

FDA Briefing Document

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

May 3-4, 2016

**Extended-release and Long-acting (ER/LA) Opioid Analgesics Risk
Evaluation and Mitigation Strategy (REMS)**

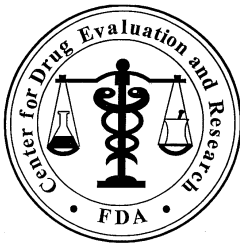
Disclaimer Statement

The briefing 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 are bringing the Extended-Release and Long-Acting (ER/LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) to this joint Advisory Committee meeting in order to gain the Committees' insights and opinions, and 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

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**Department of Health and Human Services
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1 INTRODUCTION

At this joint meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), we will be discussing the risk evaluation and mitigation strategy (REMS) for extended-release (ER) and long-acting (LA) opioid analgesic medications. The ER/LA Opioid Analgesic REMS is one

strategy among multiple national and state efforts to reduce the risk of abuse, misuse, addiction, overdose and deaths due to prescription opioid analgesics.

ER/LA opioid analgesics are 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. The ER/LA Opioid Analgesics REMS was approved on July 9, 2012, to address the serious adverse outcomes of overdose, addiction, and death that result from long-standing problems of inappropriate prescribing, misuse, and abuse of these products. The ER/LA Opioid Analgesics REMS is part of a multi-agency Federal effort to address the growing problem of prescription drug abuse and misuse.

The ER/LA Opioid Analgesic REMS is intended to reduce risks and improve safe use of ER/LA opioid analgesics while continuing to provide access to these medications for patients in pain. The central component of the ER/LA Opioid Analgesics REMS is an education program for prescribers (e.g., physicians, nurse practitioners, physician assistants). Under the REMS, application holders¹ of ER/LA opioid analgesics are required to make education programs available to healthcare providers (HCPs) who are prescribers of ER/LA opioid analgesics. The application holders are meeting this requirement by providing educational grants to accredited continuing education (CE) providers who offer training to prescribers at no or nominal cost. To be considered compliant with the ER/LA Opioid Analgesic REMS, the CE courses are required to include the content and messages of a “blueprint” developed by FDA for this purpose. The FDA Blueprint includes general and product-specific information about the ER/LA opioid analgesics; information on proper patient selection for use of these drugs; guidance for safely initiating therapy, modifying dosing, and discontinuing use of ER/LA opioid analgesics; guidance for monitoring patients; and information for counseling patients and caregivers about the safe use of these drugs.² Additionally, prescribers are provided information for how to recognize evidence of and potential for opioid misuse, abuse, and addiction.

The ER/LA Opioid Analgesics REMS also includes a patient counseling document for prescribers to assist them in properly counseling patients on their responsibilities for using these medicines safely and to provide patients with additional written instructions as needed. The labeling for ER/LA opioid analgesics includes a product-specific one-page Medication Guide to be given to patients each time they receive a prescription of their ER/LA opioid analgesic medicine. The Medication Guide contains consumer-friendly information on the safe use and disposal of ER/LA opioid analgesics and instructions for patients to consult their health care professional before changing doses, signs of potential overdose and emergency

¹ Application holders refers to all the manufacturers of the new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for ER/LA 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 FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. The FDA Blueprint contains core messages intended for use by continuing education (CE) providers to develop educational materials to train prescribers of ER/LA opioid analgesics under the REMS.

contact instructions, and advice on safe storage to prevent accidental exposure to family members.

The FDA has received four assessments of the ER/LA Opioid Analgesics REMS from the application holders of these products. FDA will present the findings from the most recent REMS Assessment, submitted in July 2015, at the May 3 and 4, 2016 joint meeting of the DSaRM and AADPAC. The goal is to seek comments from the committees as well as the public as to whether the ER/LA Opioid Analgesics REMS is meeting its goals, and assures safe use, is not unduly burdensome to patient access to the drugs, and to the extent practicable, minimizes the burden to the healthcare delivery system. FDA is also seeking input from the committees on:

