1.236	16,085	45	50,315	0.89	17,462	77	56,037	1.37
July-December 2010	112,044	325	317,682	1.023	27,335	90	87,575	1.028	17,936	69	60,784	1.14	19,145	94	66,441	1.41
January-June 2011	116,361	416	308,775	1.347	27,029	105	81,216	1.293	18,981	81	59,863	1.35	19,233	98	62,735	1.56
July-December 2011	120,215	433	326,863	1.325	25,735	106	80,934	1.310	18,984	91	63,178	1.44	19,406	110	65,658	1.68
January-June 2012	115,691	455	300,019	1.517	23,681	94	71,139	1.321	18,522	111	58,842	1.89	18,310	98	59,852	1.64
July-December 2012	116,703	400	308,017	1.299	23,030	92	72,086	1.276	18,137	86	60,340	1.43	17,656	86	60,758	1.42
January-June 2013	92,418	328	232,174	1.413	17,640	53	52,445	1.011	14,643	57	46,915	1.21	14,071	78	45,259	1.72
July-December 2013	92,291	264	231,567	1.140	17,056	39	51,849	0.752	14,186	45	46,232	0.97	13,462	69	44,474	1.55
January-June 2014	69,355	271	156,713	1.729	12,430	43	34,888	1.233	9,809	75	29,006	2.59	9,700	52	29,177	1.78
July-December 2014	64,219	219	142,824	1.533	10,814	52	31,040	1.675	8,702	37	26,105	1.42	8,547	51	26,138	1.95
January-June 2015	21,328	94	40,938	2.296	3,640	16	8,397	1.905	3,444	14	7,944	1.76	3,445	27	7,784	3.47
July-October 2015	3,969	18	3,951	4.556	652	≤10	713	1.403	717	≤10	798	5.01	765	≤10	794	3.78

	Any Methadone use				Any ER Oxymorphone use				Any IR SE Oxycodone				Any IR Hydromorphone			
	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-monhs°
All users																
July-December 2008	7,266	47	29,103	1.61	2,303	≤10	6,674	0.60	26,705	63	50,304	1.25	13,495	22	14,349	1.53
January-June 2009	7,066	46	26,516	1.73	2,520	≤10	6,946	1.01	23,496	47	43,668	1.08	14,939	31	15,321	2.02
July-December 2009	7,434	24	29,505	0.81	2,946	≤10	9,096	0.33	32,473	57	61,482	0.93	15,791	25	16,764	1.49
January-June 2010	7,535	33	27,932	1.18	3,333	≤10	9,698	1.03	37,911	68	68,862	0.99	16,259	25	16,842	1.48
July-December 2010	8,421	32	34,614	0.92	4,255	12	13,439	0.89	46,803	113	91,598	1.23	18,760	22	20,455	1.08
January-June 2011	8,285	54	31,787	1.70	4,652	25	14,483	1.73	50,787	136	95,440	1.42	19,651	37	21,152	1.75
July-December 2011	8,024	44	32,297	1.36	4,990	29	16,964	1.71	55,210	154	106,886	1.44	20,984	33	23,639	1.40
January-June 2012	7,585	58	29,312	1.98	4,381	21	14,091	1.49	55,504	160	103,544	1.55	20,322	35	22,704	1.54
July-December 2012	7,222	49	29,293	1.67	3,695	23	12,290	1.87	58,404	154	110,970	1.39	20,205	33	23,475	1.41
January-June 2013	5,662	41	21,726	1.89	2,808	21	9,055	2.32	46,199	133	83,915	1.58	16,253	40	18,990	2.11
July-December 2013	5,271	32	21,002	1.52	2,567	15	9,160	1.64	48,124	100	86,019	1.16	16,180	33	19,632	1.68
January-June 2014	3,503	24	12,703	1.89	2,036	12	6,715	1.79	39,387	106	64,860	1.63	11,078	30	12,575	2.39
July-December 2014	2,917	25	10,621	2.35	1,770	≤10	6,240	0.80	38,265	115	61,921	1.86	10,200	34	11,397	2.98
January-June 2015	1,057	≤10	2,788	2.15	524	≤10	1,536	2.60	12,183	46	18,192	2.53	3,505	≤10	3,647	2.19
July-October 2015	234	≤10	274	10.94	117	0	144	0.00	2,051	≤10	1,766	5.66	519	≤10	351	2.85

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Table 24: Rate ratios and ratio of rate ratios (RORR) for OxyContin and secondary comparators

Opioid analgesic	Exposure period category	MarketScan[i]			
		Unadjusted rate ratio (CI)	Adjusted rate ratio (CI)	Unadjusted ratio of rate ratio (CI)[iii]	Adjusted ratio of rate ratio (CI)[iii]
OxyContin	Any use[ii] (with or without concomitant opioid analgesic use periods)	0.75 (0.59-0.95)*	0.69 (0.55-0.86)*	ref	
ER Oxymorphone		1.99 (1.06-3.76)*	1.74 (0.94-3.24)	2.65 (1.35-5.22)*	2.54 (1.31-4.92)*
SE IR Oxycodone		1.28 (1.00-1.65)*	1.20 (0.94-1.54)	1.71 (1.21-2.41)*	1.75 (1.26-2.44)*
IR Hydromorphone		1.08 (0.74-1.58)	1.03 (0.72-1.47)	1.44 (0.92-2.25)	1.50 (0.99-2.29)
OxyContin	Use alone (without concomitant opioid analgesic use periods)	0.69 (0.47-1.02)	0.64 (0.44-0.94)*	ref	
ER Oxymorphone		3.28 (0.99-10.90)	2.76 (0.84-9.08)	4.74 (1.34-16.74)*	4.30 (1.23-15.04)*
SE IR Oxycodone		1.36 (1.01-1.84)*	1.29 (0.96-1.73)	1.97 (1.21-3.21)*	2.01 (1.24-3.25)*
IR Hydromorphone		0.83 (0.53-1.28)	0.83 (0.54-1.25)	1.20 (0.67-2.15)	1.29 (0.73-2.26)

(FDA generated table using data from the PMR 3051-4 study report)

Key: *=statistically significant (p<0.05), [i]= unintentional overdose outcome only, [ii]=excluding periods with concomitant comparator use; [iii]=null is 1 and OxyContin group is the reference (ratio of rate ratio or RORR > 1 means overdose rate change comparing periods favors OxyContin group, and RORR < 1 means overdose rate change comparing periods favors the comparator group)

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Table 25: Demographic and clinical characteristics

	Any use of OxyContin based treatment episodes excluding primary comparators (2.1)		Any use of primary comparator opioids treatment episodes excluding OxyContin and other primary comparators (2.1)		OxyContin alone treatment episodes (2.2)		Primary comparator alone opioid treatment episodes (2.2)	
Total treatment episodes, n (%)	378,441	36.6	654,462	63.4	142,928	13.8	269,348	26.1
Total patients, n (%)*	81,137	42.3	110,619	57.7	54,683	28.5	80,556	42.0
Mean person-time per treatment episode in months, mean (SD)	1.4	2.3	2.1	2.8	0.9	1.8	1.4	2.3
Total person-time per patient in months, mean (SD)	6.1	11.4	9.5	13.9	2.8	7.0	4.7	9.3
Demographic characteristics (treatment episode measures)								
Age (years)								
Mean, SD	51.4	12.2	53.4	11.9	52.2	12.2	54.1	11.9
Median	53		54		54		55	
Range (min, max)	16	74	16	74	16	74	16	74
Age category, n (%)								
16-34	41,247	10.9	51,821	7.9	14,366	10.1	19,437	7.2
35-64	288,850	76.3	481,294	73.5	108,024	75.6	194,676	72.3
65-74	48,344	12.8	121,347	18.5	20,538	14.4	55,235	20.5
Gender, n (%)								
Male	188,455	49.8	271,693	41.5	71,160	49.8	111,083	41.2
Female	189,986	50.2	382,769	58.5	71,768	50.2	158,265	58.8
Geographic region of patient residence (US), n (%)								
Midwest	68,298	18.0	84,987	13.0	26,572	18.6	35,936	13.3
Northeast	95,739	25.3	185,681	28.4	37,751	26.4	79,320	29.4
South	92,286	24.4	178,771	27.3	33,121	23.2	71,862	26.7
West	122,101	32.3	204,923	31.3	45,475	31.8	82,188	30.5
Missing/Unknown	17	0.0	100	0.0	≤10	0.0	42	0.0
Health plan type, n (%)								
HMO	74,828	19.8	121,282	18.5	28,316	19.8	49,573	18.4
PPO	267,971	70.8	489,324	74.8	101,247	70.8	201,635	74.9
CDHP/HDHP	35,638	9.4	43,805	6.7	13,364	9.4	18,118	6.7

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Other	≤10	0.0	50	0.0	0	0.0	21	0.0
Unknown	≤10	0.0	≤10	0.0	≤10	0.0	≤10	0.0
Year of index date, n (%)#								
2008	40,872	10.8	72,177	11.0	16,170	11.3	30,611	11.4
2009	74,696	19.7	119,965	18.3	29,299	20.5	50,364	18.7
2010	31,045	8.2	49,044	7.5	12,123	8.5	20,644	7.7
2011	70,866	18.7	117,319	17.9	26,455	18.5	48,026	17.8
2012	53,134	14.0	96,288	14.7	19,802	13.9	39,159	14.5
2013	44,874	11.9	77,422	11.8	16,378	11.5	31,267	11.6
2014	42,342	11.2	79,704	12.2	14,876	10.4	31,335	11.6
2015	20,612	5.4	42,543	6.5	7,825	5.5	17,942	6.7
Pain diagnosis, n (%)								
Abdominal pain	55,554	14.7	120,612	18.4	20,708	14.5	48,921	18.2
Amputation	2,857	0.8	5,109	0.8	1,125	0.8	2,181	0.8
Arthritis, arthropathies, osteoarthritis and musculoskeletal pain	164,603	43.5	243,429	37.2	59,366	41.5	95,544	35.5
Back pain	193,211	51.1	374,626	57.2	67,568	47.3	143,060	53.1
Chronic pain	63,456	16.8	138,170	21.1	21,503	15.0	51,716	19.2
Fibromyalgia	39,200	10.4	92,439	14.1	13,156	9.2	34,993	13.0
Headache	37,038	9.8	76,413	11.7	13,041	9.1	29,987	11.1
Malignancy	66,937	17.7	129,599	19.8	28,182	19.7	58,040	21.5
Multiple sclerosis	3,294	0.9	8,255	1.3	1,317	0.9	3,674	1.4
Neuropathic pain	10,627	2.8	26,043	4.0	4,232	3.0	10,897	4.0
Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers	15,248	4.0	32,313	4.9	5,982	4.2	13,621	5.1
Stroke	5,713	1.5	12,687	1.9	2,271	1.6	5,518	2.0
Liver disease	19,365	5.1	37,360	5.7	7,559	5.3	15,486	5.7
Renal disease	12,484	3.3	28,541	4.4	5,105	3.6	12,478	4.6
COPD	49,926	13.2	104,775	16.0	18,698	13.1	42,641	15.8
Impaired respiratory function	42,264	11.2	80,588	12.3	16,614	11.6	34,180	12.7
Deyo-Charlson comorbidity index								
Mean, SD	1.7	2.8	2.0	3.0	1.9	3.0	2.2	3.1
Median	0		1		0		1	
Range (min, max)	0	18	0	21	0	18	0	21
Psychiatric comorbidities, n (%)								
Attention deficit hyperactive disorder (ADHD)	3,000	0.8	3,770	0.6	1,055	0.7	1,434	0.5
Bipolar disorder	9,957	2.6	22,387	3.4	3,595	2.5	8,939	3.3
Borderline personality disorder	466	0.1	805	0.1	174	0.1	317	0.1
Generalized anxiety disorder	41,413	10.9	76,718	11.7	14,214	9.9	29,501	11.0
Major depression disorder	58,692	15.5	119,470	18.3	21,508	15.0	48,066	17.8

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Alcoholism	5,882	1.6	9,130	1.4	2,080	1.5	3,633	1.3
History of attempted suicide	1,071	0.3	1,898	0.3	374	0.3	761	0.3
Post-traumatic stress disorder	2,917	0.8	6,553	1.0	995	0.7	2,545	0.9
Sleep disorder	43,448	11.5	80,297	12.3	16,137	11.3	32,463	12.1
Somatoform disorder	157	0.0	567	0.1	60	0.0	211	0.1
Drug dependence								
Opioid type dependence	11,343	3.0	23,706	3.6	3,601	2.5	8,886	3.3
Non-opioid drug dependence	8,840	2.3	19,215	2.9	2,786	1.9	7,087	2.6
History of overdose/poisoning	1,110	0.3	3,160	0.5	342	0.2	1,109	0.4
Non-opioid medications of abuse potential during treatment episode, n (%)								
Depressants								
Benzodiazepines	60,818	16.1	109,074	16.7	14,984	10.5	32,087	11.9
Barbiturates	220	0.1	517	0.1	66	0.0	192	0.1
Sleep medications	37,809	10.0	71,087	10.9	10,672	7.5	22,033	8.2
Stimulants								
Amphetamines	6,627	1.8	12,392	1.9	1,689	1.2	3,823	1.4
Methylphenidate	3,032	0.8	6,085	0.9	900	0.6	2,025	0.8
Dextromethorphan	22	0.0	19	0.0	≤10	0.0	≤10	0.0
Muscle relaxants	46,593	12.3	99,258	15.2	10,816	7.6	26,734	9.9
Opioid maintenance therapy medication use during treatment episode, n (%)								
Suboxone	655	0.2	802	0.1	222	0.2	334	0.1
Subutex/sublingual buprenorphine tablets	201	0.1	253	0.0	66	0.0	102	0.0
Solution of methadone	16	0.0	148	0.0	5	0.0	81	0.0
Duration of treatment episode (months), mean (SD)	1.3	2.8	1.6	3.0	1.1	2.4	1.4	2.7
Healthcare utilization during six months prior to the index date, mean (SD)^								
All-cause office visits	8.4	6.9	9.0	7.2	8.2	7.0	8.8	7.3
All-cause ED visits	0.4	1.0	0.4	1.2	0.4	1.0	0.4	1.1
All-cause hospitalizations	0.5	1.0	0.5	1.1	0.5	1.0	0.5	1.1
Distinct medication classes (defined by the four-digit level of the GPI code) dispensed	10.6	6.2	11.9	6.4	10.6	6.1	11.7	6.4
Exposures								
OxyContin dose, n (%)								
10 mg	58,648	15.5			13,769	9.6		
15 mg	5,600	1.5			1,399	1.0		
20 mg	58,147	15.4			14,067	9.8		
30 mg	16,329	4.3			3,488	2.4		
40 mg	35,003	9.2			8,418	5.9		

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60 mg	12,806	3.4			2,385	1.7		
80 mg	26,529	7.0			6,035	4.2		
Usage, n (%)								
Existing (continuing) user	225,196	59.5	362,879	55.5	78,601	55.0	139,094	51.6
Incident (new) user	153,245	40.5	291,583	44.6	64,327	45.0	130,254	48.4
Comparator usage, any, n (%)								
ER morphine			252,960	38.7			96,702	35.9
TD Fentanyl			272,898	41.7			110,786	41.1
Methadone tabs/capsules			128,604	19.7			61,860	23.0
IR oxycodone single entity	96,452	25.5	89,639	13.7				
IR hydromorphone	17,397	4.6	46,086	7.0				
ER oxymorphone	3,602	1.0	6,200	0.9				
Other opioid use (non primary or secondary comparators)	153,387	40.5	290,985	44.5				
Transdermal delivery system (fentanyl or buprenorphine), n (%)	399	0.1	273,269	41.8	31	0.0	110,829	41.1
Buprenorphine	399	0.1	654	0.1	31	0.0	63	0.0
Prior use of opioid analgesics, n (%)								
ER opioid analgesic only	24,936	6.6	66,015	10.1	15,127	10.6	41,899	15.6
IR opioid analgesic only	41,159	10.9	59,691	9.1	4,982	3.5	9,827	3.6
Both ER and IR opioid analgesic	290,450	76.7	508,673	77.7	116,988	81.9	205,558	76.3
No opioid analgesic	21,896	5.8	20,083	3.1	5,831	4.1	12,064	4.5
Prior use of tramadol	25,255	6.7	48,768	7.5	8,086	5.7	18,366	6.8
Time since the end of the last opioid analgesic (months), mean (SD)	0.5	2.9	0.4	2.6	0.3	1.9	0.3	2.1
Number of different opioid analgesic agents (study drugs + other opioids) used, mean (SD)	1.7	0.6	1.7	0.6	1.0	0.0	1.0	0.0
Prescribing physician specialty (on index date), n (%)								
General, internal medicine or family practice physician	842	0.2	1,551	0.2	342	0.2	584	0.2
Pain specialist	24,899	6.6	72,806	11.1	4,590	3.2	18,439	6.8
Other specialist	154,297	40.8	254,207	38.8	34,962	24.5	77,976	28.9
Non-physician	31,297	8.3	48,267	7.4	4,942	3.5	11,773	4.4
Unknown	20,869	5.5	34,097	5.2	4,725	3.3	10,065	3.7
Missing	146,237	38.6	243,534	37.2	93,367	65.3	150,511	55.9
Number of prescribers of IR or ER opioid analgesics, mean (SD)	1.2	0.5	1.2	0.6	1.1	0.5	1.2	0.5
Number of pharmacies where patient obtained IR or ER opioid analgesics, mean (SD)	1.2	0.6	1.2	0.5	1.1	0.5	1.1	0.5

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Table 26: Benzodiazepine use among those dispensed OxyContin and comparator opioids, overall and by period

		Prevalence of Benzodiazepine use at baseline (within 3 months)											
		All				Pre-period (2008-2010)				Post-period (2011-2015)			
		No		Yes		No		Yes		No		Yes	
		N	%	N	%	N	%	N	%	N	%	N	%
Combined (incident and prevalent)	Any OxyContin	255,133	67.4%	123,308	32.6%	97,455	66.5%	49,158	33.5%	157,678	68.0%	74,150	32.0%
	Any ER morphine	177,116	70.0%	75,844	30.0%	57,927	68.1%	27,161	31.9%	119,189	71.0%	48,683	29.0%
	Any TD Fentanyl	177,364	65.0%	95,534	35.0%	67,315	63.8%	38,167	36.2%	110,049	65.7%	57,367	34.3%
	Any Methadone	90,912	70.7%	37,692	29.3%	35,421	70.0%	15,195	30.0%	55,491	71.2%	22,497	28.8%
	Any ER oxymorphone	17,198	66.1%	8,811	33.9%	6,459	67.2%	3,148	32.8%	10,739	65.5%	5,663	34.5%
	Any IR oxycodone single-entity	350,222	74.5%	120,099	25.5%	70,681	71.4%	28,244	28.6%	279,541	75.3%	91,855	24.7%
	Any IR hydromorphone	137,302	72.6%	51,920	27.4%	41,671	71.4%	16,658	28.6%	95,631	73.1%	35,262	26.9%
Prevalent	Any OxyContin	145,482	64.6%	79,714	35.4%	44,406	62.8%	26,315	37.2%	101,076	65.4%	53,399	34.6%
	Any ER morphine	95,229	67.9%	45,016	32.1%	23,400	64.3%	13,002	35.7%	71,829	69.2%	32,014	30.8%
	Any TD Fentanyl	92,018	63.2%	53,590	36.8%	25,743	60.4%	16,875	39.6%	66,275	64.4%	36,715	35.6%
	Any Methadone	53,543	69.5%	23,483	30.5%	15,636	68.0%	7,352	32.0%	37,907	70.1%	16,131	29.9%
	Any ER oxymorphone	9,500	63.8%	5,388	36.2%	2,912	64.2%	1,621	35.8%	6,588	63.6%	3,767	36.4%
	Any IR oxycodone single-entity	88,518	65.1%	47,470	34.9%	17,551	62.7%	10,440	37.3%	70,967	65.7%	37,030	34.3%
	Any IR hydromorphone	31,661	61.9%	19,510	38.1%	8,246	58.4%	5,882	41.6%	23,415	63.2%	13,628	36.8%
Incident	Any OxyContin	109,651	71.6%	43,594	28.4%	53,049	69.9%	22,843	30.1%	56,602	73.2%	20,751	26.8%
	Any ER morphine	81,887	72.6%	30,828	27.4%	34,527	70.9%	14,159	29.1%	47,360	74.0%	16,669	26.0%
	Any TD Fentanyl	85,346	67.0%	41,944	33.0%	41,572	66.1%	21,292	33.9%	43,774	67.9%	20,652	32.1%
	Any Methadone	37,369	72.5%	14,209	27.5%	19,785	71.6%	7,843	28.4%	17,584	73.4%	6,366	26.6%
	Any ER oxymorphone	7,698	69.2%	3,423	30.8%	3,547	69.9%	1,527	30.1%	4,151	68.6%	1,896	31.4%
	Any IR oxycodone single-entity	261,704	78.3%	72,629	21.7%	53,130	74.9%	17,804	25.1%	208,574	79.2%	54,825	20.8%
	Any IR hydromorphone	105,641	76.5%	32,410	23.5%	33,425	75.6%	10,776	24.4%	72,216	76.9%	21,634	23.1%

Table 27: NDI-linkable versus non-linkable populations

	Any use of OxyContin based treatment episodes excluding primary comparators (2.1)				Any use of primary comparator opioids treatment episodes excluding OxyContin (2.1)			
	NDI linkable		Non-NDI linkable		NDI linkable		Non-NDI linkable	
Total treatment episodes, n (%)	378,441	36.6	240,802	40.4	654,462	63.4	354,728	59.6
Total patients, n (%)*	81,137	42.3	53,411	45.9	110,619	57.7	62,865	54.1
Mean person-time per treatment episode in months, mean (SD)	1.4	2.3	1.4	2.4	2.1	2.8	2.1	2.8
Total person-time per treatment episode in months, mean (SD)	6.1	11.4	6.1	11.0	9.5	13.9	9.4	13.1
Demographic characteristics (treatment episode measures)								
Age (years)								
Mean, SD	51.4	12.2	50.9	11.5	53.4	11.9	51.1	11.1
Median	53		53		54		52	
Range (min, max)	16	74	16	74	16	74	16	74
Age category, n (%)								
16-34	41,247	10.9	24,195	10.0	51,821	7.9	30,375	8.6
35-64	288,850	76.3	195,002	81.0	481,294	73.5	291,980	82.3
65-74	48,344	12.8	21,605	9.0	121,347	18.5	32,373	9.1
Gender, n (%)								
Male	188,455	49.8	117,178	48.7	271,693	41.5	148,072	41.7
Female	189,986	50.2	123,624	51.3	382,769	58.5	206,656	58.3
Geographic region of patient residence (US), n (%)								
Midwest	68,298	18.0	52,577	21.8	84,987	13.0	51,791	14.6
Northeast	95,739	25.3	56,775	23.6	185,681	28.4	90,791	25.6
South	92,286	24.4	78,240	32.5	178,771	27.3	131,834	37.2
West	122,101	32.3	53,112	22.1	204,923	31.3	80,133	22.6
Missing/Unknown	17	0.0	98	0.0	100	0.0	179	0.1
Health plan type, n (%)								
HMO	74,828	19.8	55,891	23.2	121,282	18.5	82,208	23.2
PPO	267,971	70.8	159,175	66.1	489,324	74.8	232,229	65.5

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CDHP/HDHP	35,638	9.4	25,736	10.7	43,805	6.7	40,291	11.4
Other	≤10	0.0	0	0.0	50	0.0	0	0.0
Unknown	≤10	0.0	0	0.0	≤10	0.0	0	0.0
Year of index date, n (%)								
2008	40,872	10.8	19,338	8.0	72,177	11.0	32,022	9.0
2009	74,696	19.7	35,506	14.7	119,965	18.3	53,790	15.2
2010	31,045	8.2	13,992	5.8	49,044	7.5	21,041	5.9
2011	70,866	18.7	31,793	13.2	117,319	17.9	43,989	12.4
2012	53,134	14.0	24,484	10.2	96,288	14.7	34,184	9.6
2013	44,874	11.9	38,847	16.1	77,422	11.8	55,950	15.8
2014	42,342	11.2	49,010	20.4	79,704	12.2	71,355	20.1
2015	20,612	5.4	27,832	11.6	42,543	6.5	42,397	12.0
Pain diagnosis, n (%)								
Abdominal pain	55,554	14.7	34,331	14.3	120,612	18.4	65,282	18.4
Amputation	2,857	0.8	1,864	0.8	5,109	0.8	2,227	0.6
Arthritis, arthropathies, osteoarthritis and musculoskeletal pain	164,603	43.5	107,910	44.8	243,429	37.2	130,538	36.8
Back pain	193,211	51.1	124,755	51.8	374,626	57.2	205,432	57.9
Chronic pain	63,456	16.8	43,187	17.9	138,170	21.1	79,932	22.5
Fibromyalgia	39,200	10.4	26,127	10.8	92,439	14.1	51,729	14.6
Headache	37,038	9.8	24,582	10.2	76,413	11.7	43,109	12.2
Malignancy	66,937	17.7	39,203	16.3	129,599	19.8	64,122	18.1
Multiple sclerosis	3,294	0.9	2,142	0.9	8,255	1.3	4,074	1.1
Neuropathic pain	10,627	2.8	7,510	3.1	26,043	4.0	13,100	3.7
Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers	15,248	4.0	8,595	3.6	32,313	4.9	13,812	3.9
Stroke	5,713	1.5	3,004	1.2	12,687	1.9	5,731	1.6
Liver disease	19,365	5.1	12,363	5.1	37,360	5.7	20,163	5.7
Renal disease	12,484	3.3	8,260	3.4	28,541	4.4	12,901	3.6
COPD	49,926	13.2	32,998	13.7	104,775	16.0	51,582	14.5
Impaired respiratory function	42,264	11.2	23,908	9.9	80,588	12.3	39,028	11.0
Deyo-Charlson comorbidity index								
Mean, SD	1.7	2.8	1.6	2.7	2.0	3.0	1.8	2.9
Median	0		0		1		1	
Range (min, max)	0	18	0	19	0	21	0	18
Psychiatric comorbidities, n (%)								
Attention deficit hyperactive disorder (ADHD)	3,000	0.8	1,721	0.7	3,770	0.6	2,441	0.7
Bipolar disorder	9,957	2.6	5,763	2.4	22,387	3.4	11,968	3.4

Borderline personality disorder	466	0.1	140	0.1	805	0.1	425	0.1
Generalized anxiety disorder	41,413	10.9	27,092	11.3	76,718	11.7	43,234	12.2
Major depression disorder	58,692	15.5	38,675	16.1	119,470	18.3	65,007	18.3
Alcoholism	5,882	1.6	3,160	1.3	9,130	1.4	4,488	1.3
History of attempted suicide	1,071	0.3	692	0.3	1,898	0.3	1,165	0.3
Post-traumatic stress disorder	2,917	0.8	2,626	1.1	6,553	1.0	4,184	1.2
Sleep disorder	43,448	11.5	31,251	13.0	80,297	12.3	47,224	13.3
Somatoform disorder	157	0.0	104	0.0	567	0.1	222	0.1
Drug dependence								
Opioid type dependence	11,343	3.0	6,876	2.9	23,706	3.6	13,049	3.7
Non-opioid drug dependence	8,840	2.3	5,416	2.2	19,215	2.9	9,716	2.7
History of overdose/poisoning	1,110	0.3	722	0.3	3,160	0.5	1,591	0.4
Non-opioid medications of abuse potential during treatment episode, n (%)								
Depressants								
Benzodiazepines	60,818	16.1	37,226	15.5	109,074	16.7	58,784	16.6
Barbiturates	220	0.1	131	0.1	517	0.1	197	0.1
Sleep medications	37,809	10.0	21,900	9.1	71,087	10.9	37,190	10.5
Stimulants								
Amphetamines	6,627	1.8	3,584	1.5	12,392	1.9	6,302	1.8
Methylphenidate	3,032	0.8	1,654	0.7	6,085	0.9	3,449	1.0
Dextromethorphan	22	0.0			19	0.0	22	0.0
Muscle relaxants	46,593	12.3	30,847	12.8	99,258	15.2	57,749	16.3
Opioid maintenance therapy medication use during treatment episode, n (%)								
Suboxone	655	0.2	352	0.1	802	0.1	475	0.1
Subutex/sublingual buprenorphine tablets	201	0.1	102	0.0	253	0.0	160	0.0
Solution of methadone	16	0.0	11	0.0	148	0.0	77	0.0
Duration of treatment episode (months), mean (sd)	1.3	2.8	1.3	2.8	1.6	3.0	1.7	3.1
Healthcare utilization during six months prior to index date, mean (SD)^								
All-cause office visits	8.4	6.9	8.2	6.5	9.0	7.2	8.7	7.0
All-cause ED visits	0.4	1.0	0.4	1.1	0.4	1.2	0.5	1.2
All-cause hospitalizations	0.5	1.0	0.5	0.9	0.5	1.1	0.5	1.0
Distinct medication classes (defined by the four-digit level of the GPI code) dispensed	10.6	6.2	10.6	6.1	11.9	6.4	11.9	6.4
Exposures								

OxyContin dose, n (%)								
10 mg	58,648	15.5	39,775	16.5				
15 mg	5,600	1.5	4,247	1.8				
20 mg	58,147	15.4	37,392	15.5				
30 mg	16,329	4.3	11,902	4.9				
40 mg	35,003	9.2	21,056	8.7				
60 mg	12,806	3.4	8,202	3.4				
80 mg	26,529	7.0	13,952	5.8				
Usage, n (%)								
Existing (continuing) user	225,196	59.5	140,428	58.3	362,879	55.5	186,278	52.5
Incident (new) user	153,245	40.5	100,374	41.7	291,583	44.6	168,450	47.5
Comparator usage, any, n (%)								
ER morphine					252,960	38.7	137,901	38.9
TD Fentanyl					272,898	41.7	152,937	43.1
Methadone tabs/capsules					128,604	19.7	63,890	18.0
IR oxycodone single entity	96,452	25.5	64,439	26.8	89,639	13.7	48,429	13.7
IR hydromorphone	17,397	4.6	11,048	4.6	46,086	7.0	23,784	6.7
ER oxymorphone	3,602	1.0	2,325	1.0	6,200	0.9	3,916	1.1
Other opioid use (non primary or secondary comparators)	153,387	40.5	96,563	40.1	290,985	44.5	158,929	44.8
Transdermal delivery system (fentanyl or buprenorphine), n (%)	399	0.1	377	0.2	273,269	41.8	153,228	43.2
Buprenorphine	399	0.1	377	0.2	654	0.1	528	0.1
Prior use of opioid analgesics, n (%)								
ER opioid analgesic only	24,936	6.6	14,737	6.1	66,015	10.1	35,806	10.1
IR opioid analgesic only	41,159	10.9	26,959	11.2	59,691	9.1	33,044	9.3
Both ER and IR opioid analgesic	290,450	76.7	183,677	76.3	508,673	77.7	273,860	77.2
No opioid analgesic	21,896	5.8	15,429	6.4	20,083	3.1	12,018	3.4
Prior use of tramadol	25,255	6.7	18,747	7.8	48,768	7.5	28,889	8.1
Time since the end of the last opioid analgesic (months), mean (SD)	0.5	2.9	0.5	3.0	0.4	2.6	0.4	2.5
Number of different opioid analgesic agents (study drugs + other opioids) used, mean (SD)	1.7	0.6	1.7	0.6	1.7	0.6	1.7	0.6
Prescribing physician specialty (on index date), n (%)								
General, internal medicine or family practice physician	842	0.2	247	0.1	1,551	0.2	506	0.1
Pain specialist	24,899	6.6	10,890	4.5	72,806	11.1	26,812	7.6

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Other specialist	154,297	40.8	72,973	30.3	254,207	38.8	101,495	28.6
Non-physician	31,297	8.3	16,918	7.0	48,267	7.4	20,830	5.9
Unknown	20,869	5.5	47,966	19.9	34,097	5.2	74,213	20.9
Missing	146,237	38.6	91,808	38.1	243,534	37.2	130,872	36.9
Number of prescribers of IR or ER opioid analgesics, mean (SD)	1.2	0.5	1.2	0.6	1.2	0.6	1.2	0.6
Number of pharmacies where patient obtained IR or ER opioid analgesics, mean (SD)	1.2	0.6	1.2	0.6	1.2	0.5	1.2	0.6

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Table 28: Bi-annual rates of opioid overdose, by opioid analgesic

	Any OxyContin, Primary or Secondary Comparator use				Any OxyContin use				Any ER morphine tables and capsule use				Any Fentanyl use			
	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months
All users																
July-December 2008	58,134	212	168,937.4	1.25	15,622	66	48,017.4	1.37	9,763	49	33,543.9	1.46	11,164	40	39,110.7	1.02
January-June 2009	56,150	171	159,207.4	1.07	15,404	39	44,377.6	0.88	9,788	36	32,540.4	1.11	10,877	52	36,279.0	1.43
July-December 2009	59,003	175	169,294.9	1.03	16,476	57	50,334.7	1.13	9,481	37	33,228.0	1.11	10,274	49	35,903.0	1.36
January-June 2010	58,937	177	161,584.2	1.10	15,274	43	45,489.2	0.95	9,126	39	30,766.2	1.27	9,966	52	33,787.9	1.54
July-December 2010	61,448	199	173,548.0	1.15	15,795	52	46,859.3	1.11	9,163	33	32,809.9	1.01	10,010	48	35,663.1	1.35
January-June 2011	64,423	190	176,808.4	1.07	15,463	36	44,388.9	0.81	9,990	39	34,056.9	1.15	10,126	38	35,294.5	1.08
July-December 2011	67,293	214	191,088.7	1.12	14,855	34	44,305.3	0.77	10,299	52	37,704.1	1.38	10,275	46	37,475.6	1.23
January-June 2012	64,525	183	176,794.7	1.04	13,337	39	40,104.2	0.97	10,160	45	35,231.7	1.28	9,548	38	33,306.1	1.14
July-December 2012	65,262	197	183,191.0	1.08	12,542	32	39,484.5	0.81	10,217	46	37,449.8	1.23	9,123	42	32,754.3	1.28
January-June 2013	59,447	162	158,583.3	1.02	11,382	40	34,526.6	1.16	8,956	25	31,515.0	0.79	7,715	35	27,215.0	1.29
July-December 2013	60,018	190	159,153.4	1.19	10,918	38	34,090.3	1.11	8,607	52	31,594.9	1.65	7,391	35	26,894.6	1.30
January-June 2014	58,931	134	142,741.5	0.94	9,963	20	29,400.6	0.68	8,386	28	28,108.9	1.00	6,839	20	23,428.7	0.85
July-December 2014	62,600	177	157,616.7	1.12	9,426	38	30,110.9	1.26	8,976	43	31,888.6	1.35	6,660	31	24,639.2	1.26
January-June 2015	57,690	165	137,704.8	1.20	8,060	29	25,001.9	1.16	8,257	29	27,906.0	1.04	5,619	43	20,166.2	2.13
July-September 2015	40,537	73	61,912.9	1.18	5,407	13	10,409.6	1.25	6,254	14	12,458.7	1.12	4,120	≤10	8,512.0	1.17

	Any Methadone use				Any ER Oxymorphone use				Any IR SE Oxycodone				Any IR Hydromorphone			
	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months	N Patients	N Cases opioid fatal or non-fatal overdose	Person-months	Rate per 1000 p-months
All users																
July-December 2008	6,476	39	25,320.6	1.54	1,438	≤10	4,097.6	2.44	19,211	55	37,026.3	1.49	10,977	15	12,176.8	1.23
January-June 2009	6,221	39	23,852.8	1.64	1,538	≤10	4,516.1	0.66	16,385	28	33,002.0	0.85	11,697	16	12,751.8	1.25
July-December 2009	5,954	23	23,694.0	0.97	1,632	≤10	5,238.3	0.95	20,102	40	39,381.3	1.02	11,296	21	12,591.4	1.67
January-June 2010	5,879	22	22,863.0	0.96	1,787	≤10	5,515.7	1.09	21,864	47	41,893.9	1.12	11,098	18	12,198.9	1.48
July-December 2010	5,761	40	23,395.1	1.71	2,069	≤10	6,372.6	0.94	24,308	56	49,185.1	1.14	11,935	17	13,681.0	1.24
January-June 2011	5,865	38	22,882.6	1.66	2,229	13	7,221.2	1.80	26,509	62	54,258.6	1.14	12,331	17	14,267.5	1.19
July-December 2011	5,901	41	24,488.5	1.67	2,252	14	7,803.1	1.79	29,137	83	61,770.1	1.34	12,878	21	15,719.0	1.34
January-June 2012	5,503	25	21,715.5	1.15	1,990	≤10	6,320.8	1.42	29,798	73	61,860.5	1.18	12,035	20	14,702.8	1.36
July-December 2012	5,329	32	22,546.5	1.42	1,597	≤10	5,445.4	0.73	31,670	92	68,014.5	1.35	12,178	18	15,453.0	1.16
January-June 2013	4,589	16	18,785.4	0.85	1,490	≤10	5,046.0	0.79	29,999	76	61,400.8	1.24	10,917	17	13,446.1	1.26
July-December 2013	4,258	28	18,307.8	1.53	1,336	≤10	4,976.0	1.21	31,637	69	63,139.6	1.09	10,921	21	13,415.4	1.57
January-June 2014	4,083	20	15,821.9	1.26	1,203	≤10	4,231.1	1.65	32,757	56	59,763.8	0.94	9,912	18	11,645.8	1.55
July-December 2014	4,073	21	17,147.0	1.22	1,130	≤10	4,437.1	1.80	36,277	90	68,800.2	1.31	10,463	21	12,965.7	1.62
January-June 2015	3,590	22	14,506.9	1.52	1,032	≤10	3,960.9	1.01	34,704	70	63,201.4	1.11	9,390	20	11,321.6	1.77
July-September 2015	2,955	≤10	6,366.2	1.41	827	≤10	1,724.1	2.32	23,132	30	29,124.9	1.03	5,767	16	5,122.6	3.12

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8.5 EXPOSURE TIME DATA

Table 29: The number of overdoses (cases) and exposure time for analyses involving OxyContin and primary comparators (incident user cohort only)

Opioid analgesic[i]	Exposure period category	Medicaid				MarketScan				HIRD			
		Pre-period		Post-period		Pre-period		Post-period		Pre-period		Post-period	
		Cases	PMs	Cases	PMs	Cases	PMs	Cases	PMs	Cases	PMs	Cases	PMs
OxyContin	Any use[i] (with or without concomitant opioid analgesic use periods)	198	113,884	153	87,758	57	75,220	52	88,378	85	95,483	61	86,036
ER morphine		601	218,595	741	307,429	64	48,237	128	102,988	75	73,733	141	106,453
fentanyl		259	111,684	332	130,052	64	53,784	124	100,993	94	82,531	94	88,465
methadone		528	143,107	482	163,693	19	16,071	56	27,322	58	53,118	75	53,799
OxyContin	Use alone (without concomitant opioid analgesic use periods)	69	51,166	42	29,192	18	31,262	≤10	30,769	37	41,461	17	29,741
ER morphine		193	72,789	201	91,287	15	16,861	29	33,344	25	27,562	43	33,208
fentanyl		83	40,571	116	46,323	25	21,630	33	38,709	28	31,957	26	33,634
methadone		284	82,396	262	96,821	≤10	9,159	23	15,355	40	32,324	46	31,320

(FDA generated table from PMR 2051-4 study report)

Key: [i]=excludes periods dispensed OxyContin or primary comparator concomitantly; person-months (PMs)

Table 30: The number of overdoses (cases) and exposure time for analyses involving OxyContin and secondary comparators (combined cohort)

Opioid analgesic	Exposure period category	Medicaid				MarketScan[i]				HIRD			
		Pre-period		Post-period		Pre-period		Post-period		Pre-period		Post-period	
		Cases	PMs	Cases	PMs	Cases	PMs	Cases	PMs	Cases	PMs	Cases	PMs
OxyContin	Any use[ii] (with or without concomitant opioid analgesic use periods)	504	295,514	356	226,471	156	207,722	176	311,936	118	135,011	121	209,374
ER Oxymorphone		82	29,452	228	83,908	13	24,073	65	60,419	17	14,125	39	32,598
SE IR Oxycodone		769	342,913	1861	930,372	82	119,024	388	439,392	63	77,018	332	361,878
IR Hydromorphone		294	92,782	380	133,165	41	36,826	110	91,193	35	27,087	87	73,280
OxyContin	Use alone (without concomitant opioid analgesic use periods)	236	143,156	131	92,079	56	97,454	56	140,826	58	63,959	43	90,142
ER Oxymorphone		29	9,680	97	31,470	≤10	7,465	24	18,206	≤10	4,634	11	9,022
SE IR Oxycodone		555	262,717	1421	749,396	53	89,960	278	346,222	44	59,672	245	292,462
IR Hydromorphone		178	62,344	255	90,916	32	25,739	65	63,181	25	19,499	65	53,705

(FDA generated table from PMR 2051-4 study report)

Key: [ii]=excludes periods dispensed OxyContin or primary comparator concomitantly; numbers are based on the combined (incident and prevalent) cohort; person-months (PMs)

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8.6 UNINTENTIONAL OVERDOSE OUTCOME ANALYSES

Table 31: Rate ratios of unintentional fatal or non-fatal overdose (OD) among patients with any OxyContin use and any primary comparator use in the two years before and two years after the reformulation, Medicaid

	Ratio of Rates during Post- vs. Pre-Reformulation Periods			Ratio of Ratios for Comparator Opioids vs. OxyContin		
	Adjusted Rate Ratio	95% LCL	95% UCL	Adjusted Ratio of Rate Ratios	95% LCL	95% UCL
Any non-overlapping use^						
OxyContin	0.96	0.85	1.09	Ref	-	-
ER morphine	0.94	0.87	1.01	0.97	0.85	1.12
TD fentanyl	1.01	0.91	1.12	1.05	0.90	1.23
Methadone	0.86	0.79	0.95	0.90	0.77	1.04

Abbreviations: LCL=lower confidence limit; UCL=upper confidence limit; ER=extended release; TD=transdermal; Ref=referent; vs=versus.
^Treatment episodes that had overlapping use of more than one of the primary comparators or OxyContin at the same time were excluded.

Table 32: Rate ratios of unintentional fatal or non-fatal overdose (OD) among patients with OxyContin only use and primary comparator opioid analgesic only use in the two years before and two years after the reformulation, Medicaid

	Ratio of Rates during Post- vs. Pre-Reformulation Periods			Ratio of Ratios for Comparator Opioids vs. OxyContin		
	Adjusted Rate Ratio	95% LCL	95% UCL	Adjusted Ratio of Rate Ratios	95% LCL	95% UCL
Use without concomitant opioids ("Only use")						
OxyContin	0.81	0.64	1.02	Ref	-	-
ER morphine	1.00	0.86	1.16	1.24	0.93	1.63
TD fentanyl	1.05	0.86	1.28	1.30	0.95	1.77
Methadone	0.86	0.75	0.98	1.06	0.81	1.40

Abbreviations: ER=extended release; LCL=lower confidence limit; UCL=upper confidence limit; TD=transdermal; Ref=referent; vs=versus.

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Table 33: Rate ratios of unintentional fatal or non-fatal overdose among patients with any OxyContin use and any primary comparator opioid analgesics use in the two years before and five years after the reformulation, MarketScan

	Ratio of Rates during Post- vs. Pre-Reformulation Periods			Ratio of Ratios for Comparator Opioids vs. OxyContin		
	Adjusted Rate Ratio	95% LCL	95% UCL	Adjusted Ratio of Rate Ratios	95% LCL	95% UCL
Any non-overlapping use^						
OxyContin	0.88	0.73	1.06	Ref	-	-
ER morphine	1.01	0.82	1.23	1.14	0.87	1.50
TD fentanyl	1.06	0.88	1.27	1.20	0.93	1.55
Methadone	1.10	0.86	1.42	1.25	0.92	1.71

Abbreviations: LCL=lower confidence interval; UCL=upper confidence limit; ER=extended release; TD=transdermal; Ref=referent; vs=versus.
^Treatment episodes that had overlapping use of more than one of the primary comparators or OxyContin at the same time were excluded.

Table 34: Rate ratios of unintentional fatal or non-fatal overdose among patients with OxyContin only use and primary comparator opioid analgesics only use in the two years before and five years after the reformulation, MarketScan

	Ratio of Rates during Post- vs. Pre-Reformulation Periods			Ratio of Ratios for Comparator Opioids vs. OxyContin		
	Adjusted Rate Ratio	95% LCL	95% UCL	Adjusted Ratio of Rate Ratios	95% LCL	95% UCL
Use without concomitant opioids ("Only use")						
OxyContin	0.67	0.46	0.99	Ref	-	-
ER morphine	1.16	0.80	1.70	1.72	1.01	2.94
TD fentanyl	1.19	0.84	1.69	1.77	1.06	2.97
Methadone	1.22	0.83	1.79	1.81	1.05	3.11

Abbreviations: LCL=lower confidence interval; UCL=upper confidence limit; ER=extended release; TD=transdermal; Ref=referent; vs=versus.

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Table 35: Rate ratios of unintentional fatal or non-fatal overdose among any OxyContin use and any primary comparator opioid analgesic use in the two years before and five years after the reformulation, HIRD

	Ratio of Rates during Post- vs. Pre-Reformulation Periods			Ratio of Ratios for Comparator Opioids vs. OxyContin		
	Adjusted Rate Ratio	95% LCL	95% UCL	Adjusted Ratio of Rate Ratios	95% LCL	95% UCL
Any non-overlapping use^						
OxyContin	0.84	0.64	1.10	Ref	-	-
ER morphine	0.87	0.69	1.09	1.04	0.73	1.47
TD fentanyl	0.88	0.68	1.12	1.04	0.72	1.51
Methadone	0.99	0.75	1.31	1.18	0.81	1.73

Abbreviations: HIRD=HealthCore Integrated Research Database®; LCL=lower confidence interval; UCL=upper confidence limit; ER=extended release; TD=transdermal; Ref=referent; vs=versus.
^Treatment episodes that had overlapping use of more than one of the primary comparators or OxyContin at the same time were excluded.

Table 36: Rate ratios of unintentional fatal or non-fatal overdose among patients with OxyContin only use and primary comparator opioid analgesic only use in the two years before and five years after the reformulation, HIRD

	Ratio of Rates during Post- vs. Pre-Reformulation Periods			Ratio of Ratios for Comparator Opioids vs. OxyContin		
	Adjusted Rate Ratio	95% LCL	95% UCL	Adjusted Ratio of Rate Ratios	95% LCL	95% UCL
Use without concomitant opioids ("Only use")						
OxyContin	0.50	0.31	0.81	Ref	-	-
ER morphine	1.02	0.66	1.56	2.04	1.08	3.84
TD fentanyl	0.72	0.47	1.12	1.45	0.75	2.82
Methadone	0.90	0.62	1.31	1.81	1.00	3.28

Abbreviations: HIRD=HealthCore Integrated Research Database®; ER=extended release; LCL=lower confidence limit; UCL=upper confidence limit; TD=transdermal; Ref=referent; vs=versus.

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8.7 RESULTS OF ANALYSES WITH BENZODIAZEPINE AS A CONFOUNDER VERSUS EFFECT MODIFIER

Table 36: Rate ratios, and ratio of rate ratios, of opioid overdose (intentional and unintentional; fatal and non-fatal) among those dispensed any OxyContin (with or without other opioid analgesics concomitantly) versus any primary comparator opioid analgesic in the two years before and five years after the reformulation, HIRD database

NOTE: The adjusted rate ratios shown below are additionally adjusted for baseline benzodiazepine use (dispensing within 3 months of treatment episode initiation). The p-values for the opioid analgesic group x baseline benzodiazepine interaction (p for interaction in table) using an unadjusted model are also shown.

	Two years before [REF] vs. Five years after reformulation			OxyContin vs. Comparator Opioids			Two years before [REF] vs. Five years after reformulation			OxyContin vs. Comparator Opioids			P-interaction (by baseline benzo use)
	Rate Ratio (2 year vs. 5 year)[0]	95% LCL	95% UCL	Ratio of Rate Ratio[0]	95% LCL	95% UCL	Adjusted* Rate Ratio[0]	95% LCL	95% UCL	Adjusted* Ratio of Rate Ratio[0]	95% LCL	95% UCL	
Incident and Prevalent													
Total overdose(Fatal + Nonfatal)													
Any OxyContinˆ	0.91	0.69	1.21	Ref			0.85	0.65	1.11	Ref			
Any ER morphine	1.02	0.80	1.29	1.11	0.77	1.60	0.93	0.75	1.17	1.10	0.78	1.54	0.77
Any TD Fentanyl	0.97	0.75	1.25	1.06	0.72	1.55	0.89	0.70	1.13	1.04	0.73	1.49	0.85
Any Methadone	1.15	0.86	1.53	1.25	0.84	1.87	1.03	0.79	1.35	1.21	0.84	1.76	0.70

*Models adjusted for demographics and clinical characteristics. For all adjusted regression models in the HIRD we made the following modifications to the covariates with low sample size categories to allow for convergence:

a) classified patients with unknown geographic region to west; b) classified other and unknown health plan type to CDHP/HDHP; c) combined the 'ER' and 'ER + IR' categories in the prior use of opioid analgesics category to an 'Any ER' category; intentional overdose models adjusted only for age and sex (due to convergence limitations).

[0] Calculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

ˆAll OxyContin categories in this table exclude period w/ concomitant use of any PC, and all comparator categories in this table exclude period w/ concomitant use with Oxy or any other PC

Key: LCL = lower confidence limit; UCL = upper confidence limit

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Table 37: Rate ratios, and ratio of rate ratios, of opioid overdose (intentional and unintentional; fatal and non-fatal) among those dispensed only OxyContin (without other opioid analgesics concomitantly) versus only primary comparator opioid analgesics in the two years before and five years after the reformulation, HIRD database

NOTE: The adjusted rate ratios shown below are additionally adjusted for baseline benzodiazepine use (dispensing within 3 months of treatment episode initiation). The p-values for the opioid analgesic group x baseline benzodiazepine interaction (p for interaction in table) using an unadjusted model are also shown.

	Two years before [REF] vs. Five years after reformulation			OxyContin vs. Comparator Opioids			Two years before [REF] vs. Five years after reformulation			OxyContin vs. Comparator Opioids			P-interaction (by baseline benzo use)
	Rate Ratio (2 year vs. 5 year)[0]	95% LCL	95% UCL	Ratio of Rate Ratio[0]	95% LCL	95% UCL	Adjusted* Rate Ratio[0]	95% LCL	95% UCL	Adjusted* Ratio of Rate Ratio[0]	95% LCL	95% UCL	
Incident and Prevalent													
Total overdose(Fatal + Nonfatal)													
Use of only OxyContin (without the use of other opioids)	0.53	0.32	0.87	Ref			0.52	0.32	0.85	Ref			
Use of only ER morphine	1.21	0.78	1.87	2.29	1.18	4.45	1.14	0.75	1.75	2.18	1.17	4.07	0.4913
Use of only TD Fentanyl	0.76	0.49	1.20	1.45	0.73	2.89	0.73	0.47	1.13	1.40	0.73	2.69	0.8130
Use of only Methadone	1.03	0.70	1.52	1.96	1.04	3.71	0.91	0.63	1.31	1.74	0.97	3.13	0.7305

*Models adjusted for demographics and clinical characteristics. For all adjusted regression models in the HIRD we made the following modifications to the covariates with low sample size categories to allow for convergence:

a) classified patients with unknown geographic region to west; b) classified other and unknown health plan type to CDHP/HDHP; c) combined the 'ER' and 'ER + IR' categories in the prior use of opioid analgesics category to an 'Any ER' category; intentional overdose models adjusted only for age and sex (due to convergence limitations).

[0] Calculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

^All OxyContin categories in this table exclude period w/ concomitant use of any PC, and all comparator categories in this table exclude period w/ concomitant use with Oxy or any other PC

Key: LCL = lower confidence limit; UCL = upper confidence limit

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Table 38: Rate ratios, and ratio of rate ratios, of opioid overdose (intentional and unintentional; fatal and non-fatal) among those dispensed any OxyContin (with or without other opioids analgesics concomitantly) versus any primary comparator opioid analgesics in the two years before and two years after the reformulation, Medicaid database

NOTE: The adjusted rate ratios shown below are additionally adjusted for baseline benzodiazepine use (dispensing within 3 months of treatment episode initiation). The p-values for the opioid analgesic group x baseline benzodiazepine interaction (p for interaction in table) using an unadjusted model are also shown.

	Two years before [REF] vs. Two years after reformulation			OxyContin vs. Comparator Opioids			Two years before [REF] vs. Two years after reformulation			OxyContin vs. Comparator Opioids			P-interaction (by baseline benzo use)^
	Rate Ratio°	95% LCL	95% UCL	Ratio of Rate Ratios°	95% LCL	95% UCL	Adjusted* Rate Ratio°	95% LCL	95% UCL	Adjusted* Ratio of Rate Ratios°	95% LCL	95% UCL	
Incident and Prevalent													
Total overdose (Fatal + Nonfatal)													
Any OxyContin	1.03	0.92	1.16				1.00	0.89	1.13				
Any ER morphine	0.93	0.86	1.01	0.90	0.79	1.04	0.91	0.84	0.98	0.91	0.79	1.04	0.638
Any TD Fentanyl	1.08	0.97	1.19	1.04	0.89	1.22	1.07	0.96	1.19	1.07	0.91	1.25	0.440
Any Methadone	0.87	0.80	0.96	0.85	0.73	0.98	0.86	0.79	0.94	0.86	0.74	1.00	0.542

*Models adjusted for demographics and clinical characteristics. For all adjusted regression models in the HIRD we made the following modifications to the covariates with low sample size categories to allow for convergence:

a) classified patients with unknown geographic region to west; b) classified other and unknown health plan type to CDHP/HDHP; c) combined the 'ER' and 'ER + IR' categories in the prior use of opioid analgesics category to an 'Any ER' category; intentional overdose models adjusted only for age and sex (due to convergence limitations).

° Calculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

^All OxyContin categories in this table exclude period w/ concomitant use of any PC, and all comparator categories in this table exclude period w/ concomitant use with Oxy or any other PC

Key: LCL = lower confidence limit; UCL = upper confidence limit

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Table 39: Stratified - Among only those **with** baseline benzodiazepine dispensing: Rate ratios, and ratio of rate ratios, of opioid overdose among those dispensed any OxyContin versus any primary comparator opioid analgesics, Medicaid database

	Two years before [REF] vs. Two years after reformulation			OxyContin vs. Comparator Opioids		
	Rate Ratio°	95% LCL	95% UCL	Ratio of Rate Ratios°	95% LCL	95% UCL
Incident and Prevalent						
Total overdose (Fatal + Nonfatal)						
Any OxyContin	1.00	0.85	1.18			
Any ER morphine	0.97	0.87	1.09	0.97	0.79	1.18
Any TD Fentanyl	1.00	0.87	1.15	1.00	0.81	1.24
Any Methadone	0.83	0.73	0.96	0.83	0.67	1.03

° Calculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

Key: LCL = lower confidence limit; UCL = upper confidence limit

Table 40: Stratified - Among only those **without** baseline benzodiazepine dispensing: Rate ratios, and ratio of rate ratios, of opioid overdose among those dispensed any OxyContin versus any primary comparator opioid analgesics, Medicaid database

	Two years before [REF] vs. Two years after reformulation			OxyContin vs. Comparator Opioids		
	Rate Ratio°	95% LCL	95% UCL	Ratio of Rate Ratios°	95% LCL	95% UCL
Incident and Prevalent						
Total overdose (Fatal + Nonfatal)						
Any OxyContin	1.04	0.88	1.22			
Any ER morphine	0.91	0.82	1.00	0.88	0.72	1.06
Any TD Fentanyl	1.15	0.99	1.33	1.11	0.89	1.38
Any Methadone	0.91	0.80	1.03	0.88	0.71	1.08

° Calculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

Key: LCL = lower confidence limit; UCL = upper confidence limit

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Table 41: Rate ratios, and ratio of rate ratios, of opioid overdose (intentional and unintentional; fatal and non-fatal) among those dispensed only OxyContin (without other opioid analgesics concomitantly) versus only primary comparator opioid analgesics in the two years before and two years after the reformulation, Medicaid database

NOTE: The adjusted rate ratios shown below are additionally adjusted for baseline benzodiazepine use (dispensing within 3 months of treatment episode initiation). The p-values for the opioid analgesic group x baseline benzodiazepine interaction (p for interaction in table) using an unadjusted model are also shown.

	Two years before [REF] vs. Two years after reformulation			OxyContin vs. Comparator Opioids			Two years before [REF] vs. Two years after reformulation			OxyContin vs. Comparator Opioids			P-interaction (by baseline benzo use)^
	Rate Ratio°	95% LCL	95% UCL	Ratio of Rate Ratios°	95% LCL	95% UCL	Adjusted* Rate Ratio°	95% LCL	95% UCL	Ratio of Rate Ratios°	95% LCL	95% UCL	
Incident and Prevalent													
Total overdose (Fatal + Nonfatal)													
Use of only OxyContin (without the use of other opioids	0.86	0.69	1.08				0.85	0.68	1.07				
Use of only ER morphine	1.01	0.87	1.16	1.17	0.89	1.53	1.00	0.87	1.15	1.18	0.90	1.54	0.735
Use of only TD Fentanyl	1.09	0.90	1.32	1.26	0.94	1.70	1.08	0.89	1.31	1.27	0.94	1.72	0.903
Use of only Methadone	0.88	0.77	1.00	1.01	0.78	1.32	0.87	0.77	0.99	1.03	0.79	1.34	0.980

*Models adjusted for demographics and clinical characteristics. For all adjusted regression models in the HIRD we made the following modifications to the covariates with low sample size categories to allow for convergence:

a) classified patients with unknown geographic region to west; b) classified other and unknown health plan type to CDHP/HDHP; c) combined the 'ER' and 'ER + IR' categories in the prior use of opioid analgesics category to an 'Any ER' category; intentional overdose models adjusted only for age and sex (due to convergence limitations).

° Calculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

^All OxyContin categories in this table exclude period w/ concomitant use of any PC, and all comparator categories in this table exclude period w/ concomitant use with Oxy or any other PC

Key: LCL = lower confidence limit; UCL = upper confidence limit

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Table 42: Stratified - Among only those **with** baseline benzodiazepine dispensing: Rate ratios, and ratio of rate ratios, of opioid overdose among those dispensed only OxyContin versus only primary comparator opioid analgesics, Medicaid database

	Two years before [REF] vs. Two years after reformulation			OxyContin vs. Comparator Opioids		
	Rate Ratio°	95% LCL	95% UCL	Ratio of Rate Ratios°	95% LCL	95% UCL
Incident and Prevalent						
Total overdose (Fatal + Nonfatal)						
Use of only OxyContin (without the use of other opioids)	0.82	0.58	1.15			
Use of only ER morphine	1.06	0.84	1.33	1.30	0.86	1.95
Use of only TD Fentanyl	1.06	0.80	1.40	1.29	0.83	2.00
Use of only Methadone	0.87	0.70	1.07	1.06	0.71	1.58

° Calculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

Key: LCL = lower confidence limit; UCL = upper confidence limit

Table 43: Stratified - Among only those **without** baseline benzodiazepine dispensing: Rate ratios, and ratio of rate ratios, of opioid overdose among those dispensed only OxyContin versus only primary comparator opioid analgesics, Medicaid database

	Two years before [REF] vs. Two years after reformulation			OxyContin vs. Comparator Opioids		
	Rate Ratio°	95% LCL	95% UCL	Ratio of Rate Ratios°	95% LCL	95% UCL
Incident and Prevalent						
Total overdose (Fatal + Nonfatal)						
Use of only OxyContin (without the use of other opioids)	0.86	0.64	1.16			
Use of only ER morphine	0.98	0.82	1.18	1.14	0.80	1.62
Use of only TD Fentanyl	1.10	0.85	1.42	1.28	0.86	1.90
Use of only Methadone	0.87	0.74	1.03	1.02	0.72	1.43

° Calculated using Proc Genmod in SAS, accounting for repeated observations due to multiple treatment episodes per patient.

Key: LCL = lower confidence limit; UCL = upper confidence limit

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8.8 LITERATURE REVIEW

Author, date	Data source and patient population	Time period	Findings	Authors' Conclusions	Limitations
Coplan et al., 2016 [1] *NOTE: these 10 studies were submitted to FDA in by the sponsor as part of the 2015 labeling supplement application.*	-Truven MarketScan commercial claims and encounters databases -All patients dispensed OxyContin and comparator opioid analgesics	One year before (2009Q3-2010Q3) versus three years after (2010Q4-2013Q4) the reformulation	Rates of opioid overdose/ poisoning diagnoses decreased from 0.42 per 100 person-years of opioid use in the year before reformulation (51 cases among 85,978 people prescribed OxyContin) to 0.28 per 100 person-years of opioid use after (30 cases among 87,935 people prescribed OxyContin on average per year), reflecting a 34% (95% confidence interval [CI]: -53% to -7%) decrease, while that for the comparator opioid analgesics (ER morphine, ER oxymorphone, IR oxycodone, IR hydromorphone) remained stable or unchanged. OxyContin's percent change was statistically significantly different (p=0.027) from ER morphine (+17% [CI: -19% to +69%]), comparing the pre- and post-reformulation periods (no other opioid analgesic comparator was directly compared). IR hydromorphone increased comparing periods (10%), and ER oxymorphone (0%) and SE IR oxycodone (-1%) did not.	*"After the introduction of reformulated OxyContin with abuse-deterrent properties, there were decreases in associated abuse, overdose diagnoses, and diversion that occurred consistently across 10 studies that used different measures of abuse and its consequences."*	-Used a truncated pre- and post-period that will make longer-term trends more difficult discern -For exposure periods, no differentiation of concomitant opioid analgesic use from use alone (without other opioid analgesics) -Did not use a validated claims-based opioid overdose algorithm, and no mortality linkage -No adjustment for patient-level demographic or clinical characteristics
Larochelle et al., 2015 [2]	-Optum commercial claims data -All eligible patients who were dispensed OxyContin and comparator opioid analgesics, and all eligible patients in the database	January 1, 2003, to December 31, 2012 *Two interventions analyzed: Introduction of abuse-deterrent OxyContin formulation on August 9, 2010, and market withdrawal of propoxyphene on November 19, 2010.*	Two years after the opioid analgesic market changes (reformulation of OxyContin and propoxyphene withdrawal), total opioid dispensing decreased by 19% from the expected rate (absolute change, −32.2 mg morphine-equivalent dose per member per quarter [95% CI, −38.1 to −26.3]). By opioid subtype, the absolute change in dispensing by milligrams of morphine-equivalent dose per member per quarter at 2 years was −11.3 (95% CI, −12.4 to −10.1) for extended-release oxycodone (-39% relative change comparing periods), 3.26 (95% CI, 1.40 to 5.12) for other long-acting opioid analgesics (11% relative change comparing periods), −8.19 (95%CI, −9.30 to −7.08) for	*"Opioid dispensing and prescription opioid overdoses decreased substantially after two major changes in the pharmaceutical market in late 2010 (reformulation of OxyContin and propoxyphene withdrawal); market interventions may have value in mitigating opioid overdose."*	-Did not use a validated claims-based opioid overdose algorithm, and no mortality linkage -Prescription opioid overdose rates (and relative change) were measured overall, not separately by prescription opioid; also, overdose rates were calculated using all eligible patients, including those without any opioid dispensing

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| | | | propoxyphene (-100% relative change comparing periods), and −16.2 (95% CI, −18.8 to −13.5) for other immediate-release opioid analgesics (-16% relative change comparing periods).

Two years after the market changes (reformulation of OxyContin and propoxyphene withdrawal), the estimated overdose rate (per 100,000 members) attributed to prescription opioids decreased by 20% (absolute change, −1.10 per 100,000 members per quarter [95% CI, −1.47 to −0.74]), but heroin overdose increased by 23% (absolute change, 0.26 per 100,000 members per quarter [95% CI, −0.01 to 0.53]). | | |

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U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

S T A T I S T I CAL B RIE FIN G MAT E RI AL

OXYCONTIN POST-MARKETING REQUIREMENT STUDY 3051

Statistical Briefing Material for the Joint Meeting of the Drug Safety and Risk Management Advisory Committee and Anesthetic and Analgesic Drug Product Advisory Committee on September 10-11, 2020

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1 EXECUTIVE SUMMARY

Background: In April 2010, the United States (US) Food and Drug Administration (FDA) approved a reformulated version of OxyContin (oxycodone hydrochloride extended-release) for commercial distribution in the US. The physical properties of reformulated OxyContin potentially make it more difficult to abuse the product by crushing, as well as administering through alternate routes such as snorting and injecting. As a condition of approval, FDA required post-marketing studies on reformulated OxyContin to assess the effectiveness of the abuse-deterrent formulation (ADF) in reducing abuse and associated serious risks associated with OxyContin. In March 2016, FDA formalized these requirements and milestones, issuing a post-marketing requirement (PMR) letter to Purdue Pharma L.P. (the sponsor) that specifically asks for the conduct of four epidemiologic studies (3051-1 to 3051-4) that assess the impact of the reformulation on abuse and overdose. FDA received the following reports for PMR 3051 studies which are the subject of this statistical review:

- PMR 3051-1 final study report, dated July 2018
- PMR 3051-2 final study report, dated July 2018
- PMR 3051-3 final study report, dated April 2019
- PMR 3051-4 final study report, dated August 2019

The overarching purpose of this briefing document is to evaluate the robustness of findings and strength of evidence provided in these study reports, from a statistical perspective. The specific goals are:

(1) To discuss methodological considerations for design and analysis of PMR 3051 with an emphasis on statistical issues

(2) To demonstrate why PMR 3051 studies evaluate plausible ranges of effect estimates, rather than a single effect estimate, under various assumptions

(3) To explore results under the various assumptions

(4) To provide conclusions on totality of evidence from a statistical perspective, demonstrating what can be robustly concluded under what assumptions.

Methods: The overarching goal of PMR 3051 studies was to infer <u>causal effect</u> of OxyContin reformulation, i.e., PMR 3051 was interested in evaluating whether OxyContin reformulation <u>caused</u> a reduction in abuse and related outcomes or not. To this end, PMR 3051 aimed to evaluate changes in rates of abuse (PMR 3051-1 to 3051-3) and overdose (PMR 3051-4) of OxyContin before and after the time of OxyContin reformulation with and without comparison to those of other selected opioid analgesics, using different populations and associated data sources. However, the four data sources were observational in nature and subject to numerous sources of confounding over time that may impact change in rates of abuse and related outcomes differentially over time across opioid analgesics (see Section 4 for more details). This made it challenging to isolate the causal effect of OxyContin reformulation from observed changes in rates of abuse and overdose. To be able to explore the causal effect of OxyContin reformulation, PMR 3051 studies aimed to estimate plausible "ranges" of effect estimates by varying study parameters within studies (e.g., study period, definition of site/region/center, OxyContin, outcome measure, types of comparators, etc.). These parameters correspond to different underlying assumptions which reflect the complicated nature of data, design, and analysis to study the impact of OxyContin reformulation. Table 1 in Section 3.1 presents a summary of key study attributes and (major) varying study parameters across PMR 3051 studies.

Among the varying study parameters, definition of an outcome measure (i.e., rate) and different ways to adjust for key factors in modeling the outcome determined basic formulation of statistical models for PMR 3051-1 to 3051-3. Broadly, 3051 1-3 studies considered five types of abuse rates and corresponding statistical models (see Table 2 in Section 5.1):

1) population-based rate (model 1 and model 5)
2) drug utilization-based rate (model 2 and model 6)
3) drug utilization-based population-adjusted rate (model 2a and model 6a)
4) drug utilization-adjusted rate (model 3 and model 7)
5) population- and drug utilization-adjusted rate (model 3a and model 7a)

Here "based" means that the factor is used as denominator of a rate, whereas "adjusted" means that the factor is used as a covariate when modeling the rate. For example, population-based rate is defined as number of abuse cases divided by population size estimated using different metrics for population size (e.g., number of assessments for PMR 3051-1; US Census population or a proxy for call volume for PMR 3051-2; number of survey respondents for PMR 3051-3). Drug utilization-based rate is defined as number of abuse cases divided by dosage units dispensed. Drug utilization-based and population-adjusted rate means that the rate is defined by number of abuse cases divided by dosage unit dispensed and is modeled by adjusting for population size as a covariate. As PMR 3051 considered modeling a rate as an outcome, studies utilized Poisson regressions. The adequacy of the Poisson model was evaluated, including the issue of over-dispersion.

Unlike PMR 3051-1 to 3051-3 that considered various outcome measures (population/utilization-based or -adjusted), PMR 3051-4 considered a single measure for each outcome (rate of overdose; any overdose, fatal or non-fatal overdose) based on time at risk (person-time).

Although each PMR 3051 study presents some unique aspects due to differences in population, database, outcome, etc., major analytic goals of the entire PMR 3051 studies can be summarized as follows:

- Examine **descriptive trends** in rates of abuse/overdose
- Estimate **change** in rates of abuse/overdose before and after the time of OxyContin reformulation using (i) percent change in rates from pre-reformulation to post-reformulation period and (ii) change in levels and slopes of rates from the pre- to post-reformulation period calculated via interrupted time series (ITS) analysis
- Evaluate **these changes relative to those of comparators** using (i) a ratio of rate ratios† (RORR) and (ii) comparative ITS analysis.

Then for assessing the change in abuse/overdose rates with and without comparison to the other opioids, PMR 3051 evaluated a plausible range of effect estimates using various Poisson models that correspond to varying parameters listed in Table 1.

Methodological Considerations: This document focuses on illustrating design and methodological issues, which can be broadly summarized into **data quality and causality**, that led to the decision of considering ranges of effect estimates, from a statistical perspective.

PMR 3051 considered a "rate" outcome (rate of abuse or overdose) and examined how it changed before and after the time of the reformulation. To illustrate, suppose the following notation for a given opioid:

- Let **Apre** and **Apost** be number of '**A**'buse cases in pre-reformulation period (henceforth, the pre-period) and post-reformulation period (the post-period), respectively.
- Let **Dpre** and **Dpost** be volume of a '**D**'enominator measure in the pre-period and the post-period, respectively.
- Let $\mathbf{R_{pre}} = \frac{A_{pre}}{D_{pre}}$ and $\mathbf{R_{post}} = \frac{A_{post}}{D_{post}}$ be estimated '**R**'ate of abuse in the pre-period and the post-period, respectively.

Then these rates define estimates of target quantities that evaluate the impact of OxyContin reformulation including

- percent change = (Rpost – Rpre)/Rpre *100
- rate ratio, say RR $= \frac{R_{post}}{R_{pre}}$ that defines
- Ratio of rate ratio (RORR) $= (\frac{R_{post}}{R_{pre}}$ for a comparator$)/(\frac{R_{post}}{R_{pre}}$ for OxyContin$)$.

From above formulation, it is evident that any factors that can influence Apre and Apost differentially as well as Dpre and Dpost differentially would have an impact on the validity of the target estimates. Broadly, the following three factors that reflect observational and dynamic nature of data (i.e., **data quality**) had to be taken into consideration in design and analysis of PMR 3051:

1) inconsistencies in site participation and/or regional/program variation in database (i.e., sampling bias),
2) product misclassification, and
3) missing formulation information,

which all change over time. In addition, PMR 3051 needed to address the following questions to be able to evaluate **the causal effect of the reformulation**:

1) How to incorporate drug utilization (which has been shown to be correlated with opioid abuse) in analysis?
2) How to account for factors unrelated to OxyContin reformulation and what is appropriate choice of comparators?

To ensure consistency in site participation over time and homogeneity in selected sites (to minimize sampling bias), primary analyses in PMR 3051-1 and secondary analyses in PMR 3051-3 were limited to sites that consistently contributed to database over the study period. In order to better understand how regional-specific legislative and law enforcement actions (e.g., Florida pill mill) that might have affected changes in abuse of OxyContin and comparators, analyses were stratified by geographic region in PMR 3051-2 and PMR 3051-3 (entire US, Western regions only, entire US except Florida). As PMR 3051-3 considered populations from two different treatment programs, it considered stratified analysis by type of treatment programs. To address issues of product misclassification and missing formulation, PMR 3051-1 to 3051-3 considered multiple definitions of OxyContin such as including and excluding generic ER oxycodone, unspecified ER oxycodone, or unspecified oxycodone as a part of OxyContin endorsement. PMR 3051-2 specifically considered multiple imputation of missing formulation.

Since the time of OxyContin reformulation, utilization of Oxycontin continued to decrease. As it has been known that prescription volume correlates with opioid abuse rates, it raises a question that how much of the decrease in abuse of OxyContin (if there is any) was

†Rate ratio is defined by a ratio between rates in pre- and post-reformulation period for a single opioid. RORR is a ratio between two rate ratios (one for OxyContin; the other for a comparator) obtained from difference-in-differences type of analysis. See Section 4 for details.

due to the declined prescribing after the reformulation. It also raises a question that, if the decrease in OxyContin abuse is somewhat attributable to the decrease in its prescription volume after the reformulation, what is an appropriate way to account for the impact of the prescription volume when estimating the effect of the reformulation on abuse? Conversely, we could also raise a question that how much of the decrease in OxyContin prescribing was due to reduced demand for the drug for diversion and abuse? And if the decrease in prescribing is somewhat attributable to the reduced demand then would adjusting for utilization, which is a mediator in the causal pathway from OxyContin reformulation to abuse, be a valid approach?

It is not clear how to best account for drug utilization in analysis. This has led FDA to consider multiple outcome definitions and models, both unadjusted and adjusted for utilization, based on different assumptions, with the truth of the effect of the reformulation likely lying somewhere within this range of estimates. As described earlier, different definitions of an outcome (rate) and ways to adjust for population size or drug volume determined statistical models listed in Table 2 in Section 5.1.

Comparing abuse/overdose rates of OxyContin between the pre- and the post-period is invalid if there are time-dependent trends in these rates induced by external factors unrelated to the reformulation such as other public health efforts to mitigate the opioid epidemic or broader changes in drug abuse patterns in the community. PMR 3051 considered comparators that could potentially serve as a "counterfactual" and/or "negative control" for OxyContin, which would represent what (would have) happened in the absence of the reformulation but under the various public health efforts and secular trends. As there is no ideal single comparator, PMR 3051 considered multiple comparators where each comparator could serve as a counterfactual for OxyContin under different contextual setting.

Aforementioned design considerations led to examine the range of effect estimates under varying study parameters (e.g., study period, definition of site/region/center, OxyContin definition, outcome measure, comparators, etc.) listed in Table 1.

Statistical Findings: Overall, reduction in abuse of OxyContin was the most prominent when population-based rates of abuse were considered, rather than utilization-based rates. Comparative analysis results generally varied by the choice of outcome measure, route of administration (ROA), comparator, and definition of OxyContin.

Below we describe overview of PMR 3051-1 results in more detail as an illustrative example. Then for PMR 3051 2-4 studies, we focus on key comparative, inferential analysis results to avoid repetition between Epidemiology Reviews in background document and this document.

(1) PMR 3051-1: Descriptive trends were useful to visually inspect the impact of OxyContin reformulation with or without comparators. Trends in rate of abuse for the same opioid typically varied by considering different denominators and covariates to define the rate.

Percent change estimates for rate of non-oral abuse (based on the five different measures of the rate and corresponding statistical models) ranged from -55.6% to -29.3%, when primary definitions of OxyContin and site were used. Estimated decline in non-oral abuse rate was the largest (-70.0%) when reformulated OxyContin alone in the post-period (secondary OxyContin definition 1) was considered. Differing site definitions (broadening sites) led to smaller reductions after the reformulation, where estimated reduction in non-oral abuse went down to -8.4%, leading range of estimates -55.6% to -8.4% as compared to -55.6% to -29.3%. Total range of percent change estimates across varying OxyContin and site definitions were -70% to -8.4%.

RORR results for non-oral abuse were mostly significant and favorable to OxyContin demonstrating the effect of the reformulation in this population. As indicated by percent change results, estimated effect was the largest when reformulated OxyContin alone was considered in the post-period. RORRs from ROA analysis showed that OxyContin led to greater reduction in abuse via snorting and injecting (which it is designed to deter) but led to smaller reduction in abuse by oral routes in general, compared to those of primary comparator opioids. This resulted in mixed findings on reducing overall abuse (some are favorable to OxyContin but some others are favorable to comparators) in this population.

From ITS analysis, minimal changes in slope for all study opioids and no significant change in slope for OxyContin relative to comparators were observed. Immediate shift that represents change in outcome levels right before and after the time of the reformulation (excluding transition period) demonstrated that OxyContin is the only opioid showing significant reduction in non-oral abuse rate right after the time of the reformulation. However, the magnitude of the immediate shift for OxyContin was generally similar to those of comparators.

(2) PMR 3051-2: From primary comparative analyses, only (RORR) results based on model 1 using population-based rate consistently demonstrated the effect of the reformulation (i.e., reduction in abuse is significantly greater for OxyContin relative to all comparators).

Of note, model 1 was the least adequate model in terms of a statistical measure called the AIC, where the AIC value was 2254.99 for model 1. Briefly, a model with a lower AIC value is deemed more appropriate than the others with higher AIC values. RORRs from some other analyses using secondary definition of OxyContin (any ER oxycodone) showed even greater reduction in abuse for comparators relative to that of OxyContin.

From ROA analysis, again only RORRs based on model 1 (population-based rate) results consistently demonstrated greater reduction in oral and non-oral abuse (but not in inhalation and injection abuse) for OxyContin compared to all primary comparators. Some effect of the reformulation was observed from comparisons with IR hydrocodone and other schedule II opioids: Reduction in non-oral abuse was significant greater for OxyContin over the two comparators for most cases (model 1, 2, and 2a results for comparisons with IR hydrocodone; model 1, 2, 2a, and 3a results for comparisons with other schedule II opioids).

Change in slope for OxyContin was not apparently distinct from that of comparators. The final study report provides comparative immediate shift results based only on a limited set of models (model 5 [population-based rate], 6a [drug utilization-based, population-adjusted rate], and 7a [population- and drug utilization-adjusted rate]). Immediate shift for OxyContin was statistically significantly greater than those of IR hydrocodone based on model 5, and from other Schedule II opioids using model 5 and 7a. Considering that model 5 is an ITS version of model 1, these results are consistent with RORR results.

(3) PMR 3051-3: As in PMR 3051-2, only results based on model 1 (population-based rate) showed significantly greater reduction in OxyContin abuse compared to those of all comparators. Model 1 was the least adequate model in terms of the AIC (3281.7). In PMR 3051-3, most significant and favorable results to OxyContin were observed from comparisons with ER morphine (model 1, 3 [drug utilization-adjusted rate], and 3a [population- and drug utilization-adjusted rate] results). Comparisons with IR hydrocodone or other schedule II opioids were all insignificant except for model 1 results. Stratified by two data sources called OTP and SKIP (see attribute 2 in Table 1), the analyses revealed that most significant and favorable results for OxyContin and ER morphine comparisons were driven by data from adults entering general substance abuse treatment programs who endorsed an opioid as their primary drug of abuse (SKIP); all results from the other population (adults enrolling in methadone maintenance treatment programs; OTP) were insignificant except for model 1 results.

Changes in slope for OxyContin were mostly similar to those for comparators except for only one case: Models 7a (population- and drug utilization-adjusted rate) results for OxyContin and IR hydrocodone comparisons.

(4) PMR 3051-4: RORR results suggested that change in overdose for OxyContin is mostly similar to those of comparators across three different databases under different definitions of OxyContin use.

Data Verification and Analysis Replication: FDA requested the sponsor to submit data and analysis programs for PMR 3051 studies, except for PMR 3051-4 as it was considered infeasible to obtain commercial insurance data. The goal of this request was to confirm reproducibility of sponsor's analyses. Due to the volume of data and analyses (submission completed on February 25, 2020), FDA selected key primary analyses for the replication efforts. See Section 7 for list of verified analyses and associated study objectives. FDA has been able to reproduce the selected key primary analysis results for PMR 3051-1 to 3051-3 ensuring integrity of the analyses and selected key findings.

Conclusions: As PMR 3051 studies utilized observational data that are subject to various sources of confounding over time including the changing landscape of opioid use and abuse, isolation of the (causal) effect of OxyContin reformulation was challenging. Therefore, PMR 3051 studies were designed to explore the impact of the various factors listed in Table 1 on the estimation of reformulation effect. This is a reasonable approach, from a statistical perspective, although it somewhat complicates the interpretation of the study findings. Robustness of findings under various assumptions and qualitative synthesis of the totality of evidence were used to make final conclusions on the effect of OxyContin reformulation. Finally, evaluation of model adequacy and relative performances, coupled with FDA's efforts to verify integrity and reproducibility of sponsor's analyses, ensured quality of selected key study findings.

In PMR 3051-1, there was reasonably compelling, robust evidence that the reformulation is effective in reducing the rate of non-oral OxyContin abuse in a population entering or being assessed for substance abuse treatment. However, the evidence for a reduction in overall OxyContin abuse (via any route) in this population was weak. PMR 3051-2 and 3051-3 provided weak evidence of an effect of the reformulation, as findings were mixed and only population-based rate (which corresponds to model 1 in Table 2; the least adequate model in terms of the statistical measure AIC) consistently demonstrated significantly greater reduction in rates of (overall) abuse for OxyContin relative to primary comparator opioids. Overall, reduction in abuse of OxyContin was the most prominent when population-based rates of abuse that do not account for utilization information were considered. The totality of evidence from PMR 3051-2 supports some effect of the reformulation on reducing non-oral abuse although the non-oral abuse data in PCC are limited. PMR 3051-4 provided no compelling evidence that OxyContin reformulation reduces opioid overdose among patients prescribed OxyContin. These findings are largely consistent with those provided in Epidemiology Reviews in background document.

The investigation of the range of effect estimates under various but plausible assumptions to draw reasoned conclusions based on robustness/totality of evidence is the strength of PMR 3051 studies from a statistical perspective, particularly because analyses results confirmed that differing assumptions and study attributes could sometimes meaningfully alter the substance of findings and interpretations. However, PMR 3051 studies are still subject to limitations, some of which are untestable based on observed data (e.g., considered statistical models could [at least approximately] reflect true relationship between abuse/overdose rates, population, and drug utilization; see Section 4 for full discussion). Thus, cautions are still warranted when interpreting study findings. See Office of Surveillance and Epidemiology Summary Memorandum (henceforth referred to as *summary memorandum*) in background document. Nonetheless, these study findings enable us to explore the impact of various sources of confounding and thus provide a solid background to initiate discussions regarding questions prepared for the committee shown in background document.

2   INTRODUCTION

This briefing document assumes that readers are familiar with regulatory history of OxyContin, background for post-marketing requirement (PMR) 3051 study including goals of PMR 3051 stated in the PMR language, and study design from Epidemiology Reviews in background document. The purpose of this briefing document is as follows:
(1) To discuss methodological considerations for design and analysis of PMR 3051 from a statistical perspective
(2) To demonstrate why PMR 3051 studies evaluate plausible ranges of effect estimates, rather than a single effect estimate, under various assumptions
(3) To explore results under the various assumptions
(4) To provide conclusions on totality of evidence from a statistical perspective, demonstrating what can be robustly concluded under what assumptions.

This review focuses on key primary and secondary analyses that are mostly common to PMR 3051 1-3 (opioid abuse studies) or to all four studies for efficiency sake. This review is organized as follows: Section 3 provides a high-level overview of design and setting for all four PMR 3051 studies, emphasizing aspects pertinent to the statistical review. Section 4 discusses methodological considerations, particularly related to statistical analysis plans, that led to the investigation of ranges of effect estimates under different assumptions. Then Section 5 describes statistical methods. Section 6 summarizes the results. Section 7 describes data verification and analysis replication efforts. Section 8 briefly discusses totality and strength of evidence from a statistical perspective, then provides final conclusions from a statistical perspective.

3   STUDY DESIGN

3.1   STUDY OVERVIEW & ANALYTIC GOAL

The overarching goal of PMR 3051 studies was to infer causal effect of OxyContin reformulation, i.e., PMR 3051 was interested in evaluating whether OxyContin reformulation caused a reduction in abuse and related outcomes or not. To this end, PMR 3051 studies aimed to evaluate changes in rates of abuse (PMR 3051-1 to 3051-3) and overdose (PMR 3051-4) of OxyContin before and after the time of OxyContin reformulation with and without comparison to those of other selected opioid analgesics, using different populations and associated data sources. However, the four data sources were observational in nature and subject to numerous sources of confounding over time that may impact change in rates of abuse and related outcomes differentially over time across different opioid analgesics (see Section 4 for more details). This made it challenging to isolate the causal effect of OxyContin reformulation from observed changes in rates of abuse and overdose. To be able to explore the causal effect of OxyContin reformulation, PMR 3051 studies aimed to estimate plausible "ranges" of effect estimates by varying study parameters within studies (e.g., study period, definition of site/region/center, OxyContin, outcome measure, types of comparators, etc.). These parameters correspond to different underlying assumptions which reflect the complicated nature of data, design, and analysis to study the impact of OxyContin reformulation. Table 1 presents a summary of key study attributes and (major) varying study parameters across PMR 3051 studies. In Table 1, P represents primary and S (or SS) represents secondary or sensitivity.

Table 1. Summary of key study attributes and major varying parameters across the four PMR 3051 studies.

Attributes	Study Number			
	3051-1	3051-2	3051-3	3051-4
1. Population	Patients assessed for substance abuse problem and treatment planning	Exposure cases reported to poison control centers (PCC)	Adults treated in substance abuse treatment centers for opioid use disorder	Individuals covered by Medicaid or under some commercial insurers
2. Data Source* (see footnote for abbreviation)	Data stream that assesses pharmaceutical abuse by patients entering substance abuse treatment; ASI-MV in NAVIPPRO	Calls made to PCC in RADARS	Two substance abuse treatment center programs; OTP and SKIP in RADARS	Three claims; National Medicaid, MarketScan, HIRD

	Drug utilization information from IQVIA			
3. Period	P: 2 years pre-reformulation (pre) vs. 4 years post-reformulation (post)	P: 2 years pre vs. 5 years post		P: 2 pre vs. 5 post except for Medicaid (only 2 years post)
	S: 1 year pre vs. 3 years post			
4. Site/ Region/ Center/ Program	P: sites with ≥1 assessment/quarter	P: Entire US	P: sites with ≥1 assessment during the study period (entire US)	Linkable to National Death Index
	S1: ≥1 assessment/year	S1: US excluding Florida	S1: ≥1 assessment/quarter	
	S2: ≥1 assessment/year except for sites in New Mexico	S2: West census region	S2: ≥1 assessment/year excluding centers in S1	
			S3: all sites excluding those in S1 and S2	
			SS1: US excluding Florida	
			SS2: West census region	
			SS3: Stratified by OTP/SKIP	
5. Exposure	P: Original OxyContin (in the pre-period) vs. Original plus reformulated OxyContin (in the post-period)			Any OxyContin use regardless of other opioid use
	S1. Original OxyContin vs. Reformulated only	S1. Original OxyContin + generic ER oxycodone vs. Original OxyContin + reformulated + generic ER oxycodone	S1. Original + unspecified ER oxycodone vs. Original + reformulated + unspecified ER oxycodone	OxyContin only use (no concomitant use of other opioids)
	S2. Original OxyContin + generic ER oxycodone vs. Original OxyContin + reformulated + generic ER oxycodone	S2. S1 + unspecified oxycodone	S2. S1 + unspecified oxycodone	OxyContin with concomitant use of other opioids (further stratified by types of other opioids; e.g., primary and/or secondary comparator, IR opioids, etc.)
6. Outcome	Non-oral and overall past 30-day abuse	Intentional abuse	Past-month overall abuse ("non-medical use" is the way the survey asks)	Any overdose
				Fatal overdose
				Non-fatal overdose
7. Outcome Measure (definition of "rate†") and corresponding statistical models•	Population-based rate (model 1 and 5)			Standard person-time-based rate of overdose (person-time = treatment episode)
	Drug utilization-based rate (model 2 and 6)			
	Drug utilization-based population-adjusted rate (model 2a and 6a)			
	Drug utilization-adjusted rate (model 3 and 7)			
	Population- and drug utilization-adjusted rate (model 3a and 7a)			
8. Route of Administration	Oral swallowed intact	Oral	NA; but descriptive analyses for injection are available	NA
	Other oral (chewed, dissolved, drank)	Non-oral (inhalation, injection, and other routes)		
	Snorted	Inhalation		
	Injected	Injection		
	Any routes			
9. Primary comparators	P1: ER morphine			P1: ER morphine
	P2: IR Hydrocodone			P2: TD fentanyl
	P3: Other Schedule II opioids			P3: Methadone
10. Secondary comparators	S1: ER oxymorphone		S1: IR oxycodone	S1: ER oxymorphone
	S2: IR SE Oxycodone		S2: Methadone	S2: IR SE oxycodone
	S3: IR Oxycodone-acetaminophen		S3: Heroin	S3: IR hydromorphone
	S4: S2+ S3		S4: IR oxycodone or unknown oxycodone	
	S5: Methadone			
	S6: Heroin			

NAVIPPRO: National Addictions Vigilance Intervention and Prevention Program

ASI-MV: Addiction Severity Index-Multimedia Version in NAVIPPRO

RADARS: Researched Abuse, Diversion, and Addiction-Related Surveillance

OTP: The Opioid Treatment Program in RADARS system

SKIP: Survey of Key Informants' Patients program in RADARS system

HIRD: HealthCore Integrated Research Database

† Population-based rate: Defined by number of abuse cases/population size (e.g., number of surveys; per 3 Digit Zip-code in each quarter [3DZQ] or per calendar-quarter)

† Drug utilization-based rate: Defined by number of abuse cases/drug utilization volume (per 3DZQ or calendar-quarter)

† Drug utilization-based population-adjusted rate: Defined by number of abuse cases/drug utilization volume (per 3DZQ or calendar-quarter) and modeled using population as a covariate

† Drug utilization-adjusted rate: Defined by number of abuse cases per 3DZQ or calendar-quarter and modeled using drug utilization as a covariate

† Population- and drug utilization-adjusted rate: Defined by Abuse cases per 3DZQ or calendar-quarter and modeled using population and drug utilization as covariates

- *See Table 2 in Section 5.1 for model definition; Model 5 is interrupted time series (ITS) version of Model 1, Model 6 is ITS version of Model 2, etc.*

Although each study might present some unique aspects due to inherent differences in population, database, outcome, etc., major analytic goals of PMR 3051 studies can be summarized as follows:

- Examine **descriptive trends** in rates of abuse/overdose
- Estimate **change** in rates of abuse/overdose before and after the time of OxyContin reformulation using (i) percent change in rates from pre-reformulation to post-reformulation period and (ii) change in levels and slopes of rates from the pre- to post-reformulation period calculated via interrupted time series (ITS) analysis
- Evaluate **these changes relative to those of comparators** using (i) a ratio of rate ratios (RORR) and (ii) comparative ITS analysis.

3.2   STUDY POPUATION, DATA SOURCE, AND TIME PERIOD

Population & Data Source:

- Study population for PMR 3051-1 is patients being assessed for substance abuse problem severity and treatment planning in a treatment site within the network of in the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO). The NAVIPPRO has a surveillance system called Addiction Severity Index-Multimedia Version (ASI-MV) that collects data on overall and route-specific, past 30 days abuse of legal and illegal drugs. The NAVIPPRO ASI-MV System is dynamic as individual sites can enter or leave the network over time. Coverage of the ASI-MV network ranged from 10 to 24 states during the study period.

- Study population for PMR 3051-2 corresponds to all exposure cases reported to Poison Control Centers (PCC) participating in the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) system Poison Center Program (PCP). Coverage of RADARS PCP ranged 43 to 48 states in the US during the study period, corresponding 82.5% to 94.3% coverage of the US population.

- Study population for PMR 3051-3 is a combination of two separate groups of adults treated in substance abuse treatment centers for opioid use disorder across RADARS System centers. The Opioid Treatment Program (OTP) surveys adults enrolling in methadone maintenance treatment programs and the Survey of Key Informants' Patients (SKIP) program surveys adults entering general substance abuse treatment programs who endorsed an opioid as their primary drug of abuse. During the study period, OTP collected data from 64 to 76 sites per year from 35 states. SKIP had a key informant network including 58 to 154 sites pre year from 50 states. Individuals entering OTP or SKIP are asked to complete a standardized, self-administered survey on recent opioid use behaviors.

- Study population for PMR 3051-4 consists of individuals whose medical claims information is available in the National Medicaid or two other commercial healthcare claims database; the HealthCore Integrated Research Database (referred to as HIRD), IBM MarketScan Commercial and Medicare Supplemental Claims and Encounters database (referred to as MarketScan). Individuals are limited to those whose information is linkable to the National Death Index (NDI) database, to be able to determine fatal/non-fatal overdose status.

PMR 3051-1 to 3051-3 studies used IQVIA data to capture drug utilization (dosage units dispensed) information.

Study Period: Study period varied by each study and also by objectives. This document focuses on primary analyses that aimed to examine change in rates of abuse/overdose. For most primary analyses, study period consisted of (i) pre-reformulation period (referred to as pre-period), (ii) transition period, and (iii) post-reformulation period (referred to as post-period). Most primary analyses disregarded the transition period from analyses as it was subject to high market variability.

PMR 3051-1 to 3051-4 considered the same pre-period and transition period:
- Pre-period: 3Q2008-2Q2010 (referred to as 2-year pre-period)
- Market transition period is 3Q2010-4Q2010 (6-month)

Post-period differed by study:
- PMR 3051-1: 1Q2011 - 4Q2014 (4 years)
- PMR 3051-2 and 3051-3: 1Q2011-4Q2015 (5 years)
- PMR 3051-4: 1Q2011-4Q2015 (5 years), for MarketScan and HIRD
              1Q2011 to 4Q2012 (2 years) for Medicaid

3.3 UNIT OF ANALYSIS

Note that primary study databases for PMR 3051 are patient- or individual-level data. However, IQVIA data includes sales (prescription) information in retail pharmaceutics, hospital or clinic settings and does not include patient-level prescription data. Therefore, PMR 3051-1 to PMR 3051-3 considered 3-digit Zip Code (3DZ) as a common metric to combine individual-level (substance abuse surveillance systems) and retail-level (IQVIA) data. Accordingly, PMR 3051-1 considered <u>3DZ at each quarter</u>, referred to as 3DZQ, as a unit of analysis. PMR 3051-2 and 3051-3 further aggregated data over all 3DZs within each quarter, then used the <u>calendar-quarter</u> as a unit of analysis. For example, PMR 3051-2 study linked abuse call data and drug utilization data at each same 3DZ then aggregated number of abuse calls (as well as dosage dispensed or population size) over all available 3 DZ within each quarter to create a single observation (record) in an analysis dataset.

PMR 3051-4 is unique in the sense that it considered "active" exposure status to define exposed status, referred to as "treatment episode", which is the unit of analysis for this study. For example, a subject is in active status to a study drug from the date of dispensing to the end of its days' supply + half of the day's supply. More specifically, if a person was dispensed with a study drug that contains 30 days supply, the subject is in active exposure status for 45 days (=30 days + 0.5*30 days). A treatment episode ended when a person had opioid overdose event. A treatment episode was censored if an individual discontinued a study drug, initiated another study drug, was lost to follow-up, reached to the end of study period (6/30/2010 for pre-reformulation-period, 12/31/2010 for transition period, and the end of post-reformulation-period). Repeated, continuous dispensing of a drug formed a single treatment episode. A person could have multiple treatment episodes (even after having an outcome previously) according to new eligible opioid dispensing records. See Section 3.4.2.

3.4 OUTCOME

Primary outcome for PMR 3051-1 to 3051-3 is opioid abuse and for PMR 3051-4 is opioid overdose. PMR 3051-1 to 3051-3 considered slightly different types of abuse due to inherent differences in study populations and data sources; PMR 3051-1 concerned past 30-day non-oral abuse as primary (overall abuse and abuse via specific route as secondary), PMR 3051-2 examined intentional abuse, PMR 3051-3 considered past-month overall abuse (no route information available). Study outcome for PMR 3051-4 was "any overdose" identified by a validated algorithm that uses ICD-9 codes for opioid poisoning and ICD-10 cause of death (related to opioid poisoning) codes.[2] Then the study further examined fatal and non-fatal overdose (confirmed by the NDI data) separately.

3.4.1 PMR 3051-1 to PMR 3051-3: Rate of Abuse

For PMR 3051-1 to 3051-3, abuse outcome is measured as a "rate" using different denominators and covariates; population-based rate, drug utilization-based rate, and population and/or drug utilization-adjusted rate. Here "based" means that the factor is used as denominator of a rate whereas "adjusted" means that the factor is used as a covariate when modeling a rate. For example, population-based rate means that a variable representing a population size (e.g., number of surveys, number of individuals) is used as a denominator of the rate. Population-adjusted rate means that a variable representing population size is used as a covariate when modeling a rate. Drug utilization-based and population adjusted rate means that a variable representing drug utilization is used as a denominator of the rate while another variable representing population size is used as a covariate when modeling the drug utilization-based rate. See below for more formal definition of each rate.

3.4.1.1 Population-Based Rate

Population-based abuse rate is defined by

$$\frac{\text{number of abuse cases in a given unit of analysis}}{\text{Population size in the same unit}}.$$

Definition of population in the denominator differs across PMR 3051-1 to PMR 3051-3:
- PMR 3051-1: Number of total patients assessed by the ASI-MV (i.e., number of total assessments)
- PMR 3051-2: US Census population in 2010 (fixed over the study period), or, number of all pharmaceutical exposure cases, or, number of all intentional pharmaceutical exposure cases
- PMR 3051-3: Number of survey respondents

As mentioned in Section 3.3, unit of analysis for PMR 3051-1 is different from PMR 3051-2 and PMR 3051-3. Therefore, more specific definition of population-based abuse rate for PMR 3051-1 is

$$\frac{\text{Number of abuse cases in a given 3 digit ZIP Code in a given quarter}}{\text{Total assessments in the same 3 digit ZIP Code in the same quarter}}$$

whereas the definition changes to

$$\frac{\text{Number of abuse cases (aggreated over all 3DZ) in a given quarter}}{\text{Population size in the same quarter}}$$

for PMR 3051-2 and similarly for PMR 3051-3.

3.4.1.2 Drug Utilization-Based Rate

Drug utilization-based rate is defined by

$$\frac{\text{Number of abuse cases in a given unit of analysis}}{\text{Dosage unit dispensed in the same unit.}}.$$

FDA's guidance[3] states that both population- and drug utilization-based estimates should be included in any ADF study protocol. FDA considers drug utilization-based rate as an appropriate measure of abuse as every dosage unit dispensed has a theoretical opportunity to be abused.

3.4.1.3 Population- or Drug Utilization-Adjusted Rate

PMR 3051 1-3 considered three different types of adjusted rates:
- drug utilization-based population-adjusted rate
- drug utilization-adjusted rate
- population- and drug utilization-adjusted rate

Again, "adjusted" means that a factor is used as a covariate when modeling an abuse outcome measure. For example, drug utilization-based population-adjusted rate means that drug utilization-based rate was modeled as an abuse outcome while adjusting for population as a covariate in the model. Population- and drug utilization-adjusted rate means that both population and drug utilization are considered as covariates when modeling quarterly-based or 3DZQ-based (i.e, standard time-based) abuse rate.

3.4.1.4 Other Outcomes

PMR 3051-1 and 3051-2 examined changes in abuse by different route of administration (ROA), in order to better understand if changes in abuse via specific routes (in particular, abuse via snorting and injecting [non-oral] that ADF is designed to deter) affected alternative (i.e., switching) routes of abuse. For this purpose, secondary outcomes for OxyContin include abuse via specific ROA such as oral, snorting, injecting, other routes, etc.

ROA information was not collected for PMR 3051-3.

3.4.2 PMR 3051-4: Rate of Overdose

Rate of overdose is defined by

$$\frac{\text{Number of any overdose cases in a given treatment episode}}{\text{1000 person month in the same treatment episode}}.$$

Then PMR 3051-4 examined both unadjusted and covariate-adjusted overdose rates. Covariates includes demographic (age, gender, geographic region, etc.) and clinical characteristics (pain diagnosis, comorbidity index, etc.) See Epidemiology Review for PMR 3051-4 in background document for a full list of covariates.

Although PMR 3051-4 study report refers the outcome as to "incident overdose", it also states that approximately 10 percent of patients with opioid overdose in this study had multiple, distinct non-fatal opioid overdose during follow-up of the study (Section 6.7 of PMR 3051-4 study report; page 30). This implies that the study included several overdose cases from the same person (i.e., some may not be truly incidental) among subjects who had multiple eligible treatment episodes along the course of the study.

4 METHODOLOGICAL CONSIDERATIONS

Major issues that led to the decision of considering the range of effect estimates, from a statistical perspective, can be summarized into two categories: **data quality and causality.** This section elaborates these two issues and demonstrate how each of the issues was addressed in design, particularly in analytic strategy, for PMR 3051.

Statistical analysis plan for PMR 3051 concerned dynamic, observational nature of data and its quality, which ultimately affects accuracy (i.e., unbiasedness) of estimates for numerator and denominator that defines a "rate" outcome. To illustrate, suppose the following notation for a given opioid:

- Let **Apre** and **Apost** be number of '**A**'buse cases in the pre-period and the post-period, respectively,
- Let **Dpre** and **Dpost** be volume of a '**D**'enominator measure in the pre-period and the post-period, respectively, then
- Let $R_{pre} = \frac{A_{pre}}{D_{pre}}$ and $R_{post} = \frac{A_{post}}{D_{post}}$ be estimated '**R**"ate of abuse in the pre-period and the post-period, respectively.

These define estimates of target quantities that evaluate the impact of OxyContin reformulation including

- percent change = (Rpost – Rpre)/Rpre *100,
- rate ratio, say RR $= \frac{R_{post}}{R_{pre}}$ that defines
- Ratio of rate ratio (RORR) $= (\frac{R_{post}}{R_{pre}}$ for a comparator$)/(\frac{R_{post}}{R_{pre}}$ for OxyContin).

We can see that any factors that can influence Apre and Apost differentially as well as Dpre and Dpost (i.e., factors influence numerator and denominator of estimated rate of abuse differentially between the pre- and the post-period), would have an impact on the validity of the target estimates - percent change and RORR.

4.1 Data Quality

Statistical Issues: Key factors that might influence Apre and Apost as well as Dpre and Dpost differentially due to data quality are:
1) sampling bias
2) product misclassification
3) missing formulation
which all may change over time.
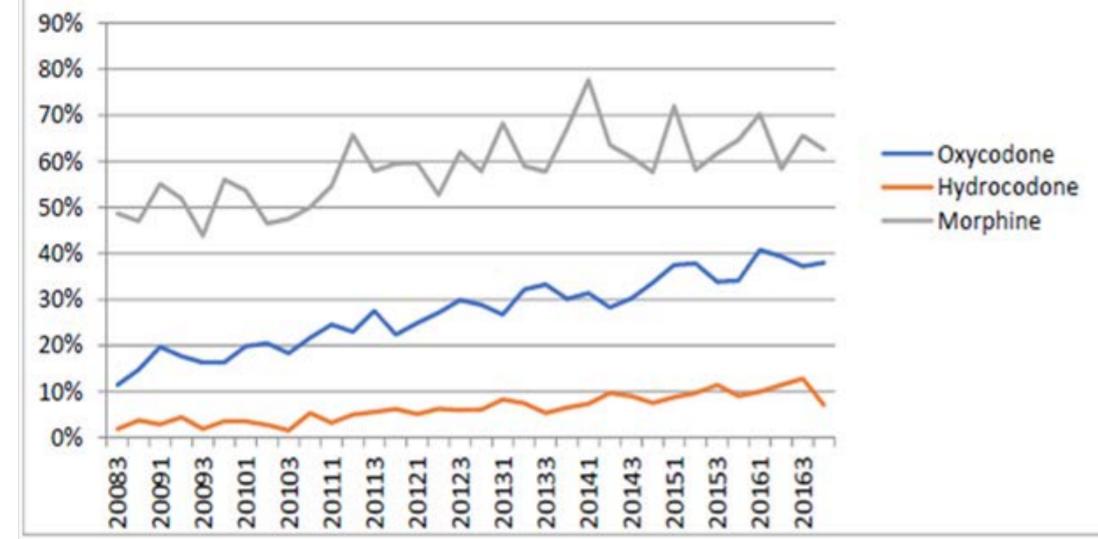
1) Sampling bias: To ensure validity of estimated rate of abuse/overdose, sampling fraction that represents proportion of opioid abuse or overdose events captured in a target population should be (approximately) constant over study period. This means that data from the ASI-MV (PMR 3051-1), PCC (PMR 3051-2), OTP/SKIP (PMR 3051-3), and medical claims (PMR 3051-4) should represent a constant, and possibly homogeneous sample of its target population over time. This might be hard to satisfy as the geographic distribution of participating sites/centers/programs, participation of each site/centers/programs, and the number and demographics of individuals being entered to each database change over time.

In addition, different geographic regions underwent different intensity of public health interventions to mediate the opioid epidemic. In particular, Florida had the legislative and law enforcement actions on Florida "pill mills" in the early post-period, which might have affected changes in abuse of OxyContin and comparators.

2) Product misclassification: The level of product misclassification might be differential between the pre- and the post-period. For example, in PMR 3051-1, the ASI-MV assessment tool has a major screen change in 2010 (and two others since 2010) which coincides with the time of reformulation.

3) Missing formulation: Figure 3 shows that percentage of exposure cases with missing product and/or formulation in PMR 3051-2 (PCC database) does change over time, differentially across drugs. These imply that the level of accuracy in Apre and Apost might be different within and between opioids, which could result in biased estimates of percent change and rate ratio for each opioid thereby biased estimate of RORR that describes the comparative effect of OxyContin reformulation (relative to the effect of comparators).

Figure 1. Percentage of exposure cases with missing (not otherwise specified) product and formulation in Poison Center Program.

Source: PMR 3051-2 Final Study Report. Appendix Figure 6-4 (p.329).

Design Consideration:

1) Sampling bias: Data used for PMR 3051 1-3 are dynamic, non-random (convenience) samples where new patients, sites, centers, and regions can be added to, or dropped from, each database over time. To ensure consistency in sampling fraction over time and homogeneity in selected sites/centers, certain key primary analyses for PMR 3051-1 and secondary analyses for PMR 3051-3 were limited to sites that consistently contributed database over the study period in the entire US. PMR 3051-2 did not control for consistent call centers as RADARS PCP includes a near census of call centers in the US. Instead, the study considered call volume, defined as either (1) all pharmaceutical exposure or (2) all intentional pharmaceutical exposure as a denominator for defining a rate in addition to Census population. PMR 3051-2 also considered call volume as a confounder because it might be associated with exposure and also with abuse of the exposure.

In order to better understand how regional-specific legislative and law enforcement actions (e.g., Florida pill mill) might have affected changes in abuse of OxyContin and comparators, analyses were stratified by geographic region in PMR 3051-2 and PMR 3051-3 (entire US, Western regions only, entire US except Florida). As PMR 3051-3 considered populations from two different treatment programs, it considered stratified analysis by type of treatment programs. See study attribute 4 in Table 1.

2-3) Product misclassification and missing formulation: PMR 3051 studies attempted to address some (but not all) of issues related to product misclassification and missing formulation by differing definitions of OxyContin. For example, Epidemiology Review for PMR 3051-1 (in background document) describes that there was a high number of endorsements of original OxyContin in the ASI-MV assessments after the time of reformulation and subsequent discontinuation of original OxyContin, indicating that most of these endorsements were likely due to misclassification, either of reformulated OxyContin as original OxyContin, or a non-OxyContin product as original OxyContin, or even of prior original OxyContin use erroneously being endorsed as past-month use. There was also endorsement of generic ER oxycodone throughout the post-period, although dispensing of generic ER oxycodone fell dramatically in January 2011 and was negligible throughout the remainder of the post-period. Therefore, PMR 3051-1 to 3051-3 considered secondary/sensitivity definitions of OxyContin that include generic ER oxycodone, unspecified ER oxycodone, or unspecified oxycodone as a part of OxyContin endorsement. See study attribute 5 in Table 1.

Some studies considered a specific objective to directly address the degree of product misclassification (e.g., secondary objective 6 of PMR 3051-1 or multiple imputation of missing formulation in PMR 3051-2). However, note that this document focuses on common issues and considerations apply to all three (PMR 3051-1 to 3051-3; abuse-related) or all the four PMR 3051 studies.

PMR 3051 studies also attempted to address issues with data quality by considering multiple comparators. This will be demonstrated in more detail in the following *Causality* Section (4.2).

Limitation: The study design and analysis still assume that changes in size of eligible sites/centers or call volume could (at least approximately) reflect changes in size of the target population over time. This is a strong, untestable assumption particularly because PMR 3051 study databases are dynamic, convenience samples.

PMR 3051 also assumed that degree of product misclassification and missing formulation are non-differential between OxyContin and comparators for some primary comparative analyses.

4.2 Causality

Statistical considerations for evaluating potential causal effect of the reformulation consist of the following three questions:

- How to incorporate drug utilization in analysis?
- How to account for factors unrelated to OxyContin reformulation?
- What is appropriate choice of comparators?

4.2.1   Drug Utilization

One of big challenges with the design and analysis of PMR 3051 was how to handle changes in drug utilization patterns, and differences in drug utilization patterns across different drugs over time. It has been known that prescription volume correlates with opioid abuse rates, perhaps because the number of tablets dispensed would be a reasonable measure for the level of availability of a drug in the community.[4] For example, Figure 2 which is taken from Dasgupta et al. (2006)[4] depicts a clear relationship between kilograms of drug dispensed per year (x-axis) and annual emergency department visits for non-medical use (y-axis) of some opioid drugs. Although these relationships seem mostly linear, the relationship may not show the same linear trend (some slopes are steeper than others) across all products and some might be even non-linear (e.g., exponential) indicated by oxycodone. Difference in these trends might be induced by difference in desirability for abuse within and between drugs. For example, oxycodone might be more highly sought after for abuse compared to morphine.

Figure 2. Relationship between drug dispensed per year and annual emergency department (ED) visit for non-medical opioid use from Dasgupta et al. (2006).
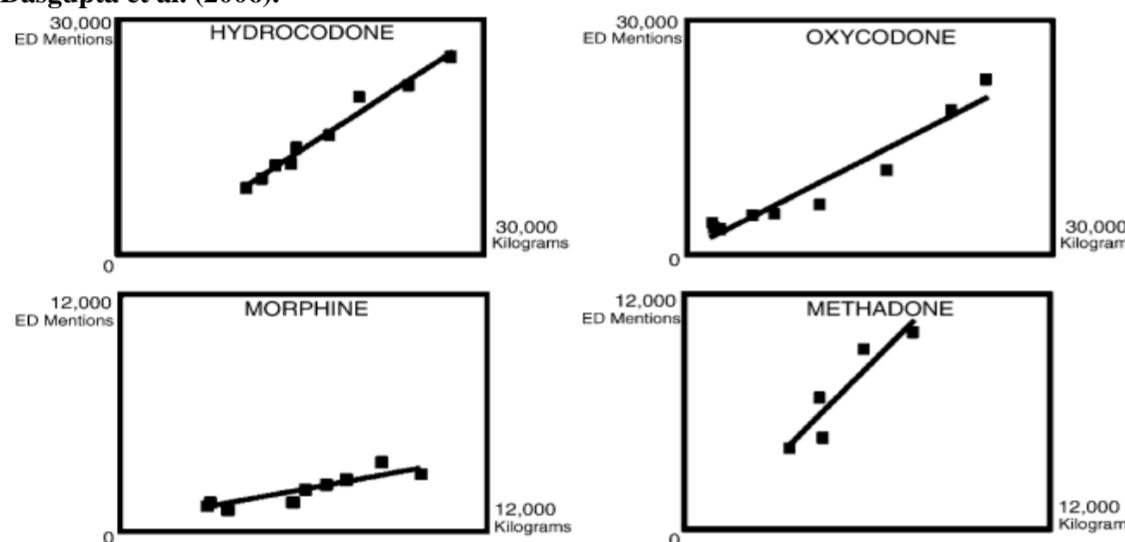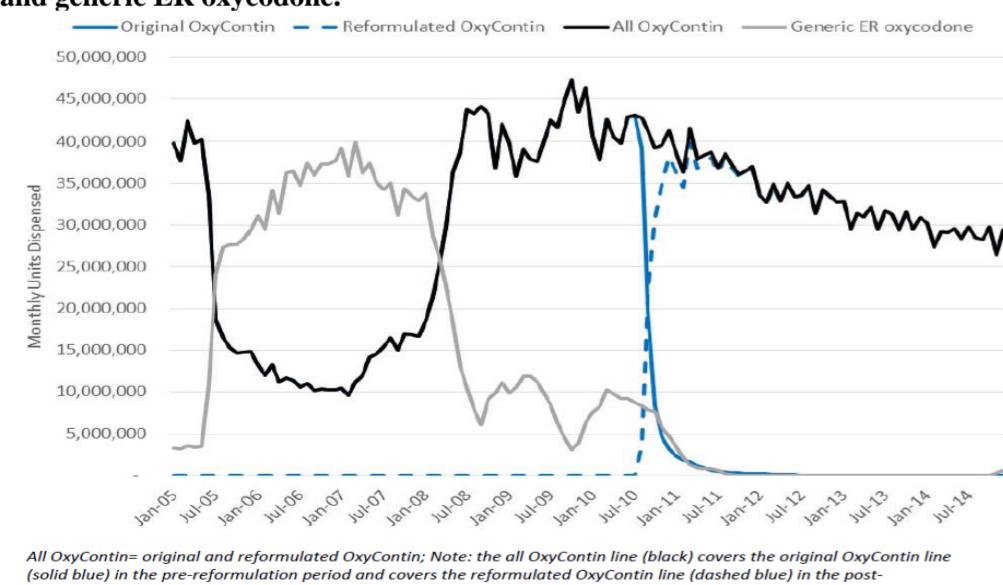
Figure 3 shows OxyContin prescribing trends from 2005-2015. This figure depicts gradual decrease in the number of tablets dispensed per month beginning around the time of reformulation. It raises a question that, if there is any decrease in OxyContin abuse (specifically non-oral abuse targeted by the ADF) after the reformulation, how much of the decrease was due to the declined prescribing after the reformulation? It also raises a question that, if the decrease in OxyContin abuse is somewhat attributable to the decrease in its prescription volume after the reformulation, what is an appropriate way to account for the impact of the prescription volume when estimating the effect of the reformulation on abuse? Should we assume that abuse rate decreases linearly with the decrease in prescription volume rather than it being decreased exponentially? Conversely, we could also raise a question that how much of the decrease in OxyContin prescribing was due to reduced demand for the drug for diversion and abuse? And if the decrease in prescribing is somewhat attributable to the reduced demand then would adjusting for utilization, which is a mediator in the causal pathway from OxyContin reformulation to abuse, be a valid approach?

Figure 3. Estimated monthly dosage units dispensed for ER oxycodone products; original and reformulated OxyContin, all Oxycontin, and generic ER oxycodone.

All OxyContin= original and reformulated OxyContin; Note: the all OxyContin line (black) covers the original OxyContin line (solid blue) in the pre-reformulation period and covers the reformulated OxyContin line (dashed blue) in the post-reformulation period; ER=extended release

Source: PMR 3051-2 Final Study Report. Figure 6-3 (p. 30).

Design consideration: It is not clear how to best account for drug utilization in analysis. This has led FDA to consider multiple outcome definitions and models, both unadjusted and adjusted for utilization based on different assumptions, with the truth of the effect of the reformulation probably lying somewhere within this range of estimates. Accordingly, PMR 3051-1 to 3 studies considered the five types of abuse rates by varying assumptions on relationships between abuse, population, and drug utilization:

1) population-based rate
2) drug utilization-based rate
3) drug utilization-based population-adjusted rate
4) drug utilization-adjusted rate
5) population- and drug utilization-adjusted rate

See study attribute 7 in Table 1.

Limitation: However, again, what is the most appropriate way to account for utilization to infer (potentially, the causal) effect of the reformulation is unclear. Therefore, PMR 3051 studies considered various model diagnostic tools to compare model performances (Section 5.4).

4.2.2 Comparators

Comparing abuse/overdose rates of OxyContin between the pre- and the post-period provides a distorted view of the causal effect of the reformulation if there are time-dependent trends in these rates induced by external factors unrelated to the reformulation. Examples of such external factors include other public health efforts to mitigate the opioid epidemic. As described in [Section 3.3.7 of PMR 3051-1 Epidemiology Review](#) in background document, some major opioid-related regulations and interventions have been enacted in the post-period; OxyContin risk evaluation and mitigation strategy (REMS) in 2010, Florida "pill mill" laws in 2011, the transmucosal immediate release fentanyl (TIRF) REMS in 2012, and the extended release/long acting (ER/LA) REMS in 2013.

If a decrease in abuse/overdose rate in the post-period for OxyContin is (somewhat) attributable to these factors that are irrelevant to the reformulation but related to nationwide public health efforts, considering a pre-post change would lead to an erroneous conclusion that the reformulation is effective on reducing abuse/overdose rate. The pre-post change estimate would be a biased, inflated measure of the effect of the reformulation, including the effect of public health efforts.

Design consideration: PMR 3051 considered comparators that could potentially serve as a "counterfactual" and/or "negative control" for OxyContin, which would represent what (would have) happened in the absence of the reformulation but under the various public health efforts and secular trends. See study attributes 9 and 10 in Table 1.

Limitation: An ideal comparator opioid for OxyContin should possess the following characteristics:

- Similar abuse potential and route of abuse preference as original OxyContin (i.e., OxyContin without having abuse-deterrent property)
- Similar market presence and utilization
- Similar baseline trends (i.e., trends in the pre-period) and abuse rate
- Not reformulated with ADF

In addition, external factors such as intervention efforts that derive secular trends in abuse/overdose should have similar influences across OxyContin and comparators.

There is no ideal comparator opioid that could satisfy all of these characteristics. Therefore, interpretation of study findings should consider

- differences in baseline abuse rates and trends in the pre-period
- differences in the impact of opioid-related interventions
- changes in the survey instrument related to ascertainment of abuse for specific products or product groups

to be able to disentangle any effects of secular trends from those due to the reformulation. In light of the absence of no ideal single comparator, PMR 3051 considered multiple comparators where each comparator could serve as a counterfactual for OxyContin under different contextual setting.

4.3 Statistical Models

Aforementioned issues and considerations led to various statistical models, particularly the choice of outcome measures. See study attribute 7 in Table 1 and summary of statistical models in Table 2 of Section 5.1. PMR 3051 repeatedly used those models under various combinations of the varying parameters such as under different definitions of OxyContin by different site definitions, etc., to estimate ranges of (potentially causal) the effect of OxyContin reformulation.

Limitation: We do not know what the most appropriate approach to model rate of abuse/overdose is. For example, what is the most appropriate way to account for utilization in analysis – should it be a denominator for defining abuse rate or a covariate? If a covariate, what is a proper way to assume the relationship between abuse rate and the utilization covariate (e.g., linear, exponential)? Some models might be more appropriate than the others which we had limited knowledge/information before the study conduct and looking at the actual abuse/overdose data.

To assess model adequacy, PMR 3051 studies examined the Akaike Information Criteria Statistic (AIC), residual plots, and observed versus predicted plots which will be described in Section 5. Although these metrics cannot tell us which model is the true model, they can inform relative performance of each model compared to the others. In particular, the AIC would be a useful tool to compare model performance simultaneously, from a statistical perspective, in an efficient way in light of the volume of analyses.

4.4 Some Other Considerations

Some other considerations include
- Would the reformation deter what it is designed to deter (i.e., abuse via snorting or injecting) without causing unintended consequences (e.g., switching abuse via other routes or other drugs)?
- Would patterns of abuse differ by potential prognostic factors such as treatment modality, pain severity (PMR 3051-1), dose strength, reasons for exposure (PMR 3051-2), etc.?

To address these questions, PMR 3051 evaluated the impact of OxyContin reformulation by ROA and considered stratified analyses by potential prognostic factors. See study attributes 8 in Table 1.

5 STATISTICAL ANALYSES

This section provides details on each model formulation, target regression parameter, and interpretation of the target parameter. For illustration purpose, we set up notation and model formulation under PMR 3051-2 and 3051-3 settings where calendar-quarter was selected as a unit of analysis. Then later we discuss how model formulations can be extended to PMR 3051-1 setting where 3DZQ was a unit of analysis.

5.1 Statistical Models for PMR 3051-1 to 3051-3

PMR 3051-1 to 3051-3 utilized a series of Poisson regression models to
1) estimate **trends** in abuse,
2) evaluate **change in abuse rate** of OxyContin between the pre- and the post-periods using **percent change**,
3) assess **ratio of rate ratios (RORR)** that compares rate ratios between OxyContin and comparator opioids, and
4) perform interrupted time series (ITS) analyses that examine **changes in level (called immediate shift) and slope** between the pre- and post-periods for OxyContin alone, and relative to comparators.

Later Sections will provide formal definitions of target parameters such as percent change and RORR (including rate ratio; Section 5.1.1) as well as changes in level and slope (Section 5.1.2). Trends in abuse described in 1) can also be estimated using observed abuse counts, population size, and drug utilization volume at each quarter (i.e., model-free).

Different measures of outcome (population- or drug utilization-based, or population- and/or drug utilization-adjusted) lead to different analytic models. Table 2 presents a list of Poisson regression models that were consistently used throughout PMR 3051-1 to 3051-3, along with corresponding study objectives.

Table 2. Poisson regression models consistently used across PMR 3051-1 to 3051-3 studies.

Model	Outcome measure	Denominator for rate	Covariate in model	Study Objective
Model 1	Population-based rate	Population	NA	Assess pre-post change in rate of abuse using percent change and RORR
Model 2	Drug utilization-based rate	Drug utilization	NA	Percent change and RORR
Model 2a	Drug utilization-based, population-adjusted rate	Drug utilization	Population	Percent change and RORR
Model 3	Drug utilization-adjusted rate	NA	Drug utilization	Percent change and RORR
Model 3a	Population- and drug utilization-adjusted rate	NA	Population, drug utilization	Percent change and RORR
Model 5	Same as model 1 (Interrupted time series [ITS] version of model 1)			Assess pre-post change in rate of abuse using ITS analysis: calculate immediate shift and change in slope

Model 6	Same as model 2 (ITS version of model 2)	Immediate shift and change in slope
Model 6a	Same as model 2a (ITS version of model 2a)	Immediate shift and change in slope
Model 7	Same as model 3 (ITS version of model 3)	Immediate shift and change in slope
Model 7a	Same as model 3a (ITS version of model 3a)	Immediate shift and change in slope

Then above models were repeatedly used for secondary/sensitivity analyses under various combination of study parameters listed in Table 1. This resulted in hundreds of different effect estimates for the same quantity of interest (that is, change in abuse) within each PMR 3051 study.

5.1.1 Models for Percent Change and RORR

5.1.1.1 Modeling population-based or utilization-based rate (Models 1 and 2)

We assume that the number of abuse cases at quarter t, denoted by A_t, follows a Poisson distribution that has mean and variance:

- $E(A_t) = \mu_t$
- $Var(A_t) = \mu_t$

Model Formulation: A general form of a Poisson regression for modeling population-based or utilization-based rate that evaluates *the pre-post change* in such a rate for OxyContin and for comparators and *compares the changes* between OxyContin and a comparator is as follow:

$$\log\left(\frac{\mu_{t,o}}{D_{t,o}}\right) = \alpha_0 + \alpha_1 P_t + \alpha_2 O_t + \alpha_3 P_t * O_t \text{ ---------- (I)}$$

where

- t denotes calendar-quarter.
- $\mu_{t,o}$ represents number of abuse cases for a specific opioid product '**O**' at quarter t.
- $D_{t,o}$ represents a volume of a selected '**D**'enominator for a specific opioid product '**O**' measured at quarter t (e.g., number of survey respondents or dosage unit dispensed at quarter t for OxyContin). This is also referred to as an "offset".
- P_t is an indicator for pre- or post-reformulation '**P**'eriod that takes a value of 1 if a quarter t belongs to the post-period [1Q2011, 4Q2015] and 0 otherwise.
- O_t is a vector of '**O**'pioid drug indicators with value of 0 for OxyContin (i.e., reference) and takes other integer values (1,2,3,…) for comparator opioids. It is possible to use a matrix consisting of indicator vectors instead of a vector of $(0,1,2,3,…)^T$.

Note that α_2 and α_3 are also vectors with the same length as the number of comparator opioids. For example, $\alpha_2 = (\alpha_{21}, \alpha_{22}, \alpha_{23})$ when primary comparators (ER morphine, IR hydrocodone, and other schedule II opioids) are of interest. Models 1 and 2 estimate a constant, mean rate within each period.

Target Parameters: With model formulation (I), $\exp(\alpha_0)$ represents expected abuse rate for OxyContin in the pre-period (say, r_{pre}) and $\exp(\alpha_0 + \alpha_1)$ represents expected abuse rate in the post-period (r_{post}). Therefore, the pre-post change in abuse rate for OxyContin, described as percent change between pre-post rates, is given by

$$\{\frac{r_{post} - r_{pre}}{r_{pre}}\} * 100 = \{ \exp(\alpha_0 + \alpha_1) - \exp(\alpha_0) \}/\exp(\alpha_0) * 100.$$

Of note, rate ratio that measures the pre-post change in abuse rate for OxyContin in <u>a ratio scale</u> is defined by $\frac{r_{post}}{r_{pre}} = \exp(\alpha_1)$.

Although rate ratio itself is not a target parameter for PMR 3051 studies, it is used to define another target parameter, RORR. For the sake of illustration, suppose that ER morphine is a comparator with O=1. Then

1) for OxyContin, the rate ratio is given by $\exp(\alpha_1)$, say rr_{Oxy}, and
2) for ER morphine, the rate ratio is given by $\exp(\alpha_1 + \alpha_3)$, say $rr_{ER\ morphine}$, based on model formulation (I).
3) Then the RORR is $\frac{rr_{ER\ morphine}}{rr_{Oxy}} = \exp(\alpha_3)$

The RORR describes the pre-post change in abuse rate for OxyContin relative to the change for ER morphine.

Interpretation: Using Poisson regression based on model formulation (I), percent change estimate can be obtained by $\{\exp(\widehat{\alpha_0} + \widehat{\alpha_1}) - \exp(\widehat{\alpha_0})\}/\exp(\widehat{\alpha_0}) * 100$. If this value is negative (<0) and corresponding 95% confidence interval (CI) excludes the null value of zero then we interpret that rate of abuse for OxyContin significantly declined after the reformulation. Although rate ratio (e.g., $\exp\{\alpha_1\}$ for OxyContin) itself is not a target parameter, it can also be used to examine whether rate of abuse for OxyContin

declined after the reformulation or not: Estimate for rate ratio $\exp(\widehat{\alpha_1}) < 1$ with its 95% CI excluding the null value of 1 indicates that the rate of abuse for OxyContin significantly declined after introduction of the reformulation.

For comparative analyses, if estimate for RORR, $\exp(\widehat{\alpha_3})$, is greater than 1 and its 95% CI excludes the null value of 1, it indicates that a statistically significant and <u>more favorable change</u> in rate for OxyContin relative to that of a comparator opioid. In this context, "favorable" could mean a greater reduction or a smaller increase in rate for OxyContin relative to that of a comparator, or no change for OxyContin but increasing rate for a comparator. In other words, such RORR suggests (some) favorable effect attributable to the reformulation (ADF), particularly when rate of abuse/overdose for OxyContin declined in the post-period (i.e., when percent change for OxyContin is negative). Note that models based on formulation (I) are equivalent to difference-in-differences model[5] that compares pre- and post-intervention means of an outcome of interest between two groups using the interaction between group and intervention period variables in the model, α_3.

Estimation: The α's are estimated by solving the generalized estimation equation (Liang and Zeger, 1986)[5] where a weight matrix (typically, AR(1) working correlation) accounts for within-opioid serial correlation induced by repeated measures over quarter t. The sandwich estimator (Liang and Zeger, 1986)[6] is used to estimate the standard errors.

5.1.1.2   Modeling population- and/or utilization-adjusted rate (Models 2a, 3 and 3a)

As a reminder, "adjusted" indicates that a factor was used as a covariate in modeling a rate outcome. Now, let
$D_{t,o}$ represents dosage unit dispensed (drug utilization) for a specific opioid product 'O' measured at quarter t, and
$C_{t,o}$ represents population size for a specific opioid product 'O' measured at quarter t.
Then PMR 3051 considered the following variation of model formulation (I) to model population- and/or utilization-adjusted rates:

- $\log\left(\frac{\mu_{t,o}}{D_{t,o}}\right) = \beta_1 \log\left(C_{t,o}\right) + \{\alpha_0 + \alpha_1 P_t + \alpha_2 O_t + \alpha_3 P_t * O_t\}$ ------- (II)

  for drug utilization-based population-adjusted rate (model 2a),

- $\log\left(\mu_{t,o}\right) = \beta_1 \log\left(D_{t,o}\right) + \{\alpha_0 + \alpha_1 P_t + \alpha_2 O_t + \alpha_3 P_t * O_t\}$ ----- (III)

  for drug utilization-adjusted rate (model 3), and

- $\log\left(\mu_{t,o}\right) = \beta_1 \log\left(D_{t,o}\right) + \beta_2 \log\left(C_{t,o}\right) + \{\alpha_0 + \alpha_1 P_t + \alpha_2 O_t + \alpha_3 P_t * O_t\}$ ----- (IV)

  for population- and drug utilization-adjusted rate (model 3a).

Unlike model 1 and 2 that estimate constant rate within each period, models 2a to 3a allow a rate to be time-varying according to the quarterly variation in the covariate(s), $D_{t,o}$ and/or $C_{t,o}$.

Of note, PMR 3051-1 considered $D_{t,o}$ and/or $C_{t,o}$ instead of $\log\left(D_{t,o}\right)$ and/or $\log\left(C_{t,o}\right)$ in model formulations (II) to (IV). This implies that model 2a to 3a for PMR 3051-1 rely on a different assumption than PMR 3051-2 and 3051-3, which will be discussed below Section 5.1.1.4.

5.1.1.3   Extension of Statistical Models to PMR 3051-1 Study

PMR 3051-1 used different unit of analysis then PMR 3051-2 and 3051-3, which is 3DZQ. To account for the difference, all notation used in model formulations (I) to (IV) should incorporate a subscript for a 3-digit Zip Code, say i. For example, PMR 3051-1 modeled a number of abuse cases <u>in a given 3-digit Zip Code i</u> at quarter t, denoted by A_{it}, thereby we assume that A_{it} follows a Poisson distribution with the following mean and variance:

- $E(A_{it}) = \mu_{it}$
- $Var(A_{it}) = \mu_{it}$

Likewise, all the other notation should include a subscript i, for example, $D_{t,o}$ should be $D_{it,o}$ to represent denominator volume in a given 3-digit Zip Code i at quarter t for an opioid O=o, and P_t should be $P_{it,o}$ to represent period indicator for the i-th Zip Code at quarter t for the opioid o.

5.1.1.4   Similarity and Difference between denominator-based and covariate-adjusted models

<u>Similarity:</u> Interpretation of percent change, rate ratio, and RORR are the same across models based on formulations (I) to (IV). As described earlier, the rate ratio for OxyContin is $\exp(\alpha_1)$, the rate ratio for a comparator opioid coded as O=1 is $\exp(\alpha_1 + \alpha_3)$, thereby the RORR is $\exp(\alpha_3)$ throughout models 1 to 3a.

<u>Difference:</u> Models based on formulations (I) and (II) that modeling population- or drug utilization-based rate (regardless of covariate adjustment) assume that mean abuse rate μ increases/decreases <u>linearly</u> by a unit change in denominator D, where the relationship is

fixed at 1 when the other covariates are fixed in each quarter t. This can be easily seen by re-arranging the denominator term in the model formulations (I) or (II). For example, re-arranging $D_{t,o}$ in the left-hand side of model formulation (I) leads to

$$\log(\mu_{t,o}) = \log(D_{t,o}) + \alpha_0 + \alpha_1 P_t + \alpha_2 O_t + \alpha_3 P_t * O_t,$$
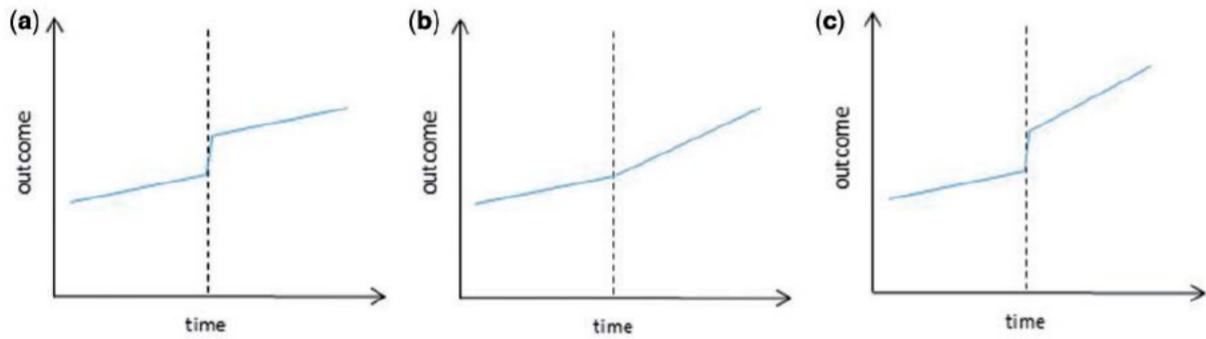
where the slope of $\log(D_{t,o})$ is fixed at 1 meaning that $\mu_{t,o}$ and $D_{t,o}$ have an exact, one-to-one monotone relationship when the other covariates are fixed. On the other hand, models based on formulations (III) and (IV) that consider D as a covariate instead of denominator assume that the linear relationship between μ and D (as well as between μ and C), described by β_1 (and/or β_2), is much more flexible as β_1 (and/or β_2) can take any values within $(-\infty, \infty)$.

Covariate-adjusted models in PMR 3051-2 and 3051-3 that used $\log(D_{t,o})$ and/or $\log(C_{t,o})$ assume that mean abuse rate μ increases/decreases <u>linearly</u> by a unit change in covariate(s). However, covariate-adjusted models (model 2a to 3a) for PMR 3051-1 that used $C_{t,o}$ instead of $\log(C_{t,o})$, for example, assume that mean abuse rate μ increases/decreases <u>exponentially</u> by a unit change in covariate C.

5.1.2   Models for Change in Levels and Slopes: Interrupted Time Series Analysis

Interrupted time series (ITS) analysis is widely used for evaluating the effectiveness of population-level health interventions which have been implemented at a clearly defined point in time.[7] It typically examines differences in trends of outcome before and after implement of an intervention, where the trend can be defined by slope of a regression line in the pre- and post-intervention period along with magnitude of outcome level (referred to as "level" in ITS analysis) attributed to the intervention. Therefore, the effect of intervention is measured by (1) the change in slope from pre-intervention to post-intervention and (2) the change in level before and after the time of the intervention. For example, see below Figure 5 taken from Bernal et al. (2017)[7] that depicts various effects of an intervention:

Figure 5. Examples of impact models used in ITS taken from Bernal et al. (2017)

In Figure 5-(a), the change in level before and after the time of an intervention describes the effect of intervention, as the slope of the two regression lines remain the same. In Figure 5-(b), change in slopes of the two lines depicts the effect of the intervention as there is no level change at the time of intervention. Similarly, Figure 5-(c) shows where both changes in levels and slopes capture the effect of the intervention.

PMR 3051-1 to PMR 3051-3 called the level change as "immediate shift", which is defined by change in (model-estimated) abuse rate from the end of the pre-period (at the second quarter of year 2010) to the beginning of the post-period (at the first quarter of year 2011).

Model Formulation: PMR 3051-2 and 3051-3 utilized the following form of Poisson ITS models for population- or drug utilization-based rates (i.e., models 5 and 6 which is ITS version of model 1 and 2, respectively) to examine change in slope for a rate of abuse:

$$\log\left(\frac{\mu_{t,o}}{D_{t,o}}\right) = \alpha_0 + \alpha_1 P_t + \alpha_2 O_t + \alpha_3 P_t * O_t$$
$$+\{(\alpha_4 + \alpha_5 P_t + \alpha_6 O_t + \alpha_7 P_t * O_t) * T\} \quad ---------- (V)$$

where T represents a calendar quarter.

Model formulation (V) is an ITS version of model formulation (I). PMR 3051-1 to 3051-3 also considered an ITS version of models 2a, 3, and 3a. For example, ITS version of model formulation (II) (i.e., ITS version of model 2a) is given by

$$\log\left(\frac{\mu_{t,o}}{D_{t,o}}\right) = \beta_1 \log(C_{t,o}) + \alpha_0 + \alpha_1 P_t + \alpha_2 O_t + \alpha_3 P_t * O_t$$
$$+\{(\alpha_4 + \alpha_5 P_t + \alpha_6 O_t + \alpha_7 P_t * O_t) * T\} \quad ---------- (VI)$$

ITS version of model formulation (III) and (IV) can be defined in a similar manner.

Target Parameter: To illustrate how models 5 and 6 that are based on formulation (V) compare two regression lines as shown in Figure 5, suppose that the goal is to compare either population- or drug utilization-based rate for OxyContin (that O=0) with that of ER morphine (O=1). Then for OxyContin,

- $\log\left(\frac{\mu_{t,OxyContin}}{D_{t,OxyContin}}\right) = \alpha_0 + \alpha_4\,T$ describes a regression line (for log of the abuse rate) in the pre-period
- $\log\left(\frac{\mu_{t,OxyContin}}{D_{t,OxyContin}}\right) = \alpha_0 + \alpha_1 + (\alpha_4 + \alpha_5)*T$ describes a regression line in the post-period

where T is a continuous integer representing calendar quarter. For example in PMR 3051-2 and 3051-3 studies, T= -7, -6, …, 18, 19 for primary analyses where T= 0 for the second quarter of year 2010 (2Q2010; the end of the pre-period) and the first quarter of year 2011 (1Q2011; the beginning of the post-period). Using this representation of T, estimated rate of abuse at the end of the pre-period for OxyContin is given by $\exp(\alpha_0)$ and at the beginning of the post-period is given by $\exp(\alpha_0 + \alpha_1)$. Therefore, immediate shift (the level change) for OxyContin measured in a ratio scale is defined by $\mathbf{exp(\alpha_1)}$. Change in slopes is $\mathbf{exp(\alpha_5)}$.

Similarly, ER morphine has the following two regression lines based on model formulation (V):

- $\log\left(\frac{\mu_{t,ER\,morphine}}{D_{t,ER\,morphine}}\right) = \alpha_0 + \alpha_2 + (\alpha_4 + \alpha_6)*T$ describes a regression line in the pre-period
- $\log\left(\frac{\mu_{t,ER\,morphine}}{D_{t,ER\,morphine}}\right) = \alpha_0 + \alpha_1 + \alpha_2 + \alpha_3 + (\alpha_4 + \alpha_5 + \alpha_6 + \alpha_7)*T$ describes a regression line in the post-period.

Then for ER morphine, $\mathbf{exp(\alpha_1 + \alpha_3)}$ represents immediate shift and $\mathbf{exp(\alpha_5 + \alpha_7)}$ represents change in slope. Presumably, these two quantities should remain relatively stable as ER morphine was not reformulated around the time of OxyContin reformulation. However, any changes in these two quantities might represent the impact of public health efforts and interventions towards the opioid epidemic, or simply reflect a secular trend.

Then immediate shift and change in slopes of OxyContin compared with those of ER morphine via ITS analysis are captured by:

- $\mathbf{exp(\alpha_3)}$ for immediate shift
- $\mathbf{exp(\alpha_7)}$ for change in slopes

based on ITS model formulation (V) and assumed representation of T (calendar quarter), O (opioid), and P (period). Similar calculations can be done for the other comparators using different values for O.

With ITS analysis, it is important to take both immediate shift and change in slopes into consideration as neither immediate shift nor change in slopes alone can properly capture the effect of the reformation. For example, immediate shift captures change at the time around the reformulation at which increase/decrease in abuse was confounded with various factors: The reformulated OxyContin became commercially available on August 9, 2010 (the time of reformulation) and was intended to replace the original formulation. By December 2010, 90% of OxyContin prescriptions dispensed were replaced with reformulated OxyContin. Therefore, there was a big market transition around the time of reformulation that might influence OxyContin availability, uptake, and prescription pattern. In addition, the immediate shift could highly inflate the effect of reformulation when drug utilization is not accounted or adjusted for. Looking at the slope change alone could also be misleading when there is no change in slopes but there do exist reduction in overall rates before and after the time of the reformulation, as shown in Figure 5-(a).

In addition, immediate shift and change in slopes should not be interpreted based on numbers (estimates, 95% CIs, and/or p-values) alone. They can be meaningfully interpreted when trends in rate of abuse that visually depict the change over time is accounted for.

5.2 Statistical Models for PMR 3051-4

PMR 3051-4 focused on unadjusted and adjusted incident overdose rates per 1,000 person-months. It used Poisson regression models similar to models based on formulation (I) (i.e., unadjusted) or formulation (II) (i.e., covariate-adjusted) using person-time as a denominator. Unit of analysis is a person-time block, which is the treatment episode. Target inferential parameters are unadjusted rate ratio or (covariate-)adjusted rate ratio, and RORR based either on unadjusted or adjusted rate ratios.

5.3 Summary of Statistical Models

Table 3 summarizes analysis models for PMR 3051-1 as an example, with explicit model specifications based on model formulations (I) to (VI), along with target quantity of estimation.

Table 3. PMR 3051-1: Summary of statistical models and corresponding study objectives.

Model	Denominator (Offset)	Covariate	Model Specification†	Target Quantity
Model 1; based on model formulation (MF) (I)	Total Assessments (TA)	N/A	$\log(\mu_{it,o}) = \log\{$ (TA for O)$_{it}$ $\}$ $+ \alpha_0 + \alpha_1\,P_{it} + \alpha_2\,O_{it} + \alpha_3\,P_{it}*O_{it}$	Percent change, RORR
Model 2; based on MF (I)	Dosage unit dispensed (DUD)	N/A	$\log(\mu_{it,o}) = \log\{$(DUD for O)$_{it}$ $\}$ $+ \alpha_0 + \alpha_1\,P_{it} + \alpha_2\,O_{it} + \alpha_3\,P_{it}*O_{it}$	Percent change, RORR
Model 2a; based on MF (II)	DUD	TA	$\log(\mu_{it,o}) = \log\{$(DUD for O)$_{it}$ $\}$ $+ \beta_1\{$(TA for O)$_{it}\}$	Percent change, RORR

			$+ \alpha_0 + \alpha_1 P_{it} + \alpha_2 O_{it} + \alpha_3 P_{it} * O_{it}$	
Model 3; based on MF (III)	N/A	DUD	$\log(\mu_{it,o}) = \beta_1 \{(\text{DUD for O})_{it}\}$ $+ \alpha_0 + \alpha_1 P_{it} + \alpha_2 O_{it} + \alpha_3 P_{it} * O_{it}$	Percent change, RORR
Model 3a; based on MF (IV)	N/A	DUD, TA	$\log(\mu_{it,o}) = \beta_1 \{(\text{DUD for O})_{it}\}$ $+ \beta_2 \{(\text{TA for O})_{it}\}$ $+ \alpha_0 + \alpha_1 P_{it} + \alpha_2 O_{it} + \alpha_3 P_{it} * O_{it}$	Percent change, RORR
Model 5; based on MF (V)	same as model 1; ITS version of model 1		$\log(\mu_{it,o}) = \log\{(\text{TA for O})_{it}\}$ $+ \alpha_0 + \alpha_1 P_{it} + \alpha_2 O_{it} + \alpha_3 P_{it} * O_{it}$ $+(\alpha_4 + \alpha_5 P_{it} + \alpha_6 O_{it} + \alpha_7 P_{it} * O_{it}) * T$	Slope change, immediate shift
Model 6; based on MF (V)	same as model 2; ITS version of model 2		$\log(\mu_{it,o}) = \log\{(\text{DUD for O})_{it}\}$ $+ \alpha_0 + \alpha_1 P_{it} + \alpha_2 O_{it} + \alpha_3 P_{it} * O_{it}$ $+(\alpha_4 + \alpha_5 P_{it} + \alpha_6 O_{it} + \alpha_7 P_{it} * O_{it}) * T$	Slope change, immediate shift
Model 6a; based on MF (VI)	same as model 2a; ITS version of model 2a		$\log(\mu_{it,o}) = \log\{(\text{DUD for O})_{it}\}$ $+ \beta_1 \{(\text{TA for O})_{it}\}$ $+ \alpha_0 + \alpha_1 P_{it} + \alpha_2 O_{it} + \alpha_3 P_{it} * O_{it}$ $+(\alpha_4 + \alpha_5 P_{it} + \alpha_6 O_{it} + \alpha_7 P_{it} * O_{it}) * T$	Slope change, immediate shift
Model 7 similar version of MF (VI)	same as model 3; ITS version of model 3		$\log(\mu_{it,o}) = \beta_1 \{(\text{DUD for O})_{it}\}$ $+ \alpha_0 + \alpha_1 P_{it} + \alpha_2 O_{it} + \alpha_3 P_{it} * O_{it}$ $+(\alpha_4 + \alpha_5 P_{it} + \alpha_6 O_{it} + \alpha_7 P_{it} * O_{it}) * T$	Slope change, immediate shift
Model 7a similar version of MF (VI)	same as model 3a; ITS version of model 3a		$\log(\mu_{it,o}) = \beta_1 \{(\text{DUD for O})_{it}\}$ $+ \beta_2 \{(\text{TA for O})_{it}\}$ $+ \alpha_0 + \alpha_1 P_{it} + \alpha_2 O_{it} + \alpha_3 P_{it} * O_{it}$ $+(\alpha_4 + \alpha_5 P_{it} + \alpha_6 O_{it} + \alpha_7 P_{it} * O_{it}) * T$	Slope change, immediate shift

†see Sections 5.1.1.1, 5.1.1.2, and 5.1.2 for notation. Scaling factors for DUD and TA are not presented here.

5.4 Model Diagnostics

PMR 3051 utilized three different model diagnostic tools to evaluate model adequacy and to compare relative model performance.

1. Akaike Information Criteria Statistic (AIC):

Given a collection of models, the AIC describes relative quality of statistical models for a given single data. AIC is an estimate of a relative distance between the unknown true likelihood function of the data and the fitted likelihood function of the model. Therefore, a model with a smaller distance, that is, a lower AIC means a better model.

2. Residual analysis:

A residual plot presents standard Pearson residuals. A model is considered adequate if residuals are randomly dispersed around zero horizontal line.

3. Observed versus predicted plots with a line of unity:

This plot presents observed outcome (rate) vs. model-estimated outcome with a line of unity. If a model is adequate, model-estimated outcome values should be close to observed values. A regression line for observed vs. model-estimated values should be close to a line of unity, and those values should spread randomly around the line of unity with no distinct pattern (e.g., upward or downward pattern).

In addition, inherent limitation of Poisson regression model is that it assumes a special mean-variance structure $[\mathrm{E}(A_t) = \mathrm{Var}(A_t)]$ where the violation of the assumption is called "over-dispersion". To address the issue of over-dispersion, some PMR 3051 studies considered including a multiplicative dispersion parameter. The other PMR 3051 studies examined directly the adequacy of the no over-dispersion assumption.

As PMR 3051 conducted hundreds of different analyses to estimate change in abuse and overdose, it is impossible to evaluate model performance based on residual plots and observed vs. predicted plots. Therefore, this document considers the AIC as a primary model diagnostic measure and uses the AIC to evaluate quality of model findings from a statistical perspective. However, we would like to emphasize that one should not determine the best effect estimate solely based on statistical diagnostic tools such as the AIC. Validity of models and model findings should always be determined and interpreted along with epidemiologic, contextual factors.

5.5 Additional Considerations

Some analyses have a low utility value or are subject to significant limitation from a statistical perspective.

1. Findings from a shorter study period (1 year pre- and 3 years post-reformulation periods) could detect changes that were more specific to the reformulation. However, analyses based on the shorter period are limited in study power and do not reflect more recent trends in drug utilization and rates of abuse. These analyses are also limited to depict sustained effect of the reformulation.

2. PMR 3051-1 to 3051-3 considered additional models not listed in Table 2 such as model 2b and model 4b using dosage unit dispensed as a categorical covariate. These models mostly showed poor model fit and/or had convergence issue. They were also not consistently used across four PMR 3051 studies and did not provide additional information on findings from models 1 – 3a (or models 5 – 7a).

3. Multiple imputation for missing formulation analysis in PMR 3051-2 used a limited set of predictors for missing formulation such as age, medical outcome, gender, center code, and time. Although such variables might be the best information captured in PCC data to predict missing formulation, there was no scientific rationale for selecting them for imputation. To conduct a valid multiple imputation analysis, first and the foremost crucial step is identification of key factors associated with missing data and making sure given data includes information on such factors as fundamental assumption for multiple imputation analysis is missing at random (i.e., missing data can be considered occurring at random given selected factors to predict missing data). Although missing at random assumption is not verifiable based on observed data, it is even harder for PMR 3051-2 to quantify the validity of the assumption because the study selected predictors for missing formulation with no scientific rationale. PMR 3051-2 study report also describes that multiple imputation approach for this study might be limited due to the lack of information on some important predictors of the missing data such as change in patient's awareness of (or ability to identify) opioid products during the study period.

4. Propensity score (PS) analysis in 3051-4 weighted individuals in the post-period to match their covariate distributions with those of individuals in the pre-period within each opioid user group (seven groups in total; OxyContin, three primary and three secondary comparators). In other words, it used average treatment effect among treated (ATT) weights to conduct PS analysis considering the pre-period as treatment group and the post-period as control group. More specifically, PS analysis was conducted as follows:

(1) The sponsor fit seven separate PS models for OxyContin and for six comparator opioids.

(2) Individuals in the pre-period served as treatment group within each opioid user cohort. Using ATT weight (i.e., 1 for those in the pre-period and PS/(1-PS) for those in the post-period), the sponsor created a control group within each opioid cohort. Then ATT weighted cohort (i.e., including individuals in the pre-period as they are weighted with 1 and weighted individuals obtained from the post-period) becomes a new cohort for each opioid group. Therefore, there were seven new (weighted) cohorts for seven different opioids.

(3) The sponsor then combined the seven ATT weighted cohorts and fit Poisson regression models to calculate RORR or adjusted RORR to evaluate the effect of OxyContin reformulation on rate of overdose.

To illustrate why this analysis might be subject to limited validity and utility, recall the goal of the standard PS analysis using ATT weight. Suppose that we are interested in the effect of OxyContin reformulation. Then the standard PS analysis based on ATT weight considering individuals prescribed OxyContin in the pre-period as "treated" (as the sponsor did) aims to create a (control) group of people representing what would have happened if the same individuals are exposed to the reformulated OxyContin. Such hypothetical control group <u>should be</u> generated by weighting individuals prescribed OxyContin in the post-period. Weighting individuals prescribed with an opioid other than OxyContin (e.g., ER morphine) in the post-period cannot serve as a control group in this setting. Then the final goal of the PS analysis is to examine difference in rate of overdose among individuals in the pre-period with that of those selected from the post-period via ATT weighting. In the absence of unmeasured confounding (and if the other necessary assumptions for causal inference such as consistency and positivity assumptions hold), the difference in rate of overdose can describe the causal effect of the reformulation <u>for patients prescribed with OxyContin</u> in the pre-period.

Therefore, the sponsor's PS analysis is of highly limited validity and utility for two reasons:

(1) In PMR 3051 setting, no unmeasured confounding assumption is unlikely to meet. Most public health efforts to mitigate the opioid epidemic occurred in the post-period. Such external factors are deemed major confounding factors where PS models are failed to account for. Consequently, the validity of the PS analysis is questionable.

(2) Secondly, using combined cohorts (seven ATT weighted cohorts based on seven different study opioids) to conduct comparative analyses to evaluate the effect of OxyContin reformulation is invalid statistical approach. PS weighting ensures covariate balance between individuals in the pre- and the post-period <u>within each opioid user cohort</u>, but not across different opioid user cohorts. The sponsor's approach is, for example, analogous to combining seven trial data based on seven different opioid products and compare one product to the others without examining covariate distributions across the seven opioid groups, assuming all necessary (causal) assumptions are met. Accordingly, RORR and adjusted RORR obtained from the sponsor's PS analyses are inappropriate to describe the effect of OxyContin reformulation.

5. Unintentional overdose results in PMR 3051-4 are likely to have limited validity. Unintentional overdose is determined by (1) identifying any overdose and intentional overdose separately by using a different algorithm for each, then (2) by subtracting intentional overdose cases from any overdose cases. Such overdose algorithms have been developed and validated from FDA PMR 3033-6 study for extended-release/long-acting (ER/LA) opioids.[8] ER/LA 3033-6 study assessed sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for evaluating algorithm performance using medical chart review result as a gold standard. Kaiser Permanente Northwest (KPNW) was the primary study site to develop and validate various overdose

algorithms. Then the study conducted assessments of algorithm portability in Kaiser Permanente Washington (KPW), Tennessee State Medicaid (TennCare), and Optum. Table 4, excerpted from Table 9 in Green et al. 2019,[8] presents performance of any overdose algorithm and intentional overdose algorithm in the four sites.

Table 4. Performance of any overdose and intentional overdose algorithms in ER/LA PMR 3033-6 study.

	Primary Site	Portability Sites		
	KPNW	KPW	Optum	TennCare
Any overdose algorithm				
Sensitivity	97.2	100.0	96.9	99.2
Specificity	84.6	89.2	100.0	92.4
PPV	87.4	84.1	100.0	91.9
NPV	96.5	100.0	96.9	99.2
Intentional overdose algorithm				
Sensitivity	70.5	74.1	63.2	44.9
Specificity	90.2	86.7	91.0	87.1
PPV	78.9	74.1	81.1	64.5
NPV	85.5	86.7	80.1	75.1

ER/LA PMR 3033-6 study showed that performance of the intentional algorithm (referred to as "overdose classified as suicide/suicide attempt" in Green et al. 2019) is not satisfactory in some settings. Sensitivity of the algorithm in KPNW was suboptimal (70.5%) and was unacceptably low in Optum and TennCare (63.2% and 44.9%, respectively). PPV of the algorithm was only 64.5 in TennCare. Given such undesirable performance of the intentional algorithm, performance of the unintentional algorithm in PMR 3051-4 that utilizes the intentional algorithm is questionable.

Of note, performance of any overdose algorithm was consistently high across all four sites; all performance metrics were nearly greater than or equal to 85%. Therefore, PMR 3051-4 study considered any overdose results as primary and unintentional overdose results as exploratory.

6. PMR 3051-4 considered a meta-analysis of two commercial data-based studies (HIRD and MarketScan) to calculate pooled incident rate ratios and RORRs. The study used DerSimonian and Laird random-effects meta-analysis.[9] Note that no matter how sophisticated the method is used, estimated between-study variability based on two studies is likely to be substantially in error. It is also known that the measure of heterogeneity used in PMR 3051-4 (where its exact form is provided in equation (3) in Section 13.3 of the statistical analysis plan for PMR 3051-4) would have very low power to detect true heterogeneity when number of studies is small.[10,11] Seide and Röver (2019)[12] further pointed out that coverage probabilities might be compromised when meta-analysis is conducted to few studies in the presence of between-study heterogeneity, especially with unbalanced study sizes. Therefore, FDA previously communicated with the sponsor that the proposed meta-analysis approach would be considered to have limited utility and the two studies would be interpreted individually.

6 RESULTS

This section overviews results from primary and some major secondary analyses (based on varying study attributes presented in Table 1) and discusses potential ranges of effect estimates for each study. See Epidemiology Reviews in background document for detailed results including some useful sensitivity analyses such as a stratified analysis by treatment modality in PMR 3051-1.

This document mostly focuses on RORR results that evaluate the effect of OxyContin reformulation compared to the other opioids. As a reminder RORR>1 (with 95% CI excluding 1) indicates potential effect of the reformulation either by a greater reduction or by a smaller increase in rate for OxyContin relative to that of a comparator, or by no change for OxyContin but increasing rate for a comparator. Review of comparative analyses is limited to those based on primary comparators, as secondary comparators were used to provide contextual information. This document provides detailed overview of PMR 3051-1 study results as an illustrative example, then briefly summarizes the substance of findings from PMR 3051-2 to 4 to avoid repetition between Epidemiology Reviews in background document and this document.

6.1 PMR 3051-1 to PMR 3051-3: Abuse
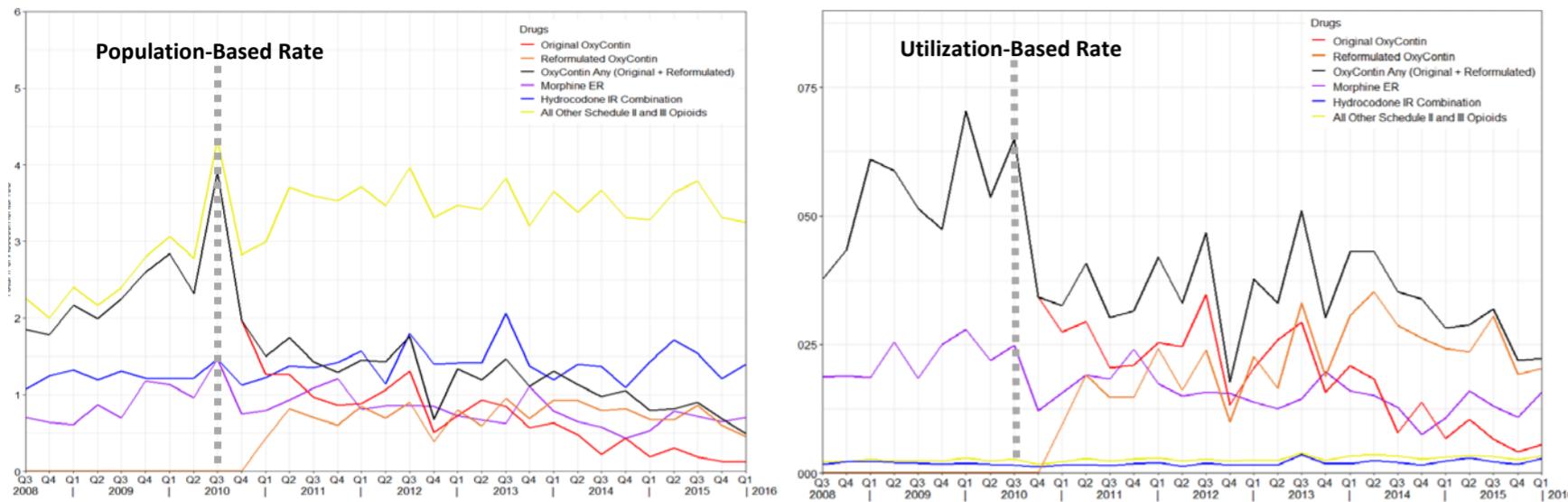
6.1.1 Overview of PMR 3051-1 Results

6.1.1.1 Descriptive Trend Analysis

Descriptive trends are useful to visually inspect the impact of OxyContin reformulation with or without comparators. Figure 6 presents trends in observed rates (both population-based and utilization-based) of non-oral abuse (primary) in PMR 3051-1. These figures

demonstrate the value of considering different denominators as they result in highly different abuse estimates and trends before and after the time of the reformulation (gray dotted line).

**Figure 6. Trends in observed rates of non-oral abuse in PMR 3051-1.**
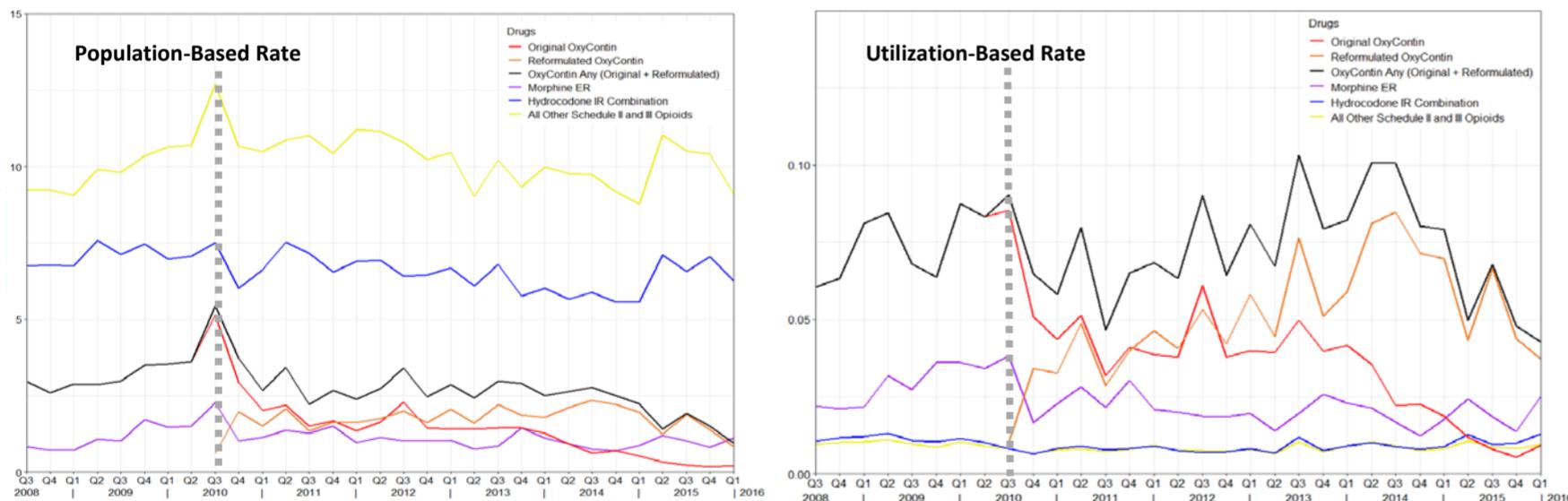
Source: Figures generated by an FDA reviewer. Grey dotted line represents the time of OxyContin reformulation.

➢ *Population-based rate = (number of non-oral abuse cases) / (number of total ASI-MV assessments/100)*
➢ *Utilization-based rate = (number of non-oral abuse cases) / (number of dosage unit dispensed)*
• *Black: Any OxyContin (original + reformulated)*
• *Red: Original OxyContin*
• *Orange: Reformulated OxyContin*
• *Purple: ER morphine*
• *Blue: IR hydrocodone*
• *Yellow: Other schedule II opioids*

Unlike Figure 6 that depicts a large decline in non-oral abuse of OxyContin following reformulation in PMR 3051-1, Figure 7 that presents trends in observed rates of <u>overall abuse</u> suggests that changes in overall abuse rates for OxyContin (black solid line) might be minimal after the time of reformulation (gray dotted line), regardless of comparisons with other opioids.

Figure 7. Trends in observed rates of overall abuse in PMR 3051-1.

Source: Figures generated by an FDA reviewer. Grey dotted line represents the time of OxyContin reformulation.

➢ *Population-based rate = (number of non-oral abuse cases) / (number of total ASI-MV assessments)*
➢ *Utilization-based rate = (number of non-oral abuse cases) / (number of dosage unit dispensed)*
• *Black: Any OxyContin (original + reformulated)*
• *Red: Original OxyContin*
• *Orange: Reformulated OxyContin*
• *Purple: ER morphine*
• *Blue: IR hydrocodone*
• *Yellow: Other schedule II opioids*

6.1.1.2 Change in Abuse for OxyContin versus Comparators

6.1.1.2.1 **Non-oral Abuse**

Percent change and RORR: This document describes percent change results here, only once, as an illustrative example, then focuses on comparative analyses results afterwards.

Table 4 presents a summary of percent change results for **<u>non-oral abuse</u>** (primary) across different OxyContin definitions and site definitions in PMR 3051-1. In the primary analyses using primary definition of OxyContin and site, percent change estimates for non-oral abuse ranged from -55.6% to -29.3%. When different OxyContin definitions were examined based on the same primary site definition, effect estimates ranged wider from -70.0% to -29.3%. Estimated decline in non-oral abuse rate was the largest when reformulated OxyContin alone in the post-period (secondary definition 1) was considered, suggesting that different definitions of OxyContin could alter findings and interpretations. Differing site definitions (broadening sites) led to smaller reductions after the reformulation, where estimated reduction in non-oral abuse went down to -8.4%, leading range of estimates -55.6% to -8.4% as compared to -55.6% to -29.3%. Total range of percent change estimates were -70% to -8.4%. The maximum estimate is highlighted in yellow the minimum estimate is highlighted in orange.

Table 5. Summary of percent change in non-oral abuse across varying OxyContin and site definitions in PMR 3051-1.

Site\OxyContin	Model	Percent Change (%) in Non-Oral Abuse			
		Original + Reformulated	Reformulated only	Original + Reformulated + generic ER oxycodone	Range of estimates*
≥1 assessment per quarter	Model 1	-30.7 (-46.9, -9.5)	-66.0 (-73.2, -56.8)	-44.8 (-59.0, -25.9)	-70.0 to -29.3 (-75.1, -9.5)
	Model 2	-31.5 (-39.4, -22.5)	-60.7 (-65.9, -54.7)	-31.6 (-38.1, -24.4)	
	Model 2a	-29.3 (-37.5, -20.1)	-59.4 (-64.8, -53.2)	-23.5 (-30.8, -15.4)	
	Model 3	-53.3 (-60.3, -45.0)	-68.9 (-74.2, -62.5)	-57.6 (-63.1, -51.3)	
	Model 3a	-55.6 (-62.3, -47.6)	<mark>-70.0 (-75.1, -63.8)</mark>	-67.4 (-71.8, -62.3)	
OxyContin\Site		≥1 assessment per quarter	≥1 assessment per year	≥1 assessment per year except NM	Range of estimates*
Original + Reformulated	Model 1	-30.7 (-46.9, -9.5)	-27.6 (-40.4, -12.2)	-26.4 (-39.7, -10.1)	-55.6 to -8.4 (-62.3, -3.1)
	Model 2	-31.5 (-39.4, -22.5)	-10.3 (-15.2, -5.2)	<mark style="background:#f0a868">-8.4 (-13.4, -3.1)</mark>	
	Model 2a	-29.3 (-37.5, -20.1)	-9.5 (-14.4, -4.4)	-9.4 (-14.3, -4.1)	
	Model 3	-53.3 (-60.3, -45.0)	Not Reliable**	-31.5 (-35.7, -27.0)	
	Model 3a	-55.6 (-62.3, -47.6)	-29.6 (-34.0, -24.8)	Not Reliable**	
Total range of estimates*		-70 to -8.4 (-75.1, -3.1)			

Numbers in parenthesis represent minimum of lower 95% CIs and maximum of upper 95% CIs.
**Estimates from these models are unreliable; Negative of Hessian is not positive definite.
- *Model 1: abuse rate defined by total assessments (TA) as a denominator (i.e., population-based rate)*
- *Model 2: abuse rate defined by dosage units dispense (DUD) as a denominator (i.e., drug utilization-based rate)*
- *Model 2a: DUD as a denominator, TA as a covariate (i.e., drug utilization-based, population-adjusted rate)*
- *Model 3: DUD as a continuous covariate (i.e., drug utilization-adjusted rate)*
- *Model 3a: TA and DUD as continuous covariates (i.e., population and drug utilization adjusted rate)*

Table 5 presents a summary of RORR results for non-oral abuse across varying OxyContin and site definitions. As most results are significant and favorable to OxyContin (RORR>1 and lower bound of 95% CI is above 1), Table 5 only highlights those that are insignificant in gray. Results are highly robust and mostly significant at 0.05 level, demonstrating compelling evidence of the effect of OxyContin reformulation on reducing non-oral rate of abuse. As indicated by percent change results, the evidence was the strongest when reformulated OxyContin was considered.

Table 6. Summary of RORR results for non-oral abuse across varying OxyContin and site definitions in PMR 3051-1.

Non-oral Abuse		RORR (95% CI) for Non-Oral Abuse					
		Sites: ≥1 assessment/quarter			≥1 assessment /year	≥1 assessment /year except NM	
Comparator	Model	Original + Reformulated	Reformulated only in the post	Original + Reformulated + generic ER oxycodone	Original + Reformulated	Original + Reformulated	Range of estimates*
ER morphine	Model 1	1.30 (0.87, 1.94)	2.66 (1.81, 3.89)	1.64 (1.08, 2.49)	1.37 (1.03, 1.83)	1.35 (1.01, 1.81)	1.04 to 3.46 (0.86, 4.78)
	Model 2	1.04 (0.84, 1.30)	1.82 (1.44, 2.29)	1.05 (0.85, 1.29)	1.21 (1.09, 1.36)	1.19 (1.06, 1.33)	
	Model 2a	1.07 (0.86, 1.33)	1.86 (1.48, 2.34)	0.97 (0.79, 1.19)	1.25 (1.12, 1.40)	1.20 (1.08, 1.34)	
	Model 3	2.14 (1.60, 2.87)	3.22 (2.37, 4.37)	2.36 (1.79, 3.12)	Not Reliable**	1.30 (1.14, 1.48)	
	Model 3a	2.33 (1.71, 3.19)	3.46 (2.50, 4.78)	3.16 (2.34, 4.27)	1.15 (1.00, 1.32)	Not Reliable**	
IR hydrocodone	Model 1	1.72 (1.19, 2.49)	3.51 (2.47, 4.98)	2.16 (1.46, 3.19)	1.46 (1.16, 1.84)	1.44 (1.13, 1.83)	1.21 to 4.04 (1.07, 5.56)
	Model 2	1.36 (1.13, 1.65)	2.38 (1.94, 2.91)	1.37 (1.15, 1.63)	1.34 (1.22, 1.46)	1.34 (1.22, 1.47)	

	Model 2a	1.30 (1.07, 1.57)	2.26 (1.85, 2.77)	1.21 (1.01, 1.44)	1.34 (1.23, 1.47)	1.34 (1.23, 1.47)	
	Model 3	2.51 (1.95, 3.23)	3.76 (2.88, 4.92)	2.76 (2.18, 3.50)	Not Reliable**	1.58 (1.40, 1.78)	
	Model 3a	2.73 (2.01, 3.71)	4.04 (2.94, 5.56)	3.70 (2.80, 4.90)	1.51 (1.33, 1.71)	Not Reliable**	
Other Schedule II	Model 1	1.90 (1.29, 2.79)	3.87 (2.68, 5.58)	2.39 (1.59, 3.60)	1.49 (1.14, 1.94)	1.45 (1.10, 1.90)	1.45 to 4.07 (1.10, 5.16)
	Model 2	1.65 (1.41, 1.93)	2.88 (2.42, 3.42)	1.66 (1.44, 1.91)	1.74 (1.62, 1.87)	1.74 (1.61, 1.87)	
	Model 2a	1.62 (1.38, 1.90)	2.82 (2.37, 3.36)	1.49 (1.29, 1.71)	1.77 (1.65, 1.91)	1.76 (1.64, 1.90)	
	Model 3	2.71 (2.18, 3.38)	4.07 (3.21, 5.16)	2.99 (2.44, 3.66)	Not Reliable**	1.96 (1.77, 2.16)	
	Model 3a	2.60 (2.06, 3.28)	3.84 (3.00, 4.93)	3.52 (2.82, 4.38)	1.79 (1.61, 1.99)	Not Reliable**	

Numbers in parenthesis represent minimum of lower 95% CIs and maximum of upper 95% CIs.

**Estimates from these models are unreliable; Negative of Hessian is not positive definite.*

- *Model 1: abuse rate defined by total assessments (TA) as a denominator (i.e., population-based rate)*
- *Model 2: abuse rate defined by dosage units dispense (DUD) as a denominator (i.e., drug utilization-based rate)*
- *Model 2a: DUD as a denominator, TA as a covariate (i.e., drug utilization-based, population-adjusted rate)*
- *Model 3: DUD as a continuous covariate (i.e., drug utilization-adjusted rate)*
- *Model 3a: TA and DUD as continuous covariates (i.e., population and drug utilization adjusted rate)*

ITS Analyses and Immediate Shift: Table 6 presents a summary of ITS analyses (change in slope and immediate shift) for non-oral abuse based on primary definitions of OxyContin and site. Values less than 0 for change in slope and immediate shift typically indicate reduction in abuse rates their trends, although as mentioned earlier, those values should be interpreted with ITS figures. Due to the volume of figures and to avoid redundancy, this document does not present ITS analysis figures as they are provided in Epidemiology Reviews in background document. Significant change in slope and immediate shift within each opioid are highlighted in yellow. Cells in green indicate that change in slope and immediate shift for OxyContin is significantly greater than that of a comparator.

Table 7. Summary of ITS results (change in slope and immediate shift) for non-oral abuse across varying OxyContin and site definitions in PMR 3051-1.

Opioid	Model	Slope in pre	Slope in post	Change in slope (95% CI)	Immediate shift (95% CI)	Range of estimates* (CIS: change in slope, IS: immediate shift)
OxyContin	Model 1	0.05	-0.03	-0.08 (-0.15, -0.01)	-0.52 (-0.87, -0.17)	CIS: -0.08 to -0.01 (-0.15, 0.08) IS: -0.57 to -0.32 (-1.11, 0.13)
	Model 2	0.04	0.01	-0.04 (-0.14, 0.07)	-0.57 (-1.11, -0.04)	
	Model 2a	0.004	-0.01	-0.01 (-0.10, 0.08)	-0.32 (-0.77, 0.13)	
	Model 3	0.05	-0.02	-0.06 (-0.17, 0.04)	-0.56 (-1.10, -0.03)	
	Model 3a	0.02	-0.03	-0.05 (-0.11, 0.02)	-0.34 (-0.66, -0.02)	
ER morphine	Model 1	0.08	-0.03	-0.12 (-0.23, -0.01)	-0.08 (-0.58, 0.42)	CIS: -0.12 to -0.06 (-0.26, 0.10) IS: -0.24 to 0.12 (-1.01, 0.66)
	Model 2	0.04	-0.03	-0.07 (-0.24, 0.10)	-0.24 (-1.01, 0.52)	
	Model 2a	0.02	-0.04	-0.06 (-0.20, 0.08)	-0.07 (-0.71, 0.58)	
	Model 3	0.07	-0.02	-0.10 (-0.26, 0.07)	-0.11 (-0.87, 0.66)	
	Model 3a	0.04	-0.04	-0.08 (-0.18, 0.02)	0.12 (-0.34, 0.58)	
IR hydrocodone	Model 1	0.004	-0.002	-0.01 (-0.10, 0.08)	0.14 (-0.29, 0.57)	CIS: -0.01 to 0.04 (-0.11, 0.17) IS: -0.16 to 0.35 (-0.82, 0.74)
	Model 2	-0.02	0.02	0.04 (-0.10, 0.17)	-0.16 (-0.82, 0.50)	
	Model 2a	-0.02	0.01	0.03 (-0.10, 0.14)	-0.09 (-0.65, 0.47)	
	Model 3	-0.01	0.01	0.02 (-0.11, 0.16)	-0.02 (-0.68, 0.64)	
	Model 3a	-0.03	-0.01	0.03 (-0.05, 0.11)	0.35 (-0.05, 0.74)	
Other schedule II	Model 1	0.05	-0.0003	-0.05 (-0.11, 0.01)	0.18 (-0.10, 0.46)	CIS: -0.05 to 0.02 (-0.11, 0.10) IS: -0.10 to 0.37 (-0.49, 0.63)
	Model 2	0.01	0.02	0.01 (-0.09, 0.10)	-0.06 (-0.49, 0.38)	
	Model 2a	-0.01	0.01	0.02 (-0.06, 0.10)	-0.10 (-0.27, 0.47)	
	Model 3	0.02	0.02	-0.01 (-0.10, 0.09)	-0.01 (-0.45, 0.42)	
	Model 3a	0.03	-0.01	-0.03 (-0.09, 0.02)	0.37 (0.11, 0.63)	

Numbers in parenthesis represent minimum of lower 95% CIs and maximum of upper 95% CIs.

- *Model 1: abuse rate defined by total assessments (TA) as a denominator (i.e., population-based rate)*
- *Model 2: abuse rate defined by dosage units dispense (DUD) as a denominator (i.e., drug utilization-based rate)*
- *Model 2a: DUD as a denominator, TA as a covariate (i.e., drug utilization-based, population-adjusted rate)*
- *Model 3: DUD as a continuous covariate (i.e., drug utilization-adjusted rate)*
- *Model 3a: TA and DUD as continuous covariates (i.e., population and drug utilization adjusted rate)*

Table 6 depicts minimal changes in slope for all study opioids and no significant change in slope for OxyContin relative to comparators. Immediate shift demonstrates that OxyContin is the only opioid showing significant level change (i.e., significant reduction in non-oral abuse rate right before and after the time of the reformulation). However, the magnitude of immediate shift for OxyContin is in general similar to that of comparators. Overall, range of estimates for change in slopes (denoted by CIS in Table 6) and immediate shift (denoted by IS in Table 6) do not show strong evidence for the effect of the reformulation.

6.1.1.2.2   Abuse by Route of Administration

Table 7 presents RORR for OxyContin compared to primary comparators by each ROA. Significant results are highlighted in yellow if reduction is greater for OxyContin, or in gray if reduction is greater for a comparator.

Table 8. ROA analyses: Summary of RORR via each ROA.

Opioid	Model	RORR (95% CI)				
		Oral Swallowed Intact	Other Oral: chewed, dissolved, drank	Snorted	Injected	Any Route
ER Morphine	1	0.72 (0.49, 1.04)	0.56 (0.40, 0.79)	1.77 (1.10, 2.85)	1.29 (0.74, 2.23)	0.97 (0.63, 1.51)
	2	0.54 (0.40, 0.71)	0.37 (0.24, 0.59)	1.22 (0.89, 1.67)	1.11 (0.84, 1.46)	0.70 (0.58, 0.84)
	2a	0.55 (0.41, 0.73)	0.38 (0.24, 0.61)	1.25 (0.91, 1.71)	1.13 (0.86, 1.50)	0.71 (0.59, 0.86)
	3	1.03 (0.69, 1.53)	0.52 (0.27, 0.99)	2.45 (1.60, 3.75)	2.11 (1.47, 3.04)	1.43 (1.11, 1.84)
	3a	1.24 (0.81, 1.91)	0.56 (0.27, 1.16)	2.64 (1.66, 4.19)	2.29 (1.55, 3.37)	1.62 (1.24, 2.13)
IR Hydrocodone	1	0.84 (0.64, 1.10)	0.62 (0.45, 0.85)	2.05 (1.38, 3.04)	0.92 (0.42, 2.01)	1.14 (0.82, 1.60)
	2	0.56 (0.48, 0.64)	0.45 (0.34, 0.59)	1.54 (1.24, 1.91)	0.55 (0.30, 1.02)	0.73 (0.65, 0.82)
	2a	0.52 (0.45, 0.60)	0.43 (0.33, 0.56)	1.47 (1.18, 1.82)	0.53 (0.28, 0.98)	0.69 (0.61, 0.77)
	3	0.93 (0.75, 1.15)	0.59 (0.40, 0.86)	2.85 (2.14, 3.81)	0.93 (0.41, 2.10)	1.34 (1.14, 1.57)
	3a	1.15 (0.91, 1.44)	0.69 (0.45, 1.04)	3.11 (2.21, 4.37)	0.93 (0.30, 2.86)	1.57 (1.32, 1.87)
Other Schedule II	1	0.90 (0.68, 1.19)	0.79 (0.55, 1.13)	2.46 (1.55, 3.90)	1.83 (1.09, 3.09)	1.21 (0.87, 1.68)
	2	0.61 (0.53, 0.70)	0.56 (0.44, 0.73)	1.90 (1.58, 2.29)	1.61 (1.26, 2.06)	0.82 (0.74, 0.91)
	2a	0.59 (0.51, 0.68)	0.55 (0.43, 0.71)	1.87 (1.55, 2.25)	1.58 (1.23, 2.03)	0.80 (0.72, 0.89)
	3	1.05 (0.84, 1.30)	0.71 (0.49, 1.03)	3.17 (2.44, 4.12)	2.39 (1.70, 3.36)	1.53 (1.30, 1.79)
	3a	1.09 (0.87, 1.36)	0.71 (0.48, 1.04)	3.05 (2.31, 4.02)	2.37 (1.65, 3.41)	1.50 (1.27, 1.77)

- *Model 1: abuse rate defined by total assessments (TA) as a denominator (i.e., population-based rate)*
- *Model 2: abuse rate defined by dosage units dispense (DUD) as a denominator (i.e., drug utilization-based rate)*
- *Model 2a: DUD as a denominator, TA as a covariate (i.e., drug utilization-based, population-adjusted rate)*
- *Model 3: DUD as a continuous covariate (i.e., drug utilization-adjusted rate)*
- *Model 3a: TA and DUD as continuous covariates (i.e., population- and drug utilization-adjusted rate)*

In general, OxyContin reformulation seemed effective on reducing abuse by snorting and injecting routes, which it is designed to deter. However, most results for abuse by oral routes indicated that reduction in comparator is more pronounced. This suggests that OxyContin abuse might have been switched from snorting/injecting to oral. Therefore, abuse by any route (overall) provided mixed results; some model results were favorable to OxyContin (i.e., RORR>1 and significant) but the others were not (i.e., RORR<1 and significant), even within the same comparator. Overall, drug utilization-base rates (model 2 and 2a) suggested that reduction in abuse for OxyContin is not substantial enough to claim the effect of the reformulation and might have led to abuse by other routes, particularly via oral. However, population- and/or drug utilization-adjusted rates (model 3 and 3a) indicated that the reformulation might be effective. These results are consistent with descriptive trend analyses.

6.1.2 Overview of PMR 3051-2 and 3051-3 Results

6.1.2.1 PMR 3051-2: Intentional Abuse

RORR: Only results based on model 1 using population-based rates demonstrated the effect of the reformulation, meaning that reduction in abuse is significantly greater (RORR>1) for OxyContin relative to all comparators. Of note, model 1 was the least adequate model in terms of the AIC (2254.99). Model 3a using population- and drug utilization-adjusted rate had the lowest AIC (1261.29) followed by model 2a (1275.91) using drug utilization-based population-adjusted rate. Some RORRs (e.g., analyses based on secondary definition of OxyContin [any ER oxycodone]) are significantly smaller than 1 implying that reduction in rates of abuse is even greater for some comparators than that of OxyContin. Mixed findings in RORR analyses demonstrated weak evidence for the effect of the reformulation.

ITS Analyses and Immediate Shift: Change in slope for OxyContin was not apparently distinct from that of comparators (no significant results observed).

The final study report provides comparative immediate shift results based only on a limited set of models (model 5 [population-based rate], 6a [drug utilization-based, population-adjusted rate], and 7a [population- and drug utilization-adjusted rate]). Immediate shift for OxyContin was statistically significantly different from IR hydrocodone based on model 5, and from other Schedule II opioids using model 5 and 7a. Considering that model 5 is an ITS version of model 1, these results are consistent with RORR results.

ROA Analyses: From ROA analysis, again only RORRs based on model 1 (population-based rate) results consistently demonstrated greater reduction in oral and non-oral abuse (but not in inhalation and injection abuse) for OxyContin compared to all primary comparators. Other than these two results (reduction in oral and non-oral based on model 1), comparisons with ER morphine results

were all insignificant. Some effect of the reformulation was observed from comparisons with IR hydrocodone and other schedule II opioids: Reduction in non-oral abuse was significant greater for OxyContin over the two comparators for most cases (model 1, 2, and 2a results for comparisons with IR hydrocodone; model 1, 2, 2a, and 3a results for comparisons with other schedule II opioids). While the totality of evidence supports some unquantifiable effect of the reformulation on reducing non-oral abuse, these data continue to generate uncertainty (see Section 5.5 of Epidemiology Review in background document). Therefore, caution is warranted when interpreting the ROA findings.

6.1.2.2 PMR 3051-3: Overall Abuse

RORR: Results were mixed again. First, only results based on model 1 (population-based rate) showed consistently significantly greater reduction in abuse compared to all comparators as in PMR 3051-2. Same as in PMR 3051-2, model 1 was again the least adequate model in terms of the AIC (3281.7) and model 3a was the most adequate (AIC=2972.5) followed by model 2a (AIC=3281.7). In PMR 3051-3, most of significant results were observed from comparisons with ER morphine (model 1, 3, and 3a results) which is the opposite from PMR 3051-2 results. Comparisons with IR hydrocodone or other schedule II opioids were all insignificant except for model 1 results.

Stratified by OTP and SKIP data sources, the analyses revealed that most significant results for OxyContin and ER morphine comparisons were driven by SKIP; all OTP results were insignificant except for model 1 results.

Results were mostly consistent when stratified by regions (entire US, western region only, or entire US excluding Florida). Model 1 results for comparisons with IR hydrocodone or other schedule II opioids remained significant, while RORR for OxyContin and ER morphine comparison became insignificant in western region and in entire US excluding Florida.
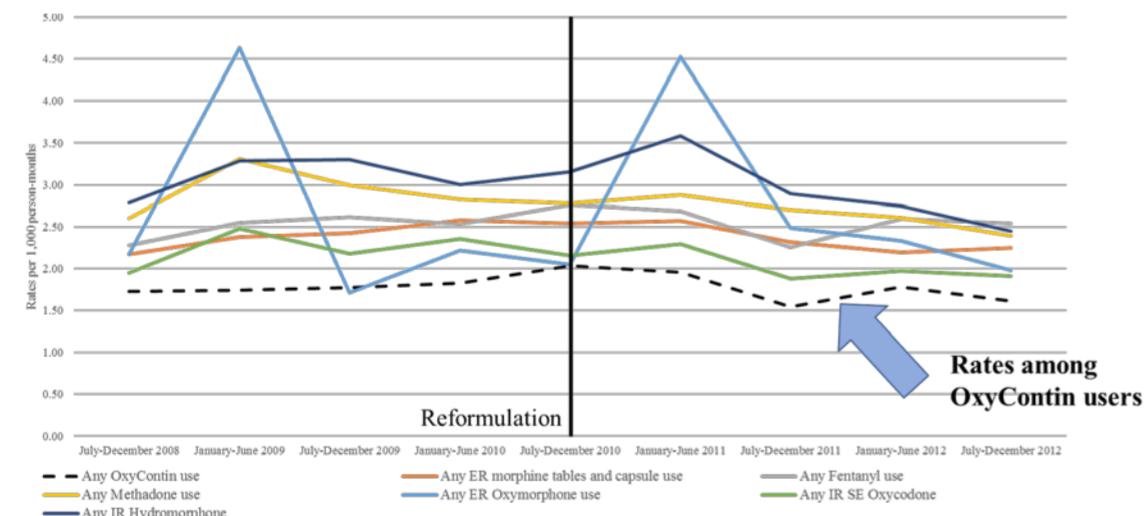
ITS Analyses and Immediate Shift: Changes in slope for OxyContin were mostly similar to those for comparators except for only one case: Model 7a (population- and drug utilization-adjusted rate) result for OxyContin and IR hydrocodone comparison.

ROA Analyses: OTP and SKIP data had no ROA information.

6.2   PMR 3051-4: Overdose

No appraent trends in any overdose (henceforth, overdose) were observed in the three claims databases. For example, see Figure 8, taken from Epidemiology Review for PMR 3051-4 in background document, that presents trends in overdose obtained from the Medicaid database.
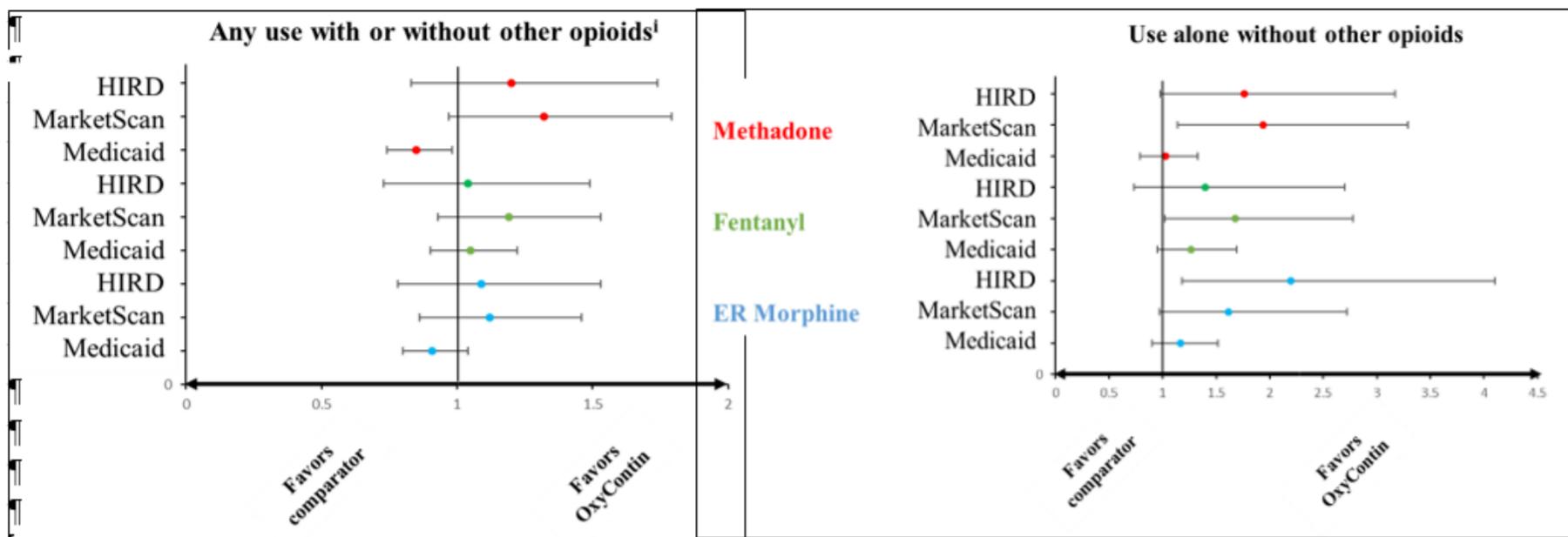
Figure 8. Trend in overdose in the National Medicaid database.

Source: Epidemiology: Review of OxyContin® Postmarketing Requirement (PMR) 3051-4 Final Study Report. Figure 3 (p 40).

As such, adjusted RORR (aRORR) results shown in Figure 9 suggest that change in overdose for OxyContin is mostly similar to those of comparators under different definitions of OxyContin use. Note that there are four significant cases where two are unfavorable to OxyContin (comparisons with methadone and ER Morphine in Medicaid; left panel of Figure 9) and the other two are favorable to OxyContin (comparisons with methadone in MarketScan and with ER morphine in HIRD; right panel of Figure 9).

Figure 9. Adjusted RORR (aRORR) results across varying OxyContin and comparator use definitions in full cohort (including both icident and prevalent opioid users).

Source: [Epidemiology: Review of OxyContin® Postmarketing Requirement (PMR) 3051-4 Final Study Report, Figure 6 (p 54 - 55)](#).

When incident users were examined instead of the full cohort (that included both prevalent and incident opioid users), all significant aRORR results (four cases) in the full cohort became insignificant, except for one case: aRORR that compares reduction in overdose between any OxyContin and (any) methadone in MarketScan database became significant, favoring OxyContin (aRORR= 2.17 with 95% CI = [1.11, 4.26]).

Due to small number of fatal overdose cases, no inferential tests seem meaningful.

7   DATA VALIDATION AND ANALYSIS REPLICATIN EFFORTS

FDA requested the sponsor to submit data and analysis programs for PMR 3051 studies, except for PMR 3051-4 as it was considered infeasible to obtain data for the study. The goal of this request was to confirm reproducibility of the sponsor's analyses. Because data and program submission was completed recently (on February 25, 2020), as well as the volume of data and analyses, FDA selected key primary and secondary analyses that were commonly done across PMR 3051-1 to 3051-3 for efficiency sake. List of study objectives associated with verified analyses are as follows:

I.   PMR 3051-1

- Primary objective 1: Impact of OxyContin reformulation on non-oral OxyContin abuse (percent change and RORR analyses)

- Primary objective 2: Changes in non-oral abuse for primary comparator opioids versus OxyContin (percent change and RORR analyses)

- Secondary objective 1: Change in trend of abuse of OxyContin and comparator opioids (descriptive trends and ITS analyses)

II.   PMR 3051-2

- Primary objective 1: Changes in intentional abuse of OxyContin (percent change and RORR analyses)

- Primary objective 2: Changes in intentional abuse rates for OxyContin compared to comparator opioids (percent change and RORR analyses; limited to primary comparators)

- Secondary objective 1: Change in trend of abuse of OxyContin and comparator opioids (ITS analysis; limited to primary comparators)

- Secondary objective 3: Changes in abuse of OxyContin versus comparator opioids by routes of administration (limited to primary comparators)

III.   PMR 3051-3

- Primary objective 1: Changes in abuse of OxyContin (percent change and RORR analyses)

- Primary objective 2: Changes in abuse for OxyContin relative to primary comparator opioids (percent change and RORR analyses)

- Secondary objective 1: Change in trends of OxyContin abuse and comparator opioids (ITS analysis; limited to primary comparators)

FDA has been able to reproduce these analyses results, ensuring integrity of the analyses and selected key findings.

8 DISCUSSION AND CONCLUSION

8.1 Summary of Study Findings and Discussion

8.1.1 Descriptive Trend Analysis

For PMR 3051-1 to 3051-3, descriptive trends in rate of abuse generally depicted a reduction in abuse of OxyContin following the reformulation. However, trends in abuse of primary comparators also demonstrate a decrease after the time of the reformulation for most cases. It is also noteworthy that rate of abuse for OxyContin was mostly higher than those of comparators before and after the reformulation across PMR 3051-1 to 3051-3. For PMR 3051-4, descriptive trend analysis shows that rate of any overdose for OxyContin remained relatively stable before and after the reformulation, or even increased slightly after the reformulation.

Figures of trends also demonstrated how different ways to define and model a rate can result in different estimates, and thus reinforced the importance to consider both population- and drug utilization-based (or adjusted) rates to evaluate the effect of reformulation. Reduction in abuse of OxyContin was mostly prominent when population-based rates of abuse was considered as shown in PMR 3051-2 and 3051-3.

8.1.2 Comparative Analyses

RORR Analysis: In general, there was reasonably compelling, robust evidence that OxyContin reformulation is effective on reducing non-oral rate of abuse from PMR 3051-1 database. However, ROA analyses revealed that increase in abuse via oral route might partially offset the benefit of deterring abuse via non-oral route, resulting in mixed effect on reducing abuse via overall routes. In PMR 3051-2 and 3015-3, there was no compelling evidence of the effect, as only population-based rate (model 1, the least adequate model in terms of the AIC) consistently demonstrated significantly greater reduction in rates of abuse for OxyContin compared to the other opioids. In PMR 3051-2, there was some evidence that the reformulation reduces abuse via non-oral route.

Although not fully described in this document, there were some variations in the decrease in rate of abuse for OxyContin by level of risk factors such as addiction severity index score (PMR 3051-1), dose strength (PMR 3051-2), etc. There were suggestions that the reformulation might have a particularly strong effect in individuals having a moderate to extreme problem with regards to opioid addiction, and/or taking higher dose tablets or capsules of opioids.

ITS analysis: Almost all ITS analyses results indicated that change in slope for OxyContin before and after the reformulation is mostly comparable to the other opioids. PMR 3051 study reports describe that Zhang et al. (2011)[13] conducted simulations to estimate the power associated with various parameters of ITS and concluded that studies with only 12 or 18 data points (equally distributed among pre- and post-reformulation periods) might suffer from low power. The study reports then argue that PMR 3051 studies might be under-powered for ITS analysis as there were only 8 data points (8 calendar-quarters) in the pre-period. Immediate shift demonstrated some effect of OxyContin attributable to the reformulation. However, the magnitude of immediate shift for OxyContin is in general similar to that of comparators.

8.1.3 Summary

In addition to descriptive trends, inferential analyses results demonstrate how differing assumptions and study attributes could (sometimes drastically) alter the substance of findings and interpretations, thus stress the value of considering range of estimates to evaluate the effect of OxyContin reformulation. For example, RORR analyses in PMR 3051-1 and 3051-2 indicated that the effect of OxyContin reformulation could change by differing OxyContin definitions and site/geographical regions. ROA analyses in PMR 3051-1 provided mixed results on overall abuse across different outcome definitions and different ways to account for population/utilization. All four studies showed different results depending on the choice of comparators.

As PMR 3051 studies utilized observational data that are subject to various sources of confounding over time including the changing landscape of opioid use and abuse, isolation of the (causal) effect of OxyContin reformulation was challenging. Findings from PMR 3051 studies enable us to explore the impact of the various factors listed in Table 1, providing a range of estimates and robustness/strength of evidence. Due to some substantial changes in the effect estimates over different study attributes, it was difficult to precisely quantify the size of the effect of the reformulation though.

8.2 Conclusion

PMR 3051 studies were designed to explore the impact of the various sources of confounding listed in Table 1 on the estimation of reformulation effect. This is a reasonable approach, from a statistical perspective, although it somewhat complicates the interpretation of the study findings. Evaluation of model adequacy and relative performances, coupled with FDA's efforts to verify integrity and reproducibility of sponsor's analyses, ensured quality of selected key study findings. Robustness of findings under various assumptions and qualitative synthesis of the totality of evidence were used to make final conclusions on the effect of OxyContin reformulation.

Descriptive trend and inferential analyses demonstrated how differing assumptions and study attributes could (sometimes drastically) alter the substance of findings and interpretations. These results reinforced the value of considering the range of estimates to evaluate the effect of OxyContin reformulation. Reduction in abuse of OxyContin was in general the most prominent when population-based rates of abuse were considered, rather than utilization-based rates.

PMR 3051-1 study provides reasonably compelling evidence that the reformulation is effective in reducing the rate of non-oral OxyContin abuse in people who are entering or being assessed for treatment. However, the evidence for a reduction in overall OxyContin abuse (via any route) in this population is weak. Findings from PMR 3051-2 to 3051-4 are not robust enough to provide compelling evidence of the effect of OxyContin reformulation on reducing (overall) rate of abuse or overdose, from a statistical perspective. The totality of evidence from PMR 3051-2 supports some effect of the reformulation on reducing non-oral abuse although the non-oral abuse data in PCC are limited. These conclusions are generally consistent with those in Epidemiology Reviews in background document.

Investigation of the range of effect estimates under various but plausible assumptions to draw reasoned conclusions based on robustness/totality of evidence is the strength of PMR 3051 studies, from a statistical perspective. However, PMR 3051 studies are still subject to limitations some of which are untestable (Section 4). Thus, cautions are still warranted when interpreting study findings (see the summary memorandum in background document).

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Literature review:
Examining the impact of reformulated OxyContin on opioid-related morbidity and mortality

Date:	May 25, 2020
Primary Reviewer(s):	Matthew Daubresse, DrPH, MHS Office of Surveillance and Epidemiology (*OSE*), *Division of Epidemiology II (DEPI)*
	Christina Greene, PhD *OSE, DEPI*
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Tertiary Reviewer(s):	Tamra Meyer, PhD, MPH *OSE, DEPI*
Associate Office Director:	Judy Staffa, PhD, RPh *OSE*
Subject:	Literature review of studies examining the impact of reformulated OxyContin on opioid-related adverse events
Drug Name(s):	OxyContin®
Application Type/Number:	NDA 022-272/S-026
Applicant/sponsor:	Purdue Pharma L.P.
OSE RCM #:	2014-2311

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ABBREVIATIONS

ADFs – Abuse Deterrent Formulations

APIs – Active Pharmaceutical Ingredients

ARCOS – Automation of Reports and Consolidated Orders System

CDER – Center for Drug Evaluation and Research

CI – Confidence Interval

DEA – Drug Enforcement Administration

DEPI –Division of Epidemiology

DPV –Division of Pharmacovigilance

ED – Emergency Department

EMS – Emergency Medical Services

ER – Extended-Release

ER/LA – Extended-Release/Long-Acting

FDA – Food and Drug Administration

IR – Immediate-Release

ITS- Interrupted Time Series

MAT – Medication Assisted Therapy

NOMAD – National Opioid Medication Abuse Deterrence

NPS - National Prescription Audit

NSDUH – National Survey on Drug Use and Health

OR – Odds Ratio

OPSA – Office of Program and Strategic Analysis

OST – Opioid Substitution Therapy

OUD – Opioid Use Disorder

PMRs – Postmarketing Requirement

RR – Risk Ratio

ROA – Route of Administration

SE – Single-Entity

UDS – Urine Drug Screen

U.S. – United States

EXECUTIVE SUMMARY

Background and methods

The FDA postmarketing required (PMR) studies 3051-1 through 3051-4 were designed to assess the impact of OxyContin reformulation on OxyContin abuse and risk of opioid overdose in the community. To supplement and contextualize the formal PMR studies submitted by the sponsor and to better understand the broader public health impact of OxyContin's reformulation, the Division of Epidemiology (DEPI) II conducted a review of peer-reviewed and selected grey literature examining the impact of reformulated OxyContin on opioid use, abuse, morbidity, and mortality.

We conducted a comprehensive literature search in the National Library of Medicine's PubMed database to identify original observational studies examining the effectiveness or public health impact of OxyContin's abuse-deterrent formulation (ADF) using either quantitative or qualitative methods. An independent reviewer conducted a secondary PubMed search to identify any additional relevant studies. We also identified and reviewed selected relevant publications (e.g., working papers) from the grey literature and editorials related to the effectiveness or public health impact of OxyContin's reformulation or ADFs in general.

Summary of findings

Our final selection consisted of 78 articles, further categorized into three main categories: PMR-related studies (15), non-PMR-related studies (31), and editorials (32). Six of the PMR-related studies and 13 of the non-PMR related studies were funded by Purdue or a Purdue-affiliated pharmaceutical company. PMR-related studies are summarized and evaluated in the reviews of the related PMR studies 3051-1 through 3051-4. We further categorized the non-PMR studies based on whether they were conducted within the United States (U.S.) and whether they used quantitative or qualitative methods (Appendix Tables 1-3).

Effect of reformulation on OxyContin dispensing

In the U.S., the transition from original OxyContin to reformulated OxyContin occurred quickly between the third and fourth calendar quarter of 2010. After reformulation, the number of prescriptions and prescription sales of OxyContin gradually declined, but overall prescriptions for ER oxycodone decreased even more sharply as generics to original Oxycontin exited the market contemporaneously with the introduction of the ADF. Canada experienced similar changes in ER oxycodone prescribing patterns after the introduction of reformulated OxyContin, and study authors noted that observed reductions in OxyContin dispensing may have been related, at least in part, to its exclusion from many provincial drug insurance plans. In Australia, OxyContin sales declined rapidly after reformulation, especially for higher strength pills (40mg, 80mg); however, OxyContin sales were already declining prior to reformulation, albeit at a slower rate. Because of the complex and constantly changing patchwork of private and public insurance coverage in the U.S., it is difficult to determine how these factors impacted OxyContin prescribing here, but formulary changes could partially explain reductions in post-reformulation sales as generic ER oxycodone exited the market. Some providers reported that patients complained about reduced efficacy or difficulty swallowing the reformulated

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product, consistent with postmarketing reports received by FDA that resulted in a safety labeling change (Warnings and Precautions: Section 5.9).

Effect of reformulation on <u>nonmedical use of OxyContin, overall and by non-oral routes</u>

Multiple published studies conducted in different populations found that the reformulation of OxyContin was associated with decreases in rates of self-reported nonmedical use of OxyContin. The findings of these studies need to be interpreted as part of the entire body of evidence on this question, including the studies conducted to fulfill PMRs 3051-1 through 3051-3 and the additional published studies using these same data sources and methods. Reviews of the PMRs and the related published studies are found elsewhere in this background package.

Published analyses of data from the National Survey on Drug Use and Health (NSDUH) found that the reformulation was associated with declines in the initiation and prevalence of nonmedical OxyContin use in the U.S.; however, neither of these studies adjusted for reductions in OxyContin dispensing post-reformulation. One study noted that the estimated prevalence of nonmedical use returned to levels similar to those seen several years prior to reformulation. An analysis of state-level NSDUH data suggested that post-reformulation changes in past-year nonmedical use of OxyContin were heavily influenced by pre-reformulation rates of nonmedical OxyContin use and oxycodone supply from manufacturers. According to this analysis, states with higher pre-existing rates of nonmedical OxyContin use experienced declines in post-reformulation nonmedical use, whereas states with lower pre-existing rates experienced increases in nonmedical OxyContin use.

Nonmedical use of oxycodone, including OxyContin, primarily occurs though the oral route, and some theorized that the crush-resistant OxyContin might prevent individuals from transitioning to non-oral routes if they were only exposed to crush-resistant formulations. However, we found no information about whether the reformulation deterred individuals from initiating non-oral abuse of OxyContin or other prescription or illicit opioids. Several U.S. studies suggest that ADF OxyContin led to a decline in nonmedical OxyContin use through non-oral routes in selected populations with a high prevalence of non-oral opioid abuse, including injection or insufflation, with some individuals reporting switching to oral abuse of OxyContin. Individuals interviewed in the Australian NOMAD cohort study reported that the reformulated product was less attractive for injection, and safe injection site data showed a large decline in the total number of visits to inject OxyContin post-reformulation.

Effect of OxyContin's reformulation on <u>broader opioid use patterns</u>

Multiple studies found that some individuals switched to other prescription opioids after OxyContin was reformulated. The evidence suggests that in some populations, individuals who had abused original OxyContin by snorting or injecting transitioned to abusing IR oxycodone via these routes. Among individuals entering treatment for opioid use disorder, one third reported that they replaced OxyContin with other drugs following the reformulation of OxyContin, including heroin, other forms of oxycodone, hydromorphone, oxymorphone, and other drugs.

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Several studies specifically examined the impact of OxyContin's reformulation on heroin overdose. Although these studies may provide some insights on shifts in abuse patterns, they did not directly measure heroin use, and the risk of overdose among those using the drug may be affected by other factors, for example the purity or potency of the opioid, increasing prevalence of heroin contamination with fentanyl or availability of naloxone. Based on the studies using NSDUH, drug shipment, and heroin mortality data, the likelihood of a shift to heroin after OxyContin's reformulation was influenced by pre-existing levels of both nonmedical oxycodone use and heroin use in the area. States with a large supply of oxycodone and higher rates of nonmedical OxyContin use and heroin deaths prior to reformulation experienced larger increases in heroin-related deaths after the reformulation, compared to other states. Several studies in both the U.S. and Australia found no clear evidence of OxyContin's reformulation increasing heroin *initiation*. In the U.S., a prospective cohort study and an analysis of NSDUH data did not find evidence of an association between reformulation and increases in heroin initiation; however, methodologic limitations preclude drawing definitive conclusions from these studies. Results from Australian studies examining shifts to heroin or injection of other opioids after reformulation were mixed. After OxyContin reformulation, the increase in average monthly visits to a Sydney safe injection site to use heroin was not statistically significant, although a visual inspection of these trends suggests some increase. Data from another Australian study showed increases in heroin-related ambulance and ED visits post-reformulation. Polysubstance abuse is common in these populations, and drug use patterns are dynamic and likely influenced by many factors, including drug availability, price, and other sociocultural factors. Nonetheless, the results of these U.S. and international studies suggest that OxyContin's reformulation may have contributed to a shift to more heroin use in certain populations and geographic areas where it was readily available.

Effect of OxyContin's reformulation on <u>opioid addiction, overdose, and related outcomes</u>

The impact of OxyContin's reformulation on the incidence or progression of opioid use disorder remains an important unanswered question. We identified no reliable, longitudinal evidence regarding the effect of OxyContin's reformulation on the risk of addiction or the progression of opioid use disorder. A difference-in-differences analysis of cross-sectional national survey data found no apparent effect of OxyContin's reformulation on the odds of prescription pain reliever use disorder.

The question of reformulated OxyContin's net impact on opioid overdose rates in the U.S. has also been exceedingly difficult to study due to the evolving and multidimensional nature of the U.S. opioid epidemic, with geographically heterogeneous increases in heroin availability and overdose, law enforcement interventions, and a multitude of policies relating to opioid analgesic prescribing, use of prescription drug monitoring programs, and naloxone dispensing. Studies examining spontaneous adverse event reports in the U.S. suggested that the reformulation was associated with a reduction in spontaneous reports of OxyContin-related deaths. However, many factors can influence spontaneous reporting over a product's lifecycle, so analyses of spontaneous adverse event reports cannot be used to make inferences on the impact of reformulated OxyContin on the risk, or incidence, of fatal overdose.

Two U.S. studies evaluated the impact of the reformulation on prescription opioid-related mortality. The first found no significant net impact of the reformulation on prescription opioid-related mortality but found that the reformulation may have led to a large increase in heroin-related mortality, based on an association

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between pre-reformulation state-level OxyContin misuse prevalence and post-reformulation increases in fatal heroin overdoses, and the lack of a similar association for other prescription pain reliever misuse. The other study estimated that the introduction of ADF OxyContin significantly reduced prescription opioid-related mortality, particularly in areas with higher exposure to oxycodone and lower exposure to heroin, suggesting that the availability of heroin might be an important factor in the effect of abuse-deterrent formulations on opioid-related mortality. This study also found a statistically significant upward inflection in heroin-related overdose mortality trends one month after the introduction of ADF OxyContin, and the increase in heroin poisoning deaths was starkest in areas with higher levels of both oxycodone use and heroin mortality prior to the reformulation. A third study using related methods assessed the impact of OxyContin's reformulation on fatal overdoses involving synthetic opioids (e.g., fentanyl) and opioids overall (including both prescription and illicit) through 2017, estimating that in the U.S., the reformulation increased overall fatal opioid overdoses by 8.7 overdoses per 100,000 individuals.

At the time of reformulation in the U.S., other efforts were being initiated to try to reduce the diversion and abuse of prescription opioids. Due to the complex mixture of concurrent interventions and secular trends in the U.S., as well as geographic differences in availability and use of OxyContin and other prescription and illicit opioids, including heroin and illicitly manufactured fentanyl, it remains difficult to determine the precise role of OxyContin's reformulation in overall opioid-involved mortality trends. Studies conducted in Australia found that the reformulation of OxyContin had little to no impact there on overdoses, ambulance runs, ED visits, calls to helplines, number of patients receiving medication-based therapy, or total treatment admissions.

Evidence of other harms associated with OxyContin's reformulation is limited. We found one study that noted an association between higher pre-reformulation OxyContin misuse rates and greater increases in post-reformulation hepatitis C infection rates at the state-level. However, such an association was not found for other prescription pain relievers in this study. We found no other studies specifically examining the impact of OxyContin's reformulation on infectious disease transmission (e.g. HIV) or other injection-related adverse outcomes (e.g., endocarditis), despite growing interest in these issues by both the National Academy of Sciences Engineering and Medicine and the Infectious Disease Society of America.

Conclusions

This review of the published literature was intended to supplement and provide context for DEPI's review of the four formal PMR studies assessing the effect of OxyContin's reformulation on abuse and overdose, and our findings must be considered in conjunction with those from the PMR studies. Published studies indicate that sales of OxyContin declined after its reformulation, in both the U.S. and other countries, although this decline may have occurred due to a variety of reasons. Rates of reported nonmedical use of OxyContin in the general U.S. population similarly declined, returning to rates observed several years before the reformulation. It remains unclear to what extent declines in OxyContin prescribing drove declines in the prevalence of its nonmedical use, versus decreases in OxyContin's abuse potential driving reduced demand and prescribing. Although the published literature in this area has serious limitations, the totality of evidence from studies employing a variety of methods suggests that OxyContin's reformulation reduced its

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attractiveness for diversion and abuse to some extent, particularly non-oral abuse in populations already abusing prescription opioids through tampering and non-oral routes.

The literature does not provide definitive answers regarding the net public health impact of OxyContin's reformulation in the U.S. We identified no reliable, longitudinal evidence regarding the effect of OxyContin's reformulation on the risk of addiction, the trajectory of opioid use disorder, or the incidence of opioid overdose. Polysubstance abuse is common, and drug use patterns are dynamic and likely influenced by many factors, including drug availability, price, and other sociocultural factors. Overall, the literature suggests that while some individuals shifted their use of OxyContin from non-oral to oral routes, others simply substituted different prescription and/or illicit opioids after OxyContin's reformulation. These apparent substitution effects varied across populations, likely reflecting heterogeneity in baseline substance abuse patterns and the availability and cost of other drugs. Some analyses suggest that OxyContin's reformulation contributed to reductions in rates of fatal overdoses involving prescription opioids in the U.S., but that these declines were offset, or more than offset, by consequent increases in fatal overdoses from illicit opioids; however, the complex mixture of concurrent interventions, secular trends, and geographical heterogeneity in opioid availability and use patterns makes it difficult to determine the precise role of ADF OxyContin in these trends.

1 INTRODUCTION

1.1 BACKGROUND

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The overarching objective of the FDA-required postmarketing study program—postmarketing required (PMR) studies 3051-1 through 3051-4—is to assess the impact of the OxyContin reformulation as an abuse-deterrent formulation (ADF) on OxyContin abuse and risk of opioid overdose in the community. To supplement and contextualize the formal PMR studies submitted by the sponsor and to better understand the broader public health impact of OxyContin's reformulation, the Division of Epidemiology (DEPI) II has conducted a review of the peer-reviewed and selected grey literature examining the impact of OxyContin's reformulation on nonmedical OxyContin use and opioid-related morbidity and mortality. Terminology and definitions around substance use vary widely in the literature. In general, we use the term *nonmedical use* to include both misuse and abuse of medications, as defined by FDA in previous regulatory documents[1]. FDA has defined *misuse* as the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed and *abuse* as the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. FDA recognizes that the term *abuse* has been identified as potentially stigmatizing to individuals with substance use disorders. This is in no way our intent; rather, we are using the term abuse as it has been previously defined specifically by FDA to describe a specific set of behaviors, or as it is used in the publications we are reviewing, when describing the findings of these studies.

1.2   REGULATORY HISTORY

Reformulated OxyContin (oxycodone hydrochloride extended-release), is a single-entity (SE) extended-release (ER) opioid product developed by Purdue Pharma L.P (Sponsor) and approved for marketing in the U.S. on April 5, 2010. Reformulated OxyContin replaced the original formulation approved on December 12, 1995. On August 5, 2010, the sponsor stopped shipping original OxyContin tablets to pharmacies, and on August 9, 2010, started shipping reformulated OxyContin tablets. In correspondence dated August 10, 2010, the sponsor notified the Food and Drug Administration (FDA) that it had ceased shipment of original OxyContin; however, pharmacies were still able to dispense their remaining stock of original OxyContin. Compared to the original formulation, data submitted by the Sponsor showed the reformulated tablet is more difficult to crush, break, or dissolve, and forms a viscous hydrogel when subjected to an aqueous environment, making it difficult to prepare for injection (see 2013 Federal Register Notice). However, abuse of OxyContin by non-oral routes, as well as the oral route, is still possible. For further details on the regulatory history of OxyContin (see OSE Summary Memorandum and Regulatory History Memorandum).

1.3   OBJECTIVES

The objective of this review was to summarize and evaluate the peer-reviewed and selected grey literature examining the impact of reformulated OxyContin on nonmedical OxyContin use and opioid-related morbidity and mortality in the United States (U.S.) and abroad. We intend the findings of this literature review to supplement DEPI's review of the formal PMR studies for OxyContin that assess the impact of reformulated OxyContin on OxyContin abuse and opioid overdose in the community.

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[1] Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-abuse-and-dependence-section-labeling-human-prescription-drug-and-biological-products-content

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2   REVIEW METHODS

We conducted our primary literature search in the National Library of Medicine's PubMed database on August 23, 2019. Appendix Table 4 provides a comprehensive list of key concepts, Boolean operators, and search terms used in our primary search, which identified a total of 143 publications. We selected search terms and Boolean operators that would limit search results to relevant observational studies involving humans. Although our interest was specifically in reformulated OxyContin, to capture publications about ADFs more generally we included search terms for other known active pharmaceutical ingredients (APIs) with formulations including abuse-deterrent properties.

On October 3, 2019, an independent DEPI reviewer conducted a secondary PubMed search to identify additional relevant studies. This review used two search strings, one limited to investigator-assigned study designs and another limited to observational study designs. Appendix Tables 5 and 6 provide a comprehensive list of key concepts, Boolean operators, and search terms used in these secondary search strings. The search excluding investigator-assigned (i.e., interventional) study designs identified 1270 publications and the search limited to observational study designs identified 1442 publications.

Prior to combining the results from the primary and secondary literature searches, each respective DEPI reviewer examined the list of publication titles to identify articles that warranted inclusion or exclusion. Overall, we aimed to include original observational quantitative and qualitative studies involving humans, including analyses of spontaneous adverse event reporting. DEPI sought additional input from the Division of Pharmacovigilance (DPV) on studies analyzing spontaneous adverse event reporting. We included review articles in our search to identify relevant articles that were not captured in our search. We did not, however, include summaries or descriptions of the review articles themselves in this document. We also included editorials related to the impact of reformulated OxyContin and broader public health considerations related to ADF opioids. Each reviewer's inclusions and exclusions were confirmed by a third independent DEPI reviewer. A total of 53 articles were selected for inclusion from the primary search and 21 articles were selected for inclusion from the secondary searches.

Finally, we included three additional economic studies from the grey literature[2] that assessed the impact of reformulated OxyContin on opioid-related morbidity and mortality. For these and other published economic studies, DEPI sought additional input from the Center for Drug Evaluation and Research (CDER), Office of Program and Strategic Analysis (OPSA) Economics Staff. Given the focus of this advisory committee meeting, we excluded studies with healthcare costs or cost-effectiveness as the primary outcome of interest and studies solely examining non-OxyContin formulations with properties to deter abuse (e.g., Hysingla, Embeda).

3   RESULTS AND REVIEWER COMMENTS

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[2] Grey literature consists of published research findings made available to the public outside of the traditional publishing and distribution channels (i.e., peer-reviewed medical, public health, and health policy journals).

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After adding observational studies from grey literature and applying exclusions, our final selection consisted of 78 articles. We categorized these articles into three main categories: PMR-related studies (15), non-PMR-related studies (31), and editorials (32). Six of the 15 PMR-related studies and nine of the 31 non PMR-related studies were funded by Purdue Pharma, the manufacturer of OxyContin, and four non-PMR-related studies were funded by Mundipharma, a pharmaceutical company affiliated with Purdue (Appendix Tables **1-2**). The non-PMR studies were further categorized based on whether they were conducted within or outside the U.S., and for the U.S. studies whether they used quantitative or qualitative methods. Methods, findings, and comments on these studies are summarized in Appendix Table 2. Tables and figures are provided to supplement select article summaries, where determined to be of value in interpreting and understanding the relevant study results.

3.1 PMR-RELATED STUDIES

Of the 78 articles we included from the peer-reviewed and grey literature, 15 used the same data sources and similar methods to the PMR 3051-1 through 3051-4 studies (Appendix Table 1). DEPI reviewers incorporated summaries and evaluations of these published PMR-related studies into the respective reviews of the related PMR studies [See Division of Epidemiology Reviews of PMRs 3051-1, 3051-2, 3051-3, and 3051-4]. Appendix Table 1 lists the 15 articles identified and the relevant PMR study reviews in which summaries of these publications can be found.

3.2 NON-PMR-RELATED U.S. STUDIES

3.2.1 Quantitative Studies

3.2.1.1 Overview of Studies

Of the 21 original non-PMR-related U.S. studies included in our review, 19 used quantitative methods (Appendix Table 2). Various quantitative study designs and data sources were used to investigate the effect of OxyContin's reformulation, on abuse-related outcomes of interest. Table 1 below provides a brief summary and description of the studies in Appendix Table 2.

Table 1. Brief description of Non-PMR-related quantitative U.S. studies

Studies	Brief Description
Hwang 2015, Severtson 2016	Used prescription claims data to estimate changes in OxyContin outpatient dispensing rates before and after the reformulation
Cheng 2018, Jones 2017, Alpert 2018	Examined changes in the prevalence of self-reported nonmedical use of OxyContin in the general population prior to and after the reformulation
Chilcoat 2016	Used prescription claims data to examine changes in rates of "doctor shopping" prior to and following the reformulation
Havens 2014, Cicero 2015	Examined self-reported post-reformulation changes in opioid drug choice and abuse behaviors in samples of individuals who had abused original OxyContin

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Lebin 2019, Severtson 2016	Used a database of anonymous online self-reports of street prices of different drugs to examine changes in OxyContin "street price" possibly resulting from the reformulation
Severtson 2016	Used drug diversion data sourced from law enforcement to examine the changes in rates of diversion cases for different products after OxyContin's reformulation
McNaughton 2014, Vosburg 2017	Used internet web posts from message boards that discussed abuse of different drugs to examine the percentage of posts endorsing abuse of OxyContin and other products before and after the reformulation
Michna 2014	Analyzed commercial medical and pharmacy claims to estimate the association between receiving an ADF opioid and subsequent opioid abuse diagnoses
Coplan 2016	Presented high-level results of 10 investigations examining the pre- and post-reformulation rates of abuse and related outcomes for OxyContin and selected comparators using multiple sources of data
Alpert 2018, Powell 2020	Used national survey and mortality data to examine state-level trends in heroin and other opioid mortality and associations with pre-reformulation rates of nonmedical use of OxyContin
Evans 2018	Used national drug product shipment and mortality data to examine state-level trends in heroin mortality and associations with pre-reformulation rates of heroin overdose fatalities and oxycodone shipment rates
Powell 2019	Used national survey and state surveillance data to examine the association between the OxyContin reformulation and rising hepatitis C infection rates at the state level
Wolff 2020	Used national survey data to investigate the association between use of original OxyContin and post-reformulation risk of heroin initiation, heroin use disorder, and pain reliever use disorder
Tuazon 2019	Used mortality data to examine changes in heroin and prescription opioid mortality rates in one state following OxyContin's reformulation
Carlson 2016	Used a prospective cohort survey study to explore trajectories of opioid abuse, including OxyContin, and risk factors for heroin initiation in a sample of people using prescription opioids nonmedically

3.2.1.2   Studies Examining the Impact of Reformulation on OxyContin Dispensing Rates, Abuse, and

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Related Outcomes

These studies reported that, compared to original OxyContin, reformulated OxyContin was associated with lower rates of Oxycontin dispensing in the outpatient setting (Hwang 2015), self-reported nonmedical use of OxyContin (Cheng 2018, Jones 2017, Alpert 2018, Havens 2014, McNaughton 2014), OxyContin "doctor shopping" (Chilcoat 2016), non-oral OxyContin abuse (Cicero 2015, Havens 2014), OxyContin "street price" (Lebin 2019, Severtson 2016), and OxyContin diversion cases (Severtson 2016). Additionally, one study found that patients using original OxyContin who switched to ADF OxyContin were less likely than those who switched to other opioids to have a subsequent medical insurance claim suggestive of opioid abuse (Michna 2014).

3.2.1.2.1 Prescription Drug Dispensing

3.2.1.2.1.1 Key Study Findings

- Hwang (2015) used IMS Health National Prescription Audit (NPA) data, a nationally representative source of outpatient retail prescription activity in the US, to investigate whether reformulated OxyContin: 1) led to a decrease in OxyContin prescription dispensing, and 2) led to the substitution of other opioid analgesics at the aggregate level. Investigators fit a regression model with OxyContin prescription counts as the outcome and adjusted for changes in dispensing of generic ER oxycodone, which began to decline in early 2010 and was removed from the market in mid-2011. OxyContin reformulation was associated with a significant decline in dispensing when adjusted for changes in generic ER oxycodone market, with an observed decrease in OxyContin dispensing of 23.8% in the first year after reformulation. Statistically significant changes in dispensing were not observed in the overall opioid market for ER and IR single entity opioid analgesic products, combined, following the reformulation. The authors hypothesized that OxyContin's reformulation may have resulted in a decline in therapeutic use of the drug. Severtson (2016) used the same data source to assess the change in prescription dispensing and also found that OxyContin prescriptions dispensed had decreased five years after the reformulation. Findings from Severtson (2016) differed from Hwang's, noting an increase in prescriptions dispensed for other opioid analgesics following the OxyContin reformulation up until the end of the study period in 2015.

3.2.1.2.1.2 Reviewer Comments

Hwang (2015) adds to our understanding of changes in the ER oxycodone market around the time of the OxyContin reformulation, in that investigators adjusted for market changes that took place at the same time (i.e., decline in the availability of generic ER oxycodone products). For OxyContin, Hwang (2015) reported a decline in OxyContin prescription dispensing 12 months following the reformulation after adjusting for generic ER oxycodone prescriptions, and Severtson (2016) reported an ongoing decline in dispensing rates over five years following the reformulation. Observed differences between Severtson (2016) and Hwang (2015) with regard to prescriptions dispensed for other opioid analgesics were likely due to differences in time periods examined, as Severtson examined prescription dispensing for a longer period of time following the reformulation. Findings
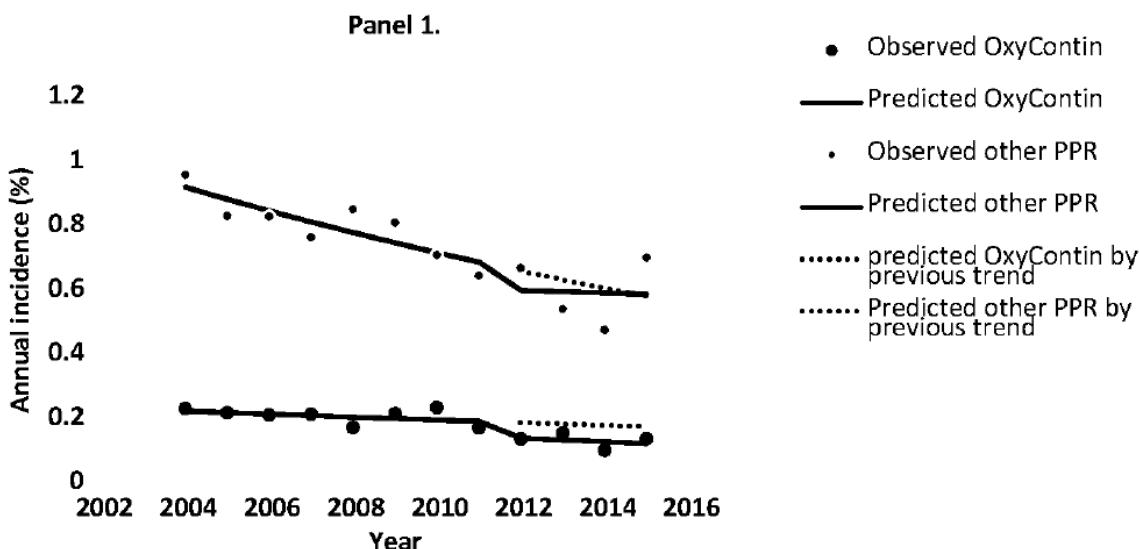
by Severtson (2016) appear to agree with the longer-term trends in OxyContin prescription dispensing rates as reported in the [DEPI Drug Utilization Review](#).

3.2.1.2.2 Nonmedical use of OxyContin

3.2.1.2.2.1 Key Study Findings

Using serial cross-sectional survey data from the National Survey on Drug Use and Health (NSDUH), Cheng (2018) conducted interrupted time series (ITS) analyses to examine the effect of the reformulation on initiation of nonmedical use of OxyContin in community-dwelling U.S. residents. The analysis found a slightly lower modeled rate of OxyContin nonmedical use initiation in 2012 compared to the predicted rate based on pre-reformulation trends in the nonmedical use of OxyContin and other prescription pain relievers (Figure 1).

Figure 1: Past-year Initiation of OxyContin and other Prescription Opioid (PPR)* Nonmedical use based on Observed and Predicted Estimates, U.S., NSDUH, 2002-2016

Source: Cheng, H.G. and P.M. Coplan, Incidence of nonmedical use of OxyContin and other prescription opioid pain relievers before and after the introduction of OxyContin with abuse deterrent properties. Postgrad Med, 2018. 130(6): p. 572, Figure 1, Panel 1.

*Other prescription opioid (PPR) include: Darvocet, Darvon, Tylenol with codeine, Demerol, Dilaudid, Fioricet, Fiorinal, Hydrocodone, Methodone, Morphine, Phenaphen, Propoxyphene, SK65, Stadol, Talacen, Talwin, Talwin-nX, Tramadol, Ultram

- Jones (2017) also used NSDUH data to examine past-year nonmedical use of OxyContin prior to and after the reformulation in community dwelling adults. This study found that the prevalence of nonmedical OxyContin use was lower in 2013 (0.5%) compared to 2010 (0.7%; p<0.05), yet the 2013 rates were similar to those observed in the earlier period spanning from 2006 to 2009. The study also found that nonmedical use of OxyContin among those meeting criteria for past-year pain reliever abuse/dependence increased numerically from 2006 to 2010, and then declined from 2011 to 2013; however, these changes were not statistically significant. Neither of these studies (Cheng 2018, Jones 2017) adjusted for the reduction in availability (i.e., number of prescription or tablets dispensed) of ER oxycodone, as described in the study by Hwang, above.

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- As part of a broader study examining OxyContin nonmedical use and heroin mortality rates, Alpert (2018) also examined the changes in self-reported past-year nonmedical OxyContin use using state-level NSDUH data in two-year periods, spanning from 2004 to 2013, defining each state's pre-reformulation OxyContin misuse rate as the population-weighted rate of past-year nonmedical OxyContin use based on pooled NSDUH data from 2004 through 2008. The authors found that the rate of past-year OxyContin misuse declined by more than 50% after the reformulation in states with the highest initial OxyContin misuse, yet the rate of OxyContin misuse *increased* slightly in states with the lowest rates of initial OxyContin misuse.

3.2.1.2.2.2 Reviewer Comments

Cheng (2018), Jones (2018), and Alpert (2018) studies found evidence of a modest decrease in both the initiation and prevalence of OxyContin nonmedical use following the reformulation, based on national survey data, although Alpert's analyses suggested that the change varied considerably by state, based on pre-reformulation levels of nonmedical use of OxyContin. A strength of these studies is that they used data from a nationally representative survey, and therefore it is valid to assess estimated trends of nonmedical use over time. Nonetheless, as only community-dwelling individuals are surveyed, important subgroups may not be represented well, including those with advanced OUD who may be in treatment for drug use disorders, incarcerated, homeless, or otherwise not captured in this survey of the non-institutionalized general population. Additionally, the "nonmedical use" measure is broad, encompassing behaviors such as taking a friend or family member's pill to relieve pain or aid with sleep, as well as taking the drug for its euphoric effect, and therefore does not directly measure non-oral abuse behaviors that were the target of the reformulation. Route of administration is not collected at the level of the drug product, and information on individual comparator opioid products (with the exception of Vicodin) was not collected in the survey. Although NSDUH data provide some important information on nonmedical use patterns of OxyContin and other prescription pain relievers in the general population, these trends may be closely tied to prescribed availability and other broad secular changes. Given the lack of information on individual comparator drug products and route of administration, it is difficult to attribute changes in the NSDUH data to the abuse-deterrent properties of reformulated OxyContin. It is likely that observed declines in OxyContin nonmedical use and some other abuse-related outcome rates may be due largely to the decline in prescriptions dispensed, and it is not entirely clear how much of the decline in OxyContin dispensing was directly caused by the reformulation's deterring abuse (i.e., a reduction in demand due to reduced interest in the drug for abuse or diversion) versus other factors, such as the 2010 OxyContin Risk Evaluation and Mitigation Strategy (REMS), or changes in insurance reimbursement policies. An adjustment of prescriptions dispensed would be helpful in determining whether the observed decline in nonmedical use prevalence persisted after accounting for reduced availability in the community.

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3.2.1.2.3 Impact of OxyContin Reformulation on Abuse of OxyContin and Other Opioids and on Opioid Abuse-related Insurance Claims

3.2.1.2.3.1 Key Study Findings

- Havens (2014) reported results from a serial cross-sectional interview study measuring past-month abuse of different oxycodone drug formulations from December 2010 to September 2011 in Kentucky in different samples of individuals who reported having abused ER oxycodone in the six months prior to OxyContin's reformulation (Havens 2014). Participants were surveyed about their abuse of OxyContin 30 days prior to the reformulation, which was four months before the start of the study period. These retrospective surveys indicated that most participants reported abusing original OxyContin (74%) and IR oxycodone (74%) in the month prior to the reformulation (Havens 2014). Reported 30-day prevalence of OxyContin abuse decreased significantly from the time of the reformulation to a later time period spanning from December 2010 to September 2011. This was true for overall abuse (Risk Ratio [RR] 0.45; 95% Confidence Interval [CI] 0.35, 0.56), snorting (RR 0.14; 95% CI 0.07, 0.26) and injecting (RR 0.01; 95% CI 0.002, 0.09). In comparison, reported non-ADF IR oxycodone abuse significantly increased from shortly after the reformulation to one year following reformulation. This was true for overall abuse (RR 1.30; 95% CI 1.19, 1.42) as well as snorting (RR 1.50; 95% CI 1.31, 1.72) and injecting (RR 1.64; 95% CI 1.36, 1.99), with the greatest increase seen for injection abuse.

- Cicero and Ellis (2015) conducted a survey of a convenience sample of individuals entering treatment for opioid use disorder (OUD) to examine the impact of ADF OxyContin on abuse patterns. In this group (n=153), one-third reported continuing abuse of OxyContin after the reformulation, another third reported replacing OxyContin with other drugs as a result of the reformulation, with 70% of those who reported switching drugs reporting switching to heroin. Approximately 3% reported that the reformulation led them to stop using opioids. Among participants who reported abuse of both OxyContin formulations 43% reported switching from injecting/inhaling the drug to swallowing it whole following the reformulation, while 34% reported being able to defeat the abuse deterrent properties and continuing to inject/inhale the drug. These study results are described in more detail in the Review of OxyContin PMR 3051-3.

- McNaughton (2014) examined internet web postings from message boards related to abuse of specific products, including OxyContin, Vicodin, and Dilaudid, comparing posts endorsing abuse of content in the period (June 2008 - July 2010) to the period (August 2010 – September 2012). Investigators found that 43% of OxyContin-related posts endorsed (i.e., encouraged) abuse of the product in the pre-reformulation period compared to 22% of OxyContin-related posts endorsing abuse of the product in the post-reformulation period. For posts that mentioned Vicodin or Dilaudid, the percent of posts that endorsed abuse of these respective products did not change from the pre-reformulation (Vicodin: 36%, Dilaudid: 46%) to post-reformulation period (Vicodin: 35%, Dilaudid: 47%). Another analysis of web posts from 2009 to 2014 explored whether the posts suggested that after the reformulation, those abusing OxyContin continued to abuse it or switched to another formulation of oxycodone or another substance altogether (Vosburg 2017). According to this study,

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some users reported tampering with the reformulated product to continue abusing it, while many reported switching to non-ADF IR opioids or, in some cases, to heroin (Vosburg 2017).

- Michna (2014) used a retrospective cohort design in a commercially insured population ages 18 to 64 years to examine switching patterns and rates of "opioid abuse" diagnosis claims, based on use of original versus reformulated ER oxycodone products. The study found that 31% of patients dispensed ER oxycodone did not switch to ADF OxyContin, but rather switched to either non-ADF Extended-Release/Long-Acting (ER/LA) opioids (21.3%) or had no further insurance claims for ER/LA opioids (9.3%). Of those who discontinued ER/LA opioids, 76% switched to IR/SA opioids, with the remaining 24% having no further insurance claims for opioids. Compared to patients who received the reformulated products, higher rates of subsequent medical insurance claims suggestive of opioid abuse were observed in patients who either switched to non-ADF ER/LA opioids (6.7% vs. 3.5%, RR: 1.9, p<0.001) or discontinued ER/LA opioid treatment (10.9% vs. 3.5%, RR: 3.1, p<0.001), agnostic of whether they switched to IR/SA opioids or had no further prescription opioid claims during the study period. The rate of medical insurance claims suggestive of opioid abuse was highest among those who switched from ER oxycodone to IR/SA opioids, and the claim rate in this group was more than three times higher than that of patients who switched to reformulated ER Oxycodone.

3.2.1.2.3.2 Reviewer Comments

- *Studies by both Havens (2014) and Cicero and Ellis (2015) found a decline in OxyContin abuse via non-oral routes in non-representative, enriched samples, with substantial switching to other available opioids. Cicero and Ellis (2015) also reported that the reformulation resulted in some people who abused OxyContin switching from injection or inhalation of OxyContin to oral abuse of the drug. A strength of both the Havens (2014) and Cicero and Ellis (2015) studies is that they examined changes in both overall and route-specific patterns of abuse following OxyContin's reformulation. Another strength of both these studies is that they gathered information on substance and route of abuse from talking to participants directly, rather than through secondary analysis of healthcare or internet data. Because these were cross-sectional studies relying on recollection of past abuse behaviors, they may be subject to reporting or recall bias, as current users of different products may report their past use differently. In the Cicero study, individuals were surveyed nearly four years following the time of the reformulation, which could lead to substantial recall bias as people currently abusing prescription or illicit opioids may report past abuse behaviors more or less accurately than people not currently using opioids. Findings from both of these studies may not be generalizable to other populations abusing opioids. Cicero's sample was limited to individuals entering treatment for OUD, and Havens' study sample was recruited with advertising flyers, and participants who were eligible were asked to recruit up to three friends or others who would be appropriate participants, an approach referred to as purposive sampling technique. Although purposive sampling is effective in obtaining eligible participants, it has inherent biases in that the study sample is not randomly selected, and subjects who are recruited may be similar and influenced by each other. Finally, because the study sampled individuals over a short period of time after the*

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reformulation, it does not provide information on longer term evolution of abuse patterns in this population. Nonetheless, these studies still provide some fairly compelling evidence that in these selected, high-risk populations, the reformulation was associated with a reduction in OxyContin non-oral abuse, accompanied by some increase in non-oral abuse of IR oxycodone, heroin, or other drugs.

- *McNaughton (2014) found that the percentage of OxyContin-related web posts endorsing (i.e., encouraging) abuse of the product declined after the reformulation yet observed no change in this percentage for Vicodin and Dilaudid over the same period of time. A study by Vosburg (2017) found that many reported switching to non-ADF IR opioids or heroin following the reformulation of OxyContin. Both of these studies (McNaughton 2014, Vosburg 2017) used novel methods, such as text matching queries, to examine reports of pre and post-reformulation abuse of specific products in a different group of people than those captured in household surveys or assessments of individuals entering substance abuse treatment. Because the internet is dynamic, it is not clear how these samples represent the behaviors of individuals who abuse OxyContin or other opioids or if these estimates represent a consistent subset of the population that uses the internet. Therefore, it is unclear whether these types of data are valid for quantitatively assessing trends in abuse practices within the community. Additionally, both these studies assumed that endorsement of OxyContin in the post-reformulation period pertained to the ADF product based on the timing of the posts. While it is likely that most post-reformulation OxyContin posts referenced the ADF product, there is still a possibility that users may have been referencing an illicitly acquired or previously stored original OxyContin formulation that was used in the post-reformulation period.*

- *Michna (2014) found that nearly a third of patients dispensed ER oxycodone switched to a non-ADF ER/LA or IR/SA opioids, and that those who switched to either non-ADF ER/LA or IR/SA opioids or who had no further prescription opioid claims were more likely to have subsequent medical insurance claims suggestive of opioid abuse, compared to those who switched to ADF OxyContin. A strength of this study was the use of a cohort design, which collects both exposure and outcome data at the level of the individual. The study was also informative in its descriptive results regarding the percent of individuals initially prescribed OxyContin who continued to receive prescriptions for OxyContin following the reformulation, switched to other ER/LA opioids or IR/SA opioids, or stopped filling opioid prescriptions altogether. A limitation, however, is that the study relied only on prescription claims and therefore did not capture cash purchases or claims submitted to other insurers. Investigators also did not compare switching patterns observed in the post-reformulation period to switching patterns of prescription opioids in a time period preceding the reformulation. The authors used ICD-9-CM codes to determine the incidence of opioid abuse claims but did not validate the algorithm used. A study by Carrell (2020) reported results from an FDA-required postmarketing study assessing the validity of ICD-9 diagnosis codes for abuse or addiction outcomes found that, among patients receiving an ER/LA opioid analgesic, code-based algorithms for abuse/addiction performed very poorly, i.e., they did not accurately identify patients who actually were identified as having opioid abuse or addiction based on manual review of the medical record. This poor performance of insurance claims may reflect the reality that substance abuse is often not*

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brought to medical attention or well documented, is associated with stigma, and may be poorly covered by insurance. Therefore, claims-based measures of abuse or addiction that rely only on ICD-9-CM codes are not useful for quantitative analyses of abuse or addiction in patients prescribed opioid analgesics.
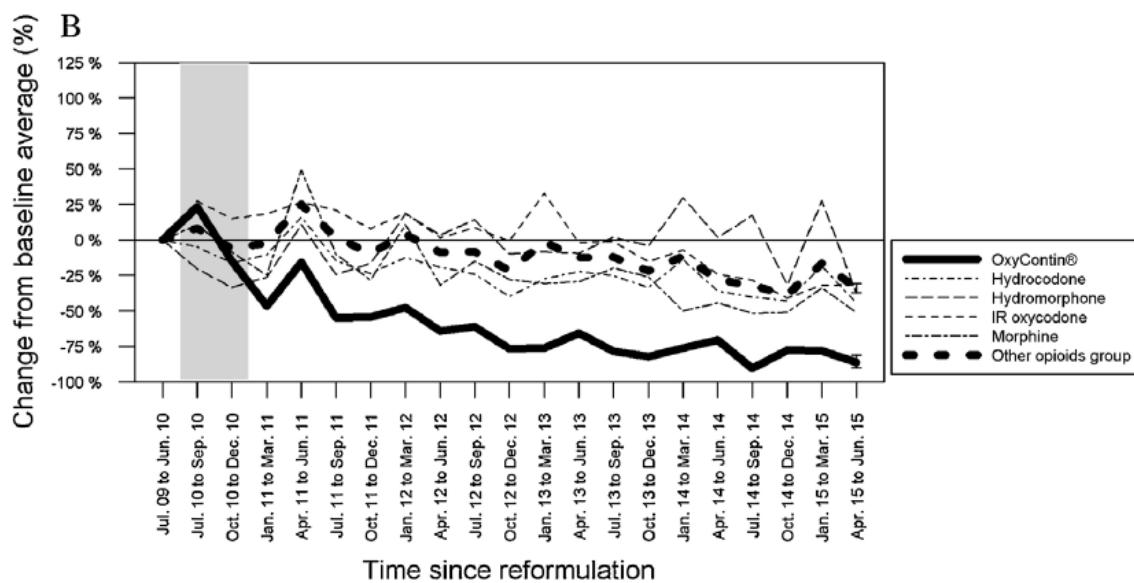
3.2.1.2.4 Street Prices and Drug Diversion of OxyContin and Other Drugs Following OxyContin's Reformulation

3.2.1.2.4.1 Key Study Findings

One cross-sectional study (Lebin 2019) examined the factors that influenced street prices of diverted oxycodone and oxymorphone using data collected from the crowdsourcing website, StreetRx, on which individuals can anonymously report street prices paid for diverted prescription drugs. The investigators compared prices reportedly paid for crushable versus crush-resistant oxycodone products between August 22, 2014 and June 30, 2016. After adjusting for time of year, dosage strength, and bulk purchase, the price of crushable oxycodone was 19.5% higher than that of crush-resistant formulations (95% CI: 14.3%, 24.9%, p<0.001).

Severtson (2016) also used Street Rx to analyze the changes in price during the five years following OxyContin's reformulation. Investigators compared prices of SE oxycodone, original OxyContin, and reformulated OxyContin, separately, from 2011 to 2015, normalized by milligram strength of unit purchased based on price per milligram. According to this study, the price of single entity oxycodone, original OxyContin, and ADF OxyContin all decreased from 2011 to 2015. The observed price difference between original and ADF OxyContin also decreased over time, from 36% higher for original OxyContin in 2011 to 13% higher for the same formulation in 2015. Additionally, this study used data from the RADARS drug diversion program, which estimates drug diversion by recording drugs involved in law enforcement cases arising from arrests or street buys. Investigators compared the rate of cases involving OxyContin and those involving other individual opioids in the year prior to the reformulation to the modeled rate for the second quarter of 2015, based on the slope of post-reformulation quarterly rates. Investigators estimated quarterly prescription rates using the projected number of prescriptions dispensed based on the method used by IMS Government solutions. The prescription-adjusted rate of OxyContin diversion cases decreased by 85.8% following the reformulation (95 CI: -89.7, -80.5), with rates declining by 8.3% each quarter after the reformulation (95 CI: -10.6, -6.1). Comparatively, the prescription-adjusted rate for cases involving other opioids (IR oxycodone, IR/ER hydrocodone, IR/ER morphine, IR/ER hydromorphone, IR/ER tramadol, IR/ER oxymorphone, IR/ER tapentadol) decreased by 31.7% following the reformulation (95 CI: -40.3, -21.8), with rates declining by 2.7% per quarter (95 CI: -3.6, -1.8) following the reformulation (Figure 2).

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Figure 2: Relative Change in Rate of Diversion Cases for OxyContin and Other Opioids*, Drug Diversion Program, 2009-2015

Source: Severtson GS, et al., Sustained reduction of diversion and abuse after introduction of an abuse deterrent formulation of extended release oxycodone. Drug Alcohol Depend, 2016. 168: p.225 Figure 3B. *Other Opioid group is comprised of IR oxycodone, IR and ER hydrocodone, IR and ER morphine, IR and ER hydromorphone, IR and ER tramadol, IR and ER oxymorphone, and IR and ER tapentadol

Chilcoat (2016) used pharmacy claims data from the IMS LRx database, to examine rates of "doctor shopping," defined as an individual obtaining prescription from at least two unique prescribers and three unique pharmacies during "overlap events," defined as at least one day of overlap between prescriptions based on start date and days' supply. The doctor-shopping rate was determined by estimating the number of individuals meeting the definition of doctor shopping divided by the number of individuals with a prescription for the product for each six-month calendar period. This study compared the doctor shopping rate for each product from a pre-reformulation period (3Q2009 to 2Q2010), to a post-reformulation period (1Q2011 to 2Q2013). Comparing pre- versus post-reformulation time periods for OxyContin and comparators (IR hydromorphone, IR oxycodone APAP, IR hydrocodone APAP, benzodiazepines, ER Morphine, IR oxycodone SE, ER oxymorphone), the rate of "doctor shopping" decreased 50% (95 CI: -53%, -47%) for OxyContin, but a similar decline was not observed for comparators.

3.2.1.2.4.2 Reviewer Comments

- *The Lebin (2019) study found that the price of crushable oxycodone was nearly 20% higher than the price of crush-resistant oxycodone formulation, after controlling for dosage strength. A limitation of this study, however, is that it only examined the prices of different products between August 2014 and June 2016, four to six years after the OxyContin reformulation, and so it was unable to compare street price for original OxyContin to IR oxycodone of the same dosage strength. Because the study analyzed prices for crushable and crush-resistant formulations of oxycodone several years following the reformulation, it is likely that the crushable oxycodone estimates largely reflect IR oxycodone prices, as original OxyContin was not likely to be easily available during the period examined. We are unaware as to whether the population of individuals who purchase opioids illicitly are well-*

represented in this sample, as these data represent individuals who have access to the internet and voluntarily choose to report street price over the internet. Furthermore, these data cannot be verified, and there has been no formal validation of how illicit drug prices sourced from StreetRx represent the actual prices paid by individuals who use prescription opioids illicitly.

- *Severtson (2016) provided information on the street price of specific oxycodone products from 2011 to 2015, finding that the observed price difference between original and ADF OxyContin decreased in the first 5 years following the reformulation. There was no baseline pre-reformulation period for comparison and given a lack of original OxyContin dispensing during the study period, it is unclear how to interpret these findings. The study also found that the utilization-adjusted rates of drug diversion cases involving OxyContin declined more than that of other prescription opioids. Drug diversion data sourced from law enforcement is a measure of law enforcement activity comprised of a convenience sample of law enforcement reporting agencies. Other factors such as changes in reporting procedures or jurisdictional priorities may also impact the ability of law enforcement to detect and record the diversion of different drugs. It is also possible that the illicit prescription drug market could shift to new jurisdictions in response to law enforcement efforts and other unmeasured factors. Another difficulty with interpreting these data is that these reports represent a variety of types of cases (e.g., street sales, forged scripts, Medicaid fraud, pill mill crackdowns, pharmacy thefts), it is not clear how accurately products are identified, and the volume of the product involved in each case is also not specified. While we must consider the limitations of the data sources in interpreting the findings discussed here, this study does suggest that the reformulation of OxyContin was associated with some degree of reduction in drug diversion, at least among reporting locations. The findings regarding whether the reformulation was associated with a decline in street price are less clear, however, due to the study investigating drug prices starting in 2011, a few months after the introduction of the reformulation.*

- *Chilcoat's (2016) study found that while the rate of "doctor shopping" decreased significantly for OxyContin, a similar decrease was not observed for other opioid analgesics over the same period. The use of a large database of retail pharmacy claims to examine "doctor shopping" rates with use of comparator opioids provides some useful information about trends in potential aberrant patient behaviors involving these products. However, it is important to consider that "doctor-shopping" metrics are not necessarily a measure of abuse or abuse-related outcomes, as they rely on an assumption that all individuals seeking drugs for abuse are seeking these substances from multiple prescribers and multiple pharmacies to avoid detection. It assumes that there is no legitimate reason for a patient to get opioids from multiple prescribers or pharmacies during a short time-period, such as the patient having to be seen at the same practice by different prescribers. While it is likely that some individuals who engage in this behavior are seeking drugs for the purpose of abuse or diversion, the exact relationship between the number of doctors and/or pharmacies associated with overlapping prescriptions for a product and the probability of abuse or diversion of that product has not been well characterized. Findings from the Extended-release/Long-Acting Opioid Analgesic*

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PMRs 3033-8, 3033-9, and 3033-10[3] suggest that doctor/pharmacy shopping metrics correlate with (i.e., are statistically associated with) various measures of abuse and addiction; however, they do a poor job of identifying these behaviors or diagnoses (i.e., distinguishing people with vs without the behaviors or diagnoses indicating nonmedical use of or addiction to opioids.

3.2.1.2.5 Coplan 2016: Selected Results of Studies Evaluating the Impact of OxyContin Reformulation

Coplan (2016) presented selected results from ten different investigations seeking to answer the question of whether the OxyContin reformulation resulted in lower rates of OxyContin-related adverse outcomes (abuse, misuse, overdose, death, doctor shopping, opioid use disorder, and drug diversion). Although not technically a review article, the selected findings reported in this paper are derived from studies for which results were also published in separate publications reviewed elsewhere in this document (Havens 2014, Severtson 2015, Cicero and Ellis 2015) or in the reviews of the formal PMR studies, as noted below:

- Butler 2013, Cassidy 2014, Butler 2011, Cassidy 2017: Described in Division of Epidemiology Review PMR 3051-1
- Severtson 2013, Coplan 2013: Described in Division of Epidemiology Review PMR 3051-2
- Cicero and Ellis 2012, Cicero and Ellis 2015[4], Dart 2015: Described in Division of Epidemiology Review PMR 3051-3
- LaRochelle 2015: Described in Division of Epidemiology Review PMR 3051-4

3.2.1.3 Studies Evaluating the Impact of OxyContin's Reformulation on Heroin Initiation, Fatal Overdose, and Hepatitis C Rates

Studies have reported that the reformulation of OxyContin was associated with increases in heroin mortality (Alpert 2018, Evans 2018, Powell 2020, Tuazon 2019) and synthetic opioid mortality (Powell 2020), as well as rising rates of acute Hepatitis C infections (Powell 2019). However, a serial cross-sectional study (Wolff 2020) found no increased risk of heroin initiation or heroin use disorder in those reporting previous nonmedical use of original OxyContin when compared to those who misused other prescription opioids prior to OxyContin's reformulation. Finally, one prospective cohort of young adults who misused prescription opioids found prior OxyContin use to be universal among those who transitioned to heroin, but it did not specifically find OxyContin's reformulation to be associated with increases in heroin initiation rates.

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[3] https://www.fda.gov/media/95546/download

[4] Part of this study is related to PMR 3051-3 and is discussed both here and in the Review of OxyContin PMR Final Study Report 3051-3

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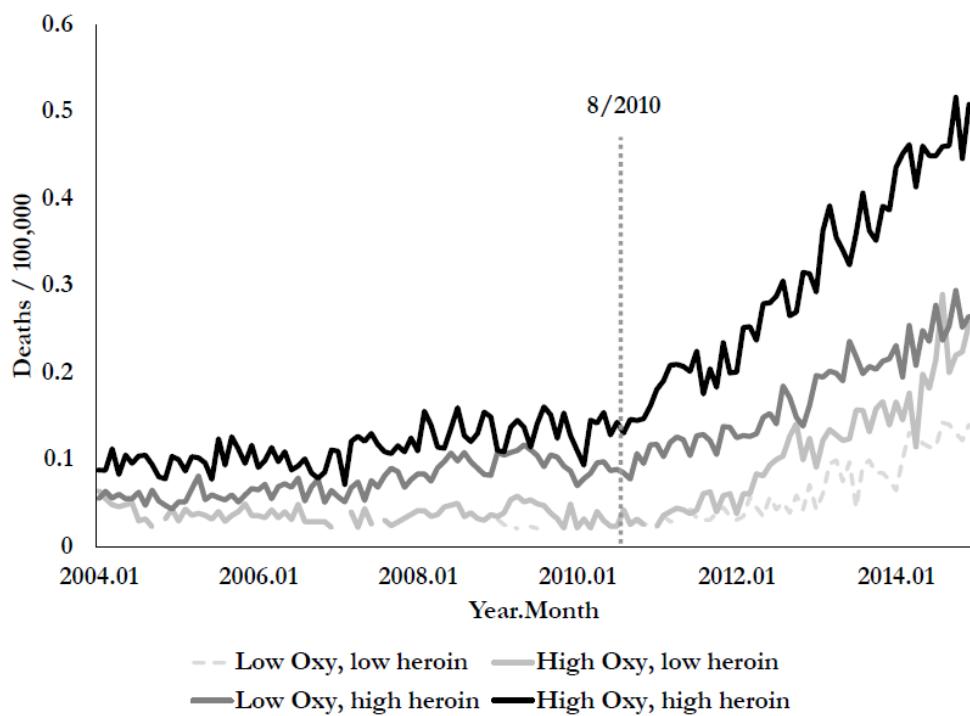
3.2.1.3.1 Quantitative Research Based on Difference-in-Differences, Event Study, and Structural Break Techniques

3.2.1.3.1.1 Key Study Findings

We reviewed five studies (Alpert 2018, Evans 2019, Powell 2019, Powell 2020, Wolff 2020) examining the impact of OxyContin reformulation on various relevant public health outcomes, such as heroin initiation, deaths due to heroin or other opioids, and hepatitis C infection rates, using methodological approaches commonly found in economics and other social sciences, including difference-in-differences, event study methods, and structural break techniques. Four of these studies (Alpert 2018, Evans 2019, Powell 2019, Powell 2020) conducted analyses at the state-level, defining pre-reformulation OxyContin misuse based on individual states' rates of non-medical use in NSDUH or state oxycodone shipments per 100,000 persons. One study examined associations between pre-reformulation OxyContin use and the pre vs. post-reformulation change in prevalence of heroin initiation, heroin use, heroin use disorder, and pain reliever misuse using NSDUH data (Wolff 2020). The analytical methods used in these studies are described in further detail in Appendix 7.

- Three studies investigated the association of the reformulation with rising heroin mortality rates. Alpert (2018) found that states with higher pre-reformulation OxyContin nonmedical use rates (2004-2009) had higher rates of heroin-related opioid deaths in the post-reformulation period, finding that each additional percentage point of OxyContin nonmedical use during the pre-period (2004-2009) was associated with 2.5 to 3.1 additional heroin-related deaths per 100,000 people in the post-period. In a follow-up analysis, Powell (2020) also found that overdose deaths involving synthetic opioids or cocaine increased more from 2013-2017 in states that had had higher pre-reformulation rates of OxyContin misuse, compared to states with lower pre-reformulation OxyContin misuse rates. States with one standard deviation higher rate of OxyContin misuse in the pre-period experienced 4.6 additional synthetic opioid overdoses and 1.3 additional cocaine overdoses per 100,000 individuals, respectively. Powell's analysis also found that any declines in natural/semi-synthetic opioid deaths were more than offset by an increase in heroin and fentanyl-involved overdoses, leading to a net increase in fatal opioid overdoses. Both studies found no association between higher rates of nonmedical use of other prescription pain relievers and increases in heroin, synthetic opioids, and overall opioid overdose deaths,

- Evans (2019) found a statistically significant trend break indicating an increase in heroin-related mortality occurring one month after the introduction of ADF OxyContin. To explore the impact of heroin and oxycodone availability prior to the reformulation, investigators grouped states into four separate categories based on pre-reformulation state-level heroin death rates and per-capita oxycodone shipments. Investigators found that the increase in heroin poisoning encounters and heroin death was greatest in areas with high levels of oxycodone use *and* high rates of heroin mortality prior to the reformulation, based on median per-capita oxycodone shipments and pre-reformulation mortality rates (**Figure 3**).

Figure 3: Monthly Heroin Death Rate by Pre-reformulation OxyContin shipments and Heroin Mortality, 2004-2014, U.S.
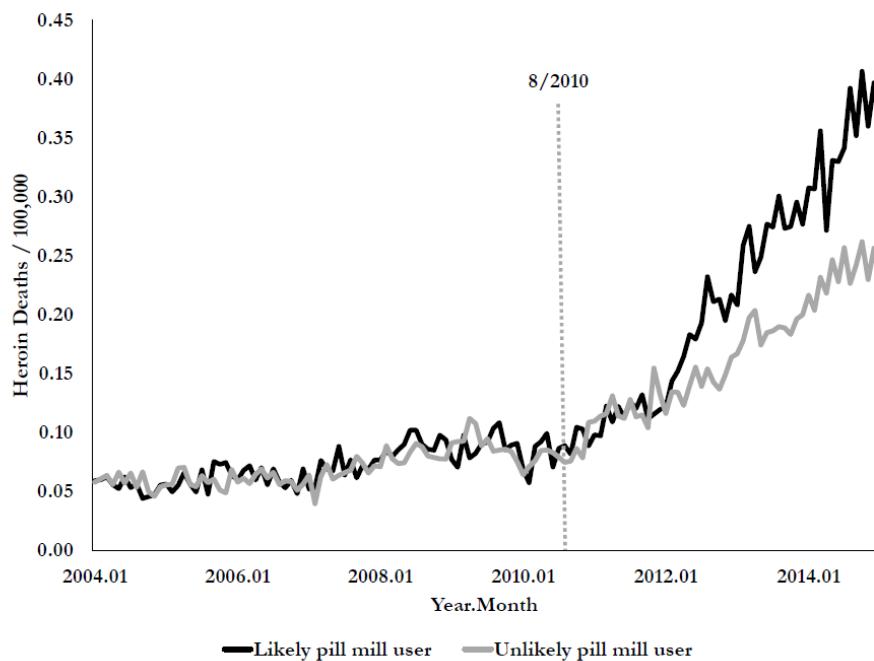

Source: Evans, W.N., E.M.J. Lieber, and P. Power, Replication data for: "How the Reformulation of OxyContin Ignited the Heroin Epidemic". 2018, Harvard Dataverse. p.30, Figure 3.

The Evans (2019) study also featured several different sensitivity analyses to determine whether other concurrent policies, particularly as the Florida pill mill crackdown, could explain some of these findings. The authors grouped Florida and eleven other states[5] that may have been impacted by the Florida pill mills and compared these states to other states that they considered not impacted by the Florida pill mills. They found that trends in heroin mortality among these two groups were very similar before the reformulation, and that both groups experienced a large change in slope coinciding with marketing of the reformulation (August 2010). However, while they found that the break in trend of heroin mortality in "non-pill mill states" occurred in August 2010, the break in trend in pill mill states occurred in October 2011; the same month in which all components of the Florida pill mill crackdown went into effect (**Figure 4**). Based on these findings, the authors concluded that the pill mill crackdown likely caused some, but a relatively small portion, of the rise in heroin mortality rates.

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[5] Alabama, Indiana, North Carolina, West Virginia, Pennsylvania, Rhode Island, Maine, New Jersey, Maryland, Mississippi, New York

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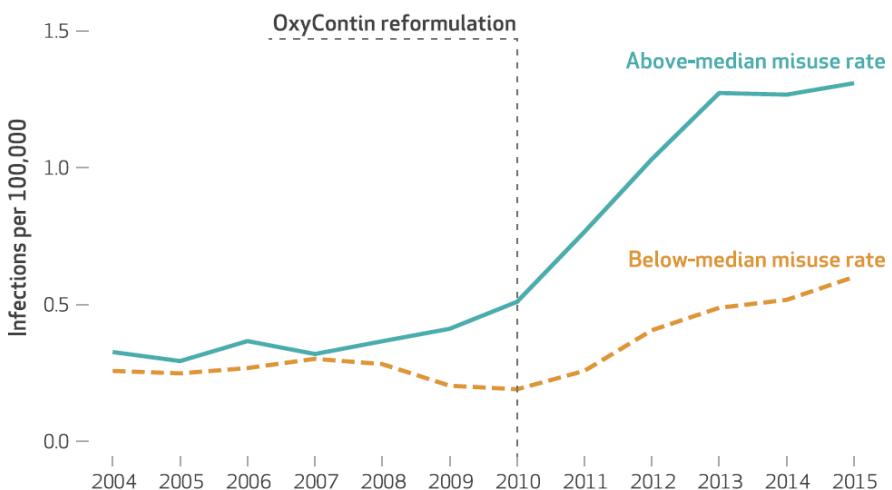
Figure 4: Monthly Heroin Death Rate for States affected and not Likely Affected by the Florida Pill Mill Crackdown, 2004 to 2012 U.S.

Source: Evans, W.N., E.M.J. Lieber, and P. Power, Replication data for: "How the Reformulation of OxyContin Ignited the Heroin Epidemic". 2018, Harvard Dataverse. p.35, Figure 12.

- Powell (2019) evaluated the relationship between the reformulation of OxyContin and hepatitis C infections and found that by 2015, five years after the introduction of the ADF OxyContin, each percentage point increase in non-medical OxyContin use prior to the reformulation was associated with an increase in hepatitis C infections by 1.32 cases per 100,000 inhabitants following the reformulation (**Figure 5**). Investigators also examined the association of pre-reformulation rates of nonmedical use of other pain relievers and hepatitis C infection rates and found no association between higher rates of nonmedical use of other pain relievers and greater increases in hepatitis C infections.

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Figure 5: Rate of Acute Hepatitis C Infection per 100,000, by State Rate of Nonmedical OxyContin Use Pre-reformulation, 2004-2015, U.S.

Source: Powell, D., A. Alpert, and R.L. Pacula, A Transitioning Epidemic: How the Opioid Crisis Is Driving the Rise In Hepatitis C. Health affairs (Project Hope), 2019. 38(2): p. 287.

- Using serial cross-sectional NSDUH data, Wolff (2020) compared adults who misused OxyContin prior to the reformulation to those who misused other prescription pain relievers (but not OxyContin) during the same time period, defining pre-reformulation use based on past reported use prior to 2011. Using a difference in differences design, they found that pain reliever misuse declined in both groups from the pre- to the post-reformulation period; the decline, however, was greater among people who misused OxyContin pre-reformulation relative to people who misused other prescription pain relievers (Odds Ratio [OR]: 0.79, 95 % CI 0.69, 0.90). Similarly, they found that heroin initiation increased in both groups post-reformulation, but the increase was smaller among people who misused OxyContin pre-reformulation (OR 0.42, 95% CI: 0.22, 0.82). There was no statistically significant difference between groups in the pre- to post-reformulation change in odds of prescription pain reliever use disorder, reported heroin use, or heroin use disorder.

3.2.1.3.1.2 Reviewer Comments

Alpert (2018) and Powell (2020) found that states that had higher rates of pre-reformulation nonmedical use of OxyContin had greater increases in fatal overdoses involving heroin, and later, synthetic opioids (e.g., illicitly manufactured fentanyl). Both of these studies aimed to answer an important question regarding the net public health impact of OxyContin's reformulation using available sources of data; however, because these analyses are ecologic in nature, they are not able to determine whether these increases were the direct result of individuals switching from OxyContin to illicit opioids because of the reformulation, rather than other differences at the state level, such as changing availability or potency of illicit opioids or impacts of pill mill crackdowns or other interventions restricting the supply of prescription opioids. Additionally, while it is possible that the reformulation may have indirectly contributed to the rise in synthetic opioid overdose deaths, it is difficult to clearly attribute this increase to the reformulation, as the rise in synthetic opioid

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mortality was not observed until three years after the OxyContin reformulation and may have been influenced by many other intervening factors.

- *Evans (2019) found that the OxyContin reformulation contributed to higher heroin mortality rates in states where there were higher rates of oxycodone shipments and heroin mortality prior to the reformulation, and that there was an inflection point in heroin mortality trends that occurred at the time of reformulated OxyContin's market introduction. A strength of this study was that the impact of the reformulation was measured separately by grouping states based on both pre-reformulation oxycodone shipments and heroin mortality, with both of these serving as proxies for community-level availability of these drugs. A limitation was that investigators relied on oxycodone shipments rather than OxyContin sales or dispensing, specifically, or actual rates of OxyContin nonmedical use. Another strength was the sensitivity analyses that suggested that the actions to close Florida pill mills did not explain most of the rise in heroin mortality rates. In aggregate, these data suggest that the availability of heroin or other substitutes might be an important factor in the net public health impact of abuse-deterrent formulations.*

- *Powell (2019) found that higher rates of pre-reformulation nonmedical OxyContin use were associated with greater increases in the rate of acute hepatitis C at the state level, but that this association was not seen for nonmedical use of other pain relievers. Again, state-level associations are valuable for generating hypotheses about possible unintended effects of OxyContin's reformulation, but they do not directly tell us whether individuals became infected with hepatitis C after changing their drug abuse behaviors because of the reformulation, e.g., switching from snorting OxyContin, to injecting heroin. Possible differences in hepatitis C reporting practices across states is another factor to consider, although it seems unlikely to entirely explain the study findings. Results from PMR 3051-1 do not suggest a post-reformulation shift from oral abuse or snorting to injecting OxyContin that would explain the apparent increase in hepatitis C infection associated with nonmedical use of OxyContin. However, the increasing trend in hepatitis C infections is similar to that of heroin overdoses, with an identified inflection point at the time of the reformulation, suggesting that the reformulation could have contributed to a rise in hepatitis C infections as opioid use patterns shifted.*

- *Wolff (2020) found that the group reporting nonmedical use of OxyContin in the pre-reformulation period had a smaller increase in odds of heroin initiation, and no difference in the change in odds of pain reliever use disorder, heroin use, or heroin use disorder, compared to the group reporting misuse of other prescription opioids during the pre-reformulation period. A strength of this study was that investigators examined the association between past nonmedical use of products and abuse-related outcomes based on individual level responses, rather than relying on state or county level estimates of both these factors. However, as different participants were surveyed each year, there was no longitudinal follow up to identify the incidence of heroin initiation associated with misuse of OxyContin, and systematic bias may have been introduced through the use of historical reporting of exposures occurring a variable interval of time (sometimes many years) prior to measurement of the*

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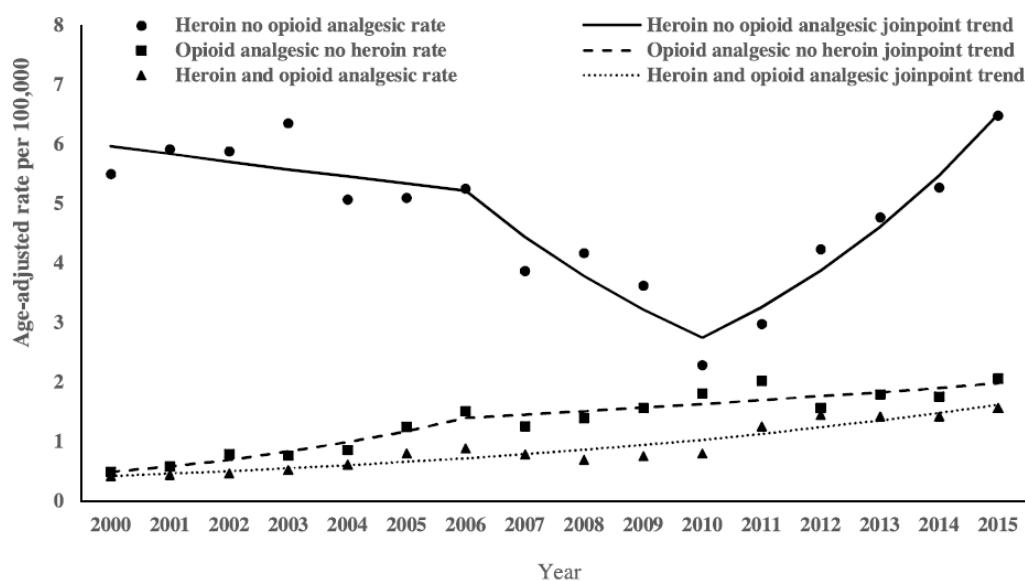
outcome. A related limitation was the potential for selection bias through potentially differential under-representation of individuals who used OxyContin nonmedically during the pre-reformulation period and subsequently developed more serious outcomes, such as advanced opioid use disorders leading to homelessness, incarceration, residential treatment, or fatal drug overdose, precluding inclusion in the survey sample.[6] As a result of these limitations, we cannot interpret these findings as longitudinal associations between the exposure to OxyContin's reformulation and subsequent changes in the risk of experiencing the outcomes examined within this study.

3.2.1.3.2 Additional Studies investigating Heroin Mortality and Initiation Following the Reformulation

3.2.1.3.2.1 Key Study Findings

- One ecologic time series study examined whether OxyContin reformulation was associated with an increase in heroin overdose deaths in a large urban area (Tuazon 2019). This study linked postmortem toxicology reports to death certificates in New York City to determine how the rates of opioid overdose deaths changed over time depending on the co-involvement of heroin (Tuazon 2019). While rates of opioid analgesic involved overdose deaths, both with and without heroin involvement, rose steadily from 2000-2015, heroin mortality rates without opioid analgesics increased an average of 18.8% per year after 2010 compared to a previously observed decline in heroin mortality rates from 2006 to 2010 (**Figure 6**).

Figure 6: Trends in overdose deaths involving heroin alone, opioid analgesic alone, and heroin with opioid analgesic, New York City, 2000-2015

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[6] Note: Three co-authors of Wolff (2020) also contributed to this literature review: L Glos, M Rosenberg, and A Schick, CDER Office of Program and Strategic Analysis, Economics Staff

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- A prospective cohort study by Carlson (2016) examined predictors of transition to heroin use among 362 young adults (ages 18 to 23) who reported use of prescription opioids that were not prescribed to them (called illicit prescription opioid use in the study) and who had no history of opioid dependence or heroin use. At baseline (May 2010) and every six months through May 2013, investigators collected information on participants' use of prescription or illicit drugs, including OxyContin, route of administration (ROA), and other items. Investigators conducted a time-to-event analysis to measure self-reported initial heroin use every six months over the 36-month follow-up period. Over the entire length of follow-up, 7.5% (n=27) of participants reported heroin initiation. Lifetime prescription opioid dependence, younger initiation of prescription opioid use, past nonmedical use of prescription opioids only for the purpose of abuse (e.g., not to manage pain), and past use by non-oral routes were significantly associated with heroin initiation (**Table 2**). All who initiated heroin reported lifetime use of OxyContin, compared to 46.3% of those who did not transition to heroin. Use of ADF OxyContin was not significantly associated with heroin initiation, although only three people (11%) who eventually initiated heroin reported ADF OxyContin use before heroin initiation. People who initiated heroin and those who did not were similar with respect to past use of IR oxycodone. Although not among the initial aims of the study, the investigators also compared heroin initiation incidence rates before and after market entry of ADF OxyContin, defining December 2010 as the start of the post-reformulation period. Investigators found that the incidence of past-6-month heroin initiation was 4.7 per 100 person-years (13 transitions in 276 person-years) from May until the end of November 2010 and 2.1 per 100 person-years (14 transitions in 658 person-years) from December 2010 until the end of the study.

Table 2: Multivariate adjusted associations between significant predictors and time to heroin initiation

Predictor	AHR	95% CI	p-value	PAR	95% CI
PO dependence (lifetime)	2.39	(1.07, 5.48)	0.0345	32%	(−2%, 64%)
Early initiation (age of initiation ≤15 years)	3.08	(1.26, 7.47)	0.0139	30%	(2%, 59%)
Has never used POs to self-medicate (only to get high) (lifetime) [a]	4.83	(2.11, 11.0)	0.0003	38%	(12%, 65%)
POs ever administered non-orally most often (since 6 months before baseline)	6.57	(2.81, 17.2)	<0.0001	63%	(31%, 86%)

[a] This 0/1 variable is expressed as 1−"Used PO to self-medicate a health problem (since 6 months before baseline)" so that all AHRs are >1, facilitating comparison of their relative sizes.

PO: Prescription Opioids; AHR: Adjusted Hazards Ratio; CI: Confidence Interval; PAR: Population Attributable Risk;
Source: Carlson, R.G., et al., Predictors of transition to heroin use among initially non-opioid dependent illicit pharmaceutical opioid users: A natural history study. Drug and Alcohol Dependence, 2016. 160: p. 132.

3.2.1.3.2.2 Reviewer Comments

- *Tuazon (2019) noted that fatal overdose rates involving heroin without any other opioid analgesics increased sharply starting in 2010, the same year OxyContin was reformulated, although the association between the reformulation and the increase in heroin overdose rates is not necessarily causal and could be due to shifting drug use patterns in the study population that are independent of the reformulation, such as changes in local heroin availability or purity. Although this study used linked postmortem toxicology data in addition to vital statistics data, possibly improving the reliability of the recorded drugs involved in the deaths examined, investigators did not examine the specific prescription opioid*

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involved in the death (e.g., oxycodone versus another opioid). Additionally, the findings of this study are only representative of mortality patterns in New York City and cannot necessarily be generalized to other populations.

- *Carlson (2016) found that use of ADF OxyContin was not significantly associated with heroin initiation, and that the rate of past-6-month heroin initiation was lower from December 2010- May 2013 compared to May 2010-November 2010; however, the interpretation of these findings is somewhat unclear. Only 28 participants reported using reformulated OxyContin, which may indicate that this product was not preferred, particularly among those who had transitioned to non-oral routes. The universal reporting of lifetime OxyContin nonmedical use, in conjunction with minimal reporting (only 3%) of prior ADF OxyContin use among heroin initiators suggests that some of those abusing original OxyContin may have switched to heroin when the drug was reformulated. However, answering this question was not the main objective of this study, and the information collected was not sufficiently detailed to draw this conclusion. While the investigators did find that the unadjusted rate of heroin initiation was higher in the earlier period, the study-defined latter period lags four months behind the introduction of ADF OxyContin, possibly contributing to a "spillover" effect as the initial 6-month period included almost four months after ADF OxyContin began replacing original OxyContin in pharmacies. It is possible that study participants included in the earlier time period initiated heroin in the first few months of market transition to the ADF (August-November 2010). Additionally, other work (Evans 2018) has found that an upward inflection in heroin mortality occurred approximately a month following the introduction of the reformulation, indicating a lag time of only about one month. Finally, we cannot assume that the hazard of heroin initiation was consistent throughout the entire study, as it could have been higher in the first six months of follow-up compared to the later months, regardless of OxyContin's reformulation. A particular strength of this study, however, was the use of a robust prospective cohort design, collecting three years of individual-level survey data, adjusting for confounding variables independently associated with heroin initiation, and employing a time-to-event analysis. Another notable strength of this study is the measure of ROA, as non-oral abuse of prescription opioids was found to be a significant predictor of heroin initiation in this analysis. This provided a good indication of individual-level factors associated with heroin initiation, although its findings regarding the impact of the reformulation on heroin initiation remain difficult to interpret.*

3.2.1.4 Studies Evaluating Spontaneous Adverse Event Reports
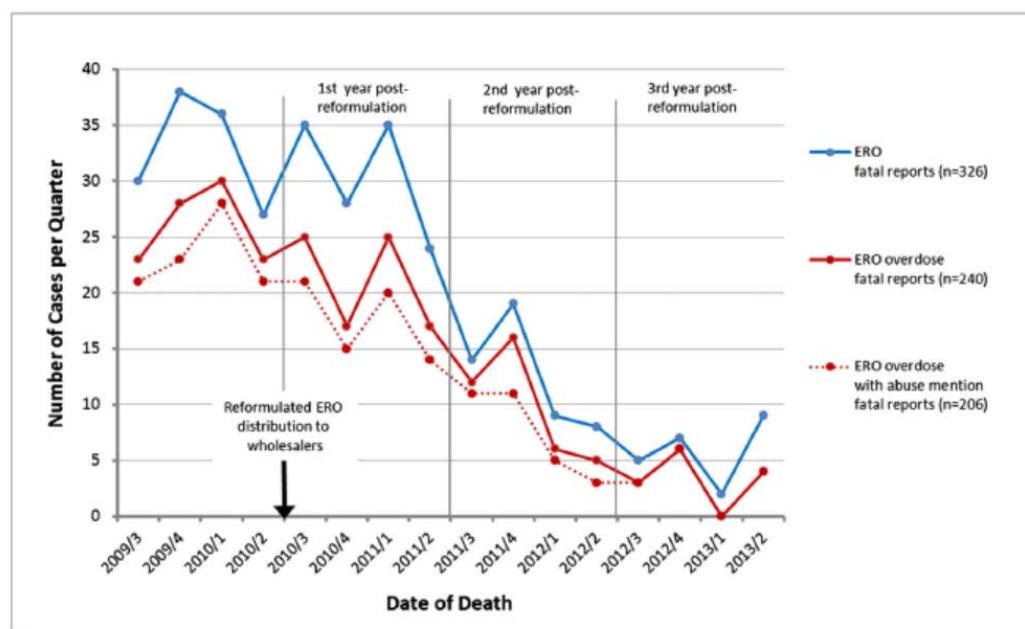
3.2.1.4.1 Overview of Studies

DEPI consulted the OSE Division of Pharmacovigilance (DPV) to review two published studies examining the impact of reformulation on trends in adverse event reports (Sessler 2014, Coplan 2016). The Sessler 2014 study used data from Purdue's spontaneous adverse event report database to evaluate the impact of OxyContin reformulation on death. The Coplan 2016 article appears to draw its conclusions, at least in part, from the Sessler study. However, the lack of in-text referencing makes it unclear if the authors summarized additional studies, thus DPV focused its critique on the Sessler study. **Appendix 8** provides a more detailed summary of findings and reviewer comments for these studies.

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3.2.1.4.2 Key Study Findings

Findings from the Sessler study suggested reformulation was associated with a reduction in spontaneous reports of OxyContin-related deaths. When examining mean fatalities, the authors reported an average value of 32.8 deaths per quarter during the year prior to reformulation, with a significant change occurring by the second year post-reformulation and persisting during the third year post-reformulation; with an average value of 5.8 deaths per quarter by the third year post-reformulation (-82% change, 95% CI (-89% to -73%)). There was not a significant reduction in mean deaths in the first year post-reformulation (−7% change, 95% −27% to 19%)). Figure 7 depicts trends in the number of fatality reports associated with extended-release oxycodone per quarter from Q3 2009 through Q2 2013.

Figure 7. Number of extended-release oxycodone (ERO) fatality reports per quarter *

3.2.1.4.3 Reviewer Comments

DPV reviewers identified four major limitations associated with the Sessler study. First, spontaneous reporting databases do not contain the totality of adverse events occurring in a given exposed population. Therefore, trends in reporting cannot be used to make inferences about trends in adverse events occurring in the exposed population. Second, the authors selected only reports with a date of death included, as well as other key variables. The authors also excluded reports associated with litigation, which may have increased in recent years. This exclusion may have biased report estimates downward in the post-period if a higher proportion of deaths (and associated reports) in the post-period were associated with litigation. Third, the authors did not attempt to identify an appropriate comparator, merely stating that there were insufficient reports for MS Contin. Finally, many factors can influence spontaneous reporting and reporting may decline over a product's life cycle (McAdams 2008). Given issues with the type of data analyzed and presented (e.g. lack of data on route of abuse), potential biases introduced by the authors' approach to select cases, and inadequate analysis of comparators in the trend analysis, DPV reviewers concluded these

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analyses cannot be used to make inferences on the impact of reformulated OxyContin on the risk, or incidence, of fatal overdose.

3.2.2 Qualitative Studies

3.2.2.1 Overview of Studies

Of the 21 non-PMR-related U.S. studies included in our review, three used qualitative methods (**Appendix Table 2**). Two surveys gathered information on abuse-related outcomes, such as drug abuse patterns and overdose, around the time of OxyContin's reformulation (Yarborough 2016, Buer 2014'). Finally, one qualitative study featured a discussion of common complaints made by patients regarding ADF opioids (Argoff 2013).

3.2.2.2 Key Study Findings

- One interview study by Yarborough (2016) sought to determine patient characteristics associated with drug overdoses using open-ended questions about specific substance use, abuse history, source of substance, route of administration, and medical treatment following events for opioid overdoses spanning the period before and after the reformulation. Researchers reported that most opioid overdoses involved polysubstance use, primarily with benzodiazepines. Researchers also reported that the lack of availability of OxyContin for abuse may have led some individuals with prescription opioid abuse histories to initiate heroin use. Other reported reasons for heroin initiation included an improved high, lower price relative to other prescription opioids, and ease of availability. However, it was unclear whether medical use of prescription opioids preceded heroin use because interviewers did not collect participants' complete drug use histories.

- Another study by Buer (2014) sought to understand changing drug use patterns resulting from the reformulation by interviewing individuals in rural Kentucky, using community outreach to recruit people who abused OxyContin. According to this study, the prescription opioids that were reportedly abused changed following the reformulation of OxyContin, as most participants refused to abuse ADF OxyContin due to the difficulty injecting or snorting the drug. Other complaints regarding the ability to abuse ADF OxyContin came from the perceived lack of potency and length of effect of the reformulation compared to the original OxyContin. Many of those who had abused original OxyContin reported replacing it with IR oxycodone, although original OxyContin was preferable if available.

- Another study by Argoff (2013) sought expert opinion from a meeting of US clinicians experienced in pain management a year following the reformulation for the purpose of exploring common objections of patients for switching from original to ADF formulations of opioid analgesics. According to these providers, patients reported difficulty swallowing pills as well as perceived reduced efficacy of the drugs compared to non-ADF formulations. Another objection to switching to ADFs was lack of coverage in formulary and higher comparative expense than previous opioids.

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3.2.2.3 Reviewer Comments

One aim of qualitative studies is to help understand factors that may be driving an observed association, in addition to providing some nuance into this relationship. As such, these studies provided some valuable information to support the interpretation of the quantitative literature studies and PMRs, which used larger and, in some cases, better defined samples, and quantitative measures of effect. An overall strength of these studies was their ability to gather detailed information on patient factors possibly associated with switching to other substances, such as drug use patterns, patient history, and concerns about drug efficacy. However, there were also several limitations noted. While one study presented here (Yarborough, 2016) identified overdoses descriptively through the different products involved in these events, the investigators did not explore whether overdoses involving heroin had a history of non-ADF or ADF OxyContin use and/or dependence. As a result, this study provides little information regarding whether previous use of original OxyContin was associated with subsequent heroin overdose after OxyContin was reformulated. Two of these qualitative studies consisted of interviewing a small number of individuals from one geographic region and, as a result, may not be representative of the larger populations of individuals who abuse prescription opioids (Argoff 2013, Buer 2014). The examinations of switching/substitution practices provided some information on why patients did not want to switch from original to ADF of prescription opioids, although the qualitative nature of the study precluded an assessment of the relative frequency with which patients actually experienced any problems with the ADF, discontinued the drug, or switched to other opioids following the reformulation (Buer 2014).

3.3   INTERNATIONAL STUDIES

We identified eight relevant international epidemiologic studies: Peacock 2015a, Degenhardt 2015, Peacock 2015b, Larance 2018, Jauncey 2018, Lam 2019, Gomes 2018, and Sankey 2016. These studies are summarized in **Appendix Table 2**. Four of these studies were associated with the National Opioid Medication Abuse Deterrence (NOMAD) study out of Australia (Peacock 2015a, Degenhardt 2015, Peacock 2015b, Larance 2018). There were two additional studies out of Australia (Jauncey 2018, Lam 2019) and two from Canada (Gomes 2018, Sankey 2016).

3.3.1   National Opioid Medication Abuse Deterrence (NOMAD) Studies- Australia

3.3.1.1   Overview of Studies

In Australia, the reformulation of OxyContin took place in April 2014, and the NOMAD study was designed to assess the impact of reformulated OxyContin on multiple opioid-related outcomes. The NOMAD study used data from pharmaceutical sales, prospective cohort interview data, annual surveys, safe injection sites, needle exchange programs, EMS, EDs, opioid-dependence treatment centers, and addiction helpline calls to determine if the reformulation had an impact on 1) the population-level use of oxycodone and other pharmaceutical opioids, 2) extra-medical use of OxyContin, 3) extra-medical (i.e. nonmedical) use of non-ADF oxycodone, 4) use of other pharmaceutical opioids and heroin, 5) attractiveness of OxyContin for abuse among people who tamper with pharmaceutical opioids, 6) methods of tampering with OxyContin, and 7) opioid overdose, and help or treatment-seeking for opioid dependence. The investigators published their protocol prior to beginning the study.

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The four NOMAD-related studies included in our review were disseminated as the main prospective NOMAD cohort study progressed. The first of these studies examined methods and predictors of tampering with reformulated OxyContin using interview data collected before (January-March 2014) and after (May-August 2014) reformulation from individuals in the prospective cohort who regularly tampered with pharmaceutical opioids (Peacock 2015a). The second study was a descriptive analysis of preliminary data from the prospective cohort study and a variety of other data sources (sales, surveys, safe injection sites, needle exchange programs) (Degenhardt 2015). The third study used data from two waves of interviews from the prospective cohort to identify latent classes of individuals who tamper with pharmaceutical opioids and assess changes in drug use and related harms following the reformulation of OxyContin (Peacock 2015b). The final study reported the main findings of the NOMAD study and included an interrupted time series analysis (Larance 2018). The time period examined varied depending on the data source. The earliest available data pre-reformulation was from 2001 and the latest post-reformulation data was from 2016.

3.3.1.2 Key Study Findings

- The findings from the Peacock (2015a) descriptive study were based on cohort interview data and suggest that among 522 individuals who regularly tampered with prescription opioids and had tampered with original OxyContin, 29% used and 18% tampered with reformulated OxyContin. Participants had a six-fold increased odds of rating reformulated OxyContin painful to inject compared to the original formulation. Compared to the original formulation, fewer people rated reformulated OxyContin as easy to cut up (79% vs 21%) and dissolve (74% vs 14%). Among the 19 participants who tampered with both original and reformulated OxyContin, less than 5% reported the original was difficult to tamper with and inject, whereas 50% and 47% reported the reformulation was difficult to tamper with and inject, respectively.

- The Degenhardt (2015) descriptive analysis of preliminary data from the NOMAD study showed that overall sales of oxycodone steadily increased between 2009 and 2014, despite a 24% decline in sales of 80mg OxyContin in the months surrounding reformulation in April 2014 (between March 2014 and June 2014). Based on annual cross-sectional interviews with people who inject drugs, in June 2013, 36% used and 31% injected oxycodone (although not necessarily OxyContin specifically) in the past six months, whereas in the June 2014 sample, 8% used and 5% injected reformulated OxyContin in the past six months. When comparing the five months pre- and post-reformulation, visits to inject oxycodone at one safe injection site declined from 62% to 5% of visits for all drugs. During this same time period, the proportion of visits to two needle exchange programs where the last drug injected was pharmaceutical opioids (other than methadone and buprenorphine) dropped from an average of 10% to 6% of client visits. In the NOMAD cohort of people who regularly tampered with pharmaceutical opioids, the proportion of individuals who reported past-month extra-medical use of OxyContin 80mg declined from 56% in the three months preceding reformulation to 24% (16% original Oxycontin; 8% reformulated OxyContin) three months after reformulation. The authors also reported reductions in any past-month use and injection of other individual prescription opioids with no offsetting increases in reported use or injection of other individual prescription opioids in the period immediately post-reformulation. Past-month heroin use was not assessed at

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baseline; however, pre-reformulation, 64% of the cohort reported heroin use in the past six months. People who used heroin reported injecting on a median of 27% of days in the past six months pre-reformulation and 36% of days in the past month post-reformulation. Results from cohort interview data also suggested that after reformulation, reformulated OxyContin was cheaper and less attractive for tampering than the original formulation.

- Peacock (2015b) used the first of two waves of interview data from the prospective cohort to conduct a latent class analysis, identifying four primary groups of individuals who regularly tamper with prescription opioids: frequent opioid substitution therapy (OST; buprenorphine/methadone) 39%, mixed OST/heroin 7%, infrequent pharmaceutical/heroin use 44%, and frequent oxycodone use 11%. Follow-up interviews conducted after OxyContin's reformulation in the total sample indicated that 8% percent of individuals reported past-month use of reformulated 80mg OxyContin, compared to 55% pre-reformulation. The largest reduction occurred in the frequent oxycodone group (past-month use of OxyContin 80mg: 100% pre-reformulation, 19% post-reformulation). All groups also experienced statistically significant declines in past-month use of other drugs, including MS Contin, which was the only other prescription opioid for which results were reported, and heroin. The groups had varying levels of use of prescribed OST, and the proportion of individuals in the frequent oxycodone group reporting past-month OST use increased from 7% pre-reformulation to 21% post-reformulation. Compared to other groups, a larger proportion of individuals in the frequent oxycodone group reported tampering and successfully tampering with reformulated oxycodone in the prior month. All groups experienced declines in past-month tampering and non-serious injection drug related injuries. Only the frequent OST group experienced declines in past-month injection of any drug. However, the mixed OST/heroin and the frequent oxycodone groups experienced declines in daily injections. Both the frequent OST and frequent oxycodone groups experienced declines in non-serious, potentially serious, and serious injection drug related injuries. Needle sharing and accidental overdose did not differ significantly over time for any group. Loss to follow-up (i.e., the proportion of participants from Wave 1 who did not participate in Wave 2) was low and similar across groups, ranging from 7% to 12%.

- The main NOMAD study (Larance 2018) reported that reformulation was associated with reduced sales of 40mg and 80mg strengths of OxyContin but was not associated with a net change in overall opioid, oxycodone, or other pharmaceutical opioid sales due to steady increases in oxycodone-naloxone dispensing since its introduction in 2014. Pharmacy dispensing data show sales of OxyContin began to decline prior to reformulation, around October 2011. The authors report, prior to reformulation, 80mg OxyContin tablets were the least commonly prescribed strength but were frequently sought after by individuals who tamper with pharmaceutical opioids. Based on analyses of data from the prospective cohort, surveys of people who inject drugs, and clients of supervised injecting facilities or needle and syringe programs the authors concluded that OxyContin's reformulation was associated with reductions in OxyContin tampering and injection, with no clear evidence of switching to heroin or other drugs. Some data from the NOMAD cohort suggest the attractiveness of other oxycodone formulations and opioids for abuse after OxyContin's

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reformulation and visits to supervised injecting facilities to inject heroin did increase after the reformulation, although these changes were not statistically significant. Of the individuals in the NOMAD cohort, 18% reported attempting to tamper with reformulated OxyContin 1 to 4 months after introduction; after 12 months, attempts to tamper had increased to 27%. Analyses of ambulance calls, ED visits, helpline calls, and overall treatment admissions found no evidence of an association between reformulation and changes in these outcomes; however, the authors reported an average of 17 fewer new or subsequent treatment admissions per month where oxycodone was the primary opioid of concern.

3.3.1.3 Reviewer Comments

The NOMAD studies have multiple strengths and limitations. One of the main strengths of these studies is the authors' use of a published pre-specified study protocol. The subsequent published studies appeared to adhere to this protocol. The NOMAD study evaluated the impact of reformulation using a wide variety of data sources that measured both behaviors and harms associated with drug abuse. Third, compared to the U.S., it appears that there were fewer, if any, competing interventions taking place at the time of OxyContin reformulation in Australia, allowing for a clearer interpretation of results than may have been possible had the study been conducted in the U.S.

The two NOMAD studies (Peacock 2015a, Peacock 2015b) based on interview data share some limitations due to similarities in study design. Both studies collected interview data, once prior to reformulation and again one to three months post-reformulation when reformulation may have had the greatest impact on tampering practices. Final results from the NOMAD cohort included a third wave of interviews and suggested reductions in tampering may attenuate over time.

The first descriptive study (Peacock 2015a) found a decline in the percentage of participants who tampered with OxyContin after reformulation, which suggests the reformulation was less attractive for tampering; however, the study did not specifically assess the prevalence of poly-opioid or polysubstance abuse or rates of switching to other pharmaceutical or illicit opioids post-reformulation. After dividing the sample into four groups in the latent class analysis (Peacock 2015b) and restricting to respondents in both survey waves, the conclusions regarding changes in use and tampering after reformulation were based on a small number of participants, particularly the frequent oxycodone group (58 respondents). In this study, latent classes were determined based on past-month drug use and did not assess changes in drug use that may have affected class membership post-reformulation.

The publication reporting main findings from the NOMAD study builds upon the prior preliminary descriptive study (Larance 2018) by including additional data sets, a longer post-reformulation follow-up period, and an interrupted time series analysis, which was not possible in the prior study due to a lack of post-reformulation data from an extended time period. Again, this publication shared many of the strengths mentioned above, but there were some notable caveats when interpreting the findings. The NOMAD study did not account for decreases in OxyContin sales when estimating changes in the proportion of individuals reporting injecting oxycodone pre- and post-reformulation. We expect some correlation between OxyContin sales and prevalence of OxyContin abuse, and this correlation may be particularly strong for the higher strength dosage forms. Although it is plausible that some of the decline in OxyContin sales, particularly of

high strength tablets, was due to reduced demand for abuse or diversion following the reformulation, the growing sales of oxycodone/naloxone and other market or societal factors may also have influenced OxyContin prescribing. Data from safe injection sites, needle exchange programs, ambulance runs, ED visits, and treatment seeking lacked OxyContin-specific endpoints and were only able to provide aggregated information on oxycodone or opioids. Some of these data originated from limited geographical areas. For example, data from safe injection site visits came from one area (Sydney) and data from needle exchange visits came from two areas (Sydney and Queensland). Drug abuse patterns are likely geographically heterogeneous (as they certainly are in the U.S.) and depend on pre-existing prevalence of drug abuse, availability of substitutes, and treatment options. Due to the limited geographic coverage of these data, it is possible that some post-reformulation changes in drug abuse patterns went undetected.

Interview data from the NOMAD cohort provided detailed information on nonmedical opioid use and tampering behaviors. However, individual drug use patterns are complex and may change frequently, particularly given that, at baseline, most individuals were using multiple substances, including both prescription and illicit opioids. In retrospect, an additional wave of interviews during the pre-reformulation period may have been useful in determining how drug use patterns were changing prior to reformulation and to what extent the observed changes in pre- to post-reformulation drug use could be attributed to OxyContin's abuse-deterrent properties. It is unclear how drug use patterns in this cohort would have changed in the absence of the reformulation and if the prevalence of tampering and abuse of some prescription drugs would decline naturally over time in a population selected specifically for these behaviors. The observed reductions in the use of multiple opioids, while encouraging, are difficult to attribute solely to the reformulation of OxyContin. Other factors, like receipt of OST, changing social circumstances, or even regular contact with research staff, may have also contributed to the observed reductions in reported abuse of prescription opioids.

Based on the results of the NOMAD studies, it remains unclear if the observed declines in OxyContin abuse were predominantly due to OxyContin's abuse-deterrent properties or other factors affecting retail sales and black-market demand. The data presented suggest OxyContin sales, individuals injecting oxycodone, and visits to needle exchange programs were declining prior to reformulation. For example, pharmacy sales of OxyContin had been declining since October 2011, the proportion of participants who reported use or injection of oxycodone in the past six months had been declining since 2012, and visits to needle exchange program sites for oxycodone had been declining since 2013. The most prominent and statistically significant decline post-reformulation occurred in monthly visits to safe injection sites. The interrupted time series approach does account for pre-reformulation trends; however, without adjusting for the sharp declines in sales of 80mg and 40mg OxyContin tablets or other factors influencing sales, it is unclear to what extent declines in visits to safe injection sites were due to OxyContin's ADF properties. Finally, due to the exclusion of individuals who have not yet tampered with pharmaceutical opioids, this study was unable to examine the effect of OxyContin's reformulation on initiation of tampering or abuse of opioids via non-oral routes, which is an important question in considering the public health impact of OxyContin's reformulation.

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3.3.2 Other International studies- Australia

3.3.2.1 Overview of Studies

We reviewed two international studies from Australia that were not associated with the NOMAD study (Jauncey 2018, Lam 2019). These studies used an interrupted time series approach to examine changes in outcome trends over time. The first Australian study (Jauncey 2018) examined the impact of reformulated OxyContin on the number of safe injection site visits and the number and type of opioid overdoses occurring onsite. It appears that data for this study came from the same safe injection site used in the NOMAD study. The other Australian study (Lam 2019) described trends in opioid-related ambulance and ED attendance before and after the reformulation of OxyContin in April 2014. The data for this study originated from Victoria, whereas ambulance and overdose data in the NOMAD study originated from other states in Australia.

3.3.2.2 Key Study Findings

- The Australian safe injection site study (Jauncey 2018) found average monthly visits to a single site declined from approximately 6000 pre-reformulation (February 2007 to March 2014) to 5000 visits post-reformulation (April 2014 to February 2016). The average monthly decline comparing pre to post-reformulation was -1061 visits per month (95% CI: -195, -1928) or 18%. This decrease was largely explained by a reduction in visits to inject OxyContin but was partially offset by increased visits to inject morphine or fentanyl after reformulation. Similarly, onsite overdoses involving OxyContin decreased after reformulation; however, due to increases in heroin and morphine overdoses, there was no significant change in the number of total onsite overdoses per month following reformulation.

- The Lam (2019) trend analysis of Australian ambulance and ED data found that, prior to reformulation, the quarterly rate of ED visits involving pharmaceutical opioids was increasing by 0.06 ED visits per 100,000 people. In the post-reformulation period, there was a slight (-0.08) but statistically significant decrease in the trend of quarterly ED visits involving pharmaceutical opioids per 100,000 people. There was no significant difference in the rate of prescription opioid related ambulance attendances after reformulation. Prior to reformulation, trends in heroin-related ambulance attendance and ED visits were stable. However, after reformulation, there was a significant increase in rates of heroin-related ambulance attendance and ED visits. Rates of heroin related ambulance attendance increased from 9.9 per 100,000 persons in 2013 to 13.9 per 100,000 persons in 2018 and rates of ED visits increased from 1.82 per 100,000 persons in 2013 to 2.55 per 100,000 persons in 2018.

3.3.2.3 Reviewer Comments

Data from safe injection sites, ambulance services, and EDs provide valuable information and a deeper understanding of how OxyContin reformulation may have had an impact on opioid abuse and related harms more broadly. Findings from the Australian safe injection site study, which suggest reformulation was associated with fewer site visits to inject OxyContin, fewer OxyContin-related overdoses, more visits for

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morphine and fentanyl, and increased morphine- and heroin-related overdoses, suggest that some individuals substituted OxyContin with other opioids post-reformulation. However, it remains unclear to what extent these changes in drug use are a direct result of the ADF properties versus other factors, such as reductions in OxyContin dispensing, increases in availability of other drugs, or decreases in the price of other drugs. The results of this study may not be generalizable to all people who inject drugs for two reasons. First, this study examined data from a small subset of people who inject drugs who visited one safe injection site, many of whom had a long history of injection drug use. Second, these data do not capture all instances of an individual's injection drug use.

The Australian EMS and ED study also has some notable limitations. First, OxyContin-related ambulance attendance and ED visits were combined with those involving other prescription opioids, making it difficult to determine whether a reduction in OxyContin-related ED visits, specifically, was driving the slight decrease in pharmaceutical opioid-related ambulance attendance and ED visits. Second, the authors state that OxyContin reformulation in Australia occurred in isolation from any other policy changes or interventions designed to curb opioid misuse and abuse. However, like the safe injection site study, this analysis did not account for decreases in OxyContin dispensing after reformulation or any possible changes in heroin supply or cost.

3.3.3   Other International Studies- Canada

3.3.3.1   Overview of Studies

We reviewed two international studies from Canada, Gomes (2018) and Sankey (2016). In Canada, reformulated OxyContin was introduced to the market in February of 2012. These two studies examined different data sources and outcomes. The first study (Gomes 2018) used IQVIA dispensing data from community pharmacies to examine rates of dispensing and market share of ADF OxyContin and generic non-ADF ER oxycodone. The second study (Sankey 2016), used medical chart review and patient surveys to examine post- reformulation changes in the prevalence of oxycodone-positive urine drug screens (UDS) in opioid-dependent patients receiving methadone maintenance therapy.

3.3.3.2   Key Study Findings

- The analysis of dispensing data across Canada (Gomes 2018) found that after reformulation, the national dispensing rate of OxyContin declined 44.6% from 26.4 tablets per 100 persons in February 2012 to 14.6 tablets per 100 persons in April 2016. The authors reported that insurance plans either chose not to list this new form of OxyContin on their formularies or made its access contingent on meeting strict eligibility criteria. Although dispensing for generic ER oxycodone increased after reformulation, compared to the three-year period prior to reformulation, approximately two million fewer doses of oxycodone were dispensed per month after reformulation (February 2012 to April 2016). Uptake of generic ER oxycodone following OxyContin reformulation also varied widely by province.

- The descriptive chart review study (Sankey 2016) among Canadian individuals receiving methadone maintenance therapy found a reduction in the average per-patient percentage of oxycodone-positive

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UDSs from 22.4% pre-reformulation to 10.5% post-reformulation. Of the 250 patients who had oxycodone-positive UDSs during the baseline period, 90 patients had zero oxycodone positive UDSs during the transition period and 130 patients had zero during the post-OxyContin reformulation period. Morphine-related-positive UDSs remained stable during the same period.

3.3.3.3 Reviewer Comments

The dispensing study (Gomes 2018) collected dispensing data from a large geographic area over an eight-year period which suggests these results may be nationally representative. We found it noteworthy that the authors linked the decline in reformulated OxyContin sales to its exclusion from provincial drug formularies, indicating that changes in OxyContin dispensing after the reformulation may be driven by factors other than direct effects of the abuse-deterrent formulation on desirability for abuse.

The chart review study (Sankey 2016) in patients receiving methadone maintenance therapy had similar limitations to the Australian studies. First, it did not account for other potential factors, such as changes in OxyContin dispensing and diversion, that may be associated with reductions in oxycodone misuse and abuse. Second, given the inclusion only of patients in methadone maintenance treatment, the small sample size, and small geographic area covered in this study limit the generalizability of these findings.

3.4   EDITORIALS

In addition to our review of original studies, we also examined editorials to look for any new information or other studies referenced that might be relevant to understanding the impact of ADF OxyContin. Of the 32 editorials we reviewed, 12 focused primarily on ADF Oxycontin, and 20 provided commentary on ADFs in general. We did not identify relevant new data in any of the editorials. Among those that specifically commented on ADF OxyContin, opinions differed with respect to the effectiveness and public health impact of the reformulation. Some editorials took a positive view of the effect of the reformulation (Schaeffer 2012, Dart 2015, Kunins 2015, Bigal 2019, Cicero and Ellis 2015-Reply, Alexander 2019), others a more negative view (Ruan 2015, Manchikanti 2015), and still others a relatively balanced view, pointing out both potential benefits as well as limitations of OxyContin's ADF properties (Cicero and Ellis 2015(2), Dasgupta 2015, Jamison 2013, By 2018). Among the editorials commenting on ADF opioids in general, again, some presented a mostly positive view of ADFs' role in addressing prescription opioid abuse, noting that any reduction in non-oral abuse should confer an important safety benefit for these products (Jones 2014, Jones 2016, Pergolizzi 2018, DePriest 2014, Papagallo 2012, Bannwarth 2012). Others took a more negative view, noting ADF's lack of effect on the most common route of abuse (oral) and raising concerns about potential unintended consequences such as higher cost and shifting abuse to more dangerous illicit opioids (Brooks 2018, Kibbe 2018, Med Lett Drugs Ther 2018, Singer 2018). Most expressed mixed views about the role of ADF opioids (s, Litman 2018).

4   DISCUSSION

We identified and reviewed original observational studies examining the impact of OxyContin's reformulation on opioid use, morbidity, and mortality. Our review included 78 publications from the peer-reviewed and selected manuscripts from the grey literature. Fifteen of these publications analyzed the same data sources used in formal PMR studies designed to evaluate the impact of OxyContin's reformulation on

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OxyContin abuse and overdose in various U.S. populations, and discussion of these fifteen studies can be found in the relevant PMR study reviews. The 61 remaining publications provide some valuable information that supplements and contextualizes the results of the four PMR studies. Nonetheless, most of the studies have substantial limitations, as noted in the reviewer comments sections above. In addition, with a few exceptions, the published studies lacked pre-specified protocols. Although this is common for observational studies in the peer-reviewed literature, the inability to distinguish between pre-specified and post-hoc analyses limits our understanding of the rationale for comparator, time period, and outcomes selection, and the extent to which negative findings were not published.

4.1   EFFECT OF REFORMULATION ON OXYCONTIN DISPENSING

In the U.S., the transition from original OxyContin to reformulated OxyContin occurred quickly between the third and fourth calendar quarter of 2010. After reformulation, the number of prescriptions and prescription sales of OxyContin gradually declined (Hwang 2015), but overall prescriptions for ER oxycodone decreased even more sharply as generics to original Oxycontin exited the market contemporaneously with the introduction of the ADF. DEPI analyses of retail pharmacy data, shows dispensing of IR oxycodone increased after OxyContin's reformulation which suggests a possible shift in prescribing from generic ER oxycodone to IR oxycodone ([DEPI Drug Utilization Review](#)). A retrospective cohort study among commercially insured patients found that almost one-third of patients dispensed ER oxycodone did not switch to ADF OxyContin after the reformulation, instead switching to non-ADF ER or IR opioids (Michna 2014). Because the study did not compare between switching patterns for patients prescribed opioids before and following the reformulation, we are unaware of the reasons the patients may have switched or discontinued opioids, complicating the interpretation of the switching data and subsequent rates of abuse based on insurance claims. These findings were consistent with analyses done in Marketscan claims data as part of the PMR 3051-4 protocol development.

After reformulation, Canada experienced similar changes in ER oxycodone prescribing patterns as the U.S. (Gomes 2018, Hwang 2015). The authors of the Canadian study noted that observed reductions in OxyContin dispensing after its reformulation may have been related, at least in part, to its exclusion from many provincial drug insurance plans there. Because of the complex and constantly changing patchwork of private and public insurance coverage in the U.S., it is difficult to determine how these factors impacted OxyContin prescribing here. In one U.S. study, providers reported that some patients complained about reduced efficacy or difficulty swallowing the reformulated product (Argoff 2013). These findings are consistent with postmarketing reports received by FDA that resulted in a safety labeling change (Warnings and Precautions: Section 5.9) about difficulty swallowing, as well as rare cases of intestinal obstruction and exacerbation of diverticulitis, associated with reformulated OxyContin (OxyContin label 2015). In Australia, OxyContin sales declined rapidly after reformulation, especially for higher strength pills (40mg, 80mg). OxyContin sales were already declining prior to reformulation, albeit at a slower rate, as sales of oxycodone-naloxone combination products increased (Larance 2018). Although the Australian studies we reviewed examined numerous data sources and reported reductions in OxyContin abuse, tampering, and injection, none of the analyses accounted for this observed decrease in OxyContin sales.

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4.2 EFFECT OF REFORMULATION ON NONMEDICAL USE OF OXYCONTIN, OVERALL AND BY NON-ORAL ROUTES

Multiple published studies examining different populations found that the reformulation of OxyContin was associated with decreases in rates of self-reported nonmedical use or abuse of OxyContin (Cheng 2018, Jones 2017, Alpert 2018, Havens 2014, McNaughton 2014, Wolff 2019, Larance 2018). The findings of these studies need to be interpreted as part of the entire body of evidence on this question, including the studies conducted to fulfill PMRs 3051-1 through 3051-3 and the published studies using these same data sources and methods. Reviews of the PMRs and the related published studies are found elsewhere in this background package.

Published analyses of national survey data (NSDUH) data suggest that the reformulation was associated with declines in the initiation and prevalence of nonmedical OxyContin use; however, neither of these studies adjusted for reductions in OxyContin dispensing post-reformulation (Cheng 2018, Jones 2017), and one study noted that the estimated prevalence returned to levels similar to that seen several years before the reformulation (Jones 2017). An analysis of state-level NSDUH data suggested that post-reformulation changes in past-year nonmedical use of OxyContin were heavily influenced by pre-reformulation rates of nonmedical OxyContin use, and trends in nonmedical OxyContin use appeared correlated with trends in oxycodone supply from manufacturers (Alpert 2018). According to this analysis, states with higher pre-existing rates of nonmedical OxyContin use experienced declines in post-reformulation nonmedical use, whereas states with lower pre-existing rates experienced increases in nonmedical OxyContin use (Alpert 2018).

Several studies examined outcomes that are related to, but do not directly measure abuse. These studies suggested that OxyContin reformulation was associated with decreases in "doctor shopping" (Chilcoat 2016) and diversion cases (Severtson 2016) involving OxyContin. Studies examining street prices (Lebin 2019, Severtson 2016), suggested street prices for reformulated OxyContin were lower compared to other, non-ADF opioids. These lower street prices may, at least in part, be due to increased difficulty manipulating and injecting the reformulation (Buer 2014). Although it is unclear how well metrics like doctor shopping, street price, and number of diversion cases correlate with the true prevalence of abuse of a product, these data are consistent with the hypothesis that reformulated OxyContin is less attractive for diversion and abuse than original Oxycontin or other, non-ADF IR oxycodone products currently on the market.

Nonmedical use of oxycodone, including OxyContin, primarily occurs though the oral route, (Cicero and Ellis 2015), and some theorized that the crush-resistant OxyContin might prevent individuals from transitioning to non-oral routes if they were only exposed to crush-resistant formulations. However, we found no information about whether the reformulation deterred individuals from initiating non-oral abuse of OxyContin or other prescription or illicit opioids. . Several studies from within the U.S. suggested that ADF OxyContin led to a decline in nonmedical OxyContin use through non-oral routes in selected populations with a high prevalence of non-oral opioid abuse, including injection or insufflation (Havens 2014, Cicero and Ellis 2015), with some reporting shifting to oral abuse of OxyContin (Cicero and Ellis 2015). Individuals interviewed in the Australian NOMAD cohort study reported that the reformulated product was less attractive for injection, and safe injection site data showed a large decline in the total number of visits to inject OxyContin post-reformulation (Larance 2018).

4.3 EFFECT OF OXYCONTIN'S REFORMULATION ON BROADER OPIOID USE PATTERNS

Multiple studies suggest that some individuals switched to other prescription opioids after OxyContin was reformulated. This finding is consistent with reformulated OxyContin having an abuse-deterrent effect, although it raises the larger question about whether the reformulation led to any net reduction in harms. The evidence suggests that in some populations, individuals who had abused original OxyContin by snorting or injecting transitioned to abusing IR oxycodone via these routes (Havens 2014). Among individuals entering treatment for opioid use disorder, one third reported that they replaced OxyContin with other drugs following the ADF, including heroin, other forms of oxycodone, hydromorphone, oxymorphone, and other prescription opioid and non-opioid drugs (Cicero and Ellis 2015). Analyses of internet posts provided some additional support for the theory that OxyContin's reformulation led some individuals to switch from OxyContin to other prescription opioids (McNaughton 2014, Vosburg 2017) or heroin (Vosburg 2017).

Several studies specifically examined the impact of OxyContin's reformulation on heroin overdose (Alpert 2018, Evans 2018, Powell 2020, Tuazon 2019). Although these studies may provide some insights on shifts in abuse patterns, they did not directly measure heroin use, and the risk of overdose among those using the drug may be affected by other factors, for example the purity or potency of the opioid or availability of naloxone. Based on the studies using NSDUH, drug shipment, and heroin mortality data, the likelihood of a shift to heroin after OxyContin's reformulation appears to depend on pre-existing levels of both nonmedical oxycodone use and heroin use in the area. States with high pre-reformulation supply of oxycodone, nonmedical OxyContin use, and heroin deaths experienced larger increases in heroin-related deaths after the reformulation, compared to other states (Alpert 2018, Evans 2018, Powell 2020). This same separation was not observed between higher and lower levels of non-medical use for other prescription opioids, suggesting, but not proving, that OxyContin's reformulation had some causal role in these observed increases (Powell 2020).

Several studies in both the U.S. and Australia found no clear evidence of OxyContin's reformulation increasing heroin *initiation* (Wolff 2020, Carlson 2016, Larance 2018). In the U.S., findings from a prospective cohort study and an analysis of NSDUH data did not find evidence of an association between reformulation and increases in heroin initiation; however, methodologic limitations preclude drawing definitive conclusions from these studies. In Australia, the evidence was mixed on shifts to heroin or injection of other opioids resulting from the reformulation (Larance 2018, Lam 2019). Although the proportion of individuals in the NOMAD cohort reporting recent heroin use declined (64% past six-month use at baseline, compared to 44% past-month use twelve months post-reformulation), the frequency of heroin injection increased modestly (median 27% of days in past month to median of 36% of days in past month). The difference in referent time periods (past six-month versus past-month use) made these data difficult to interpret. After OxyContin reformulation, the increase in average monthly visits to a Sydney safe injection site to use heroin was not statistically significant, although a visual inspection of these trends suggested some increase (Larance 2018). Data from another Australian study showed increases in heroin-related ambulance and ED visits post-reformulation (Lam 2019). Taken together, the results of studies conducted in the U.S. and Australia suggest that OxyContin's reformulation may have contributed to a shift to heroin use in certain populations and geographic areas where heroin was readily available. The data suggest that this shift may have been driven predominantly by individuals with some history of heroin use in

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addition to non-oral abuse of prescription opioids, rather than new initiators of heroin, although this is speculative. Polysubstance abuse is common, and drug use patterns are dynamic and likely influenced by many factors, including drug availability, price, and other sociocultural factors.

4.4 EFFECT OF OXYCONTIN'S REFORMULATION ON OPIOID ADDICTION, OVERDOSE, AND RELATED OUTCOMES

We identified no reliable, longitudinal evidence regarding the effect of OxyContin's reformulation on the risk of addiction or the progression of opioid use disorder. Using a difference-in-differences analysis of cross-sectional survey data, Wolff (2020) found no apparent effect of OxyContin's reformulation on the odds of prescription pain reliever use disorder. The impact of OxyContin's reformulation on the incidence or progression of opioid use disorder remains an important unanswered question. The question of reformulated OxyContin's net impact on opioid overdose rates in the U.S. has also been exceedingly difficult to study due to the evolving and multidimensional nature of the U.S. opioid epidemic, with geographically heterogeneous increases in heroin availability and overdose, law enforcement interventions, and a multitude of policies relating to opioid prescribing, prescription drug monitoring programs, and naloxone dispensing.

Studies examining spontaneous adverse event reports in the U.S. suggested reformulation was associated with a reduction in spontaneous reports of OxyContin-related deaths. However, many factors can influence spontaneous reporting over a product's lifecycle so analyses of spontaneous adverse event reports cannot be used to make inferences on the impact of reformulated OxyContin on the risk, or incidence, of fatal overdose.

Two studies (Alpert 2018, Evans 2019) evaluated the impact of the reformulation on prescription opioid-related mortality. While Alpert (2018) found no significant net impact of the reformulation on prescription opioid-related mortality, Evans et al. (2018), in contrast, found that the introduction of ADF OxyContin significantly reduced prescription opioid-related mortality, especially in areas with "high" exposure to oxycodone and "low" exposure to heroin, and suggested that the availability of heroin might be an important factor in the effect of abuse-deterrent formulations on opioid-related mortality. However, Alpert (2018) also found that the reformulation may have led to a large increase in heroin-related mortality. Similarly, Evans (2018) found a statistically significant trend break in heroin poisoning encounters and heroin-related mortality one month after the introduction of ADF OxyContin. Evans also showed that the increase in heroin poisoning encounters and heroin death was starkest in areas with "high" levels of oxycodone, and "high" levels of heroin availability prior to the reformulation. Using similar methods to Alpert (2018), Powell (2020) extended the follow-up period to explore the impact of OxyContin's reformulation on fatal overdoses involving synthetic opioids (e.g., fentanyl) and opioids overall (including both prescription and illicit). They estimated that in the U.S., the reformulation has increased overall fatal opioid overdoses by 8.7 overdoses per 100,000 individuals as of 2017.

The national-level impact of OxyContin's reformulation on opioid overdose and other abuse-related outcomes likely depends on the backdrop against which the intervention took place, with regard to factors such as availability of treatment and other opioids as well as other policy interventions. In Australia, it appears the reformulation had little to no impact on overdoses, ambulance runs, ED visits, calls to helplines, number of patients receiving MAT, or total treatment admissions (Larance 2014). However, one Australian

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study found a decline in treatment episodes for oxycodone (Larance 2014) post-reformulation and another found increases in both ED visits and ambulance rides associated with heroin use (Lam 2019). At the time of OxyContin's reformulation in the U.S., other efforts were being initiated to try to reduce the diversion and abuse of prescription opioids. Many of these efforts were focused on reducing the excess prescription of OxyContin and other oxycodone formulations originating from unregulated pain clinics, or "pill mills," which were heavily concentrated in Florida. An analysis by Evans (2018) exploring the impact of the Florida "pill mill crackdown" estimated that these actions explained about 25% of the observed increase in U.S. heroin mortality rates following OxyContin's reformulation. Nonetheless, due to the complex mixture of concurrent interventions and secular trends, as well as geographic differences in availability and use of OxyContin and other prescription and illicit opioids, including both heroin and illicitly manufactured fentanyl, it remains difficult to determine the precise role of OxyContin's reformulation in overall opioid-involved mortality trends.

Evidence of other outcomes associated with OxyContin's reformulation is limited. We found one study (Powell 2019) that noted an association between higher pre-reformulation OxyContin misuse rates and greater increases in post-reformulation hepatitis C infection rates at the state-level. We found no other studies specifically examining the impact of OxyContin's reformulation on infectious disease transmission (e.g., HIV) and other injection-related adverse outcomes (e.g., endocarditis), despite the growing interest in these issues by both National Academy of Sciences Engineering and Medicine (NASEM 2020) and Infectious Disease Society of America (IDSA 2018).

5   CONCLUSIONS

This review of the published literature was intended to supplement and provide context for DEPI's review of the four formal PMR studies assessing the effect of OxyContin's reformulation on abuse and overdose, and our findings must be considered in conjunction with those from the PMR studies. Published studies indicate that sales of OxyContin declined after its reformulation, in both the U.S. and other countries, although this decline may have occurred due to a variety of reasons. Rates of reported nonmedical use in the general U.S. population similarly declined, returning to rates observed several years before the reformulation. It remains unclear to what extent declines in OxyContin prescribing drove declines in the prevalence of its nonmedical use, versus decreases in OxyContin's abuse potential driving reduced demand and prescribing. Although the published literature in this area has serious limitations, the totality of evidence from studies employing a variety of methods suggests that OxyContin's reformulation reduced its attractiveness for diversion and, to some extent, abuse, particularly non-oral abuse in populations already abusing prescription opioids through tampering and non-oral routes.

The literature does not provide definitive answers regarding the net public health impact of OxyContin's reformulation in the U.S. We identified no reliable, longitudinal evidence regarding the effect of OxyContin's reformulation on the risk of addiction, the trajectory of opioid use disorder, or the incidence of opioid overdose. Polysubstance abuse is common, and drug use patterns are dynamic and likely influenced by many factors, including drug availability, price, and other sociocultural factors. Overall, the literature suggests that some individuals shifted their use of OxyContin from non-oral to oral routes, while others

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switched to other prescription and/or illicit opioids after OxyContin's reformulation. These apparent substitution effects varied across populations, likely reflecting heterogeneity in baseline substance abuse patterns and the availability and cost of substitutes. Some data suggest OxyContin's reformulation was associated with reductions in rates of fatal overdoses involving prescription opioids in the United States, but these declines were offset by increases in fatal overdoses from illicit opioids. However, the complex mixture of concurrent interventions, secular trends, and geographical heterogeneity in opioid availability and use patterns makes it difficult to determine the precise role of ADF OxyContin in these trends.

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6 APPENDICIES

Appendix Table 1: PMR Related Studies (N=15)

Author, Year	Title	Data source	Funding source	Relevant PMR review
Butler, 2011	Abuse risks and routes of administration of different prescription opioid compounds and formulations	NAVIPRO-ASIMV	Purdue	PMR 3051-1
Butler, 2013	Abuse rates and routes of administration of reformulated extended-release oxycodone: initial findings from a sentinel surveillance sample of individuals assessed for substance abuse treatment	NAVIPRO-ASIMV	Purdue	PMR 3051-1
Butler, 2018	Relative Abuse of Crush-Resistant Prescription Opioid Tablets via Alternative Oral Modes of Administration	NAVIPRO-ASIMV	Collegium Pharmaceutical	PMR 3051-1
Cassidy, 2014	Changes in prevalence of prescription opioid abuse after introduction of an abuse-deterrent opioid formulation	NAVIPRO-ASIMV	Endo Pharmaceutical	PMR 3051-1
Cassidy, 2017	Abuse of reformulated OxyContin: Updated findings from a sentinel surveillance sample of individuals assessed for substance use disorder	NAVIPRO-ASIMV	Purdue	PMR 3051-1
Cicero and Ellis, 2015	Abuse-deterrent formulations and the prescription opioid abuse epidemic in the United States: lessons learned from OxyContin.	SKIP-RAPID*	Denver Health and Hospital Authority	PMR 3051--3
Cicero and Ellis, 2016	A tale of 2 ADFs: differences in the effectiveness of abuse-deterrent formulations of oxymorphone and oxycodone extended-release drugs.	SKIP-RAPID*	Washington University, RADARS System	PMR 3051-3
Cicero, 2012	Effect of abuse-deterrent formulation of OxyContin	RADARS-OTP/SKIP	Denver Health and Hospital Authority	PMR 3051--3
Coplan, 2013	Changes in oxycodone and heroin exposures in the National Poison Data System after introduction of extended-release oxycodone with abuse-deterrent characteristics	NPDS	Purdue	PMR 3051--2

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Coplan, 2016	The effect of an abuse-deterrent opioid formulation (OxyContin) on opioid abuse-related outcomes in the postmarketing setting	RADARS, PCC, Marketscan, Kentucky, FAERS, IQVIA NPA	Purdue	PMR 3051-1 to 4
Coplan, 2017	Corrigendum: The effect of an abuse-deterrent opioid formulation (OxyContin) on opioid abuse-related outcomes in the postmarketing setting	Correction	Not applicable	PMR 3051-1 to 4
Dart, 2015	Trends in opioid analgesic abuse and mortality in the United States	RADARS-TCP/PCC	Denver Health and Hospital Authority	PMR 3051-2 & 3051-3
Larochelle, 2015	Rates of opioid dispensing and overdose after introduction of abuse-deterrent extended-release oxycodone and withdrawal of propoxyphene	Optum claims	Health Resources and Services Administration, Ryoichi Sasakawa Fellowship, Harvard Pilgrim Health Care Institute	PMR 3051-4
Severtson, 2013	Reduced abuse, therapeutic errors, and diversion following reformulation of extended-release oxycodone in 2010	RADARS-PCC	Purdue	PMR 3051--2
Severtson, 2016	Sustained reduction of diversion and abuse after introduction of an abuse deterrent formulation of extended release oxycodone	RADARS-OTP/SKIP/StreetRx	Denver Health and Hospital Authority, RADARS System	PMR 3051-3

*Researchers and Patients Interacting Directly

Appendix Table 2: Non-PMR-Related Studies (N=31)

Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Alpert, 2018	Supply-side drug policy in the presence of substitutes: evidence from the introduction of abuse-deterrent opioids," NBER Working Paper no. 23031	National Bureau of Economic Research (NBER)/ RAND	NSDUH, DEA ARCOS, National Vital Statistics System (NVSS)	Objective: Evaluate impact of OxyContin reformulation on rates of nonmedical use of OxyContin and heroin mortality at the state-level Design: Difference-in-difference study using serial cross-sectional data sourced from community-dwelling adults in NSDUH (2004-2013) Population: United States Exposure: State-level rates of nonmedical use of OxyContin prior to reformulation (2004-2009) Outcome: State-level rates of nonmedical use of OxyContin and heroin mortality post-reformulation (2010-2013)	Each additional percentage point of initial OxyContin misuse associated with a decrease in OxyContin misuse of 0.8 percentage points and 2.5 to 3.1 additional heroin deaths per 100,000 population, depending on model adjustment. Rates of past-year OxyContin misuse declined by more than 50% after reformulation in states with the highest initial OxyContin misuse. Rate of OxyContin misuse increased slightly in states with the lowest rates of initial OxyContin misuse. Reformulation does not appear to affect overdose rates for all opioids in three-year period following reformulation. Reformulation associated with increases in heroin mortality, especially in states with high rates of oxycontin misuse. Nonmedical use of other pain relievers is not associated with increase in heroin mortality.	Impact of reformulation beyond 2013 is unclear, as opioid mortality beyond this point was not examined. No data were provided on route of abuse, nor changes in routes of abuse following the reformulation. No examination of past-year initiation of other prescription opioid misuse or heroin over the same time period. Examined drug overdose mortality, but not heroin use or non-fatal overdose. No examination of differences in prescription opioid overdose deaths due to natural and semi-synthetic opioids, methadone, and synthetic opioids (such as fentanyl), as deaths from these substances were aggregated.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Argoff, 2013	Validity testing of patient objections to acceptance of tamper-resistant opioid formulations	Endo	Clinical experience	Objective: Describe common reported patient objections to being switched from original to ADF opioids Design: Qualitative/ Descriptive study (August 2011) Population: Convenience sample of three pain management clinicians Exposure: ADF OxyContin Outcome: Reported patient objections to switching to ADF	Patients reported difficulty swallowing pills and feeling that the drug was not working. Patients also report no coverage in formulary and higher expense than previous opioids.	Patient objections reported by clinicians, may not be fully representative of patient experience. No information on frequency of patient objections to ADFs nor whether patients switched to non-ADF opioids or other drugs.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Buer, 2014	Does the new formulation of OxyContin® deter misuse? A qualitative analysis	Purdue	Interviews	Objective: Examine changing drug use patterns as a result of the reformulation of OxyContin

Design: Qualitative /Descriptive study (December 2010-September 2011)

Population: Adults living in rural Appalachian county in Kentucky who had misused OxyContin (N=25).

Exposure: Reformulation of OxyContin in August 2010

Outcome: Drug use patterns (drug preference and route of abuse) after the reformulation | Most commonly misused prescription opioids changed after reformulation. Most participants did not think ADF OxyContin could be injected or snorted and did not want to try. Other participants believed OxyContin ADF was difficult to inject or snort, less potent and long lasting compared to the original formulation. Misuse of original OxyContin was replaced with IR oxycodone post-reformulation, although original OxyContin was still preferable. | Small number of participants, all recruited from community centers in rural Appalachia. Reported behavior and changes in abuse patterns not generalizable to larger US population. Participants represent a select group of individuals with past abuse of original formulation OxyContin. |

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Carlson, 2016	Predictors of transition to heroin use among initially non-opioid dependent illicit pharmaceutical opioid users: A natural history study	National Institute of Drug Abuse (NIDA) Grant	study interviews	Objective: Investigate predictors of transition to heroin use Design: Prospective Cohort (May 2010-May 2013) Population: Individuals between 18-23 years who used prescription opioids illicitly and had no history of opioid dependence or heroin use at baseline (N=362) Exposure: Original or ADF OxyContin use, non-oral route of abuse, past use of illicit POs to get high, age of PO initiation Outcome: Time to initiation of heroin use	Over 36 months, 7.5% (n=27) of participants-initiated heroin use; rate of heroin initiation was 2.8% per year. From May 2010 until November 2010, incidence rate was 4.7 per 100 person-years (13 transitions in 276 person years). From December 2010 to May 2013, incidence rate was 2.1 per 100 person-years (14 transitions in 658 person-years). Mean length of prescription opioid use at first reported heroin use was 6.2 years. 100% of heroin initiators and 45% of those who did not initiate heroin use during the study reported lifetime use of Oxycontin. Lifetime prescription opioid (PO) dependence, early age of PO initiation, using illicit POs to get high but not to self-medicate a health problem, and ever using PO non-orally most often were significant predictors of heroin initiation in adjusted analyses. Use of ADF OxyContin was not a significant predictor of heroin initiation.	Small number of individuals exposed to ADF OxyContin compared to original OxyContin. Refusal to switch from original to ADF was not measured. Comparison of heroin initiation rates in initial period (May -November 2010) and later period (December 2010- May 2013) difficult to interpret, since ADF OxyContin marketed for about half of initial period. Limited generalizability given recruited sample was young, with some participants still financially dependent on family.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Cheng, 2018	Incidence of nonmedical use of OxyContin and other prescription opioid pain relievers before and after the introduction of OxyContin with abuse deterrent properties	Purdue	NSDUH	Objective: Examine trends of past-year initiation of nonmedical OxyContin use before and after OxyContin ADF Design: Ecologic Study (Time series: 2004-2015) Population: NSDUH sample of community residents ages 12 and older, excluding those with past nonmedical OxyContin use more than a year prior to survey. Exposure: OxyContin reformulation Outcome: Incident rates of past-year initiation of nonmedical OxyContin use based on weighted number of newly incident users divided by person-year count for that year.	Interrupted time series analysis found lower observed incidence of past-year initiation of nonmedical use of OxyContin after 2010 when compared to predictions based on pre-2010 trends, resulting in ~137,400 fewer incident cases. Past-year initiation of OxyContin misuse declined following reformulation. Sub-analysis restricted to 12-21-year-old respondents found incidence of initiation of nonmedical use of OxyContin was lower in 2012 than in 2010, after controlling for age and cohort-related variations. In sub-analysis, same finding was not observed for initiation of nonmedical use of other prescription opioids.	Not clear whether decline in nonmedical use of OxyContin directly attributable to reformulation, since it does not account for other policy interventions, changes in prescription volume, or other factors potentially affecting rates of incident nonmedical OxyContin use. Study reports sub-analysis results in 12-21 year-old-respondents, but does not explore this association among respondents of other ages. Study not able to compare past-year initiation of nonmedical OxyContin use with comparable formulations (e.g., other ER/LAs), only compared with nonmedical use rates of all other prescription pain relievers.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Chilcoat, 2016	Decreased diversion by doctor-shopping for a reformulated extended release oxycodone product (OxyContin)	Purdue	Claims (IQVIA LRx)	Objective: Examine whether "doctor-shopping" of OxyContin and other opioid products in the periods decreased following the reformulation Design: Ecologic pre-post study (2009-2013) Population: National un-projected longitudinal data from patients in IMS LRx database which covers approximately 65% of retail prescriptions in the United States. Exposure: OxyContin reformulation Outcome: "Doctor shopping" rates for six-month calendar intervals spanning before and after reformulation. "Doctor shopping" definition: individuals with prescriptions from at least two unique prescribers and three unique pharmacies during "overlap events" defined as at least one day of overlap between prescriptions based on start date and days' supply	Comparing pre- versus post-reformulation time periods for OxyContin and comparators, the rate of "doctor shopping" decreased 50% (95 CI: -53%, -47%) for OxyContin, but a similar decline not observed for comparators. Largest decreases in rates among young adults (73%), individuals paying with cash (61%), and individuals receiving highest available dose (62%).	"Doctor-shopping" metrics not a direct measure of abuse, given assumption all individuals seeking drugs for abuse are seeking these substances from multiple prescribers and multiple pharmacies to avoid detection. May be an association between these behaviors and abuse/diversion but use of multiple prescribers and pharmacies potentially a poor predictor of actual abuse-related behavior.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Cicero and Ellis, 2015	Abuse-Deterrent Formulations and the Prescription Opioid Abuse Epidemic in the United States: Lessons Learned from OxyContin	Denver Health and Hospital Authority (DHHA)	SKIP, RAPID	Objective: Investigate whether ADF OxyContin discouraged abuse overall, caused for a shift in preference to other drugs, or altered routes of administration. Design: Cross-sectional study using a mixed methods approach involving structured surveys and qualitative interviews (May- July 2014) Population: Clients ages 18 and above entering treatment for OUD who agreed to participate in online survey interview (RAPID participants, n=244). Exposure: Use of original or ADF OxyContin and/or other opioids Outcome: Continued abuse of OxyContin and/or other opioids and change in routes of abuse.	62.7% participants indicated any lifetime abuse of original OxyContin. Among these, 33.3% indicated continued abuse of OxyContin after reformulation, 33.3% reported replacing OxyContin with other drugs as a result of the ADF, 3% reported ADF influenced their choice to stop using drugs, 30% indicated not using the drug enough to change their choice. Of those who reported switching drugs because of ADF, 70% reported using heroin. Past month use of heroin increased during 4-year period after ADF, 65% of individuals who switched from OxyContin to heroin reported doing so because it was more readily available and cheaper. Some participants reporting abuse of both OxyContin formulations also reported switching from injection/inhalation to swallowing whole following reformulation. Others reported defeating abuse deterrent properties and continuing to inject/inhale.	Cross-sectional study measuring past use of substances retrospectively, possibly influenced by recall bias if current users of different substances recall or report past use differently. Individuals surveyed nearly four years following reformulation, thus high likelihood of recall bias. Small sample of individuals seeking treatment for OUD not likely representative of entire population potentially affected by the reformulation or those who seek treatment for OUD.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Coplan, 2016	The effect of an abuse-deterrent opioid formulation (OxyContin) on opioid abuse-related outcomes in the postmarketing setting.	Purdue	RADARS (multiple data streams), NPDS, Marketscan, Kentucky, FAERS, IQVIA NPA	Objective: Examine changes in opioid abuse via oral and nonoral routes, doctor-shopping in 10 separate investigations, 3.5 years following reformulation. Design: Review of multiple studies Exposure: ADF OxyContin Outcomes: Results of these studies were published/reviewed elsewhere.	Abuse of OxyContin varied following the reformulation based on poison center surveillance, drug treatment, and prescription claims data. Doctor-shopping and overdose fatalities reported decreases over the same time period. Abuse of other non-ADF opioids also decreased based on various data, although observed declines were smaller. Declines in OxyContin abuse were greater for nonoral routes.	Limited details on study methods. Each data source and analysis has limitations (majority discussed elsewhere in this review). Results reflective of a selected, subset of findings and analyses from larger studies.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Degenhardt, 2015	The introduction of a potentially abuse deterrent oxycodone formulation: Early findings from the Australian National Opioid Medications Abuse Deterrence (NOMAD) study	Mundipharma Australia, Australian Government, National Health and Medical Research Council.	NOMAD prospective cohort study, sales, surveys, safe injection sites, needle exchange programs	Objective: To examine the potential impact of the April 2014 introduction of ADF OxyContin in Australia Design: Descriptive analysis of preliminary data from the prospective cohort study and other data sources Population: people who inject drugs regularly, individuals visiting supervised injecting centers and needle-syringe programs 2009-2014, a cohort of 606 people tampering with pharmaceutical opioids Exposure: OxyContin Reformulation Outcome: OxyContin and other opioid sales, visits to supervised injection sites and needle exchange programs, past-month abuse of OxyContin and other opioids	Oxycodone sales steadily increased 2009-2014, 24% decline in sales of 80mg OxyContin units sold after reformulation (April 2014). Comparing the five months pre- and post-reformulation, visits to inject oxycodone at one safe injection site declined from 62% to 5% of visits for all drugs. In NOMAD cohort proportion of individuals who reported past-month nonmedical use of OxyContin 80mg declined from 56% in the three months pre-reformulation to 24% (16% original Oxycontin; 8% reformulated OxyContin) three months post-reformulation.	Interrupted time series analysis not possible due to a lack of sufficient post-reformulation data points. Study did not account for decreases in OxyContin sales when estimating changes in proportion of individuals reporting injecting oxycodone pre- and post-reformulation. Data from safe injection sites, needle exchange programs lacked OxyContin-specific endpoints and only able to provide information on oxycodone or opioids in aggregate.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Evans, 2018	How the reformulation of OxyContin ignited the heroin epidemic—working paper	Natural Bureau of Economic Research (NBER)	ARCOS, NSDUH, NVSS, Marketscan	Objective: Examine whether ADF OxyContin was responsible for the rising rate of heroin and overall opioid overdose deaths Design: Ecologic/ Trend (2004-2014) Population: United States Exposure: Pre-reformulation, state-level oxycodone shipment rates (2004-2009) and pre-reformulation heroin mortality rates (2008-2009) Outcome: Post-reformulation state-level (2010-2014) heroin, prescription opioid, and overall opioid mortality	Statistically significant trend break indicating increase in heroin-related mortality one month after the introduction of ADF OxyContin (September 2010). States with above median per-capita pre-reformulation oxycodone shipments experienced post-reformulation heroin death rates rise from <0.1 to >0.4; below-median states experienced smaller increases. In states with high levels of pre-reformulation oxycodone use and limited heroin availability, reformulation may have slowed increase in total opioid-related deaths, but in states with high exposure to both oxycodone and heroin, combined opioid death rates increased. Additional analyses estimated that concurrent interventions (Florida pill mill crackdown, PDMPs) explained a maximum of 25% of the change in heroin mortality.	Due to ecological design, can only examine the impact of the reformulation at the state-level. Possible impact of other interventions not fully accounted for using analytic approach. Rates of pre-reformulation oxycodone shipments may not be a good measure of OxyContin availability or use and rates of pre-reformulation heroin deaths may not be a good measure of heroin use at the state-level.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Gomes, 2018	Trends and uptake of new formulations of controlled-release oxycodone in Canada	Canadian Institutes of Health Research. Grant Number: DSE-146021 The Canadian Network for Observational Drug Effect Studies (CNODES)	IQVIA dispensing data from community pharmacies in Canada	Objective: To examine rates of dispensing and market share of ADF OxyContin and generic non-ADF ER oxycodone before and after reformulation Design: serial cross-sectional study of ER oxycodone dispensing from community pharmacies across Canada between October 2007 and April 2016 Population: 6000 community pharmacies across Canada Exposure: OxyContin reformulation Outcome: dispensing rates of ER oxycodone	National dispensing rate of OxyContin declined 44.6%, from 26.4 tablets per 100 persons (February 2012) to 14.6 tablets per 100 persons (April 2016). Although dispensing for generic ER oxycodone increased after reformulation, rate of overall ER oxycodone dispensing decreased after reformulation. Uptake of generic ER oxycodone after OxyContin reformulation varied widely by province.	No major limitations. Decline in reformulated OxyContin sales could be due to exclusion from provincial drug formularies or other factors.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Havens, 2014	The impact of a reformulation of extended-release oxycodone designed to deter abuse in a sample of prescription opioid abusers	Purdue	Structured interview	Objective: Determine how ADF OxyContin was abused relative to other opioids Design: Cross-sectional survey (December 2010-September 2011) Population: Individuals with past history of OxyContin abuse in the past six months residing in rural Kentucky (N=189) Exposure: original/ADF OxyContin, non-ADF IR oxycodone Outcome: Past-30-day OxyContin or IR oxycodone abuse, overall and via snorting and injection	Most participants reported abusing original OxyContin (74%) and IR oxycodone (74%) one month prior to the reformulation. Reported past 30-day OxyContin abuse decreased significantly from time of reformulation to September 2011. Declines observed for overall abuse, snorting, and injecting. Non-ADF IR oxycodone abuse increased during first year after reformulation, increases observed for overall abuse, snorting, and injecting.	Cross-sectional study using retrospective reports of past abuse, subject to misclassification and recall bias. Study sampled people over a short time period and unable to provide information on changes in abuse patterns over longer period. Sample recruited using purposive sampling technique (PST) leading to non-random and similar sample with respect to abuse patterns. Results likely reflective of a small subset of OxyContin abusers based on geographic location.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Hwang, 2015	Impact of abuse-deterrent OxyContin on prescription opioid utilization	AHRQ and Robert Wood Johnson grants	IQVIA NPA	Objective: Examine whether ADF OxyContin led to decrease in OxyContin dispensing and/or substitution of other opioids at an aggregate level Design: Ecologic/Pre-post study Population: Prescription dispensing data (IQVIA) from 2008-2012 Exposure: ADF OxyContin Outcome: Change in prescription dispensing for OxyContin and other prescription opioids	After adjusting for changes in the generic ER Oxycodone market, OxyContin prescription dispensing decreased by 17.6K prescriptions per month following reformulation, representing a change from a 4.9% increase in dispensing pre-reformulation to a 23.8% decrease in dispensing post-reformulation. Analyses of IR oxycodone and hydrocodone did not reveal significant differences in prescription volume or slope after the reformulation. Decline in dispensing of ER oxycodone products leveled out within a year after reformulation.	Did not examine whether decline in oxycodone ER led to switching to other prescription opioid analgesics. Unable to explain reason for decline in prescriptions after reformulation. Short length of follow-up after reformulation.

Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Jauncey, 2018	The impact of OxyContin reformulation at the Sydney Medically Supervised Injecting Centre: Pros and cons	No funding information provided	Australian Safe injection site data	Objective: To assess impact of reformulated OxyContin on the number of safe injection site visits and the number and type of opioid overdoses occurring onsite Design: Interrupted time series February 2007 to February 2016 Population: Individuals visiting safe injection sites in Sydney, Australia Exposure: OxyContin reformulation Outcome: monthly counts of site visits	Observed declines in OxyContin-related visits and overdoses at one Syndey, Australia supervised injection center. Declines were offset by increases in visits for morphine and fentanyl. Declines in overdoses offset by increases in heroin- and morphine-related overdoses.	Unclear to what extent changes in nonmedical OxyContin use were a result of the ADF properties versus other factors, such as OxyContin sales and availability, or price of other drugs. The results of this study may not be generalizable to all injection drug user populations or geographic areas.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Jones, 2017	Trends in the nonmedical use of OxyContin, United States, 2006 to 2013	Federal- US Department of Health and Human Services (HHS)	NSDUH	Objective: Examine changes in nonmedical use of OxyContin following reformulation Design: Ecologic serial cross-sectional study (2006-2013) Population: Non-institutionalized U.S. population ages 12 and above Exposure: ADF OxyContin (2010) Outcome: Self-reported past-year nonmedical use of OxyContin (2006-2013)	Prevalence of past-year OxyContin nonmedical use in 2013 (0.5%), 3 years after reformulation, prevalence significantly lower than the prevalence in reformulation year (2010, 0.7%, p<0.05), but similar to years pre-reformulation (2006-2009) and post-reformulation (2011-2012). Those reporting lifetime injection drug use past-year pain reliever abuse/dependence did not differ with respect to prevalence of past-year nonmedical OxyContin use pre- and post-reformulation.	Study did not examine or adjust for differences in prescription dispensing rates of OxyContin, which are likely related to prevalence of nonmedical OxyContin use.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Lam, 2018	Trends in heroin and pharmaceutical-opioid related harms in Victoria, Australia up to 2018	Faculty of Medicine, Nursing and Health Sciences, Monash University	Australia ambulance and ED data	Objective: Examine impact of reformulation on opioid-related ambulance and ED attendance in Victoria, Australia Design: Interrupted time series January 2012 to October 2018 Population: Individuals in Victoria, Australia aged 12+ years Exposure: OxyContin reformulation Outcome: rates of quarterly ED and ambulance attendence	Post-reformulation slight (-.08) but statistically significant decrease in quarterly ED visits involving pharmaceutical opioids per 100,000 people. No significant difference in rate of prescription opioid related ambulance attendances after reformulation. Pre-reformulation trends in heroin-related ambulance and ED visits stable. After reformulation, significant increase in rates of heroin-related ambulance and ED visits.	Lack of OxyContin specific outcomes. Analysis did not account for decreases in OxyContin dispensing after reformulation or any possible changes in heroin supply or cost.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Larance, 2018	The effect of a potentially tamper-resistant oxycodone formulation on opioid use and harm: main findings of the National Opioid Medications Abuse Deterrence (NOMAD) study	Mundipharma Australia, Australian Government, National Health and Medical Research Council.	NOMAD prospective cohort study, sales, surveys, safe injection sites, needle exchange programs, ambulance use, ED visits, treatment admissions	Objective: To examine the potential impact of the April 2014 introduction of ADF OxyContin in Australia Design: assesses changes in outcomes pre and post-reformulation using interrupted time series Population: people who inject drugs regularly, individuals visiting supervised injecting centers and needle-syringe programs, cohort of people tampering with pharmaceutical opioids Exposure: OxyContin reformulation Outcome: OxyContin and other opioid sales, visits to supervised injection sites and needle exchange programs, past-month abuse of OxyContin and other opioids, ambulance calls, ED visits, helpline calls, treatment admissions	Reduction in sales of higher strength OxyContin tablets. Reductions in OxyContin tampering and injection among those who tampered with prescription opioids pre-reformulation. In NOMAD cohort, 18% attempted tampering with reformulated OxyContin 1-4 months after introduction; after 12 months, tampering attempts increased to 27%. Analyses of ambulance calls, ED visits, helpline calls, and overall treatment admissions found no evidence of an association between reformulation and changes in these outcomes. Authors report an average of 17 fewer new or subsequent treatment admissions per month where oxycodone was primary opioid of concern.	Did not account for decreases in OxyContin sales when estimating changes in the proportion of individuals reporting injecting oxycodone pre- and post-reformulation. Data from safe injection sites, needle exchange programs, ambulance runs, ED visits, treatment seeking lacked OxyContin-specific endpoints, thus only able to provide information on oxycodone or opioids in aggregate. No examination of changes in drug use patterns among individuals in cohort during pre-reformulation comparison period. Due to limited geographic coverage of these data, possible that some post-reformulation changes in drug abuse patterns went undetected.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Lebin, 2019	Scoring the best deal: Quantity discounts and street price variation of diverted oxycodone and oxymorphone	DHHA	Street Rx database	Objective: Compare changes in the geometric mean price of crushable to non-crushable oxycodone products Design: Descriptive study of crowdsourced data (2014-2016) Population: Anonymous street drug price reports from a crowdsourcing website that reports street prices for diverted drugs. Exposure: Crush or non-crush resistant formulation of product reported Outcome: Street price of product	In unadjusted model, price of crushable products was 30.4% higher compared to crush resistant products. In adjusted model, price of crushable products was 19.5% higher compared to ADFs. Higher dosage strength was associated with lower price per milligram as was bulk purchase. Time of year not significantly associated with a lower/higher price when adjusted. Lower potency/drug likability, high dosage strength, crush-resistant opioids, and bulk purchases were significantly cheaper.	Study examined prices of different products 4-6 years after OxyContin reformulation and unable to compare street price for original OxyContin to IR oxycodone for same dosage strength. Likely that crushable oxycodone estimates largely reflect IR oxycodone prices, as original OxyContin not easily available during the study period. Reported drug price information subject to selection bias and unclear how well the data represents the population of individuals who engage in nonmedical OxyContin or other prescription opioid use.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
McNaughton, 2014	Monitoring of internet forums to evaluate reactions to the introduction of reformulated OxyContin to deter abuse	National Institute of Health (NIH) grant	Inflexxion Web monitoring	Objective: Examine prevalence of web posts from individuals who reported abuse of specific products to evaluate changes in endorsement Design: Cross-sectional study of web posts (June 2008-September 2012) Population: Web posts from self-reported individuals who reported abuse of OxyContin, Dilaudid, and Vicodin from Internet message boards encouraging or discouraging product abuse Exposure: Reformulated OxyContin Outcome: Encouragement of product abuse	43% of OxyContin posts endorsed abuse of the product in the pre-reformulation period compared to 22% in the post-reformulation period. Percent of posts for Vicodin and Dilaudid encouraging abuse did not change from pre-reformulation (Vicodin: 36%, Dilaudid: 46%) to post-OxyContin reformulation period (Vicodin: 35%, Dilaudid: 47%).	Did not collect information on changing routes of abuse or switching from original OxyContin to other substances (e.g. Vicodin or Dilaudid). Representativeness of web posts compared to actual population that abuses these specific substances unclear.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Michna, 2014	Use of prescription opioids with abuse-deterrent technology to address opioid abuse	Purdue	Marketscan	Objective: Examine frequency of transitioning to ADF OxyContin or other non-ADF opioids, and the rate of future opioid abuse claims based on opioid prescription filled following reformulation Design: Retrospective Claims Cohort study (2010-2012) Population: Commercially insured individuals between 18 and 64 with primary ER/LA opioid of ER oxycodone from February-August 2010. Exposure: ADF OxyContin prescription Outcomes: Switching to other prescription opioids, future opioid abuse healthcare claims	31% of ER Oxycodone recipients did not switch to ADF OxyContin after reformulation, instead switching to non-ADF ER/LA opioids (21.3%), IR/SA opioids (7.1%), or having no further claims (2.2%). Higher rate of opioid abuse diagnosis claims observed for patients who switched to non-ADF ER/LA opioids (Relative Risk: 1.89, p<0.001) or discontinued ER/LA opioid treatment (Relative Risk: 3.08, p<0.001). The rate of opioid abuse claims highest among those who switched from ER oxycodone to IR/SA opioids (Relative Risk: 3.19, p<0.001).	Cash payments or use of drugs obtained outside of prescription not captured. Claims-based ascertainment of opioid abuse has low sensitivity and specificity for opioid abuse or use disorder. Limited duration of follow-up, abuse may develop or be detected later. Did not account for differences in exposed person-time among patients who did and did not switch to non-ADF opioids or discontinued opioids altogether when examining rate of subsequent opioid abuse claims. No control time period allowing for assessment of opioid switching patterns or abuse outcomes unrelated to reformulation, so unable to determine if change attributable to reformulation or other factors.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Peacock, Degenhardt, Hordern, 2015a	Methods and predictors of tampering with a tamper-resistant controlled-release oxycodone formulation	Mundipharma	Interviews from prospective cohort in NOMAD study	Objective: Examine methods and predictors of tampering with reformulated OxyContin Design: Prospective cohort study Population: Individuals who tamper with prescription opioids in Australia Exposure: OxyContin reformulation Outcome: ever and past-month use and tampering	Among individuals who regularly tampered with prescription opioids and had tampered with original OxyContin, 29% subsequently ever used and 18% ever tampered with reformulated OxyContin. Participants had six-fold increased odds of rating reformulated OxyContin painful to inject compared to original formulation.	Study did not assess rates of switching to other pharmaceutical or illicit opioids post-reformulation. Results of studies based on self-reported data are susceptible to recall and social desirability bias. No examination of changes in drug use patterns among individuals in cohort during pre-reformulation comparison period.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Peacock, Degenhardt, Larance, 2015b	A typology of people who tamper with pharmaceutical opioids: responses to introduction of a tamper-resistant formulation of controlled-release oxycodone	Purdue	NOMAD prospective cohort study	Objective: To identify categories of people who tamper with pharmaceutical opioids and assess to changes in drug use and related harms following the reformulation of OxyContin

Design: Latent class analysis

Population: Individuals who tamper with prescription opioids in Australia

Exposure: OxyContin reformulation

Outcome: past-month use, tampering, and harms | Identified four primary groups of individuals who regularly tamper with prescription opioids: frequent opioid substitution therapy (OST; buprenorphine/methadone) 39%, mixed OST/heroin 7%, infrequent pharmaceutical/heroin use 44%, and frequent oxycodone use 11%. Largest reduction occurred in the frequent oxycodone group (past-month use of OxyContin 80mg: 100% pre-reformulation, 19% post-reformulation). Compared to other groups, larger proportion of individuals in frequent oxycodone group reported tampering and successfully tampering with reformulated oxycodone in past month. | Unable to assess effects of reformulation more than 4 months after introduction of reformulation (Wave 2). Results may change if Wave 3 results included. Findings based on a small number of participants, particularly frequent oxycodone group (n=58). Latent classes determined based on past-month drug use and did not assess changes in drug use that may have affected class membership post-reformulation. Other factors may have contributed to observed reductions. |

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Powell, 2019	A transitioning epidemic: how the opioid crisis is driving the rise in hepatitis C	National Institute of Drug Abuse (NIDA) Grant	NSDUH and CDC National Notifiable Diseases Surveillance System.	Objective: Examine whether states with higher rates of OxyContin misuse before the reformulation experienced faster growth of hepatitis C infections Design: Ecologic study using difference-in-difference methods (2004-2015) Population: United States Exposure: Pre-reformulation (2004-2015) rates of nonmedical use of OxyContin at the state level Outcome: Rate of acute hepatitis C infections at the state level (2004-2015)	Hepatitis C infections increased three times faster in states most affected by reformulation—states with above-median rates of initial OxyContin misuse vs. states with below-median rates. This differential increase began immediately after reformulation in 2010. Five years after reformulation, each percentage point of non-medical OxyContin use prior to reformulation increased hepatitis C infections by 1.32 cases per 100,000 inhabitants. Before reformulation, almost no difference in hepatitis C infection rates across two groups of states.	Possible that other factors, such as changes in availability of prescription opioids or increased availability of inexpensive heroin, contributed to rise in hepatitis C infection rates nationally. Hepatitis C infection may be differentially under-reported across states. Did not account for impact of reformulation of Opana ER, introduced in 2012, which resulted in shift from snorting to injecting this product.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Powell, 2020	The Evolving Consequences of OxyContin Reformulation on Drug Overdoses	National Bureau of Economic Research (NBER)	ARCOS, NSDUH, NVSS, Marketscan	Objective: Evaluate the association between pre-reformulation (2004-2009) rates of nonmedical use of OxyContin and post-reformulation (2010-2017) mortality rates for heroin, synthetic opioids, cocaine (with and without opioids), and opioids overall at the state-level. Design: Difference-in-difference study using serial cross-sectional data from separate sources Population: United States Exposure: State-level rates of nonmedical use of OxyContin and other prescription pain relievers prior to the reformulation (2004-2009). Outcome: State-level heroin, synthetic opioid, cocaine (with and without opioids), and overall mortality rates following the reformulation (2010-2017).	Found no evidence of pre-existing trend in heroin mortality rates pre-reformulation. Increase in heroin mortality began in 2011, continuing until 2016, then decreasing in 2017. Pattern of synthetic opioid mortality was similar to heroin but delayed, with rise in synthetic opioid overdoses from 2013. 4.6 additional synthetic opioid overdoses per 100,000 observed in states with higher rates of pre-reformulation nonmedical OxyContin use. States with higher rates of pre-reformulation OxyContin misuse had additional 1.3 deaths involving opioids and cocaine per 100,000. Reformulation may have had small beneficial effect on opioid overdose mortality initially, but subsequent increase in heroin and fentanyl overdoses overshadowed reductions in natural/semi-synthetic prescription opioid deaths. State-level rates of nonmedical use of prescription pain relievers not related to increases in heroin, synthetic opioid, cocaine, and opioid overdose mortality.	Did not examine rates of past-year initiation of misuse of other prescription opioids or initiation of heroin, fentanyl, or cocaine prior to the reformulation. Study did not account for state-level differences in pre-reformulation rates of cocaine or heroin deaths, which could contribute to observed rising mortality rates in certain states.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Sankey, 2016	Opioid use following the introduction of an extended-release oxycodone formulation with tamper-resistant properties: Prospective historical chart review in methadone-maintained patients	No funding information provided	Chart review and survey of patients on MAT in Canada	Objective: To compare oxycodone positive drug screens before, during and after the transition from oxycontin to ADF oxycontin Design: Descriptive study based on chart reviews Population: patients receiving MAT Exposure: OxyContin reformulation Outcome: percentage of oxycodone positive UDS per patient	Average per-patient percentage of oxycodone-positive UDS decreased from 22.4% pre-reformulation to 10.5% post-reformulation. Of 250 patients with oxycodone-positive UDS during the baseline period, 90 patients had no oxycodone positive UDSs during the transition period and 130 patients had no oxycodone positive UDS during the post-OxyContin period. Morphine-related-positive UDS remained stable during the same period.	Descriptive study design does not account for other potential factors, such as changes in OxyContin dispensing and diversion, potentially associated with reductions in oxycodone misuse and abuse. Not able to distinguish use of OxyContin from use of other oxycodone products. Small sample size and geographic area covered limits generalizability of findings.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Sessler, 2014	Reductions in reported deaths following the introduction of extended-release oxycodone (OxyContin) with an abuse-deterrent formulation	Purdue	Purdue adverse event report database	Objective: Evaluate the impact of OxyContin reformulation on OxyContin-related fatalities Design: analysis of trends using spline regression Population: US fatality reports submitted to manufacturers pharmacovigilance database Exposure: OxyContin reformulation Outcome: quarterly number of OxyContin-related fatalities	Mean quarter number of OxyContin-related fatalities decreased from 32.8 deaths per quarter during the year prior to reformulation, with a significant decrease beginning in the second year post-reformulation, persisting the third year re-formulation; to an average value of 5.8 deaths per quarter by the third year re-formulation (-82% change, 95%CI (-89% to -73%).	Spontaneous reporting databases do not contain totality of adverse events occurring in given exposed population. Trends in reporting cannot be used to make inferences about trends in the incidence of deaths or other adverse events occurring in exposed population. Authors selected only reports with a date of death included, as well as other key variables. Study lacked comparators.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Severtson, 2016	Sustained reduction of diversion and abuse after introduction of an abuse deterrent formulation of extended release oxycodone.	DHHA	RADARS OTP SKIP StreetRx	Objective: Analyze changes in rates of prescription units dispensed, drug diversion cases, and prices possibly resulting from the reformulation of OxyContin. Design: Ecologic study/ pre-post (2010-2015) Population: Prescription data from IMS Health (2010-2015) Street prices of products reported anonymously (2011-2015) Drug diversion cases involving product mention Exposure: Reformulation of OxyContin, OxyContin ADF Outcome: Rate of unit dispensed for opioid product, prescription-adjusted rates of drug diversion for product, reported street price of drug (2011-2015)	Large decrease in rate of units dispensed for OxyContin following the reformulation, which was significantly greater than for Other Opioid group. Median reported street price of single entity IR oxycodone, original OxyContin, and ADF OxyContin all decreased 2011-2015. Median reported street price for original OxyContin was 36% higher than for reformulated OxyContin in 2011 and 13% higher in 2015. Prescription-adjusted rate of OxyContin diversion cases decreased by 85.8% following reformulation (95 CI: -89.7, -80.5). Prescription-adjusted rate for cases involving other opioids decreased by -31.7% (95% CI: -40,3, -21.8) following reformulation.	Interpretation of price comparison between original and ADF OxyContin 2011-2015 unclear, since availability of original OxyContin extremely limited following the reformulation. Did not identify prices for original OxyContin in the pre-reformulation period compared to prices post-reformulation. Drug diversion data from convenience sample of law enforcement agencies, possibly influenced by factors impacting the detection and reporting of diversion of different drugs, for example, changes in reporting procedures or jurisdictional priorities.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Tuazon, 2019	Examining opioid-involved overdose mortality trends prior to fentanyl: New York City, 2000-2015	New York Department of Health	State death certificates linked to postmortem toxicology	Objective: Examine changes in unintentional overdose mortality rates based on opioid substance involved Design: Ecologic time series (2000-2015) Population: New York City Exposure: Year of OxyContin reformulation (2010) Outcome: Three mutually exclusive categories of opioid deaths: 1) heroin without opioid analgesics, 2) opioid analgesics without heroin, 3) both heroin and opioid analgesics	Rate of unintentional overdose deaths involving heroin without opioid analgesics declined from 2006-2010 then increased after 2010 at a rate of 18.8% per year. Rate of unintentional overdose deaths involving opioids without heroin increased 18.9% per year from 2000-2006 and increased 3.9% per year from 2006-2015. Rate of unintentional overdose deaths involving both heroin and opioids increased 9.3% per year 2000-2015. Increase in deaths involving heroin and opioid analgesics was highest among those ages 15-34 and 55-84. Overall rate of heroin only deaths was higher than opioid analgesics alone and opioid analgesics in combination with heroin. Increase in the rate of heroin only deaths only observed from 2010.	Findings only reflective of deaths in one city and state, potentially not representative of different geographic areas. Did not examine which specific substances (e.g., oxycodone, hydrocodone) were involved in prescription opioid deaths with or without heroin. Only examined overdose deaths classified as unintentional and did not examine rates of opioid-involved overdose deaths due to other intents typically included in overdose mortality analyses (e.g. assault, suicide, or undetermined intent).

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Vosburg, 2017	Changes in drug use patterns reported on the web after the introduction of ADF OxyContin: findings from the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System Web Monitoring Program	DHHA	RADARS web monitoring program	Objective: Examine encouragement of tampering or switching to other substances following ADF OxyContin Design: Cross-sectional study of web posts (2009-2014) Population: Web posts mentioning generic or branded oxycodone products Exposure: ADF OxyContin exposure Outcome: Reported changes in tampering with medications and/or switching to other substances	Some users still tampered with their medications, including ADF OxyContin. Many reported switching from OxyContin to non-ADF IR opioids, and heroin.	Web posts represent unknown selection of all individuals abusing OxyContin and other opioids. Internet use is dynamic, and individuals may migrate from one preferred site to another in non-random ways that create selection bias over time.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Wolff, 2020	The impact of the abuse-deterrent reformulation of extended-release OxyContin on Prescription Pain Reliever Misuse and Heroin Initiation	SAMHSA Contract	NSDUH	Objective: Assess impact of OxyContin reformulation on non-fatal abuse-related outcomes by comparing adults reporting past nonmedical use of OxyContin prior to the reformulation to those reporting nonmedical use of other prescription pain relievers during this time. Design: Difference-in-differences, using serial cross-sectional study of NSDUH data 2004-2013 Population: Community-dwelling respondents ages 18+ who reported nonmedical use of prescription pain relievers in 2010 or before Exposure: Reported nonmedical use of OxyContin in 2010 or before Outcome: Prescription pain reliever misuse, pain reliever use disorder, heroin initiation, heroin use, and heroin use disorder, changes analyzed using difference-in-difference methods	Following reformulation, prescription pain reliever misuse declined among individuals who used OxyContin and other prescription pain relievers prior to the reformulation. Decline was larger in those who had used OxyContin nonmedically in the pre-period (OR:0.79, 95% CI:0.69, 0.90). Heroin initiation increased among nonmedical OxyContin and other prescription pain reliever users after the reformulation. Increase was smaller among pre-reformulation misusers of OxyContin (OR 0.42, 95% CI: 0.22, 0.82). No statistically significant effect of reformulation on prescription pain reliever use disorder, heroin use, and heroin use disorder comparing both groups of individuals misusing prescription pain relievers.	Attempts to draw longitudinal conclusion from cross-sectional data. Findings possibly biased due to differential survivorship of exposure groups. Not able to examine the effect of the reformulation on different routes of abuse. Different pre-reformulation misuse populations (OxyContin vs other prescription opioids) potentially not comparable with regard to risk of outcomes, given nonmedical use of OxyContin was independently associated with outcomes (e.g., heroin use). Bias potentially introduced by variable time intervals between exposure (pre-reformulation use of OxyContin or other rx opioids) and measurement of outcome.

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Author, Year	Title	Funding source	Data source	Brief description	Main findings	Major limitations and/or biases
Yarborough, 2016	Understanding opioid overdose characteristics involving prescription and illicit opioids: A mixed methods analysis	Purdue	Interviews	Objective: Examine opioid overdoses among members of a large integrated health system following the introduction of OxyContin® ADF Design: Qualitative description of interviews (June 2012-February 2014, N=87) Population: Patients who had an opioid overdose identified in electronic medical records and an active opioid prescription Exposure: OxyContin reformulation Outcome: causal opioids, concomitant medications, contributing alcohol or illicit drug use, prescribed dose and frequency, source and route of administration for each substance, indication of abuse or misuse for each substance and, if available, any indication of suicidal intent	Individuals experiencing opioid overdoses abused and misused multiple medications/drugs; experienced dose-related miscommunications or medication-taking errors; had mental health and/or substance use conditions; reported chronic pain; or had unstable resources or family/social support. Most overdose events involved polysubstance use, often including benzodiazepines. Participants reported lack of availability of OxyContin for abuse possibly led some individuals with prescription opioid abuse histories to initiate heroin use. Reported reasons for heroin initiation included an improved high, lower price relative to other prescription opioids, and ease of availability.	Interview not primarily focused on OxyContin reformulation. Small sample size, limited generalizability. Did not explore whether individuals with overdoses involving heroin had a history of non-ADF or ADF OxyContin use and/or dependence. Results possibly affected by selection bias, given high refusal rate and many participants unable to be reached.

AHRQ- Agency for Healthcare Research and Quality
ARCOS- Automation of Reports and Consolidated Orders System
DEA- Drug Enforcement Agency
FAERS- FDA Adverse Events Reporting System
NOMAD-National Opioid Medications Abuse Deterrence

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NPA-National Prescription Activity
NSDUH-National Survey on Drug Use and Health
NVSS-National Vital Statistics System
OTP- Opioid Treatment Program
RADARS-Researched Abuse, Diversion, and Addiction-Related Surveillance System
RAPID-Researchers and Participants Interacting Directly
SKIP-Survey of Key Informants' Patients

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Appendix Table 3: Editorials (N=32)

Author, Year	Title
[No authors listed] Med Lett Drugs Ther, 2018	Roxybond--an abuse-deterrent formulation of short-acting oxycodone.
[No authors listed], Med Lett Drugs Ther. 2017	Arymo ER--a new abuse-deterrent morphine formulation.
Alexander, 2014	Development and impact of prescription opioid abuse deterrent formulation technologies.
Ballantyne, 2015	Preventing prescription opioid abuse.
Bannwarth, 2012	Will abuse-deterrent formulations of opioid analgesics be successful in achieving their purpose?
Bigal, 2019	Abuse-Deterrent OxyContin And Hepatitis C.
Brooks, 2018	ADF: Abuse-Deterrent Formulation or Another Disillusioned Formulation?
By, 2018	Important statistical considerations in the evaluation of post-market studies to assess whether opioids with abuse-deterrent properties result in reduced abuse in the community.
Cicero, Ellis, 2015 (2)	Abuse Deterrent Formulations of Prescription Opioids--Reply.
Cicero, Ellis, 2015 (3)	Anticipated and unanticipated consequences of abuse deterrent formulations of opioid analgesics.
Dart , 2015	Abuse-Deterrent Formulations of Prescription Opioids.
Dasgupta, 2015	Commentary on Degenhardt et al (2015): a new formulation for research.
DePriest, 2014	Oxycodone/Naloxone: role in chronic pain management, opioid-induced constipation, and abuse deterrence.
Humphreys, 2019	Evaluating dynamic impacts of abuse-deterrent prescription opioids formulations
Jamison, 2013	Is there support for abuse-deterrent and tamper-resistant opioid formulations?
Jauncey, 2019	What are our aims, and why?
Jones, 2014	Addressing prescription opioid overdose: data support a comprehensive policy approach.
Jones, 2015	Preventing prescription opioid abuse--reply.
Jones, 2016	Drug Formulation Advances in Extended-Release Medications for Pain Control.
Kibbe, 2018	Oxycodone hydrochloride immediate-release analgesic for managing severe pain: abuse-deterrent formulations.
Kunins, 2015	Abuse-deterrent opioid formulations: part of a public health strategy to reverse the opioid epidemic.
Litman, 2018	Abuse-deterrent opioid formulations
Manchikanti, 2015	The effect of abuse-deterrent extended-release oxycodone leads to inappropriate conclusions with over estimation of safety of abuse-deterrent formulations.
Nelson, 2019	Are abuse-deterrent opioid formulations all they are crushed up to be?
Pappagallo, 2012	The implications of tamper-resistant formulations for opioid rotation.
Peacock, 2019	Post-marketing studies of pharmaceutical opioid abuse-deterrent formulations: A framework for research design and reporting
Pergolizzi, 2018	Managing severe pain and abuse potential: the potential impact of a new abuse-deterrent formulation oxycodone/naltrexone extended-release product.
Ruan, 2015	Abuse-Deterrent Formulations of Prescription Opioids.
Schaeffer, 2012	Abuse-deterrent formulations, an evolving technology against the abuse and misuse of opioid analgesics.
Schneider, 2010	Abuse-deterrent and tamper-resistant opioid formulations: what is their role in addressing prescription opioid abuse?

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Singer, 2018	Abuse-deterrent opioids and the law of unintended consequences
Twillman, 2014	Potential cost-shifting and hidden costs and risks in the economic analysis of opioid abuse-deterrent formulations.

Appendix Table 4: Concepts, operators, and search terms for primary literature search

CONCEPT	OPERATOR	TERMS
ACTIVE PHARMACEUTICAL INGREDIENTS	n/a	(MorphaBond[tiab] OR Arymo[tiab] OR Embeda[tiab] OR Hysingla[tiab] OR RoxyBond[tiab] OR OxyContin[tiab] OR Xtampza[tiab] OR "morphine-naltrexone"[tiab] OR morphine[tiab] OR hydrocodone[tiab] OR oxycodone[tiab])
ABUSE DETERRENT FORMULATIONS	AND	AND (deter[tiab] OR deterrent[tiab] OR "abuse deterrent"[tiab] OR "abuse-deterrent"[tiab] OR ADF[tiab] OR reformulated[tiab] OR reformulation[tiab] OR reformulations[tiab] OR formulations[tiab])
OUTCOMES	AND	AND (misuse[tw] OR abuse[tw] OR "non-medical use"[tw] OR nonmedical[tw] OR "non medical use"[tw] OR recreational[tw] OR substance[tw] OR addiction[tw] OR addictive[tw] OR dependence[tw] OR overdose[tw] OR death[tw] OR mortality[tw])
STUDY DESIGNS	NOT	NOT ("randomized control trial"[tw] OR "randomized-control trial"[tw] OR "randomized control trials"[tw] OR "randomized-controlled trials"[tw] OR "randomized controlled trial"[tw] OR "randomized controlled trials"[tw] OR "randomized-controlled trial"[tw] OR "randomized-controlled trials"[tw] OR "randomised control trial"[tw] OR "randomised-control trial"[tw] OR "randomised control trials"[tw] OR "randomised-controlled trials"[tw] OR "randomised controlled trial"[tw] OR "randomised controlled trials"[tw] OR "randomised-controlled trial"[tw] OR "randomised-controlled trials"[tw] OR RCT[tw] OR "randomized trial"[tw] OR "randomised trial"[tw]OR "randomized control"[tw] OR "randomised control"[tw] OR "cluster-randomized trial"[tw] OR "cluster-randomised trial"[tw] OR "randomized double-blind"[tw] OR "clinical trial"[tw] OR "clinical trials"[tw] OR "clinical study"[tw] OR "clinical studies"[tw] OR "clinical conference"[tw] OR "clinical conferences"[tw] OR "phase I"[tw] OR "phase II"[tw] OR "phase III"[tw] OR autobiography[tw] OR biography[tw] OR "patient education handout"[tw] OR webcast[tw]) NOT (cell[tw] OR "cell line"[tw] OR cellular[tw] OR tissue[tw] OR "in vitro"[tw] OR "in vivo"[tw] OR spectroscopic[tw] OR spectrometer[tw] OR spectrophotometry[tw] OR "transformation products"[tw] OR "gene variants"[tw] OR plant[tw] OR pharmacokinetic[tw] OR pharmacodynamic[tw] OR microscopy[tw] OR chromatography[tw] OR "mass spectrometry"[tw] OR spectroscopy[tw] OR "Hot-Melt"[tw] OR "injection-molding"[tw] OR "laboratory-based"[tw] OR excipients[tw] OR bioequivalence[tw] or "dissolution studies"[tw])
ANIMALS	NOT	NOT (animals[tiab] OR animal[tiab] OR "Pogona vitticeps"[tiab] OR mice[tiab] OR mus[tiab] OR mouse[tiab] OR murine[tiab] OR woodmouse[tiab] OR rats[tiab] OR rat[tiab] OR murinae[tiab] OR muridae[tiab] OR cottonrat[tiab] OR cottonrats[tiab] OR hamster[tiab] OR hamsters[tiab] OR cricetinae[tiab] OR rodentia[tiab] OR rodent[tiab] OR rodents[tiab] OR pigs[tiab] OR pig[tiab] OR swine[tiab] OR swines[tiab] OR piglets[tiab] OR piglet[tiab] OR boar[tiab] OR boars[tiab] OR "sus scrofa"[tiab] OR ferrets[tiab] OR ferret[tiab] OR polecat[tiab] OR polecats[tiab] OR "mustela putorius"[tiab] OR "guinea pigs"[tiab] OR "guinea pig"[tiab] OR cavia[tiab] OR callithrix[tiab] OR marmoset[tiab] OR marmosets[tiab] OR cebuella[tiab] OR hapale[tiab] OR octodon[tiab] OR chinchilla[tiab] OR chinchillas[tiab] OR gerbillinae[tiab] OR gerbil[tiab] OR

gerbils[tiab] OR jird[tiab] OR jirds[tiab] OR merione[tiab] OR meriones[tiab] OR rabbits[tiab] OR rabbit[tiab] OR hares[tiab] OR hare[tiab] OR diptera[tiab] OR flies[tiab] OR fly[tiab] OR dipteral[tiab] OR drosphila[tiab] OR drosophilidae[tiab] OR cats[tiab] OR cat[tiab] OR carus[tiab] OR felis[tiab] OR nematoda[tiab] OR nematode[tiab] OR nematoda[tiab] OR nematode[tiab] OR nematodes[tiab] OR sipunculida[tiab] OR dogs[tiab] OR dog[tiab] OR canine[tiab] OR canines[tiab] OR canis[tiab] OR sheep[tiab] OR sheeps[tiab] OR mouflon[tiab] OR mouflons[tiab] OR ovis[tiab] OR goats[tiab] OR goat[tiab] OR capra[tiab] OR capras[tiab] OR rupicapra[tiab] OR chamois[tiab] OR haplorhini[tiab] OR monkey[tiab] OR monkeys[tiab] OR anthropoidea[tiab] OR anthropoids[tiab] OR saguinus[tiab] OR tamarin[tiab] OR tamarins[tiab] OR leontopithecus[tiab] OR hominidae[tiab] OR ape[tiab] OR apes[tiab] OR pan[tiab] OR paniscus[tiab] OR "pan paniscus"[tiab] OR bonobo[tiab] OR bonobos[tiab] OR troglodytes[tiab] OR "pan troglodytes"[tiab] OR gibbon[tiab] OR gibbons[tiab] OR siamang[tiab] OR siamangs[tiab] OR nomascus[tiab] OR symphalangus[tiab] OR chimpanzee[tiab] OR chimpanzees[tiab] OR prosimians[tiab] OR "bush baby"[tiab] OR prosimian[tiab] OR "bush babies"[tiab] OR galagos[tiab] OR galago[tiab] OR pongidae[tiab] OR gorilla[tiab] OR gorillas[tiab] OR pongo[tiab] OR pygmaeus[tiab] OR "pongo pygmaeus"[tiab] OR orangutans[tiab] OR pygmaeus[tiab] OR lemur[tiab] OR lemurs[tiab] OR lemuridae[tiab] OR horse[tiab] OR horses[tiab] OR pongo[tiab] OR equus[tiab] OR cow[tiab] OR calf[tiab] OR bull[tiab] OR chicken[tiab] OR chickens[tiab] OR gallus[tiab] OR quail[tiab] OR bird[tiab] OR birds[tiab] OR quails[tiab] OR poultry[tiab] OR poultries[tiab] OR fowl[tiab] OR fowls[tiab] OR reptile[tiab] OR reptilia[tiab] OR reptiles[tiab] OR snakes[tiab] OR snake[tiab] OR lizard[tiab] OR lizards[tiab] OR alligator[tiab] OR alligators[tiab] OR crocodile[tiab] OR crocodiles[tiab] OR turtle[tiab] OR turtles[tiab] OR amphibian[tiab] OR amphibians[tiab] OR amphibia[tiab] OR frog[tiab] OR frogs[tiab] OR bombina[tiab] OR salientia[tiab] OR toad[tiab] OR toads[tiab] OR "epidalea calamita"[tiab] OR salamander[tiab] OR salamanders[tiab] OR eel[tiab] OR eels[tiab] OR fish[tiab] OR fishes[tiab] OR pisces[tiab] OR catfish[tiab] OR catfishes[tiab] OR siluriformes[tiab] OR arius[tiab] OR heteropneustes[tiab] OR sheatfish[tiab] OR perch[tiab] OR perches[tiab] OR percidae[tiab] OR perca[tiab] OR trout[tiab] OR trouts[tiab] OR char[tiab] OR chars[tiab] OR salvelinus[tiab] OR "fathead minnow"[tiab] OR minnow[tiab] OR cyprinidae[tiab] OR carps[tiab] OR carp[tiab] OR zebrafish[tiab] OR zebrafishes[tiab] OR goldfish[tiab] OR goldfishes[tiab] OR guppy[tiab] OR guppies[tiab] OR chub[tiab] OR chubs[tiab] OR tinca[tiab] OR barbels[tiab] OR barbus[tiab] OR pimephales[tiab] OR promelas[tiab] OR "poecilia reticulata"[tiab] OR mullet[tiab] OR mullets[tiab] OR seahorse[tiab] OR seahorses[tiab] OR mugil curema[tiab] OR "atlantic cod"[tiab] OR shark[tiab] OR sharks[tiab] OR catshark[tiab] OR anguilla[tiab] OR salmonid[tiab] OR salmonids[tiab] OR whitefish[tiab] OR whitefishes[tiab] OR salmon[tiab] OR salmons[tiab] OR sole[tiab] OR solea[tiab] OR "sea lamprey"[tiab] OR lamprey[tiab] OR lampreys[tiab] OR pumpkinseed[tiab] OR sunfish[tiab] OR sunfishes[tiab] OR tilapia[tiab] OR tilapias[tiab] OR turbot[tiab] OR turbots[tiab] OR flatfish[tiab] OR flatfishes[tiab] OR sciuridae[tiab] OR squirrel[tiab] OR squirrels[tiab] OR chipmunk[tiab] OR chipmunks[tiab] OR suslik[tiab] OR susliks[tiab] OR vole[tiab] OR voles[tiab] OR lemming[tiab] OR lemmings[tiab] OR muskrat[tiab] OR muskrats[tiab] OR lemmus[tiab] OR otter[tiab] OR

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		otters[tiab] OR marten[tiab] OR martens[tiab] OR martes[tiab] OR weasel[tiab] OR badger[tiab] OR badgers[tiab] OR ermine[tiab] OR mink[tiab] OR minks[tiab] OR sable[tiab] OR sables[tiab] OR gulo[tiab] OR gulos[tiab] OR wolverine[tiab] OR wolverines[tiab] OR minks[tiab] OR mustela[tiab] OR llama[tiab] OR llamas[tiab] OR alpaca[tiab] OR alpacas[tiab] OR camelid[tiab] OR camelids[tiab] OR guanaco[tiab] OR guanacos[tiab] OR chiroptera[tiab] OR chiropteras[tiab] OR bat[tiab] OR bats[tiab] OR fox[tiab] OR foxes[tiab] OR iguana[tiab] OR iguanas[tiab] OR "xenopus laevis"[tiab] OR parakeet[tiab] OR parakeets[tiab] OR parrot[tiab] OR parrots[tiab] OR donkey[tiab] OR donkeys[tiab] OR mule[tiab] OR mules[tiab] OR zebra[tiab] OR zebras[tiab] OR shrew[tiab] OR shrews[tiab] OR bison[tiab] OR bisons[tiab] OR buffalo[tiab] OR buffaloes[tiab] OR deer[tiab] OR deers[tiab] OR bear[tiab] OR bears[tiab] OR panda[tiab] OR pandas[tiab] OR "wild hog"[tiab] OR "wild boar"[tiab] OR fitchew[tiab] OR fitch[tiab] OR beaver[tiab] OR beavers[tiab] OR jerboa[tiab] OR jerboas[tiab] OR capybara[tiab] OR capybaras[tiab])

Appendix Table 5: Concepts, operators, and search terms for secondary literature search excluding investigator-assigned study designs

CONCEPT	OPERATOR	TERMS
ACTIVE PHARMACEUTICAL INGREDIENTS	n/a	(MorphaBond[tw] OR Arymo[tw] OR Embeda[tw] OR Hysingla[tw] OR RoxyBond[tw] OR OxyContin[tw] OR Xtampza[tw] OR Targiniq[tw] OR Vantrela[tw] OR Oxaydo[tw] OR Troxyca[tw] OR Opana[tw] OR "Opana ER"[tw] OR "morphine-naltrexone"[tw] OR morphine[tw] OR hydrocodone[tw] OR oxycodone[tw] OR "oxycodone-naloxone"[tw] OR oxymorphone[tw] OR "oxycodone-naltrexone"[tw])
ABUSE DETERRENT FORMULATIONS	AND	(deter[tw] OR deters[tw] OR deterred[tw] OR deterrent[tw] OR "abuse deterrent"[tw] OR "abuse-deterrent"[tw] OR ADF[tw] OR reformulate[tw] OR reformulated[tw] OR reformulation[tw] OR reformulations[tw] OR formulations[tw] OR formulation[tw] OR "tamper resistant"[tw] OR "tamper-resistant"[tw] OR resist[tw] OR resists[tw] OR resisted[tw] OR tamper[tw] OR tampers[tw] OR tampered[tw] OR barrier[tw] OR barriers[tw] OR prevent[tw] OR prevents[tw] OR prevented[tw] OR prevention[tw])
OUTCOMES	AND	(misuse[tw] OR abuse[tw] OR "non-medical use"[tw] OR nonmedical[tw] OR "non medical use"[tw] OR "extra-medical"[tw] OR "unintended misuse"[tw] OR recreational[tw] OR substance[tw] OR addiction[tw] OR addictive[tw] OR dependence[tw] OR overdose[tw] OR death[tw] OR mortality[tw] OR "substance use disorder"[tw] OR SUD[tw] OR "opioid use disorder"[tw] OR OUD[tw] OR "overdose death"[tw] OR "opioid overdose death"[tw] OR "overdose related hospitalization"[tw] OR withdrawal[tw] OR "non-fatal overdose"[tw] OR "non fatal overdose"[tw] OR diversion[tw] OR "drug diversion"[tw] OR "intravenous drug use"[tw] OR "IV drug use"[tw] OR "injection drug use"[tw] OR inhale[tw] OR inhalation[tw] OR inhales[tw] OR inhaled[tw] OR inhaling[tw] OR snort[tw] OR snorts[tw] OR snorting[tw] OR snorted[tw] OR intranasal[tw] OR crush[tw] OR crushed[tw] OR chew[tw] OR chewed[tw] OR inject[tw] OR injection[tw] OR injects[tw] OR injected[tw] OR "people who inject"[tw] OR "people who inject drugs"[tw] OR PWID[tw] OR "people who use drugs"[tw] OR PWUD[tw] OR poisoning[tw] OR suicide[tw] OR phlebitis[tw] OR "skin infection"[tw] OR "skin infections"[tw] OR "thrombotic microangiopathy"[tw] OR "thrombotic thrombocytopenic purpura"[tw] OR "TTP"[tw] OR "adverse effects"[tw])
STUDY DESIGNS (part 1)	NOT	("randomized control trial"[tw] OR "randomized-control trial"[tw] OR "randomized control trials"[tw] OR "randomized-controlled trials"[tw] OR "randomized controlled trial"[tw] OR "randomized controlled trials"[tw] OR "randomized-controlled trial"[tw] OR "randomized-controlled trials"[tw] OR "randomised control trial"[tw] OR "randomised-control trial"[tw] OR "randomised control trials"[tw] OR "randomised-controlled trials"[tw] OR "randomised controlled trial"[tw] OR "randomised controlled trials"[tw] OR "randomised-controlled trial"[tw] OR "randomised-controlled trials"[tw] OR RCT[tw] OR "randomized trial"[tw] OR "randomised trial"[tw] OR "randomized control"[tw] OR "randomised control"[tw] OR "cluster-randomized trial"[tw] OR "cluster-randomised trial"[tw] OR "randomized double-blind"[tw] OR "clinical trial"[tw] OR "clinical trials"[tw] OR "clinical study"[tw] OR "clinical studies"[tw] OR "clinical conference"[tw] OR

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		"clinical conferences"[tw] OR "phase I"[tw] OR "phase II"[tw] OR "phase III"[tw] OR autobiography[tw] OR biography[tw] OR "patient education handout"[tw] OR webcast[tw])
STUDY DESIGNS (part 2)	NOT	(cell[tw] OR "cell line"[tw] OR cellular[tw] OR tissue[tw] OR "in vitro"[tw] OR "in vivo"[tw] OR spectroscopic[tw] OR spectrometer[tw] OR spectrophotometry[tw] OR "transformation products"[tw] OR "gene variants"[tw] OR plant[tw] OR pharmacokinetic[tw] OR pharmacodynamic[tw] OR microscopy[tw] OR chromatography[tw] OR "mass spectrometry"[tw] OR spectroscopy[tw] OR "Hot-Melt"[tw] OR "injection-molding"[tw] OR "laboratory-based"[tw] OR excipients[tw] OR bioequivalence[tw] OR "dissolution studies"[tw])
ANIMALS	NOT	(animals[tw] OR animal[tw] OR "Pogona vitticeps"[tw] OR mice[tw] OR mus[tw] OR mouse[tw] OR murine[tw] OR woodmouse[tw] OR rats[tw] OR rat[tw] OR murinae[tw] OR muridae[tw] OR cottonrat[tw] OR cottonrats[tw] OR hamster[tw] OR hamsters[tw] OR cricetinae[tw] OR rodentia[tw] OR rodent[tw] OR rodents[tw] OR pigs[tw] OR pig[tw] OR swine[tw] OR swines[tw] OR piglets[tw] OR piglet[tw] OR boar[tw] OR boars[tw] OR "sus scrofa"[tw] OR ferrets[tw] OR ferret[tw] OR polecat[tw] OR polecats[tw] OR "mustela putorius"[tw] OR "guinea pigs"[tw] OR "guinea pig"[tw] OR cavia[tw] OR callithrix[tw] OR marmoset[tw] OR marmosets[tw] OR cebuella[tw] OR hapale[tw] OR octodon[tw] OR chinchilla[tw] OR chinchillas[tw] OR gerbillinae[tw] OR gerbil[tw] OR gerbils[tw] OR jird[tw] OR jirds[tw] OR merione[tw] OR meriones[tw] OR rabbits[tw] OR rabbit[tw] OR hares[tw] OR hare[tw] OR diptera[tw] OR flies[tw] OR fly[tw] OR dipteral[tw] OR drosphila[tw] OR drosophilidae[tw] OR cats[tw] OR cat[tw] OR carus[tw] OR felis[tw] OR nematoda[tw] OR nematode[tw] OR nematoda[tw] OR nematode[tw] OR nematodes[tw] OR sipunculida[tw] OR dogs[tw] OR dog[tw] OR canine[tw] OR canines[tw] OR canis[tw] OR sheep[tw] OR sheeps[tw] OR mouflon[tw] OR mouflons[tw] OR ovis[tw] OR goats[tw] OR goat[tw] OR capra[tw] OR capras[tw] OR rupicapra[tw] OR chamois[tw] OR haplorhini[tw] OR monkey[tw] OR monkeys[tw] OR anthropoidea[tw] OR anthropoids[tw] OR saguinus[tw] OR tamarin[tw] OR tamarins[tw] OR leontopithecus[tw] OR hominidae[tw] OR ape[tw] OR apes[tw] OR pan[tw] OR paniscus[tw] OR "pan paniscus"[tw] OR bonobo[tw] OR bonobos[tw] OR troglodytes[tw] OR "pan troglodytes"[tw] OR gibbon[tw] OR gibbons[tw] OR siamang[tw] OR siamangs[tw] OR nomascus[tw] OR symphalangus[tw] OR chimpanzee[tw] OR chimpanzees[tw] OR prosimians[tw] OR "bush baby"[tw] OR prosimian[tw] OR "bush babies"[tw] OR galagos[tw] OR galago[tw] OR pongidae[tw] OR gorilla[tw] OR gorillas[tw] OR pongo[tw] OR pygmaeus[tw] OR "pongo pygmaeus"[tw] OR orangutans[tw] OR pygmaeus[tw] OR lemur[tw] OR lemurs[tw] OR lemuridae[tw] OR horse[tw] OR horses[tw] OR pongo[tw] OR equus[tw] OR cow[tw] OR calf[tw] OR bull[tw] OR chicken[tw] OR chickens[tw] OR gallus[tw] OR quail[tw] OR bird[tw] OR birds[tw] OR quails[tw] OR poultry[tw] OR poultries[tw] OR fowl[tw] OR fowls[tw] OR reptile[tw] OR reptilia[tw] OR reptiles[tw] OR snakes[tw] OR snake[tw] OR lizard[tw] OR lizards[tw] OR alligator[tw] OR alligators[tw] OR crocodile[tw] OR crocodiles[tw] OR

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| | | turtle[tw] OR turtles[tw] OR amphibian[tw] OR amphibians[tw] OR amphibia[tw] OR frog[tw] OR frogs[tw] OR bombina[tw] OR salientia[tw] OR toad[tw] OR toads[tw] OR "epidalea calamita"[tw] OR salamander[tw] OR salamanders[tw] OR eel[tw] OR eels[tw] OR fish[tw] OR fishes[tw] OR pisces[tw] OR catfish[tw] OR catfishes[tw] OR siluriformes[tw] OR arius[tw] OR heteropneustes[tw] OR sheatfish[tw] OR perch[tw] OR perches[tw] OR percidae[tw] OR perca[tw] OR trout[tw] OR trouts[tw] OR char[tw] OR chars[tw] OR salvelinus[tw] OR "fathead minnow"[tw] OR minnow[tw] OR cyprinidae[tw] OR carps[tw] OR carp[tw] OR zebrafish[tw] OR zebrafishes[tw] OR goldfish[tw] OR goldfishes[tw] OR guppy[tw] OR guppies[tw] OR chub[tw] OR chubs[tw] OR tinca[tw] OR barbels[tw] OR barbus[tw] OR pimephales[tw] OR promelas[tw] OR "poecilia reticulata"[tw] OR mullet[tw] OR mullets[tw] OR seahorse[tw] OR seahorses[tw] OR mugil curema[tw] OR "atlantic cod"[tw] OR shark[tw] OR sharks[tw] OR catshark[tw] OR anguilla[tw] OR salmonid[tw] OR salmonids[tw] OR whitefish[tw] OR whitefishes[tw] OR salmon[tw] OR salmons[tw] OR sole[tw] OR solea[tw] OR "sea lamprey"[tw] OR lamprey[tw] OR lampreys[tw] OR pumpkinseed[tw] OR sunfish[tw] OR sunfishes[tw] OR tilapia[tw] OR tilapias[tw] OR turbot[tw] OR turbots[tw] OR flatfish[tw] OR flatfishes[tw] OR sciuridae[tw] OR squirrel[tw] OR squirrels[tw] OR chipmunk[tw] OR chipmunks[tw] OR suslik[tw] OR susliks[tw] OR vole[tw] OR voles[tw] OR lemming[tw] OR lemmings[tw] OR muskrat[tw] OR muskrats[tw] OR lemmus[tw] OR otter[tw] OR otters[tw] OR marten[tw] OR martens[tw] OR martes[tw] OR weasel[tw] OR badger[tw] OR badgers[tw] OR ermine[tw] OR mink[tw] OR minks[tw] OR sable[tw] OR sables[tw] OR gulo[tw] OR gulos[tw] OR wolverine[tw] OR wolverines[tw] OR minks[tw] OR mustela[tw] OR llama[tw] OR llamas[tw] OR alpaca[tw] OR alpacas[tw] OR camelid[tw] OR camelids[tw] OR guanaco[tw] OR guanacos[tw] OR chiroptera[tw] OR chiropteras[tw] OR bat[tw] OR bats[tw] OR fox[tw] OR foxes[tw] OR iguana[tw] OR iguanas[tw] OR "xenopus laevis"[tw] OR parakeet[tw] OR parakeets[tw] OR parrot[tw] OR parrots[tw] OR donkey[tw] OR donkeys[tw] OR mule[tw] OR mules[tw] OR zebra[tw] OR zebras[tw] OR shrew[tw] OR shrews[tw] OR bison[tw] OR bisons[tw] OR buffalo[tw] OR buffaloes[tw] OR deer[tw] OR deers[tw] OR bear[tw] OR bears[tw] OR panda[tw] OR pandas[tw] OR "wild hog"[tw] OR "wild boar"[tw] OR fitchew[tw] OR fitch[tw] OR beaver[tw] OR beavers[tw] OR jerboa[tw] OR jerboas[tw] OR capybara[tw] OR capybaras[tw]) |

Appendix Table 6: Concepts, operators, and search terms for secondary literature search limited to observational study designs

CONCEPT	OPERATOR	TERMS

ACTIVE PHARMACEUTICAL INGREDIENTS	n/a	(MorphaBond[tw] OR Arymo[tw] OR Embeda[tw] OR Hysingla[tw] OR RoxyBond[tw] OR OxyContin[tw] OR Xtampza[tw] OR Targiniq[tw] OR Vantrela[tw] OR Oxaydo[tw] OR Troxyca[tw] OR Opana[tw] OR "Opana ER"[tw] OR "morphine-naltrexone"[tw] OR morphine[tw] OR hydrocodone[tw] OR oxycodone[tw] OR "oxycodone-naloxone"[tw] OR oxymorphone[tw] OR "oxycodone-naltrexone"[tw])
ABUSE DETERRENT FORMULATIONS	AND	(deter[tw] OR deters[tw] OR deterred[tw] OR deterrent[tw] OR "abuse deterrent"[tw] OR "abuse-deterrent"[tw] OR ADF[tw] OR reformulate[tw] OR reformulated[tw] OR reformulation[tw] OR reformulations[tw] OR formulations[tw] OR formulation[tw] OR "tamper resistant"[tw] OR "tamper-resistant"[tw] OR resist[tw] OR resists[tw] OR resisted[tw] OR tamper[tw] OR tampers[tw] OR tampered[tw] OR barrier[tw] OR barriers[tw] OR prevent[tw] OR prevents[tw] OR prevented[tw] OR prevention[tw])
OUTCOMES	AND	(misuse[tw] OR abuse[tw] OR "non-medical use"[tw] OR nonmedical[tw] OR "non medical use"[tw] OR "extra-medical"[tw] OR "unintended misuse"[tw] OR recreational[tw] OR substance[tw] OR addiction[tw] OR addictive[tw] OR dependence[tw] OR overdose[tw] OR death[tw] OR mortality[tw] OR "substance use disorder"[tw] OR SUD[tw] OR "opioid use disorder"[tw] OR OUD[tw] OR "overdose death"[tw] OR "opioid overdose death"[tw] OR "overdose related hospitalization"[tw] OR withdrawal[tw] OR "non-fatal overdose"[tw] OR "non fatal overdose"[tw] OR diversion[tw] OR "drug diversion"[tw] OR "intravenous drug use"[tw] OR "IV drug use"[tw] OR "injection drug use"[tw] OR inhale[tw] OR inhalation[tw] OR inhales[tw] OR inhaled[tw] OR inhaling[tw] OR snort[tw] OR snorts[tw] OR snorting[tw] OR snorted[tw] OR intranasal[tw] OR crush[tw] OR crushed[tw] OR chew[tw] OR chewed[tw] OR inject[tw] OR injection[tw] OR injects[tw] OR injected[tw] OR "people who inject"[tw] OR "people who inject drugs"[tw] OR PWID[tw] OR "people who use drugs"[tw] OR PWUD[tw] OR poisoning[tw] OR suicide[tw] OR phlebitis[tw] OR "skin infection"[tw] OR "skin infections"[tw] OR "thrombotic microangiopathy"[tw] OR "thrombotic thrombocytopenic purpura"[tw] OR "TTP"[tw] OR "adverse effects"[tw])
STUDY DESIGNS (part 1)	AND	("systematic review"[tw] OR cohort[tw] OR "matched-cohort"[tw] OR "matched cohort"[tw] OR "case-control"[tw] OR "cross sectional"[tw] OR "cross-sectional"[tw] OR survey[tw] OR observational[tw] OR "prevalence study"[tw] OR "longitudinal study"[tw] OR "before-after study"[tw] OR "pre-intervention"[tw] OR "post-intervention"[tw] OR "pre-post"[tw] OR "real world"[tw] OR "real-world"[tw] OR "interrupted time-series"[tw] OR "interrupted time series"[tw] OR "interrupted-time-series"[tw] OR "population-based"[tw] OR "case report"[tw] OR "case-report"[tw] OR "case series"[tw] OR "case-series"[tw] OR retrospective[tw] OR prospective[tw] OR "pooled analysis"[tw] OR crossover[tw] OR "meta-analysis"[tw] OR "meta analysis"[tw] OR incidence[tw] OR prevalence[tw])
STUDY DESIGNS (part 2)	NOT	(cell[tw] OR "cell line"[tw] OR cellular[tw] OR tissue[tw] OR "in vitro"[tw] OR "in vivo"[tw] OR spectroscopic[tw] OR spectrometer[tw] OR spectrophotometry[tw] OR "transformation products"[tw] OR "gene

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		variants"[tw] OR plant[tw] OR pharmacokinetic[tw] OR pharmacodynamic[tw] OR microscopy[tw] OR chromatography[tw] OR "mass spectrometry"[tw] OR spectroscopy[tw] OR "Hot-Melt"[tw] OR "injection-molding"[tw] OR "laboratory-based"[tw] OR excipients[tw] OR bioequivalence[tw] OR "dissolution studies"[tw])
ANIMALS	NOT	(animals[tw] OR animal[tw] OR "Pogona vitticeps"[tw] OR mice[tw] OR mus[tw] OR mouse[tw] OR murine[tw] OR woodmouse[tw] OR rats[tw] OR rat[tw] OR murinae[tw] OR muridae[tw] OR cottonrat[tw] OR cottonrats[tw] OR hamster[tw] OR hamsters[tw] OR cricetinae[tw] OR rodentia[tw] OR rodent[tw] OR rodents[tw] OR pigs[tw] OR pig[tw] OR swine[tw] OR swines[tw] OR piglets[tw] OR piglet[tw] OR boar[tw] OR boars[tw] OR "sus scrofa"[tw] OR ferrets[tw] OR ferret[tw] OR polecat[tw] OR polecats[tw] OR "mustela putorius"[tw] OR "guinea pigs"[tw] OR "guinea pig"[tw] OR cavia[tw] OR callithrix[tw] OR marmoset[tw] OR marmosets[tw] OR cebuella[tw] OR hapale[tw] OR octodon[tw] OR chinchilla[tw] OR chinchillas[tw] OR gerbillinae[tw] OR gerbil[tw] OR gerbils[tw] OR jird[tw] OR jirds[tw] OR merione[tw] OR meriones[tw] OR rabbits[tw] OR rabbit[tw] OR hares[tw] OR hare[tw] OR diptera[tw] OR flies[tw] OR fly[tw] OR dipteral[tw] OR drosphila[tw] OR drosophilidae[tw] OR cats[tw] OR cat[tw] OR carus[tw] OR felis[tw] OR nematoda[tw] OR nematode[tw] OR nematoda[tw] OR nematode[tw] OR nematodes[tw] OR sipunculida[tw] OR dogs[tw] OR dog[tw] OR canine[tw] OR canines[tw] OR canis[tw] OR sheep[tw] OR sheeps[tw] OR mouflon[tw] OR mouflons[tw] OR ovis[tw] OR goats[tw] OR goat[tw] OR capra[tw] OR capras[tw] OR rupicapra[tw] OR chamois[tw] OR haplorhini[tw] OR monkey[tw] OR monkeys[tw] OR anthropoidea[tw] OR anthropoids[tw] OR saguinus[tw] OR tamarin[tw] OR tamarins[tw] OR leontopithecus[tw] OR hominidae[tw] OR ape[tw] OR apes[tw] OR pan[tw] OR paniscus[tw] OR "pan paniscus"[tw] OR bonobo[tw] OR bonobos[tw] OR troglodytes[tw] OR "pan troglodytes"[tw] OR gibbon[tw] OR gibbons[tw] OR siamang[tw] OR siamangs[tw] OR nomascus[tw] OR symphalangus[tw] OR chimpanzee[tw] OR chimpanzees[tw] OR prosimians[tw] OR "bush baby"[tw] OR prosimian[tw] OR "bush babies"[tw] OR galagos[tw] OR galago[tw] OR pongidae[tw] OR gorilla[tw] OR gorillas[tw] OR pongo[tw] OR pygmaeus[tw] OR "pongo pygmaeus"[tw] OR orangutans[tw] OR pygmaeus[tw] OR lemur[tw] OR lemurs[tw] OR lemuridae[tw] OR horse[tw] OR horses[tw] OR pongo[tw] OR equus[tw] OR cow[tw] OR calf[tw] OR bull[tw] OR chicken[tw] OR chickens[tw] OR gallus[tw] OR quail[tw] OR bird[tw] OR birds[tw] OR quails[tw] OR poultry[tw] OR poultries[tw] OR fowl[tw] OR fowls[tw] OR reptile[tw] OR reptilia[tw] OR reptiles[tw] OR snakes[tw] OR snake[tw] OR lizard[tw] OR lizards[tw] OR alligator[tw] OR alligators[tw] OR crocodile[tw] OR crocodiles[tw] OR turtle[tw] OR turtles[tw] OR amphibian[tw] OR amphibians[tw] OR amphibia[tw] OR frog[tw] OR frogs[tw] OR bombina[tw] OR salientia[tw] OR toad[tw] OR toads[tw] OR "epidalea calamita"[tw] OR salamander[tw] OR salamanders[tw] OR eel[tw] OR eels[tw] OR fish[tw] OR fishes[tw] OR pisces[tw] OR catfish[tw] OR catfishes[tw] OR siluriformes[tw] OR arius[tw] OR heteropneustes[tw] OR sheatfish[tw]

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| | | OR perch[tw] OR perches[tw] OR percidae[tw] OR perca[tw] OR trout[tw] OR trouts[tw] OR char[tw] OR chars[tw] OR salvelinus[tw] OR "fathead minnow"[tw] OR minnow[tw] OR cyprinidae[tw] OR carps[tw] OR carp[tw] OR zebrafish[tw] OR zebrafishes[tw] OR goldfish[tw] OR goldfishes[tw] OR guppy[tw] OR guppies[tw] OR chub[tw] OR chubs[tw] OR tinca[tw] OR barbels[tw] OR barbus[tw] OR pimephales[tw] OR promelas[tw] OR "poecilia reticulata"[tw] OR mullet[tw] OR mullets[tw] OR seahorse[tw] OR seahorses[tw] OR mugil curema[tw] OR "atlantic cod"[tw] OR shark[tw] OR sharks[tw] OR catshark[tw] OR anguilla[tw] OR salmonid[tw] OR salmonids[tw] OR whitefish[tw] OR whitefishes[tw] OR salmon[tw] OR salmons[tw] OR sole[tw] OR solea[tw] OR "sea lamprey"[tw] OR lamprey[tw] OR lampreys[tw] OR pumpkinseed[tw] OR sunfish[tw] OR sunfishes[tw] OR tilapia[tw] OR tilapias[tw] OR turbot[tw] OR turbots[tw] OR flatfish[tw] OR flatfishes[tw] OR sciuridae[tw] OR squirrel[tw] OR squirrels[tw] OR chipmunk[tw] OR chipmunks[tw] OR suslik[tw] OR susliks[tw] OR vole[tw] OR voles[tw] OR lemming[tw] OR lemmings[tw] OR muskrat[tw] OR muskrats[tw] OR lemmus[tw] OR otter[tw] OR otters[tw] OR marten[tw] OR martens[tw] OR martes[tw] OR weasel[tw] OR badger[tw] OR badgers[tw] OR ermine[tw] OR mink[tw] OR minks[tw] OR sable[tw] OR sables[tw] OR gulo[tw] OR gulos[tw] OR wolverine[tw] OR wolverines[tw] OR minks[tw] OR mustela[tw] OR llama[tw] OR llamas[tw] OR alpaca[tw] OR alpacas[tw] OR camelid[tw] OR camelids[tw] OR guanaco[tw] OR guanacos[tw] OR chiroptera[tw] OR chiropteras[tw] OR bat[tw] OR bats[tw] OR fox[tw] OR foxes[tw] OR iguana[tw] OR iguanas[tw] OR "xenopus laevis"[tw] OR parakeet[tw] OR parakeets[tw] OR parrot[tw] OR parrots[tw] OR donkey[tw] OR donkeys[tw] OR mule[tw] OR mules[tw] OR zebra[tw] OR zebras[tw] OR shrew[tw] OR shrews[tw] OR bison[tw] OR bisons[tw] OR buffalo[tw] OR buffaloes[tw] OR deer[tw] OR deers[tw] OR bear[tw] OR bears[tw] OR panda[tw] OR pandas[tw] OR "wild hog"[tw] OR "wild boar"[tw] OR fitchew[tw] OR fitch[tw] OR beaver[tw] OR beavers[tw] OR jerboa[tw] OR jerboas[tw] OR capybara[tw] OR capybaras[tw]) |

Appendix 7: Economic Methodology Review of Quantitative Research Based on Difference-in-Differences, Event Study, and Structural Break Techniques

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

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Office of Program and Strategic Analysis
Office of Surveillance and Epidemiology

Memo

Date: May 28, 2020

Reviewer(s): Lukas Glos, MA
Office of Program and Strategic Analysis (OPSA), Economics Staff

Christina Greene, PhD
Office of Surveillance and Epidemiology (OSE),
Division of Epidemiology II (DEPI)

Secondary Reviewer(s): Matthew Rosenberg, MSPPM
OPSA, Economics Staff

Jana McAninch, MD MPH MS
OSE, DEPI

Tertiary Reviewer(s): Andreas Schick, PhD
OPSA, Economics Staff

Tamra Meyer, PhD MPH
OSE, DEPI

Associate Office Director: Judy Staffa, PhD RPh
OSE

Product Name(s): OxyContin® (Oxycodone)

Subject: Critique of published articles using economic analysis methods to assess impact of reformulation of OxyContin

Applicant/Sponsor: Purdue Pharma

OSE RCM #: 2019-1681

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Introduction

In November 2019, the Division of Epidemiology (DEPI, Non-Medical Use) and the Economics Staff provided review and critique of five epidemiologic studies conducted by economists. These studies used nationally available data sources to explore whether the OxyContin reformulation was associated with an increase in other adverse outcomes, including heroin mortality, synthetic opioid mortality, and hepatitis C.

Methods and Materials

DEPI reviewed five studies published by economists, four of which were published in journals and one of which was found in the grey literature. DEPI consulted with CDER's Economics Staff for assistance and guidance with interpreting these studies, particularly the application of the methodology used. Together DEPI and CDER's Economics Staff reviewed and summarized the results, interpretation, and potential methodological issues from these studies.

Results

We have identified and reviewed five studies (Alpert 2018, Evans 2019, Powell 2019, Powell 2020, Wolff 2020[7]) that assessed the impact of the introduction of an abuse-deterrent formulation (ADF) of OxyContin to the U.S. market in 2010 on various outcomes using methodological approaches commonly found in social sciences, such as difference-in-differences and event study (Alpert 2018, Powell 2019, Powell 2020, Wolff 2020) methods (operationalized in form of regression analysis), and structural break techniques (Evans 2019).

These methods relied on real world data to mimic randomized assignment; the difference-in-differences and event study methods used in these studies compared changes in outcomes before-and-after the reformulation between populations that were exposed to the reformulation and populations that were not, or only partially, exposed to the reformulation. The difference in those changes was interpreted as the net impact of the reformulation on the exposed populations relative to the unexposed populations. While the difference-in-differences methods produced averaged results for the before-and-after periods, the event study techniques produced results for each year included in these studies. The structural break technique used in one of the studies identified changes in trends (or trend breaks) in U.S. markets for prescription opioids and heroin and estimated the timing of their occurrence.

Among the four studies (Alpert 2018, Powell 2019, Powell 2020, Wolff 2020) that utilized difference-in-differences and event study techniques, the studies by Alpert (2018), Powell (2019) and Powell (2020) conducted their analyses on the state-level and considered states with higher rates of OxyContin misuse prior to the reformulation as exposed and states with lower rates of OxyContin misuse prior to the reformulation as unexposed. In contrast, Wolff (2020) utilized individual-level data and considered individuals who misused OxyContin prior to the introduction of ADF OxyContin as exposed and individuals who misused other prescription pain relievers in the same time period as unexposed. Evans (2018) used time series data and structural break techniques to identify changes in trends, based on the timing of the reformulation.

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[7] Some authors of this study are employees of the U.S. Food and Drug Administration and participated in drafting this literature review

Three studies that we have reviewed (Alpert 2018, Evans 2019, Wolff 2020) assessed the impact of the reformulation on prescription pain relievers use, use disorder, and misuse. Evans (2019) found a statistically significant trend break in oxycodone utilization in the third quarter of 2010, the same quarter in which the reformulation occurred. They found no trend breaks for any other opioid product they have evaluated during the same time period. Similarly, Alpert (2018) found a significant net reduction in OxyContin misuse following the reformulation, and Wolff (2020) found a significant net reduction in prescription pain relievers misuse, but no effect on prescription pain reliever use disorder following the introduction of ADF OxyContin. Two studies (Alpert 2018, Evans 2019) evaluated the impact of the reformulation on opioid-related (opioids other than heroin) mortality. While Alpert (2018) found no significant net impact of the reformulation on opioid-related mortality, Evans et al. (2018), in contrast, showed that the introduction of ADF OxyContin significantly reduced opioid-related mortality, especially in areas with "high" exposure to oxycodone and "low" exposure to heroin, and suggested that the availability of heroin might be an important factor in the effect of abuse-deterrent formulations on opioid-related mortality.

Four studies (Alpert 2018, Evans 2018, Powell 2020, Wolff 2020) also assessed the impact of the introduction of ADF OxyContin on heroin initiation, heroin use, heroin use disorder, heroin poisoning encounters and heroin-related mortality. Wolff (2020) found a significant net reduction in heroin initiation after the introduction of ADF OxyContin but no impact of heroin use, and heroin use disorder. They suggested that any increase in heroin-related mortality that occurred after the reformulation was likely not due to individuals switching for the first time from OxyContin to heroin. In contrast, both Alpert (2018) and Powell (2020) found that the reformulation led to a large increase in heroin-related mortality and suggested that reformulation led some individuals to switch from prescription opioids to illicitly-produced and illicitly-sold opioids, including heroin. Similarly, Evans (2018) found a statistically significant trend break in heroin poisoning encounters and heroin-related mortality one month after the introduction of ADF OxyContin. However, they also showed that the increase in heroin poisoning encounters and heroin death was starkest in "high risk areas" with "high" levels of oxycodone, and "high" levels of heroin availability prior to the reformulation. They suggested that in these areas it would have taken only one and a half years to double the pre-reformulation heroin-related death rate.

One study by Powell (2020) explored the impact of the reformulation of OxyContin on fatal overdoses from synthetic opioids (e.g. fentanyl), opioids overall (including heroin), as well as cocaine. They found, that states with a one standard deviation higher rate of OxyContin misuse in the pre-period experienced 4.6 additional death from synthetic opioid overdoses and 1.3 additional cocaine-related overdoses per 100,000 individuals, respectively. However, they have not observed this trend for fatal overdoses involving cocaine only, suggesting a co-exposure of cocaine with opioids. To assess the effect of the reformulation on opioid-related mortality overall, the investigators created a counterfactual model that compared a 'hypothetical country' unexposed to the reformulation to the United States; based on this model, they estimate, that the reformulation has increased overall fatal opioid overdoses by 8.7 overdoses per 100,000 individuals as of 2017.

Finally, one study by Powell (2019) evaluated the relationship between the reformulation of OxyContin and hepatitis C infections and found that the reformulation significantly increased the number of hepatitis C cases in the United States. The authors showed that by 2015, five years after the introduction of the ADF of OxyContin, each percentage point of non-medical OxyContin use prior to the reformulation increased hepatitis C infections by 1.32 cases per 100,000 inhabitants.

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Appendix 8: Review of Spontaneous Adverse Event Reporting Studies

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Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Pharmacovigilance Memo

Date: March 16, 2020

Reviewer(s):   Mallika Mundkur, MD MPH

Office of Surveillance and Epidemiology (OSE),

Division of Pharmacovigilance II (DPV II)

Division Director(s):   S. Christopher Jones, PharmD, MPH, MS
OSE, DPV II

Product Name(s):   OxyContin® (Oxycodone)

Subject: Critique of published articles using adverse event reporting data
to assess impact of reformulation of OxyContin

Applicant/Sponsor: Purdue Pharma

OSE RCM #:   2019-1681

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Introduction

In November 2019, the Division of Epidemiology (DEPI, Non-Medical Use) requested the Division of Pharmacovigilance II (DPV II) to critique two published articles that included use of spontaneous reporting data to evaluate abuse-related outcomes (e.g., death) prior to and following reformulation of OxyContin®. A summary of this critique would be included in background material provided to an Advisory Committee (scheduled for September 2020) discussing the results from postmarketing requirements for OxyContin®.

Methods and Materials

DEPI provided two articles for DPV to review (Sessler, 2014; Coplan, 2016).[1, 2] DPV reviewed and summarized these articles, with a focus on assessing strength of study design, and identifying potential issues with methodology, if any. We also reviewed an erratum for one publication (Coplan, 2016) for relevant information.[2]

## Results

Sessler, 2014
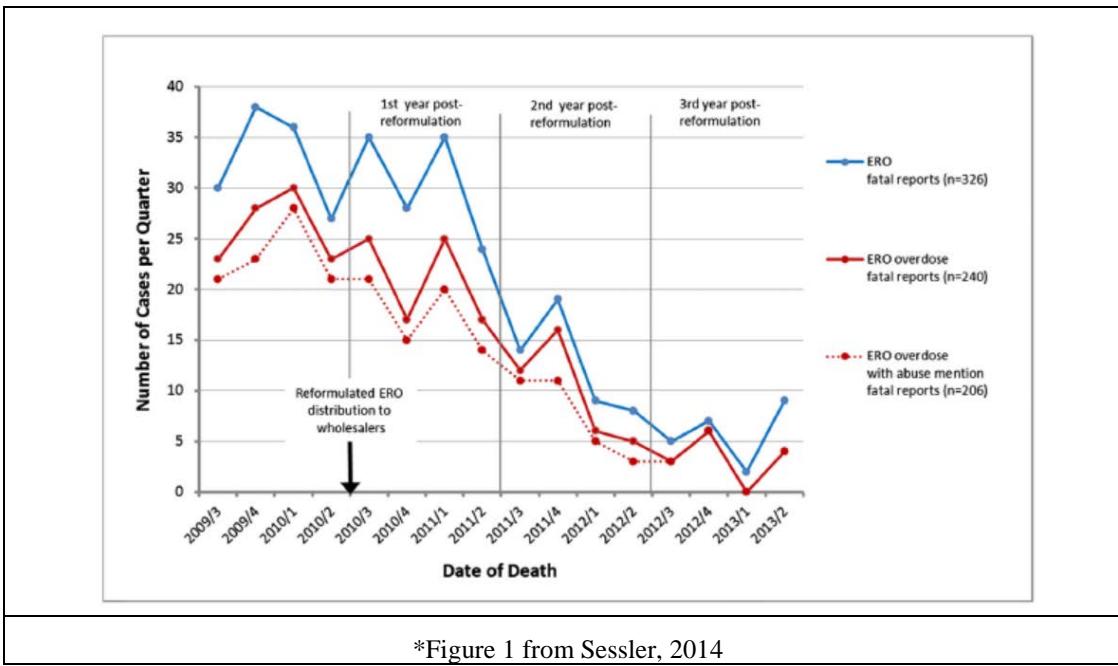
Study methods
This study used a single data source, Purdue Pharma's spontaneous report adverse event database, to evaluate the impact of introduction of reformulated OxyContin® on deaths. The primary outcome of interest in the study was death, as measured by deaths reported to the manufacturer, *with* a reported date of death (including month and year). For the main analysis, the authors excluded reports of death without a date, and those without key reporting elements (e.g., patient, reporter, suspect product or adverse event). In addition, the authors excluded reports deriving from litigation or postmarketing studies such as the manufacturer's patient assistance program.

The study focused on death reports during the timeframe 2009-2013, dividing this into four periods. Additionally, the authors calculated mean fatalities per quarter (of each year), which were subsequently used to model fatality trends (Poisson). Changes in trends were evaluated by spline regression with an inflection point set to the time of the introduction of reformulated OxyContin®. The authors also conducted numerous sensitivity analyses to account for factors such as the following: number of prescriptions dispensed, exclusion of reports without a date of death, the impact of reports describing intentional harm, and the impact of delayed reporting.

Study results

The authors describe 326 fatal cases involving OxyContin® meeting the selection criteria outlined above, of which 195 occurred following reformulation (3Q2010-2Q2013) and 131 occurred prior to reformulation (3Q2009-2Q2010). For the subset of cases involving fatal overdose (n=240), 136 occurred following reformulation, and 104 occurred prior to reformulation. When examining mean fatalities (with date of death reported), the authors report an average value of 32.8 deaths per quarter during the year prior to reformulation, with a significant change occurring by the second year post-reformulation and persisting the third year re-formulation; with an average value of 5.8 deaths per quarter by the third year re-formulation (reported -82% change, 95%CI (-89% to -73%)). The authors note that the change in slope at the pre-defined inflection point (introduction of reformulated OxyContin®) was statistically significant (p=0.0015), with a change of -20.7%, 95%CI (31% to 9%). Figure 1 from the article is reproduced below.

Figure 1. Number of extended-release oxycodone (ERO) fatality reports per quarter *

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*Figure 1 from Sessler, 2014

Although the methods did not detail a planned analysis to include comparators, in the results, the authors report that quarterly reports for extended release morphine (MSContin®) were too few to provide an adequate comparator trend. In addition, the authors state that non-fatal reports for OxyContin were 384 per quarter in the the year pre-reformulation compared with 3129, 395, and 294 per quarter in the first, second, and third year post-reformulation.

Authors' conclusions

The authors concluded that trends in non-fatal reports demonstrated "reductions in fatalities involving ERO post-reformulation were not due to temporal changes in reporting patterns."

Coplan, 2016

This article provides a high-level summary of results from ten studies that were used to fulfill a FDA postmarketing requirement, including but not limited to Purdue Pharma's spontaneous report adverse event database. The authors state that the studies were designed to attempt to address the question of whether OxyContin with abuse-deterrent properties resulted in "lower rates of abuse."

The studies summarized in the article addressed varied outcomes (e.g., misuse, abuse, diagnosed opioid use disorder, overdose fatalities, fatalities, drug diversion events, and doctor shopping) and utilized a number of data sources (e.g., RADARS PC, NPDS, NAVIPPRO ASI-MV, RADARS SKIP/OTP, IMS prescription data).

To assess overdose and fatalities, the authors referred to an analysis of an adverse event database of reports to Purdue Pharma *(Reviewer comment: presumably referencing results from the Sessler study above, listed as Reference 43 of this article, but not referenced in the text).* The authors state that reports of death and overdose fatalities involving OxyContin "containing date of death" decreased by 60% and 65%, while death and overdose death reported decreased by 80% and 85%, respectively *(Reviewer comment: These numbers are not more clearly specified so it is not clear if the authors are referring to changes in mean quarterly reports, total reports, or other).*

The authors note that reports of nonfatal adverse events involving OxyContin, such as constipation or nausea, did not change over the same period of time, inferred by the authors to mean "there was no generally decreased reporting of adverse events associated with OC."

Reviewer's Comments

Sessler, 2014

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The Sessler study was subject to at least three major methodologic issues as outlined below.

Data source
Spontaneous reporting databases do not contain the totality of adverse events occurring in a given exposed population. Accordingly, trends in reporting cannot be used to make inferences about trends in adverse events occurring in the exposed population at large. Thus, the author's use of spontaneous reporting data to examine changes in the occurrence of an adverse event among individuals exposed to OxyContin before and after reformulation is not valid. We also note that the spontaneous data used by the authors was itself an incomplete representation of the totality of spontaneous reports, as it only included reports submitted to Purdue Pharma.

Inclusion and exclusion criteria

Apart from the issue with the data source used for this analysis, the authors used selection criteria that could bias results. For example, the authors selected only reports with a date of death included, as well as other key variables. In addition, they excluded reports associated with litigation. Such selection criteria may have substantial impact on apparent trends in reporting, particularly if litigation reports increased in recent years. Reporting trends, which might include missingness of other variables, such as event date, from spontaneous reports could also be problematic. The authors did not report analyzing trends in litigation or missingness of key variables, which might have addressed some of these questions.

Trend analysis
When attempting to draw a conclusion about the impact of a specific event on a trend, the use of a comparator or "control" is essential.[3] On this point, the authors did not appear to attempt to identify an appropriate comparator, merely stating that there were insufficient reports for MSContin. When evaluating all non-fatal reports for OxyContin, it was not clear that the authors performed a trend analysis, thus even this comparison was inadequate. We also note that the increase in non-fatal reports following introduction of the reformulated product reported by the authors may have been due to litigation reports, a possibility not addressed by the authors, underscoring the problems with case selection as outlined in the point above. We also note in Figure 1 above that reports vary considerably over time, and while the overall trend in fatal case reports meeting selection criteria appears to decrease over time, the variability in reporting appears to weaken any inference that one can make regarding the impact of a specific event, without a comparator. Without use of a comparator, the author's statement that "reductions in fatalities involving ERO post-reformulation were not due to temporal changes in reporting patterns" is not substantiated. Finally, the authors do not specify why they used a relatively short pre-period (3Q2009- 2Q2010) to estimate trends prior to reformulation—inferences about pre-reformulation trends would be more reliable with a larger number of data points.

Summary

In summary, this analysis of spontaneous reports cannot be used to make inferences about the impact of reformulated OxyContin upon the outcome of death, due to issues with the type of data (spontaneous reports) selected, biases introduced by the approach the authors used to select cases, and suboptimal trend analysis.

Coplan, 2016

This article reviews other studies, and does not appear to provide new data, though it is difficult to ascertain the latter based upon the referencing format selected by the authors. Apart from mentioning the different data sources used to assess the same outcomes, the review does not describe in detail the rationale used to justify inclusion of these data sources, nor does it highlight other potentially important methodologic differences (e.g., inclusion/exclusion, outcome measurement) among studies attempting to assess the same outcomes. The authors' lack of in-text referencing to link summarized findings to specific studies, together with lack of detail regarding methodologic characteristics of the various studies prevent the reviewer from determining whether or not the authors' aggregation of results to support inferences about specific outcomes (e.g., death, abuse), is appropriate.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

Date:	March 27, 2020
Reviewer:	Danielle Molnar, PharmD, BCPS, Safety Evaluator Division of Pharmacovigilance II
Team Leader:	Mallika Mundkur, MD, MPH, Acting Team Leader DPV II
Division Director:	S. Christopher Jones, PharmD, MS, MPH DPV II
Product Name(s):	OxyContin (oxycodone hydrochloride, extended release)
Subject:	Thrombotic microangiopathy (TMA)
Application Type/Number:	NDA 022272
Applicant:	Purdue Pharma L.P.
OSE RCM #:	2019-2642

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates reports from the FDA Adverse Event Reporting System (FAERS) and published medical literature case for an association between intravenous use of OxyContin and thrombotic microangiopathy (TMA). This review updates DPV's assessment of TMA FAERS cases involving OxyContin that were included in the 2017 OSE integrated review of reformulated Opana ER, presented during the Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) Meeting on March 13-14, 2017 (McAninch et al. 2017). We are providing this update to support FDA's preparation for the Joint Meeting of the DSaRM and AADPAC meeting about the OxyContin Abuse Deterrent Formulation scheduled for September 10-11, 2020.

Our FAERS search identified six non-fatal cases that comprised the case series of TMA associated with intravenous abuse of reformulated OxyContin; three of these cases were also summarized in the previous review. Four cases were also published in the medical literature. All six cases in the series reported intravenous abuse of reformulated OxyContin, and half provided a brief description of the tampering method, all involving thermal manipulation. All reported event dates occurred after introduction of reformulated OxyContin to the market where the event took place (2 in the United States, 4 in Australia).

The six reports were received over six years (2014-2019), indicating an ongoing, but minimally reported event. A common thread is apparent through all six cases. The patients presented with anemia, thrombocytopenia, evidence of hemolysis, and additional laboratory markers consistent with drug-induced TMA after intravenous use of OxyContin. Our analysis found that these cases appear to be consistent with the risk of TMA already described in OxyContin labeling.

The cases in the series included several aspects that supported a causal association between intravenous OxyContin abuse and TMA. The reported sequence of events and clinical evidence indicates a strong temporal association between intravenous abuse of OxyContin and TMA for all the cases in our series. Additionally, we did not identify an alternative etiology for TMA in five of the six cases. All cases resolved, or showed signs of resolving, with abstinence of OxyContin IV abuse (positive dechallenge) and either supportive care only, or supportive care plus plasma exchange, steroids, and/or eculizumab. Five cases provided evidence of positive dechallenge and two cases provided evidence of positive rechallenge.

In addition to the factors supporting a causal association, the presence of PEO in OxyContin provides plausibility by which reformulated OxyContin may be associated with TMA. Data from animal models have linked PEO of varying molecular weights to acute manifestations of TMA (Hunt et al 2017, D'Agostino 2020, and Persich et al. 2020). However, the number of cases our search uncovered (six) is much lower than the 59 TMA cases identified for reformulated Opana ER in previous reviews (McAninch et al. 2017). Differences in the number of reports should be interpreted with caution given known limitations of spontaneous reports, such as product misclassification or stimulated reporting. If the observed difference in the number of TMA events is true beyond FAERS, numerous factors apart from the presence of PEO in drug products

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may contribute to the difference, for example, relative rates of abuse, size of the PEO polymer, manufacturing process, and tampering methods.

In conclusion, we find an association between intravenous abuse of reformulated OxyContin and TMA. However, TMA associated with intravenous abuse of OxyContin is a known, labeled event. Our assessment of the case series against the current OxyContin labeling indicates the description of potential risk of TMA following intravenous abuse of OxyContin remains accurate and adequately described. Based on this review, DPV does not propose any recommendations at this time.

2

1   INTRODUCTION

This review evaluates reports from the FDA Adverse Event Reporting System (FAERS) and published medical literature cases for an association between intravenous use of OxyContin and thrombotic microangiopathy (TMA). This review updates DPV's assessment of TMA FAERS cases involving OxyContin that were included in the 2017 OSE integrated review of postmarketing safety data on reformulated Opana ER (oxymorphone extended-release), presented during the Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) Meeting on March 13-14, 2017 (McAninch et al. 2017). We are providing this update to support FDA's preparation for the Joint Meeting of the DSaRM and AADPAC meeting about the OxyContin Abuse Deterrent Formulation scheduled for September 10-11, 2020.

1.1   BACKGROUND

Drug characteristics

OxyContin, marketed under NDA 022272 and henceforth referred to as reformulated OxyContin, is a schedule II controlled-release oxycodone hydrochloride product designed with physiochemical properties intended to discourage abuse by injection or intranasal route (FDA 2010). The product is formulated with a polyethylene oxide (PEO) polymer matrix intended to thicken and become gel-like in aqueous solutions for abuse deterrence (Joshi et al. 2018). OxyContin's reformulation contains PEO with a molecular weight of ~4,000,000 Da (D'Agostino 2020).[a]

Reformulated OxyContin is also marketed in countries outside the U.S. For example, controlled-release oxycodone in Australia was replaced with the tamper-resistant, PEO-containing, formulation of OxyContin in April 2014 (Schaffer et al. 2018).[b] There may be slight differences in the manufacturing of OxyContin marketed in the U.S. versus other countries, such as the tablet coating process, the manufacturing location, or ingredient suppliers. It not known whether possible differences in manufacturing by country could play a role in the success of tampering with OxyContin for purposes of intravenous abuse, or whether they influence risk of TMA after intravenous abuse of OxyContin.

TMA

TMA encompasses a spectrum of clinical syndromes characterized by thrombosis in arterioles and capillaries, manifesting clinically as microangiopathic hemolytic anemia and thrombocytopenia. Types of TMA include thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). Published reports of TMA after intravenous use of reformulated Opana ER indicate the patients had anemia, thrombocytopenia and evidence of

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[a] For comparison, Opana ER's reformulation contains PEO with a molecular weight ~7,000,000 Da

[b] Australian Product Information – Oxycontin (oxycodone hydrochloride) modified release tablets. 2019. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-02353-1&d=202001301016933

hemolysis, with a negative direct Coombs test and normal ADAMTS13 (a disintegrin and metalloprotease with a thrombospondin type 1 motif member 13) activity (Nataatmadja et al. 2016). Hemolytic anemia, thrombocytopenia, and negative Coombs test are consistent with TTP. However, normal ADAMTS13 activity is consistent with drug-induced TMA, not TTP wherein ADAMTS13 activity is reduced because of autoantibodies or inherited deficiency (Sadler 2016). Anuric or oliguric renal failure typically occurs in HUS and causal factors include *Shiga* toxin-producing *Escherichia coli* and defects in alternative complement pathway regulation (Sadler 2016).

Secondary TMA can be associated with certain predisposing medical conditions, such as pregnancy or systemic infections like hepatitis, as well as certain drugs, such as chemotherapy. Other drugs associated with secondary TMA include quinine, cyclosporine, and tacrolimus, although there are approximately 44 drugs with evidence to support a compelling association with secondary TMA (Sadler 2016). The known mechanisms of drug-induced TMA are immune-mediated, direct toxicity to endothelium, or both (Sadler 2016). Severe ADAMTS13 deficiency very rarely occurs in secondary TMA, and intervention with plasma exchange, rituximab, or eculizumab is not known to be beneficial over correcting the underlying condition (Sadler 2016).

Previous cases of OxyContin-associated TMA

Following reports of injection drug users in Tennessee who had developed TMA in 2012, the Centers for Disease Control and Prevention (CDC) determined the illnesses were associated with dissolving and injecting another opioid analgesic product (i.e., reformulated Opana ER) (CDC 2013). In 2017, OSE conducted an integrated review of postmarketing data to identify cases of opioid-associated TMA. At that time, DPV identified three cases of TMA associated with OxyContin, all of which were reports from Australia, and 59 cases associated with intravenous abuse of reformulated Opana ER from December 9, 2011 through June 1, 2016 (McAninch et al. 2017). OSE presented these and other results at an advisory committee meeting held in March 2017 regarding postmarketing safety issues related to reformulated Opana ER, and TMA was one of the safety issues discussed. Subsequently, the applicant for reformulated Opana ER removed its product from the market in 2017 following FDA's request (FDA 2017).

High molecular weight PEO and TMA

PEO provides a possible biological mechanism underlying these cases of drug-induced TMA. PEO is a water-soluble polymer and is available in a range of molecular weights (100,000-7,000,000 Da) (Joshi et al. 2018). Studies in animal models demonstrated the potential for high molecular weight (HMW) PEO-based formulations (approximately 7,000,000 Da) to cause acute hematotoxicity, TMA, and end organ injury in the setting of intravenous abuse (Hunt et al. 2017). Additional data to date suggests potential TMA risk if HMW PEO ($\geq$ 2 million) is extracted and injected (D'Agostino 2020 and Persich et al. 2020). The mechanistic role of PEO as a causal agent in these cases of TMA appears to be direct toxicity to the endothelium, as demonstrated in guinea pig models, through alteration of blood flow leading to shear stress on vessel walls and mechanical red cell damage (Saleem et al. 2018, Hunt et al. 2017, and Nataatmadja et al. 2016).

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PEO-containing drug product formulations may not carry the same risk of TMA when injected. Differences in risk of PEO-associated TMA may theoretically be dependent on manufacturing processes, such as curing methods; PEO molecular weight used; tampering and preparation methods for intravascular abuse; and patterns of abuse of the drug (Mellon 2018).

1.2   RELEVANT REGULATORY HISTORY

Reformulated OxyContin is approved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate in adults; and in opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20mg oxycodone orally or its equivalent.[c]

FDA approved reformulated OxyContin (NDA 022272) on April 5, 2010. The Applicant ceased shipments of the original OxyContin formulation (NDA 20553) in August 2010 when the reformulated product was commercially launched (Purdue 2013 and 2019). Labeling describing abuse-deterrent properties of the reformulated product was not approved until April 16, 2013 reflecting results of abuse potential studies conducted by the Applicant.[c]

On April 18, 2013, FDA determined that original OxyContin (NDA 20553) was withdrawn from the market for safety reasons, in light of extensive and well-documented history of abuse, per the *Federal Register* (78 FR 23273 at 23274). This determination of withdrawal for safety reasons also meant that generic versions of the original OxyContin formulation could not be marketed.

On September 26, 2018, FDA approved the Applicant's request (NDA prior approval supplement 39) to add language to the reformulated OxyContin label regarding increased risk of embolism and death, and thrombotic microangiopathy with parenteral drug abuse of reformulated OxyContin.[c]

1.3   RELEVANT PRODUCT LABELING

9 DRUG ABUSE AND DEPENDENCE [c]

9.2 Abuse

Risks Specific to Abuse of OXYCONTIN

OXYCONTIN is for oral use only. Abuse of OXYCONTIN poses a risk of overdose and death. The risk is increased with concurrent use of OXYCONTIN with alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved OXYCONTIN enhances drug release and increases the risk of overdose and death. With parenteral abuse, the inactive ingredients in OXYCONTIN can be expected to result in local tissue necrosis, infection,

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[c] Approval dates and history, letters, labels, reviews for NDA 022272. Drugs@FDA, http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=022272

pulmonary granulomas, increased risk of endocarditis, valvular heart injury, embolism, and death. Cases of thrombotic microangiopathy (a condition characterized clinically by thrombocytopenia and microangiopathic hemolytic anemia) associated with parenteral abuse have been reported.

Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

We utilized a broad case definition to capture all potential cases of TMA described with intravenous use of OxyContin, recognizing that individual cases may report signs and symptoms of TMA but not specific diagnosis. We used the following case definition, modeled after previous OSE reviews of reformulated Opana ER and TMA, to identify cases of TMA reported with OxyContin.[d]

Inclusion Criteria: 1, 2, and 3
1. Patient known to have injected OxyContin.
2. A) Diagnosis of TMA (which includes TTP or hemolytic uremic syndrome [HUS])
   OR
   B) Thrombocytopenia AND anemia with evidence of hemolysis. (Evidence of hemolysis includes: red cell fragmentation on peripheral drug smear [e.g., schistocytes], elevated lactate dehydrogenase [LDH], elevated reticulocyte count [without evidence of blood loss] or elevated total bilirubin [without evidence of hepatitis.])
3. Absence of definitive evidence of an alternative etiology of TMA.

2.2 CAUSALITY CRITERIA

We used an adaptation of the WHO-UMC Causality Assessment System, shown in Table 1, to assess the relationship of thrombotic microangiopathy and intravenous use of reformulated OxyContin.

Table 1. Modified WHO Causality Assessment System (Uppsala 2018)	
Causality Term	**Assessment Criteria***
Probable	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear

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[d] Previous reviews of Opana ER and TMA considered multiple products for inclusion criterion #1 (McAninch et al. 2017). In contrast, our review focuses on a single product, OxyContin.

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Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unassessable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

* All points should be reasonably complied with.

2.3 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of Search	December 30, 2019
Time Period of Search	All reports through December 29, 2019
Search Type	FBIS Quick Query
Product Terms	Product Name: OxyContin or NDA: 022272
MedDRA Search Terms (Version 22.1)	HLGT: 1. *Coagulopathies and bleeding diatheses (exclude thrombocytopenic)* 2. *Haemolyses and related conditions* 3. *Haematological disorders NEC* 4. *Platelet disorders*

* See Appendix A for a description of the FAERS database.

2.4 LITERATURE SEARCH

DPV searched the medical literature in PubMed@FDA and EMBASE with the strategy described in Table 3 to identify case reports of TMA associated with OxyContin.

Table 3. Literature Search Strategy	
Date of search	January 23, 2020

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Table 3. Literature Search Strategy	
Search terms used on PubMed@FDA	(("oxycodone"[MeSH Terms] OR "oxycodone"[All Fields] OR "oxycontin"[All Fields]) OR ("oxycodone"[MeSH Terms] OR "oxycodone"[All Fields])) AND (microangiopathy[All Fields] OR ("purpura, thrombotic thrombocytopenic"[MeSH Terms] OR ("purpura"[All Fields] AND "thrombotic"[All Fields] AND "thrombocytopenic"[All Fields]) OR "thrombotic thrombocytopenic purpura"[All Fields] OR ("thrombotic"[All Fields] AND "thrombocytopenic"[All Fields] AND "purpura"[All Fields])) OR ("haemolytic uraemic syndrome"[All Fields] OR "hemolytic-uremic syndrome"[MeSH Terms] OR ("hemolytic-uremic"[All Fields] AND "syndrome"[All Fields]) OR "hemolytic-uremic syndrome"[All Fields] OR ("hemolytic"[All Fields] AND "uremic"[All Fields] AND "syndrome"[All Fields]) OR "hemolytic uremic syndrome"[All Fields]))
Search terms used in EMBASE	('oxycodone'/exp OR oxycodone OR 'oxycontin'/exp OR oxycontin) AND (microangiopathy OR 'thrombotic thrombocytopenic purpura' OR 'hemolytic uremic syndrome')
Years included in searches	All dates through date of search

2.5 PERIODIC SAFETY REPORTS

DPV screened the following periodic safety report for the Applicant's assessment of thrombotic microangiopathy with OxyContin use:

- Periodic Safety Update Report (PSUR) for oxycodone hydrochloride, April 13, 2019 – October 12, 2019, and FDA Addendum to PSUR, April 13, 2019 - October 12, 2019.

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved 194 reports. A total of 188 reports were not included in the final analysis for the following reasons:
- Duplicate reports (n= 40)
- Did not meet case definition in Section 2.1 (n= 148)

The remaining six cases were included in the case series of TMA reported with intravenous use of reformulated OxyContin, and the series is summarized in Table 4. Appendix B contains a line listing of the six cases in this case series.

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Table 4. Descriptive Characteristics of TMA Reported with Intravenous Abuse of Reformulated OxyContin in This FAERS Case Series, Received by FDA through December 30, 2019[*] (N=6)		
Sex	Male	4
	Female	2
Age in years (n=6)	Mean	39
	Median	39
	Range	28-56
Reporter's Country	Australia	4
	United States	2
Initial FDA Received Year	2014	1
	2015	1
	2016	1
	2017	2
	2019	1
Event Year	2014	2
	2015	1
	2016	1
	NR	2
Report Type	Direct	1
	Expedited (15-Day)	5
Serious Outcomes[†]	Death	0
	Hospitalization	6
	Life-threatening	2
	Other serious	4
Preferred Terms[‡]	Drug Abuse	4
	Incorrect route of product administration	3
	Microangiopathic hemolytic anemia	3
	Thrombocytopenia	3
	Thrombotic microangiopathy	2
	Vomiting	2
	Abdominal pain	2
Time to Onset (n=4)	6 days	1
	2 weeks	1
	20 days	1
	5 weeks of regular IV OxyContin use	1
Platelet Count on Admission (n= 6)[§] (RI: 150-450 x10^9/L) [**]	Median	53.5 x10^9/L
	Range	8-61 x10^9/L
Hemoglobin on Admission (n= 6)[§‖] (RI: Female 12-16 g/dL; Male 14-18 g/dL) [**]	Median	8 g/dL
	Range	5.9-9.3 g/dL
SCr on Admission (n=6)[‖] (RI: Female 0.50-1.10	Above normal	4
	Normal	2

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Table 4. Descriptive Characteristics of TMA Reported with Intravenous Abuse of Reformulated OxyContin in This FAERS Case Series, Received by FDA through December 30, 2019[*] (N=6)		
mg/dL; Male 0.70-1.30 mg/dL) [**]		
ADAMSTS13 Activity (n= 4) [¶] (Normal: >60%) [**]	Median	80%
	Range	68%-98%
LDH (n= 6) [§] (RI: 80-225 U/L) [**]	Median	1084.5 U/L
	Range	406-1630 U/L
Schistocytes (n=6)	Present	5
	Not reported	1
Hepatitis C (n= 6)	Positive	0
	Negative	3
	Previously diagnosed	1
	NR	2
Infectious comorbid conditions (n= 6)	Negative	2
	Hepatitis C	1
	None Reported	3
Treatment [††]	Plasma exchange	4
	Prednisone or prednisolone	3
	Eculizumab	1
	Supportive Care	4

ADAMSTS13 = A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13; LDH = Lactate dehydrogenase; NR= Not Reported; RI = Reference Interval; SCr = Serum Creatinine

[*] This includes 3 cases previously described in McAninch et al 2017.

[†] One case may report more than one outcome.

[‡] Most frequently reported MedDRA preferred terms with N≥2.

[§] Two cases did not report units. Because the reported values resembled others with reported units, we assumed the same units for this table.

[‖] SCr was reported as µmol/L for 3 cases, mg/dL for one case, and "normal kidney function" for one case. A value without units or description was reported for one case and is presumed above normal because the value is higher than other SCr levels described as above normal.

[¶] One additional case reported "normal" ADAMSTS13 results.

[**] Reference intervals varied by reporter, if provided at all. The reference intervals shown on this table are from the American Board of Internal Medicine (ABIM 2020).

[††] One case may report more than one treatment.

All cases reported intravenous abuse of reformulated OxyContin, and half provided a brief description of the tampering method, all involving thermal manipulation. The majority of reports were not only submitted to FAERS, but also published as case reports in the medical literature. Most were reported from Australia while two are domestic reports. All reported event dates occurred after introduction of reformulated OxyContin to the market where the event took place (April 2010 in the U.S. and April 2014 in Australia).

None of the cases resulted in death; however, all case patients were hospitalized. All were described as presenting with anemia and thrombocytopenia, and most with impaired renal function. All reported some evidence of hemolytic processes, including elevated LDH and red

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blood cell fragmentation (schistocytes), with ADAMTS13 activity in normal range, consistent with drug-induced TMA.

Our case series contains six cases of TMA with intravenous abuse of reformulated OxyContin. All six cases are summarized below. We acknowledge that the last three cases were previously described by McAninch et al. and presented in the FDA Briefing Document for the Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) on March 13-14, 2017 during the meeting held to discuss postmarketing safety issues related to reformulated Opana ER (McAninch et al. 2017). We summarized those three cases again in this review for completeness.

FAERS Case #15860040, Received January 25, 2019, United States, Literature (Di et al. 2018)
A 43-year-old male with a history of untreated chronic hepatitis C, insulin-dependent diabetes mellitus, IV polysubstance abuse complicated by recent necrotizing fasciitis, and peripheral inserted central catheter associated deep vein thrombosis (DVT), had been at a community hospital for 14 days for treatment of a soft tissue abscess in the left upper extremity. He was treated with one dose of sulfamethoxazole/trimethoprim on day 1, then was started on clindamycin and piperacillin/tazobactam, subcutaneous heparin to day 17, oral acetaminophen, oral long-acting oxycodone, and hydromorphone IV as needed. He developed thrombocytopenia and was found to have microangiopathic hemolytic anemia on day 18 (platelets 54 x10^9/L from a baseline of 400 x10^9/L). He received packed red blood cells (PRBC) and fresh frozen plasma (FFP). He was transferred to a different institution on day 21, after finishing the course of antibiotics, where he was found to have a creatinine level of 1.8 mg/dL (baseline 1.1mg/dL). Physical exam was unremarkable, but labs on admission were significant for thrombocytopenia (8x10^9/L) anemia (7.4 g/dL), and leukocytosis (12.7 x10^9/L) with elevated reticulocytes and schistocytes on peripheral blood smear. Labs also showed indirect hyperbilirubinemia (total bilirubin 3.7 mg/dL, direct bilirubin 0.5 mg/dL), elevated LDH (1489 IU/L), and low haptoglobin (<8 mg/dL) with a negative direct antiglobulin test. (Reference intervals [RI] were not provided.) Folate and vitamin B12 were normal. D-dimer was elevated and PT mildly prolonged, but PTT, INR and fibrinogen were normal. Autoimmune labs showed mildly elevated ANA titer and negative anti-SCL and double-stranded DNA antibody. Hepatitis C viral load was markedly elevated. Other infectious disease workups were negative. ADAMTS13 activity was 98%. Plasma exchange was started, as was prednisone 60mg and folic acid 3mg daily. Oral long-acting oxycodone and IV hydromorphone were continued for pain management. Heparin was held. His platelets increased on plasma exchange and were stable until dropping again on day 28. On that day, a nurse witnessed him crushing long-acting oxycodone pills in his bed that he had partially liquified in his mouth. There was concern he was self-injecting crushed long-acting oxycodone into his IV, but that was never witnessed. On day 29, his platelets decreased to 16 x10^9/L, long-acting oxycodone was discontinued, and plasma exchange was held. Platelet level increased to 74 x10^9/L on day 30, then to 141 x 10^9/L on day 31. It remained above 150 x10^9/L throughout the remainder of the hospital stay.

Reviewer Comments: The initial TTP diagnosis, initially supported by labs and clinical presentation, was excluded after ADAMTS13 returned normal. An untreated hepatitis C infection could have provided a potential alternative etiology for the thrombocytopenia and hemolytic anemia. However, reported improvement of thrombocytopenia without treatment of the

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underlying infection renders hepatitis C an unlikely etiology in this case. Less convincing potential etiologies were ruled out by the reporters, including recent skin grafting and antibiotics. The major weakness of this case compared with others in the series is that intravenous abuse was not witnessed nor reported by the patient. However, witnessed tampering with OxyContin in temporal association with the events, followed by prompt and steady improvement of thrombocytopenia with removal of OxyContin and plasma exchange, is a convincing demonstration of positive dechallenge.

Causality assessment: probable

FAERS Case #13828986, Received September 28, 2017, Australia, Literature (Robson et al. 2017)

A 35-year-old male with a history of schizoaffective disorder (treated with intramuscular risperidone), chronic pain (treated with paracetamol), smoker, and intermittent IV drug user described 48 hours of fatigue, sweats and epigastric discomfort at presentation. He reported IV use of heroin, obtained from an unfamiliar supplier, 4 days prior. He was hypertensive at presentation with a temperature of 37.8°C and had palpable lymphadenopathy in the right axilla. Hemoglobin (Hb) was 5.9 g/dL and platelets were 61 x10^9/L (RIs not provided). He received 4 units of red cells by transfusion and lymph node biopsy showed reactive changes only. Upon transfer to a tertiary hospital 48 hours later, areas of superficial thrombophlebitis on his forearms were noted on physical exam but he was negative for peripheral stigmata of endocarditis, rash, and cardiac murmur. Jugular venous pressure was not elevated and there was no peripheral edema. Blood tests showed thrombocytopenia (platelets 69 x10^9/L) and anemia (8.5 g/dL), evidence of hemolysis (elevated LDH of 722 U/L [RI <250] and reticulocytes 239x10^9/L [RI 20-100]), and undetectable haptoglobin (<0.1 g/L). Blood films confirmed microangiopathic hemolytic anemia, demonstrating red cell fragmentation. The coagulation profile was normal. Deteriorating renal function was noted 48 hours after presentation (SCr 191 µmol/L; RI not provided) and urinalysis was positive for blood and protein. He was treated with plasma exchange and prednisolone 75mg daily. Renal biopsy 4 days after admission showed evidence of TMA: arterioles contained fibrin thrombi and fragmented red cell; glomeruli showed ischemic change; and mild patchy chronic tubulointerstitial damage. ADAMTS13 activity was 80% (normal >70). Antinuclear antibody, rheumatoid factor, and antineutrophil cytoplasmic antibody were negative. There was no evidence of hepatitis B or hepatitis C, cytomegalovirus or Epstein Barr virus. C3 and C4 were within normal range (1.33 g/L [RI 0.90-1.80) and 0.25 g/L [RI 0.16-0.47] respectively). Three sets of blood cultures showed no growth. Transthoracic echocardiograph showed normal valves and normal left ventricle. Stool culture excluded infection. Plasma exchange was continued over 12 days with improving Hb and platelets but continuing abnormal renal function, elevated LDH, and elevated reticulocytes. Eculizumab was initiated and plasma exchange was stopped. The patient was discharged home 4 weeks after presentation with Hb 12.9 g/dL, platelets 337 x10^9/L, reticulocytes 83x109/L, haptoglobin 0.3g/L, LDH 253 U/L, and SCr 170 µmol/L. He was readmitted 6 weeks later due to recurrent anemia and deteriorating renal function (SCr 242 µmol/L). He disclosed that he had been regularly injecting tamper-resistant OxyContin, obtained from someone else for whom it was prescribed, and had been regularly injecting this formulation before the initial presentation. LDH, bilirubin and haptoglobin were within normal limits and blood film showed no red cell fragmentation. His Hb and creatinine improved during admission without further intervention

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other than abstinence from IV drug use. Eculizumab was stopped after 6 months of treatment, and the patient engaged in substance abuse counselling.

Reviewer Comments: Like several cases in this series, health care providers were not made aware of the patient's history of intravenous abuse of OxyContin until after empiric treatments and workups were well underway. In this case, temporal association of the events to intravenous abuse of OxyContin was not established until a second presentation, but this second presentation provides evidence of a positive rechallenge after a positive dechallenge, all supported by thorough laboratory workup and exclusion of alternative etiologies. The role of eculizumab therapy in this case is unclear as some, but not all, signs and symptoms improved with coinciding abstention from IV drug abuse during the first and second admissions. We acknowledge that recent IV heroin abuse could have played a contributory role for the first admission. However, the totality of evidence and patient history provided by the end of the report indicates an unlikely role for heroin in this case.

Causality assessment: probable

FAERS Case #13089022, Received January 4, 2017, United States, Direct Report
A 43-year-old female with remote history of drug abuse presented with complaints of abdominal pain and was found to have thrombocytopenia, anemia, evidence of hemolysis, schistocytes on peripheral smear, elevated LDH, and a syndrome suggesting a TTP-like TMA. After two courses of plasma exchange for presumed idiopathic TTP, and initial denial of IV drug use, she admitted to one instance (six days before admission) of dissolving and heating OxyContin 60mg she got from a relative, drawing it into a syringe through a cigarette filter, and then intravenously injecting it. She denied any use of Opana ER. She had a normal complete blood count (CBC) three months before admission. Labs taken the day after admission showed: Hb 7.9, platelet count 11,000, bilirubin 2.6, LDH 406, haptoglobin < 10, peripheral smear with fragmentation and schistocytes, normal kidney function, no evidence of hepatitis, and normal ADAMTS13 activity. (Units and RIs were not provided.) No additional plasma exchange occurred after her admission of IV OxyContin use, and the syndrome resolved. Her CBC normalized. The reporter noted the similarity of this patient's presentation to past Opana ER cases at his Tennessee institution.

Reviewer Comments: Although this case lacks medical history of the patient and provides fewer laboratory and workup details, it does provide a clear temporal relationship and specific time-to-onset of six days without apparent alternative etiology. Improvement without treatment outside of supportive care and cessation of OxyContin abuse demonstrates a positive dechallenge.

Causality assessment: probable

FAERS Case #11617284, Received October 9, 2015, Australia, Literature (Tate et al. 2015)
A 56-year-old male with no clinically significant medical history presented with a 3-day history of periumbilical abdominal pain. He reported IV use of OxyContin over a period of months, and injection of the new tamper-resistant formula for the 5 weeks before presentation because he could not access the discontinued form. Results of cardiovascular and respiratory exams were

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unremarkable and there was no injection site infection or axillary lymphadenopathy. Labs on admission showed Hb 8.7 g/dL (RI 13.5-18.0 g/dL), total white cell count 15x10^9/L (RI 4-11x10^9/L), neutrophils 10.84x10^9/L (RI 2-8x10^9/L), monocytes 1.47x10^9/L (RI 0.1-1.0x10^9/L), and platelets 53x10^9/L (RI 140-400x10^9/L). SCr was normal at 66 µmol/L. His unconjugated bilirubin level was 34 µmol/L (RI <20 µmol/L) and LDH was 769 U/L (RI 150-280 U/L). Other liver function tests were normal. His reticulocyte count was 168x10^9/L (RI 10-100x10^9/L), haptoglobin 0.04 g/L (RI 0.36-1.95 g/L), and Coombs test was negative. Three percent of his red blood cells were fragmented and polychromasia was present, reported to be consistent with microangiopathic hemolytic anemia. ADAMTS13 activity was 70% (RI 40%-130%). He was negative for hepatitis B, hepatitis C, and HIV. Vitamin B12, folate, lupus anticoagulant, anticardiolipin, anti-B2 glycoprotein I, antinuclear antibody, extractable nuclear antigen and complement levels were normal. His ferritin was elevated but transferrin saturation was normal. Activated partial thromboplastin time and prothrombin time were normal and his fibrinogen level was elevated at 5.4g/L (RI 1.7-4.5 g/L). A random urine test showed proteinuria at 340mg/L (RI <100mg/L) and protein-to-creatinine ratio of 66 g/mol (RI <15g/mol). The microangiopathic hemolysis resolved, demonstrated by improved lab parameters, through supportive care.

Reviewer Comments: The laboratory evidence and workup reported in this case supports drug-induced TMA more so than other types of TMA. We note that white blood cells were elevated, but the reporter did not indicate other signs or symptoms indicating a systemic infection that otherwise may have provided alternative etiology for the TMA. Temporal association of the events in this case to IV OxyContin use is clear, although time-to-onset of 5 weeks is imprecise given reported regular abuse throughout that period. A positive dechallenge is again demonstrated by clinical response in the absence of treatment other than supportive care and drug abstinence.

Causality assessment: probable

FAERS Case #10299601, Received July 11, 2014, Australia, Literature (Nataatmadja et al. 2016)
A 29-year-old female with a medical history of depression (for which she took desvenlafaxine daily) was treated for migraine and discharged but re-presented three days later. Labs at presentation showed Hb 7 g/dL (RI 11.5-16 g/dL) and platelets of 17x10^9/L (RI 150-400x10^9/L). She was treated with PRBC and FFP and was transferred to a tertiary center. Her creatinine was 90 µmol/L (RI 46-90 µmol/L). Her LDH and bilirubin were elevated (970 U/L [RI 150-280 U/L] and 34 µmol/L [<20 µmol/L], respectively), haptoglobin reduced (0.02 g/L [RI 0.36-1.95 g/L]), and fragments were present on blood film. ADAMTS13 activity was normal (94%). Plasma exchange was initiated for presumed TTP. Blood tests normalized with eight sessions of plasma exchange. She was lost to outpatient follow-up but presented to the hospital again 2 weeks later with hemolytic anemia (Hb 8.1 g/dL) and thrombocytopenia (8 x10^9/L), and renal impairment (SCr 118 µmol/L). LDH was 1630 U/L, bilirubin 51 µmol/L, haptoglobin 0.03 g/L. Urine showed mild hematuria of 20x10^6/L and albumin: creatinine ratio of 6.4 g/mol (RI not provided). She reported new visual disturbances and was found to have retinal ischemia. Plasma exchange and prednisolone were initiated. Repeat ADAMTS13 again showed normal activity. Atypical HUS was considered (test results months later were negative for aHUS-associated mutations). During this second admission, the patient admitted that she and her husband had been injecting immediate-release oxycodone and OxyContin tablets prescribed for her husband's back pain. For

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the past two months they had been using reformulated OxyContin by breaking the tablets with kitchen shears, then soaking and heating the pieces in water which made it easier to remove the coating. Plasma exchange was discontinued, and the patient was lost to follow-up after discharge. The outcome of retinal ischemia was not reported.

Reviewer Comments: The patient's history of IV OxyContin abuse was discovered after a second TMA admission providing evidence for a positive dechallenge during the first admission, followed by a positive rechallenge leading to the second presentation. Reported two months of abuse provides a temporal association as well as a time-to-onset of two weeks to the second admission. Plasma exchange was provided empirically during the first admission, but the subsequent clinical response given the reported abuse history could have been due to coinciding cessation of IV OxyContin abuse during that admission.

Causality assessment: probable

FAERS Case #11906673, Received January 11, 2016, Australia
A 28-year-old male presented to the emergency department with abdominal pain and vomiting. Labs showed creatinine 218, LDH 1400, bilirubin 112 and platelets 59. (Units and RIs were not provided.) He self-discharged and then presented again five days later for abdominal pain with creatinine 283, platelets 90, Hb 93, LDH 586, haptoglobin 0.03, ADAMTS13 >68%. He was diagnosed with atypical HUS. He was discharged three days after admission, with creatinine 216, LDH 392, Hb 94, platelets 302, and bilirubin 11. He reported that on only one occasion, approximately 20 days before the first presentation to the emergency room, he dissolved three 80mg tablets of OxyContin in water with no other substance. He then boiled the mixture, and injected half into his vein in the morning, half in the evening.

Reviewer Comments: Details regarding the patient's medical history and treatment during his three-day hospital stay are lacking; however, this case provides a temporal relationship supported by a time-to-onset of 20 days from IV abuse of OxyContin to the initial presentation. However, he was diagnosed with aHUS and no labs were reported to rule out that diagnosis, nor is it clear what contributed to improvement of the reported labs at discharge or whether improvement was spontaneous.

Causality assessment: possible

3.2 LITERATURE SEARCH

We did not identify additional literature cases of TMA associated with OxyContin.

3.3 PERIODIC SAFETY REPORTS

In the periodic safety report screened by DPV, the Applicant assessed TMA/TTP-like illnesses involved with intravenous abuse of reformulated OxyContin. The Applicant found six cases relevant to the intravenous abuse of OxyContin. The same six cases comprise our FAERS case series. Of these six cases, the Applicant found one that reported a positive rechallenge, and five that showed probable causality with the reported events.

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The Applicant designated the issue as an ongoing signal that they would monitor for additional 12 months due to its potential for seriousness.

4   DISCUSSION

We identified six FAERS cases of TMA associated with intravenous abuse of reformulated OxyContin. The six reports were received over six years (2014-2019), indicating an ongoing, but minimally reported event. The event dates reported for the six cases in our series coincide with the presence of reformulated OxyContin on the market, and zero cases were retrieved prior to the approval of reformulated OxyContin. A common thread is apparent through all six cases. The patients presented with anemia, thrombocytopenia, and evidence of hemolysis with normal ADAMTS13 activity after intravenous use of OxyContin. In most cases, accurate diagnosis and clinical decision-making were hampered by later discovery of the patient's intravenous OxyContin abuse, after empirical treatments based on alternative etiologies had begun. Our analysis found that these cases appear to be consistent with the risk of TMA already described in OxyContin labeling.

The cases in the series included several aspects that supported a causal association between intravenous OxyContin abuse and TMA. Although half lacked a precise time-to-onset, the reported sequence of events and clinical evidence indicates a strong temporal association between intravenous abuse of OxyContin and TMA for all the cases in our series. Not only did the clinical courses and reported laboratory data provide robust evidence of TMA following IV abuse of reformulated OxyContin, the descriptions are consistent with previous descriptions of individuals with TMA known to have intravenously abused reformulated Opana ER (McAninch et al 2017). Additionally, we did not identify an alternative etiology for TMA in five of the six cases. All cases resolved, or showed signs of resolving, with abstinence of OxyContin IV abuse (positive dechallenge and either supportive care only, or supportive care plus plasma exchange, steroids, and/or eculizumab. Five cases provided evidence of positive dechallenge and two cases provided evidence of positive rechallenge.

In addition to the factors supporting a causal association, the presence of PEO in OxyContin provides plausibility by which reformulated OxyContin may be associated with TMA. As noted earlier, data from animal models have linked PEO of varying molecular weights to acute manifestations of TMA, and PEO was also present in reformulated Opana ER (Hunt et al 2017, D'Agostino 2020, and Persich et al. 2020). However, the number of cases our search uncovered (six) is much lower than the 59 TMA cases identified for reformulated Opana ER in previous reviews (McAninch et al. 2017). Although differences in the number of reports should be interpreted with caution given known limitations of spontaneous reports (see below), if the observed difference in the number of TMA events are true beyond FAERS, numerous factors apart from the presence of PEO in drug products may contribute to the difference, for example, rates of abuse, size of the PEO polymer, manufacturing process, and tampering methods.

One of the general limitations of spontaneous reporting data, such as FAERS, is under-reporting. FAERS data cannot be used to determine rates of abuse or abuse-related events, such as TMA, and while comparisons in reporting levels between products (e.g., OxyContin versus Opana ER) is hypothesis-generating, these differences should be interpreted with caution given issues affecting spontaneous reports such as product misclassification or stimulated reporting, the latter

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of which was particularly relevant for reformulated Opana ER. We acknowledge that our ability to assess the Australian cases is limited because it is unknown whether differences manufacturing location, coating process, or source of PEO may factor into risk of TMA after intravenous abuse of OxyContin. Finally, our six cases illustrate practical challenges in diagnosing TMA and in obtaining accurate or timely history from abusers, which could result in under- diagnosis and under-reporting of events in general.

The current labeling for OxyContin states, in section 9.2 Abuse: "Cases of thrombotic microangiopathy (a condition characterized clinically by thrombocytopenia and microangiopathic hemolytic anemia) associated with parenteral abuse have been reported." Given the findings of our assessment of the case series, the current labeling continues to remain appropriate in that it identifies a product-specific risk specific to a particular form of abuse of administration of the product.[e] Moreover, the treatment approaches described in the case series varied and, therefore, do not provide evidence sufficient to add implications for patient management.

5   CONCLUSION

In conclusion, we find an association between intravenous abuse of reformulated OxyContin and TMA. We identified six FAERS cases of TMA associated with intravenous abuse of reformulated OxyContin. The six reports were received over six years (2014-2019), indicating an ongoing, but minimally reported event. However, TMA associated with intravenous abuse of OxyContin is a known, labeled event. Our assessment of the case series against the current OxyContin labeling indicates the description of potential risk of TMA following intravenous abuse of OxyContin remains accurate and adequately described.

6   RECOMMENDATIONS

Based on this review, DPV does not propose any recommendations at this time.

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[e] The draft guidance Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products - Content and Format (July 2019) is available on the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents#guidancesearch.

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8   APPENDICES

8.1   APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.2 APPENDIX B. FAERS LINE LISTING OF THE CASE SERIES: TMA REPORTED WITH INTRAVENOUS ABUSE OF REFORMULATED OXYCONTIN

[Duplicate reports are shown in brackets.]

	FAERS Case #	Version #	Manufacturer Control #	Initial FDA Received Date	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	10299601	6	AU-NAPPMUNDI-GBR-2014-0019072	7/11/2014	Expedited	29	F	Australia	HO, OT
2	11617284	2	AU-PURDUE-USA-2015-0126524	10/9/2015	Expedited	56	M	Australia	HO, OT
3	11906673	2	AU-MUNDIPHARMA DS AND PHARMACOVIGILANCE-GBR-2016-0033409	1/11/2016	Expedited	28	M	Australia	HO, LT
4	13089022 [13343330]	1 [1]	[US-MUNDIPHARMA DS AND PHARMACOVIGILANCE-USA-2017-0137162]	1/4/2017 [3/16/2017]	Direct [Expedited]	43	F	USA	HO [HO, OT]
5	13828986	5	AU-NAPPMUNDI-USA-2017-0140117	8/3/2017	Expedited	35	M	Australia	HO, OT
6	15868840	2	US-PURDUE-USA-2019-0145684	1/23/2019	Expedited	43	M	USA	HO, LT, OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: HO=hospitalization, LT= life-threatening, OT=other medically significant

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POSTMARKET MEDICATION ERROR REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Review:	March 31, 2020
Application Number:	NDA 22272
Product:	Oxycontin (oxycodone) extended-release tablet, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg
Applicant/Sponsor/Manufacturer:	Purdue Pharma LP
OSE RCM #:	2019-1681
Tracked Safety Issue #:	N/A
Requesting Office or Division:	Office of Surveillance and Epidemiology (OSE)
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Lead:	Otto L. Townsend, PharmD
DMEPA Deputy Director:	Irene Z. Chan, PharmD, BCPS
DMEPA Division Director (Acting):	Lubna Merchant, MS, PharmD
Subject:	New or unique medication errors related to the abuse-deterrent formulation of Oxycontin

This review contains:

☒ No Recommendations (no action indicated)

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1   PURPOSE OF REVIEW

This review provides our findings from a search of the FDA Adverse Event Reporting System (FAERS) for new or unique types of medication errors associated with Oxycontin since it was reformulated with abuse-deterrent properties in 2010.

We initiated this review at the request of the Office of Surveillance and Epidemiology (OSE) team who is planning a joint meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC). The joint meeting is intended to discuss the 1) results of postmarketing-required studies and other postmarketing data on the effectiveness of the current (abuse deterrent) formulation of Oxycontin, and 2) broader health impact of Oxycontin.

To inform the joint meeting discussion, the OSE planning team requested that we search FAERS to determine if there were new or unique medication errors (specifically related to cutting, splitting, dissolving, chewing, breaking, or crushing) with the current (abuse-deterrent) formulation of Oxycontin compared to the original Oxycontin formulation.

2   FINDINGS

This section summarizes relevant findings from our review of Oxycontin product information and FAERS medication error cases.

2.1   PRODUCT INFORMATION

- Oxycontin is an extended-release formulation of the active ingredient, oxycodone hydrochloride.
- Oxycontin (oxycodone controlled-release tablets) was originally approved on December 12, 1995 under NDA 20553.
- On April 5, 2010, an abuse-deterrent formulation of Oxycontin was approved under NDA 22272 that replaced the original formulation marketed under NDA 20553. The abuse-deterrent formulation was intended to increase resistance to chemical and physical manipulation, making the product less easy to chew, crush, or dissolve.[a]
- The approval of NDA 22272 included post-marketing requirements for the Applicant to conduct studies to assess whether the abuse-deterrent formulation reduced abuse, misuse, fatal and non-fatal overdose associated with Oxycontin.
- Oxycontin is currently available as 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg extended-release tablets supplied in unit dose blisters (for hospital use) and bottles.
- The current (abuse-deterrent) formulation of Oxycontin includes similar statements as the original formulation of Oxycontin on the container label, carton labeling and Prescribing Information related to taking tablets whole and not manipulating by other means prior to administration.

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[a] See the FDA Summary Review for Oxycontin, NDA 22-272 (April 5, 2010). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022272s000SumR.pdf.

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2.2 FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

Using the methods described in Appendix A, our FAERS search didn't identify any Oxycontin medication errors that were new or unique since it was reformulated with abuse-deterrent properties in 2010.

3 DISCUSSION

None of the U.S. Oxycontin medication error reports in FAERS that we considered for this review described errors that were new or unique to the current (abuse-deterrent) formulation of Oxycontin. It is possible that there are errors related to the abuse-deterrent formulation of Oxycontin. Medication errors are underreported (the reporting of medication errors to FAERS is voluntary) and the public may not be aware that an error is specifically related to the abuse-deterrent formulation of Oxycontin.

4 CONCLUSION

We did not identify any case reports that described new or unique medication errors related to the current (abuse-deterrent) formulation of Oxycontin.

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Appendix A. FDA Adverse Event Reporting System (FAERS)

A.1   Methods

On November 21, 2019, we searched FAERS using the criteria in Table 1 below, and identified 540 cases. The 540 cases were downloaded to Excel, and limited to cases where the MedDRA Preferred Term (PT) was *Medication error* (n=10)*, Intercepted product administration error* (n=2)*, Accidental overdose* (n=86)*,* or *Wrong technique in product usage process* (n=246). We individually reviewed the cases with PT *Medication error, Intercepted product administration error, and Accidental overdose*. For cases coded with the PT *Wrong technique in product usage process* (246 cases), we individually reviewed cases (n=108) that included the terms cut, split, chew, crush, dissolve, or break in the case narrative. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[b]

Table 1. Criteria Used to Search FAERS	
Initial FDA Receive Dates:	August 10, 2010 to November 1, 2019
Product Name:	Oxycontin (primary suspect)
Event:	SMQ *Medication errors* (Narrow)
Country (Derived):	USA

A.2   Results

Using the methods described in A.1, our search did not identify any cases that described a new or unique medication error signal related to the abuse-deterrent formulation of Oxycontin. Furthermore, we note that none of the cases described new or unique risks related to users cutting, splitting, breaking, crushing, dissolving or chewing the abuse-deterrent formulation of Oxycontin. The cases that we reviewed described errors related to misuse, drug abuse, accidental exposure to product by child, product dispensing error, product prescribing error, incorrect frequency of administration, wrong product administered, incorrect dose administered (which were not unique to the abuse-deterrent formulation of Oxycontin), or there was insufficient information to determine if a medication error occurred.

A.3   Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic

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[b] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Available from: https://www.nccmerp.org/taxonomy-medication-errors-now-available.

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products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonization. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 7, 2011
To:	Bob Rappaport, MD, Director Division of Anesthesia and Analgesia Products (DAAP) Office of New Drugs
Through:	Bindi Nikhar, MD, Deputy Director Lauren Choi, Pharm.D, Team Leader Division of Pharmacovigilance II (DPV II) Office of Surveillance and Epidemiology
From:	Afrouz Nayernama, PharmD Safety Evaluator Division of Pharmacovigilance II (DPV II) Office of Surveillance and Epidemiology
Subject:	Postmarketing safety review of choking, dysphagia, nasal and intestinal obstruction, and medication residue in the stool
Drug Name(s):	Reformulated OxyContin (OxyContin RF)
Application Type/Number:	NDA 22-272
Applicant/sponsor:	Perdue LP
OSE RCM #:	2010-2441

CONTENTS

EXECUTIVE SUMMARY

This DPVII –initiated[1] safety review evaluates 38 AERS[2] cases possibly related to the new abuse-deterrent formulation of OxyContin, including choking (25), dysphagia (2), nasal or intestinal obstruction (3), exacerbation of diverticulitis (1), and medication residue in the stool (8).[3]

The reformulated OxyContin (OxyContin RF) is designed to be more resistant to crushing and dissolving than the original formulation, making the extraction of oxycodone difficult for abuse (via snorting or injection); it contains polyethylene oxide (PEO), which provides hydro-gelling and muco-adhesive properties to mitigate the risk of abuse and misuse by turning into a viscous gel-like substance upon contact with moisture or tampering of the tablet. Pharmacokinetic studies were conducted to establish bioequivalence; clinical safety and efficacy studies were not conducted during the drug development program for this new abuse-deterrent formulation of OxyContin.

AERS cases suggest that in some instances, the tablet turns into a "glue-like" substance upon contact with oral/nasal mucosa, causing choking or obstruction. The pills are also noted to not dissolve adequately and in some cases, pass through the GI tract intact without absorption (e.g. in the stool). No serious outcomes were reported except in 4 patients who had underlying gastrointestinal disorders, such as colon cancer or diverticulitis. The patients required hospitalization (2), an emergency room visit (1), and/or a surgical procedure to remove the tablet (3). It is unclear if the new labeling and medication guide (MG) revisions will be sufficient to have an impact on reduced cases of choking; the majority of the AERS cases reported ingesting one tablet per dose.

Overall, review of AERS data suggest that cases of choking, dysphagia, medication residue in the stool, etc. may be related to the newly reformulated abuse-deterrent formulation of Oxycontin, which contains a polymer, polyethylene oxide used in extended-release drug formulations. Currently available data suggest that no serious outcomes have been reported for such events (except in patients with underlying gastrointestinal disorders), and DPV II will continue routine pharmacovigilance monitoring. It is recommended that DAAP take into consideration the need to further evaluate manufacturing and formulation issues related to this drug product.

1   BACKGROUND

1.1   INTRODUCTION

This DPVII-initiated safety review evaluates AERS cases of choking, dysphagia, nasal and intestinal obstruction, exacerbation of diverticulitis, and medication residue in the stool[4] associated with the newly reformulated OxyContin (OxyContin RF). During the assessment of REMS[5] for OxyContin RF on November 16, 2010, DPVII informed the Division of Anesthesia

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[1] Division of Pharmacovigilance II

[2] Adverse Event Reporting System

[3] Two cases were also reported under other events.

[4] MedDRA Preferred Terms : Medication Residue (PT) for tablet in stool (LLT)

[5] Risk Evaluation and Mitigation Strategy

and Analgesia Products (DAAP) that the above events may be related to the new formulation and that the sponsor's recent labeling and Medication Guide revisions may not be sufficient to mitigate the risk of choking. Subsequently, DPVII initiated this safety review.

Oxycodone is a pure mureceptor opioid agonist whose principal therapeutic action is analgesia.[6] The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.[8] Oxycontin is a modified-release formulation of oxycodone that was initially approved on December 12, 1995. The reformulated OxyContin contains polyethylene oxide (PEO) that provides hydro-gelling properties to mitigate the risk of abuse and/or misuse by turning into a viscous gel-like substance upon contact with moisture or tampering of the tablet. The sponsor discontinued the distribution of the original formulation upon marketing of the new abuse deterrent formulation.

1.2 NDA 22,272 (OXYCONTIN RF) REVIEW [7,8,9, 10]

Per the review of NDA 22,272, the reformulated Oxycontin (OxyContin RF) is intended to reduce the abuse liability of the product by making the modified-release characteristics more robust. The changes to the formulation such as including PEO are purported to result in a tablet that is more difficult to crush or dissolve, and more resistant to the extraction of oxycodone by chemical means. Exposure to moisture results in the swelling of the tablet matrix, rendering the particles disagreeable to snorting. Welling of the tablet matrix makes IV abuse unfavorable and unsuccessful due to the small amount of viscous liquid available for injection.

During the development of this new formulation, the applicant and the Division agreed that clinical efficacy and safety studies would not be required if the new formulation was bioequivalent to the original formulation. Six pharmacokinetic (PK) studies were submitted in support of this application. As the new formulation was demonstrated to be bioequivalent to the original formulation, no clinical efficacy and safety studies were performed.

Adapted from Dr. Ellen Field's CDTL memo for NDA 22,272

The Applicant submitted a safety update containing data gathered after the March 31, 2009, resubmission for NDA 22,272. A total of 277 healthy subjects received doses ranging from 5 mg through 80 mg, in either the fed or fasted state, with or without naltrexone blockade. The adverse event profiles were similar for both the reformulated OxyContin and OxyContin treatments. The most common treatment-emergent adverse events reported were those known to be associated with opioids such as nausea, headache, dizziness, and vomiting. There were no unexpected safety findings. Results of laboratory tests, vital signs measurements, and SpO2 evaluations raised no safety concerns for any of the study treatments. Overall, the safety profiles of the reformulated

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[6] OxyContin Labeling: Full Prescribing Information. Nov 15, 2010.

[7] FDA: NDA (22-272) Review; Chemistry review, ONDQA, Division I, Branch II .Jan 16, 2008.

[8] FDA: NDA (22-272) Review; Pharmacology Review. May 1, 2008.

[9] FDA: NDA (22-272) Review; Cross-Discipline Team Leader Review and Deputy Director Memo. May 2008

[10] FDA: NDA (22-272) Review, Medical officer Review. Dec 30, 2009.

OxyContin® as well as OxyContin® were as expected for oxycodone administered to fasted and fed, healthy, adult subjects with or without naltrexone HCl blockade.

A joint meeting of the Anesthesia and Life Support and the Drug Safety and Risk Management Advisory Committees was held on September 19, 2009 to discuss the new data submitted to define the product's tamper-deterrent features. The committee members voted 14 to 4 with 1 abstention to approve the application. The consensus of the committee was that the reformulated product (all strengths) demonstrated an incremental increase in tamper resistance, although it clearly maintained the previously acknowledged high risk for people who misused or abused the product by taking higher than safe doses of intact tablets. (**See Appendix A** for the complete summary of the Advisory Committee meeting).

1.3   REGULATORY HISTORY

OxyContin RF was approved in the U.S. on April 5, 2010 and marketed on August 9, 2010.There has been 1 labeling revision (11/15/2010) since the approval to include the risk of choking in the postmarketing Adverse Reactions section of the package insert and Medication Guide.

A Dear Healthcare Professional Letter (HCP) was disseminated in the U.S. on October 4, 2010 to notify HCPs of the launch of the reformulated OxyContin and to address the reports of difficulty swallowing (**See Appendix B** for the Dear Health Care Professional letter).

1.4   PRODUCT LABELING

OxyContin RF Product Labeling Information:

The labeling information pertaining to this consult is as follows (**See Appendix B** for a complete listing of relevant labeling for OxyContin RF)

ADVERSE REACTIONS -Postmarketing Experience (6.2)

- Choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet
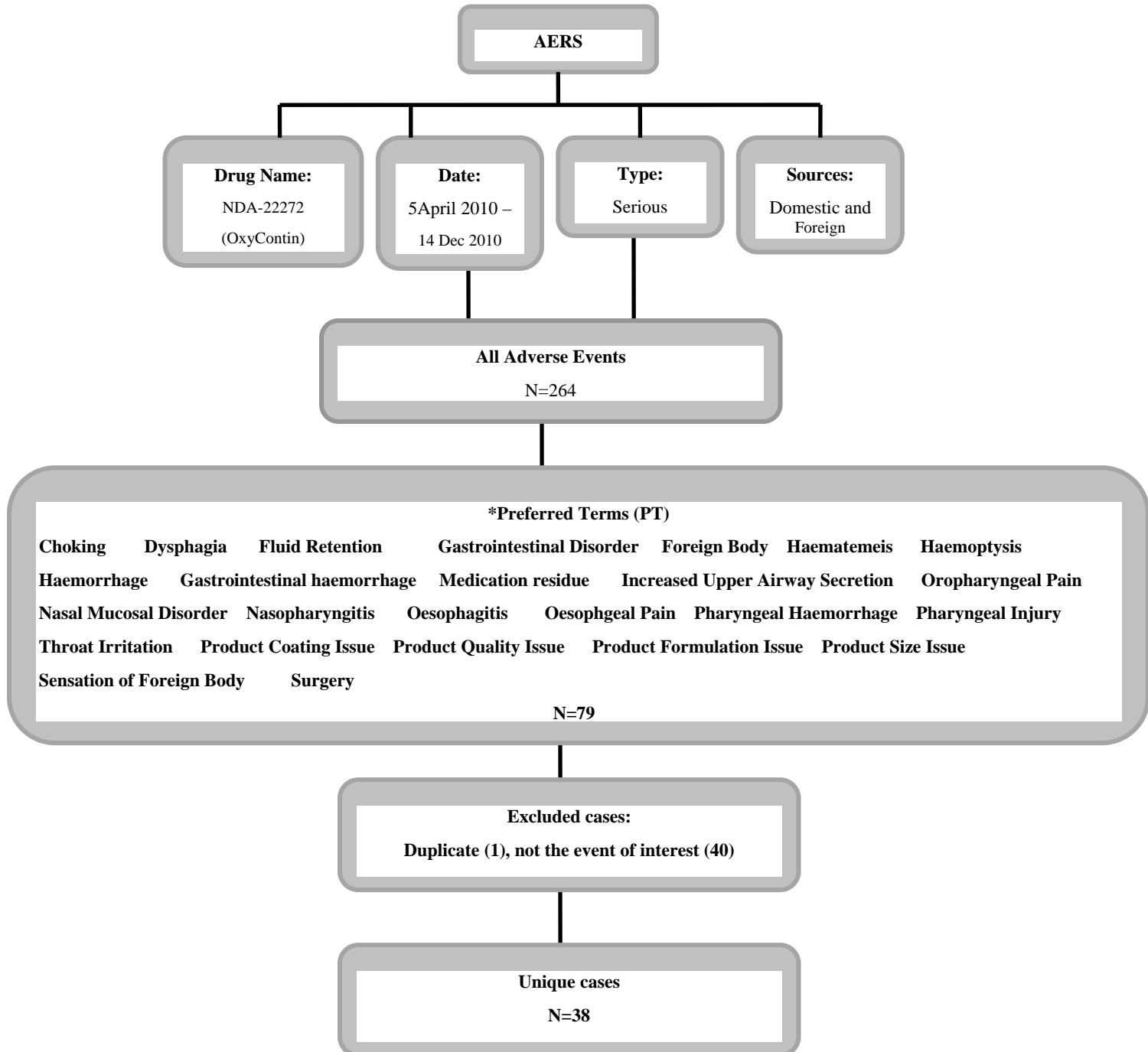
2.   METHODS AND MATERIALS

2.1   AERS SELECTION OF CASES

As of December 14, 2010 the AERS database contained a total of 264 adverse events reports associated with the use of OxyContin RF (NDA 22272). **See Appendix C** for AERS limitations.

The AERS search criteria are shown in figure 1.

Figure1. AERS Search criteria


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                              ┌──────────────┐
                              │     AERS     │
                              └──────────────┘
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Drug Name:
NDA-22272
(OxyContin)

Date:
5April 2010 –
14 Dec 2010

Type:
Serious

Sources:
Domestic and Foreign

All Adverse Events
N=264

*Preferred Terms (PT)

Choking   Dysphagia   Fluid Retention   Gastrointestinal Disorder   Foreign Body   Haematemeis   Haemoptysis

Haemorrhage   Gastrointestinal haemorrhage   Medication residue   Increased Upper Airway Secretion   Oropharyngeal Pain

Nasal Mucosal Disorder   Nasopharyngitis   Oesophagitis   Oesophgeal Pain   Pharyngeal Haemorrhage   Pharyngeal Injury

Throat Irritation   Product Coating Issue   Product Quality Issue   Product Formulation Issue   Product Size Issue

Sensation of Foreign Body   Surgery

N=79

Excluded cases:
Duplicate (1), not the event of interest (40)

Unique cases
N=38

*Preferred Terms (PT) that reflect potential product formulation issues were selected from all adverse events associated with OxyContin RF.

3   RESULTS

3.1 AERS CASES

A total of 38 cases remained for further review and analysis. Associated attributes and demographics for these cases, as they relate to formulation issues are illustrated in Table 1.

Table 1. Demographics and characteristics of adverse event cases associated with OxyContin RF (N=38)	
Age (N=17)	Range: (16-77), Mean (50), Median (50 years)
Gender	Male (20), Female (17), not reported (1)
Dosage regimen	Range: 20 mg-560 mg daily (33) , not reported (5)
*Outcomes	Hospitalization (6), Life-threatening (1) , other [(32); emergency room visit (1), walk-in clinic (1)]
Event date	2010 (38)
Sources	U.S (38)
Reporter Type	Health Care Professional (5) Consumer (33)
Type of Report	Expedited {15 –day, (38)}

*More than one outcome was reported per case.

DPVII identified 38 AERS cases possibly related to the new formulation of OxyContin as follows: choking (25), dysphagia (2), nasal and intestinal obstruction (3), exacerbation of diverticulitis (1), and medication residue in the stool (8)[11].

Choking

DPV II identified 25 AERS cases of choking associated with OxyContin RF. In all cases, the event occurred shortly after taking OxyContin RF tablet, suggesting a strong temporal association. In addition, none of the cases reported a co-suspect medication. It is unclear if adequate amounts of water had been taken with the tablets.

Among the cases that reported age (n=14), 13 were younger than 55 years old with a median of 48 years, indicating that an old age with difficulty swallowing was unlikely to be a contributory factor. Two cases reported that the tablet turned into a glue-like or "slime" substance that "hung in the back of the throat" or "closed up the throat". Five cases also reported coughing up or vomiting gel-like or gooey substances. In 3 cases, the patients reported that they could not breathe due to the tablets becoming stuck in their throats; in another case, the patient described that with each dose, he felt his throat swell up and he was bringing up whitish phlegm.

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[11] Two cases were also discussed under other events.

Among the cases that reported a dosage regimen (n=20), 13 cases reported that only one tablet was ingested per dose, suggesting that the choking was unlikely to be due to the ingestion of multiple tablets at one time. The majority of the cases did not report how they dislodged the tablet; three cases reported that a Heimlich maneuver (2) or a slap (1) on the back was required to dislodge the tablet. In a fourth case, the patient swallowed 7 tablets of 80 mg OxyContin RF and reported that it took him about 2.5 hours to dislodge the tablets; he was gagging and injured the back of his throat, resulting in bleeding for about 1.5 hours. In a fifth case, the patient reported that he felt sick in his stomach, and spit-up phlegm and then blood.

Four cases that reported choking also reported hypersensitivity reactions. All 4 cases reported prior use of original OxyContin formulation without experiencing hypersensitivity reactions. The first patient experienced hive-like blisters over her face and scalp after the second dose of OxyContin RF. The patient took Benadryl. However, the hives turned into blisters (the size of a quarter) on the face and head; she also had facial swelling. The patient was prescribed prednisone. She recovered from the events but the blisters left scars on her face. The patient had a history of allergies to sulfa, penicillin, codeine, and latex. The second patient reported itching, body turning red and hypothermia (93.2 F). The patient was treated with Benadryl. The 3rd and 4th cases reported swelling of the lips, face and eyes.

Dysphagia

In a patient with esophageal cancer, an OxyContin RF tablet became stuck and "gummed up" in the esophagus and had to be "sucked out". In another case, a patient with a history of gastric bypass and an unspecified intestinal surgery reported that OxyContin RF became stuck in his esophagus and required an emergency room visit to be removed. The patient also reported vomiting a jelly-like substance and passing pills in his stool.

Intestinal Obstruction

In a colon cancer patient, Oxycontin RF tablets blocked the narrow passage (due to colon cancer) from the small intestine to the large intestine, requiring a surgery.

Exacerbation of diverticulitis

A patient with a medical history of diverticulitis reported that OxyContin RF is like "eating peanuts, gelling up and filling up pockets in the colon and intestine." The patient was hospitalized due to diverticulitis flare and fever. The patient had used the original OxyContin previously without problems.

Nasal obstruction (Abuse/misuse)

Two cases reported abuse/misuse of OxyContin RF. In both cases, the patients attempted to crush and snort OxyContin RF; they had a gel-like substance gummed up in their nostrils, which required a medical procedure to remove the substance. One of the cases also reported a severe nostril burn. The outcome of the event was reported in one case; the patient recovered and was discharged from the hospital without any complication. The outcome was not reported in the other case.

Medication Residue (e.g. tablets found in the stool)

Eight AERS cases reported finding OxyContin RF tablets in the stool. Six of 8 patients reported that the drug was not being effective and they were not getting any pain relief; the 2 remaining cases reported experiencing withdrawal symptoms. One of the two patients that reported withdrawal symptoms was hospitalized due to a seizure, severe headaches, and shaking; she reported not digesting OxyContin RF and seeing the tablets in her vomit and stool. Two cases that reported the lack of efficacy involved cancer patients (prostate and colon cancer). The patient with colon cancer reported seeing the tablets in her colostomy bags; she experienced a headache and loss of vision in addition to no pain relief from OxyContin RF, requiring hospitalization. In a pediatric case, a 16 year-old female with a medical history of cerebral palsy developed gastroesophageal reflux disease (GERD) and began to aspirate after taking OxyContin RF. She was taken to a walk-in clinic for possible aspiration. The patient's mother reported that Oxycontin RF tablets were found in her stool; in addition she had a headache, an upset stomach, and inadequate pain control.

4   DISCUSSION

4.1   AERS CASES

The reformulated Oxycontin (OxyContin RF) is intended to reduce the abuse liability of the product by making the modified-release characteristics more resistant to misuse/abuse via crushing, dissolving, snorting or injection. OxyContin RF contains polyethylene oxide, which provides hydro-gelling and muco-adhesive properties to mitigate the risk of abuse and misuse by turning into a viscous gel-like substance upon contact with moisture or tampering of the tablet. Polyethylene oxide is a polymer used in extended-release drug formulations.

Per the review for NDA 22,272 (OxyContin RF), the new formulation was found to be bioequivalent (based on PK studies) to the original formulation. Additional clinical safety and efficacy studies were not required prior to its approval. Safety analysis of the NDA revealed no deaths, serious adverse events or discontinuation of the drug due to adverse events. The most common treatment-emergent adverse events reported were those known to be associated with opioids such as nausea, headache, dizziness, and vomiting. There were no unexpected safety findings.

In a recent PSUR[12], the sponsor stated that within two months of launching OxyContin RF, the volume of the received adverse events (AEs) increased by approximately 10-fold compared to the number of reports received, historically, for the original formulation. The AEs received for Oxycontin RF included an increased number of reports involving hypersensitivity reactions, foreign body related terms (e.g. tablet being stuck in the throat), gastrointestinal symptoms, and lack of /reduced efficacy compared to the original formulation. The sponsor associated many of the GI and foreign body related events to the swelling and hydro-gelling properties of the tablet and the muco-adhesive properties of the excipient, polyethylene oxide (PEO).

This DPVII-initiated review evaluates 38 AERS cases possibly associated with OxyContin RF. The reported events include choking (25), dysphagia (2), nasal or intestinal obstruction (3),

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[12] Periodic Safety Update Report, April 13, 2010-October 12, 2010.

exacerbation of diverticulitis (1), and medication residue in the stool (8)[13]. These adverse events are likely due to the hydro-gelling and muco-adhesive properties of the new formulation.

Ingesting multiple tablets at one time does not appear to be the main cause of choking since the majority of the cases reported a dosage regimen that required one tablet per dose. A total of 5 cases also reported vomiting gel-like or gooey substances. It appears that Oxycontin RF turns into a gel or glue-like substance once it mixes with oral mucosa and/or gastric juice. Ingestion of OxyContin RF resulted in dysphagia, intestinal obstruction, and exacerbation of diverticulitis in patients with underlying GI disorders such as esophageal cancer or colon cancer with a small lumen requiring hospitalization (2), an emergency room visit (1) and/or surgical procedure to remove the tablet (3). Although these cases were confounded by comorbidities, we could not exclude the contributory role of Oxycontin RF due to its hydro-gelling and muco-adhesive properties. Some cases also reported seeing an intact tablet in the stool and experiencing inadequate pain relief due to the drug being ineffective. It is noteworthy that we also identified cases where the patients who tolerated the original formulation reported having hypersensitivity reactions to the new formulation. No serious outcomes were reported in the majority of the cases except in 4 patients with underlying comorbidities as discussed above.

Overall, while adverse events such as choking, dysphagia, tablets in stool etc., discussed above appear to be related to the new abuse-deterrent formulation of OxyContin, the extent to which the hydro-gelling and muco-adhesive properties of a polymer such as the polyethylene oxide can contribute to these events is unknown. Given that no clinical safety and efficacy studies were conducted during the development program of this new abuse-deterrent formulation, there is no additional safety data to corroborate these findings.

It is unclear if the new labeling and MG revisions, which advised patients to take one tablet at a time with plenty of water will help reduce the risk of choking.

5   CONCLUSIONS

Based on the review of 38 AERS cases, DPVII concludes that adverse events outlined in this review, such as choking, dysphagia, tablets in stool, etc. appear to be related to the new formulation of OxyContin, specifically the hydro-gelling property of the tablets. Upon contact with oral/nasal mucosa, the tablets appears to become a "jelly-like" substance, causing the patients to choke or the tablet to become stuck in different parts of the GI tract. In some cases, the pills are also noted to dissolve inadequately and appear to be passing through the GI tract intact without absorption; this could result in inadequate pain relief. No serious outcomes have resulted from these adverse events, except in patients with underlying gastrointestinal disorders. While the contribution of a polymer such as polyethylene oxide towards these adverse events is unclear, description of the adverse events appear to be related to its physico-chemical properties. It is unclear if recently implemented labeling and MG revisions will help mitigate such adverse events. DPV II will continue routine pharmacovigilance monitoring for this drug product.

6   RECOMMENDATIONS

It is recommended that DAAP take into consideration the need to further evaluate manufacturing and formulation issues related to this drug product.

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[13] Two cases were also discussed under other events.

APPENDICES

APPENDIX A: ADVISORY COMMITTEE MEETING[14]

A joint meeting of the Anesthesia and Life Support and the Drug Safety and Risk Management Advisory Committees was held on September 19, 2009 to discuss the new data submitted to define the product's tamper-deterrent features. The committee members voted 14 to 4 with 1 abstention to approve the application. The consensus of the committee was that the reformulated product (all strengths) demonstrated an incremental increase in tamper resistance, although it clearly maintained the previously acknowledged high risk for people who misuse or abuse the product by taking a higher than safe doses of intact tablets. The advantages of the new formulation include:

- Perhaps most importantly, it cannot be crushed or chewed by standard mechanisms that may result in the ingestion of a lethal "immediate-release" dose by a casual or recreational abuser, or by a patient, e.g., when a nurse or caretaker attempts to crush and administer via a nasogastric tube.
- It cannot be altered to a consistency (i.e., powder) that can be insufflated or dissolved for injection using the standard household tools that the more hard-core abusers generally use.
- When dissolved in water it becomes a thick, gelatinous substance that cannot be syringed or injected with the usual needles and syringes used by hard-core abusers. The committee members acknowledged that the reformulated OxyContin tablets can be crushed and/or extracted by unusual means and, therefore, those intent on abusing the products by defeating the extended-release mechanism will still be able to do so.

The committee members also acknowledged that that those abusing or misusing the product by ingesting more intact tablets or higher doses of intact tablets would not be provided with any protection from overdose with this reformulated product. Finally, the committee members were generally in consensus that a post-marketing epidemiology study to assess the impact of the reformulation on actual abuse in the community is essential to fully understand the value of the product and the level of risk management it will need, and that this study should be required as a postmarketing requirement for approval.

APPENDIX B: LABELING

2 DOSAGE AND ADMINISTRATION

2.1 Safe Administration Instructions

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[14] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022272s000MedR.pdf

OxyContin tablets should be taken one tablet at a time. Take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth *[see Patient Counseling Information (17.1)]*.

6 ADVERSE REACTIONS

6.2 Postmarketing Experience

In addition to the events listed above, the following have also been reported, potentially due to the swelling and hydro-gelling property of the tablet: choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet.

17 PATIENT COUNSELING INFORMATION

See <u>MEDICATION GUIDE</u> as appended at the end of the full prescribing information

17.1 Information for Patients and Caregivers

Provide the following information to patients receiving OxyContin or their caregivers:
•   Advise patients that OxyContin contains oxycodone, which is a morphine-like substance.
•   Advise patients that OxyContin is designed to work properly only if swallowed whole. Taking cut, broken, chewed, crushed, or dissolved OxyContin Tablets can result in a fatal overdose.
•   Advise patients that OxyContin tablets should be taken one tablet at a time.
•   Advise patients not to pre-soak, lick or otherwise wet the tablet prior to placing in the mouth.
•   Advise patients to take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth.
•   Advise patients to report adverse experiences, and episodes of increased or incident pain occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
•   Advise patients not to adjust the dose of OxyContin without consulting the prescribing professional.
•   Advise patients that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
•   Advise patients not to combine OxyContin with alcohol or other central nervous system depressants (e.g. sedatives, hypnotics) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.

Reference ID: 2863891
•   Advise women of childbearing potential who become, or are planning to become, pregnant to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
•   Advise patients that OxyContin is a drug with known abuse potential. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
•   Advise patients that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. If tapering is appropriate, their prescriber can provide a dose schedule to gradually discontinue the medication.

- Advise patients to keep OxyContin in a secure place out of the reach of children. When OxyContin is no longer need

MEDICATION GUIDE

OXYCONTIN® (ox-e-KON-tin) (CII) (oxycodone hydrochloride controlled-release)

How should I take OxyContin?
- See "What is the most important information I should know about OxyContin?"
- **Take OxyContin exactly as prescribed. Do not change your dose unless your healthcare provider tells you to**.
- **Swallow OxyContin tablets whole. Do not cut, break, chew, crush, or dissolve the tablets.**
-
• In order to reduce the possibility of choking on the tablets or having difficulty swallowing the tablets:
  - OxyContin tablets should be taken one tablet at a time.
  - Do not pre-soak, lick or otherwise wet the tablet prior to placing in your mouth.
  - Take each tablet with enough water to ensure complete swallowing immediately after placing in your mouth.

Dear Health Care Professional Letter

October 4, 2010

Dear Healthcare Professional:

On April 5, 2010, the U.S. Food and Drug Administration (FDA) approved Purdue Pharma L.P.'s New Drug Application for a reformulation of OxyContin® (oxycodone hydrochloride controlled-release) Tablets. Purdue elected to reformulate OxyContin to be bioequivalent to the original formulation and in an effort to make the tablet more difficult to manipulate for the purpose of intentional misuse and abuse, however, there is no evidence that the reformulation of OxyContin is less subject to misuse, abuse, diversion, overdose, or addiction. **Since introducing reformulated OxyContin to the market on August 9, 2010, Purdue has received reports that some patients are encountering difficulties with swallowing the reformulated tablet. Purdue encourages you to counsel your patients on appropriately taking this medication and to remind them that:**

• OxyContin Tablets should be taken one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth

• Multiple tablets should not be swallowed together

• Tablets should not be dampened, soaked, licked, or otherwise wet prior to placing them in the mouth for immediate swallowing

Reformulated OxyContin is a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Please see Important Safety Information and Boxed Warning which is included at the end of this letter. Please report any adverse event information associated with the use of OxyContin Tablets to Purdue Pharma L.P. at 1-888-726-7535, (prompt #2), or the FDA MedWatch system by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, or via the Internet at www.FDA.gov/medwatch.

OxyContin continues to be a CII controlled substance with all the attendant risks of Schedule II opioids, specifically that the drug has a high potential for abuse. Use, misuse, or abuse of the drug may lead to physical dependence or addiction (addiction is sometimes referred to as "psychological dependence"). In addition, alteration of the tablet in any manner poses significant risks of overdose and death. The Full Prescribing Information contains warnings about the potential for abuse, diversion, overdose, and addiction, including a Boxed Warning.

Purdue Pharma L.P.

One Stamford Forum

Stamford, CT 06901-3431

The Full Prescribing Information for OxyContin Tablets contains the following **Boxed Warning:**

We have enclosed the Full Prescribing Information for reformulated OxyContin®, which is also available at http://www.purduepharma.com/pressroom/news/OxyContinPI.pdf. Should you have any questions regarding OxyContin, please call our Medical Services Department at

1-888-726-7535.

Sincerely,

Craig Landau, MD

Vice President and Chief Medical Officer

http://www.purduepharma.com/pdfs/dearHCPletter.pdf

APPENDIX C: LIMITATIONS OF ADVERSE EVENT REPORTING SYSTEM (AERS)

The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Hence, when considering these figures, the accumulated case reports cannot be used to calculate incidences or estimates of drug risk for a particular product, as reporting of adverse events is a voluntary process, and underreporting exists. Further, because of the multiple factors that influence reporting, comparisons of drug safety usually cannot be made from these data. Some of these factors include the length of time a drug is marketed, the market

share, size and sophistication of the sales force, publicity about an adverse event and regulatory actions.

It should also be noted that in some of these cases, the reported clinical data was incomplete, and there is no certainty that these drugs caused the events reported. A given event may actually have been due to an underlying disease process or to another coincidental factor.

APPENDIX D: CASE REPRESENTATIVES

ISR# 6945957

A male patient of unspecified age reported that he was taking OxyContin RF (oxycodone hydrochloride controlled-release) for pain related to Crohn's disease at doses of 40 mg, 60 mg and 80 mg. He had taken the original OxyContin formulation in the past for a year and a half without any problem. The reformulated OxyContin tablet got stuck in his esophagus and he had to go to the emergency room to have it removed. The patient also developed an allergic reaction and he experienced hives. His face and eyes were swollen and his blood pressure increased to 188/144. He was throwing up a jelly like substance, passing pills and releasing gel in his stools. The patient also indicated that "the gel from OxyContin tablets was getting stuck to his scar tissue" (unspecified). The patient indicated that he was suffering from withdrawal and his Crohn's disease was acting up. The outcome of the events was not reported. His medical history also included a gastric bypass surgery and an intestinal surgery. Concomitant medications were not reported.

ISR# 7035868, U.S.

A female patient of unspecified age reported that she started taking the reformulated OxyContin 80 mg four times a day for an unspecified indication on Sep 16, 2010. The patient reported that she was not digesting OxyContin RF and finding them in her vomit and stool. She had withdrawal symptoms, severe headaches, and a seizure. She coded and was hospitalized. The outcome of these events was not specified. Her medical history and concomitant medications were not reported. The patient had taken OxyContin (controlled-release oxycodone hydrochloride) in the past.

ISR#7012896, U.S.

A pharmacist reported that a female with an unspecified age started OxyContin RF 80 mg for her back pain. The patient took a total of 4 tablets and each time, the tablet made her sick in her stomach (cramp), nauseated, and vomit foam and gel like substance within 45 minutes. The gel like substance was stuck in her throat and she had to pull it out. The patient also indicated that she felt like she could not breathe when the tablet was stuck in her throat and had a panic attack. The outcome of the events was reported as not resolved. The past medical history included a stroke and 4 back surgeries.

APPENDIX E: ISR NUMBERS OF INCLUDED CASES

6945957	7002917	7045943	7108945	7137846
6955921	7010219	7045948	7111115	7137853
6957918	7012896	7048361	7113565	7141928

6960552	7013315	7051839	7113672	7146458
6978337	7035868	7077639	7114101	7146486
6981317	7036037	7086489	7114154	7149349
6981323	7039537	7086493	7114382	7149355
7024995	7039678	7121273	7129539	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AFROUZ R NAYERNAMA
03/08/2011

LAUREN Y CHOI
03/08/2011

BINDI M NIKHAR
03/08/2011

ROBERT M BOUCHER
03/08/2011

Reference ID: 2915136

To:
Jana Mcaninch, MD, Judy Staffa
CDER Office of Surveillance and Epidemiology

From:
Paula Rausch, PhD, RN
Associate Director for Research and Risk Communications
CDER/Office of Communications (OCOMM)

Re: Summary overview of OCOMM's social science research on abuse-deterrent formulation opioids for Oxycontin ADF Advisory Committee meeting

Date: Updated May 29, 2020

The following overview summarizes OCOMM's general ADF-related social and behavioral science research and preliminary findings that will be presented at the AC meeting.

Background and Purpose

Currently available ADFs have properties that are expected to deter some forms of abuse. However, findings from a multi-phase, mixed-method broad opioid-related research project OCOMM undertook uncovered considerable variability in health care professionals' (HCPs) awareness of, knowledge about, attitudes toward, and experience with ADFs. This lack of awareness and knowledge – as well as potential misunderstandings – among HCPs about ADFs and the terminology used to describe them were of significant concern to FDA. At the direction of senior leaders from FDA and its Center for Drug Evaluation and Research (CDER), social scientists from OCOMM and other areas of FDA designed a comprehensive, three-phase qualitative and quantitative research strategy aimed at providing detailed and comprehensive evidence the Agency could use to inform its ADF-related policy, regulatory, and communication decisions, including related to alternative language that may be necessary to describe and explain these products. The purpose of this ADF research, which is currently underway, is to build on the findings from an earlier initial broad opioid research project OCOMM conducted by exploring and assessing the ADF-related knowledge, attitudes, and behaviors among opioid prescribers and dispensers/pharmacists and to explore possible alternative language for describing these products. Obtaining this research-based evidence is critical to ensuring that any alternative ADF language used or adopted does not further confuse or additionally complicate this complex topic.

The objectives of this project include enhancing FDA's understanding of the following:
1. How health care providers understand the terms abuse, addiction, and abuse deterrent formulation (ADF) in the context of prescription drugs.

2. What are health care providers' attitudes toward, perceptions about, and experiences with, abuse-deterrent opioid analgesics and abuse deterrence. For example:

    - knowledge gaps and misperceptions
    - prescribing decisions, practices, and guidelines
   - potential barriers to using ADFs

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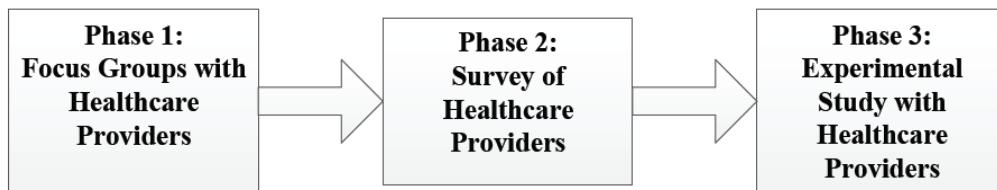
- potential use of ADFs to address the opioid epidemic
- the quality and understandability of the nomenclature used to describe them
- underlying reasons for health care provider attitudes and perceptions

3. What health care providers think is the best course of action for minimizing any confusion about ADFs among health care providers, such as the kinds of training or education they think are needed and the language and/or terms they believe would best convey the concept of abuse deterrence to health care providers.

4. Informed by the qualitative feedback obtained in the Phase 1 focus groups, conduct a survey to identify how prevalent health care professionals' knowledge, attitudes, behaviors, and perceptions are as identified in Objectives 1 to 3.

5. Informed by the Phase 1 focus groups and the Phase 2 survey, conduct an experimental study whose main objective is to determine the terminology most effective in conveying to health care providers the concept of abuse deterrence, and in addressing misunderstandings that ADFs may still be abused and can still lead to addiction.

This project, which is being led by OCOMM, involves an FDA Project Advisory Group that consists of several experienced social and behavioral scientists from OCOMM, CDER's Office of Prescription Drug Promotion and the Center for Food Safety and Nutrition, as well as opioid and ADF subject matter experts from CDER's offices of Communications, New Drugs, Surveillance and Epidemiology, and from its Controlled Substances Staff.

Study Design

The mixed-method social and behavioral science approach being undertaken for this project consists of three separate but iterative phases. Each phase will be informed in important ways by the previous phase. Also, each phase will draw from samples of the same target populations, but participants will not be included in multiple phases.

This sequence of phases not only ensures that FDA will be able to gather broad, detailed feedback from a limited number of HCPs who share their experiences in their own language through focus groups discussions, but also that we can leverage the internal and external validity strengths of survey and experimental designs. Survey methodology will allow us to gain an understanding about ADFs from larger and potentially more representative groups of HCPs. We can then use this evidence to develop language and content that can be tested experimentally.

The HCPs include opioid prescribers (physicians, physician assistants, and nurse practitioners) practicing in a variety of medical fields known to prescribe the greatest proportions of opioids and pharmacists who dispense opioids. These medical fields include those practicing in primary care, including family practice, and general and internal

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medicine; and in rheumatology, neurology, anesthesiology, pain management, emergency medicine, surgery, orthopedics, and physical medicine/rehabilitation. Participants are geographically and sociodemographically diverse, including related to types of practice, years in practice, location of practice (rural, urban, suburban), opioid prescribing volumes, gender, race/ethnicity, and age.

Key Findings to be Presented

To date, the Phase 1 qualitative focus group data collection and analysis for this ADF-specific research has been completed and reporting of findings is underway.
- Prior knowledge of the term 'abuse-deterrent formulation' opioid was uncommon among prescribers and pharmacists, especially notable because about half of participants chose the names of ADFs as opioids they had prescribed when presented a complete list of opioid names.
- OxyContin was the most commonly prescribed ADF, which might explain some discrepancy between prescribing behavior and awareness of the term ADF.
- Most who were unfamiliar with the ADF term guessed incorrectly when explaining what they thought it means. Common misperceptions included:
  - ADFs are formulated to make someone sick when they are using an opioid or when someone takes too high a dose of opioids; similarity to Antabuse was mentioned
  - ADFs do not provide any type of high or euphoric feeling
  - ADF refers to a "policy" or "plan of care"
  - ADFs offer non-narcotic pain relief
  - Single participants also said each of the following: ADFs had higher addiction potential, had higher abuse potential, were intended to end opioid use, and are a form of physical therapy.
- Some were confused about whether ADFs could be modified at all and about how they work/mechanism of action; discussion suggested HCPs had only a general sense of how these drugs work, and some thought that all ADFs use the same mechanism.
- Most commonly, participants who explained why they did not prescribe ADFs cited cost and insurance issues (lack of coverage and preauthorization requirements).
- Some also worried prescribing an ADF could lead to potential feelings of patient dissatisfaction with care or stigmatization, and some did not use the term ADF specifically or referred to policies, laws or practices mandating use of ADFs (vs. non-ADFs)
- A few noted they hadn't prescribed ADFs due to perceived ineffectiveness in their ability to prevent misuse, abuse, or addiction.
- Other barriers to use included the need for more information about them before prescribing them, including for data/studies specifically proving their efficacy in reducing abuse and addiction and the extent of those decreases, and about their side effects and mechanisms of action/how they work.
- Across all groups, participants reported limited training and education on ADFs

As noted, OCOMM also completed a previous broad, mixed-method social and behavioral science opioid-related research project that included a survey among HCPs containing questions related to ADFs and which informed the current ADF-specific study described above. This general opioids survey was fielded in 2018 among 320 healthcare

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professionals (physicians, PAs, NPs and dentists) who had prescribed opioids to at least five different patients over the past month. Generally, these findings suggested, in part, that 1) significant work was needed to increase general knowledge about ADFs among prescribers as well as understanding about their benefits, who can prescribe them, and when they should be used, and 2) more research was needed to better understand knowledge, attitudes, and prescribing practices related to ADFs, including related to the ADF term itself. Specific ADF findings included:

- Overall prescriber knowledge about ADF opioids was low, e.g., nearly half (48.8%) thought that ADFs have been proven to reduce the most common [oral] route of abuse, 45% thought an ADF was less addictive, and just 33.4% knew that non-ADF and ADF opioids have the same addictive potential. In a 5-item knowledge index, 12.5% (n=40) did not answer a single question correctly, with only nine (2.8%) answering all five questions correctly.

- Prescriber opinions about ADF benefits varied, with 30.3% agreeing that "ADFs don't decrease abuse; it's just a marketing designation," with just 38.1% disagreeing; and 52.8% agreeing that ADFs reduce morbidity and mortality and that greater use would decrease misuse and abuse (50.6%).

- ADF knowledge was negatively associated with perceived effectiveness of ADFs for reducing opioid abuse (b=-.13, p=.02).

- Although only 12.2% reported having never experiencing patient misuse, abuse and/or addiction, 67% said they never/rarely/occasionally prescribed ADFs when facing these issues.

- Confidence in prescribing ADFs was also low among some prescribers, with 30.1% of primary care and 44.6% of specialists reporting no/very little/a little confidence.

- There was also strong agreement overall that ADFs have barriers, including cost (70.0%), lack of insurance coverage (49.1%), and lack of system or practice access (52.8%). Other barriers included respondents saying that "providers don't know enough about ADFs to prescribe them" (73.8% agreement); they don't think they have patients who need them (60.0%), ADFs of the opioids they prescribe are not available (34.4%), and patients would react poorly to them (32.8%).