- 1) alternative methodologies for evaluating the overall impact of the program on knowledge and behavior by prescribers and patients;
- 2) the overall impact of the REMS on the adverse events it is intended to mitigate
- 3) whether the FDA Blueprint or other tools (e.g., Medication Guide or Patient Counseling Document) should be revised and/or expanded;
- 4) the use of the continuing education as a component of the REMS as a mechanism for providing prescriber training;
- 5) whether to expand the REMS program to include immediate-release (IR) opioid analgesics; and
- 6) how additional REMS tools or elements to assure safe use (ETASU) such as required prescriber or pharmacist training and/or required patient agreements, if recommended, may impact the healthcare delivery system and patient access to the ER/LA and IR (if applicable) opioid analgesics.

2 BACKGROUND

2.1 Opioid Treatment for Pain

Pain can be categorized according to many characteristics including duration, acute or chronic. Acute pain is defined as pain that is self-limited and generally requires treatment for no more than up to a few weeks (e.g., postoperative or acute musculoskeletal pain). Chronic pain is defined as either pain persisting for longer than 1 month beyond resolution of the underlying insult, or pain persisting beyond 3 months. In the 1990's there was raised awareness of the inadequate treatment of pain. This led to the publication of pain management guidelines by various specialty groups.³ In 1999, the Joint Commission on the Accreditation of Healthcare Organizations declared pain to be the fifth vital sign.⁴ In late 2000, Congress passed into law a provision that declared the 10-year period that began January 1, 2001, as the Decade of Pain

³ JAMA. 1995 Dec 20;274(23):1874-80.

⁴ Joint Commission Perspectives, September/October 1999.

Control and Research.⁵ According the 2011 Institute of Medicine Report, chronic pain constitutes a major public health problem in the United States.⁶ Since the mid-nineties, the use of opioid analgesic drug products to treat non-cancer, chronic pain has increased sharply in response to the new focus on pain management.^{7,8} Over the last 20 years, numerous new formulations of opioid drugs have been developed, in part as an effort to provide treatment options for patients living with inadequately treated pain.

ER/LA opioid analgesics are opioid drug products 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. This class of products comprises two distinct subsets: 1) extended-release formulations that are designed to release the opioid analgesic over an extended duration of time; and 2) long-acting opioids that have pharmacokinetic profiles that permit long dosing intervals. Thus, ER/LA opioid analgesic products include: a) extended-release, solid, oral dosage forms containing hydrocodone, hydromorphone, morphine, oxycodone, tapentadol, or oxymorphone, and fentanyl-containing transdermal delivery systems, and b) oral formulations of methadone, and buccal and transdermal delivery formulations of buprenorphine. In 2013, the FDA required class-wide labeling changes for ER/LA opioid analgesics that included modifications to the products' indications, limitations of use, and warnings, including boxed warnings to more effectively communicate to prescribers the serious risks of misuse, abuse, addiction, overdose and death associated with these drugs.

Immediate-release (IR) opioid analgesics are a class that contains a wide variety of products that are generally indicated for the management of acute pain with variations to reflect use for pain varying from mild to severe intensity. The IR opioid analgesics are formulated as oral tablets, capsules, and oral solutions; and injectable solutions for intravenous, intramuscular, epidural, and intrathecal administration. The IR opioid analgesics contain many of the same active opioid ingredients as the extended-release opioid analgesic formulations. Some IR opioid analgesics contain just the opioid while others contain a non-opioid, such as acetaminophen in combination with the opioid. On March 22, 2016, the Agency announced required class-wide safety labeling changes for IR opioid analgesics similar to those for ER/LA opioid analgesics. Among the changes, is a boxed warning about the serious risks of misuse, abuse, addiction, overdose and death. This is part of the Agency's overall effort to help inform prescribers about the importance of balancing the serious risks of opioids with their role in managing pain.

Drug use data indicate high numbers of prescriptions for opioid analgesics, predominantly the IR opioid analgesics. Prescriptions for both the IR and ER/LA opioid analgesics have been increasing from 2005 through about 2011, but started decreasing since the peak in 2011-2012; trends vary for specific agents within each class.

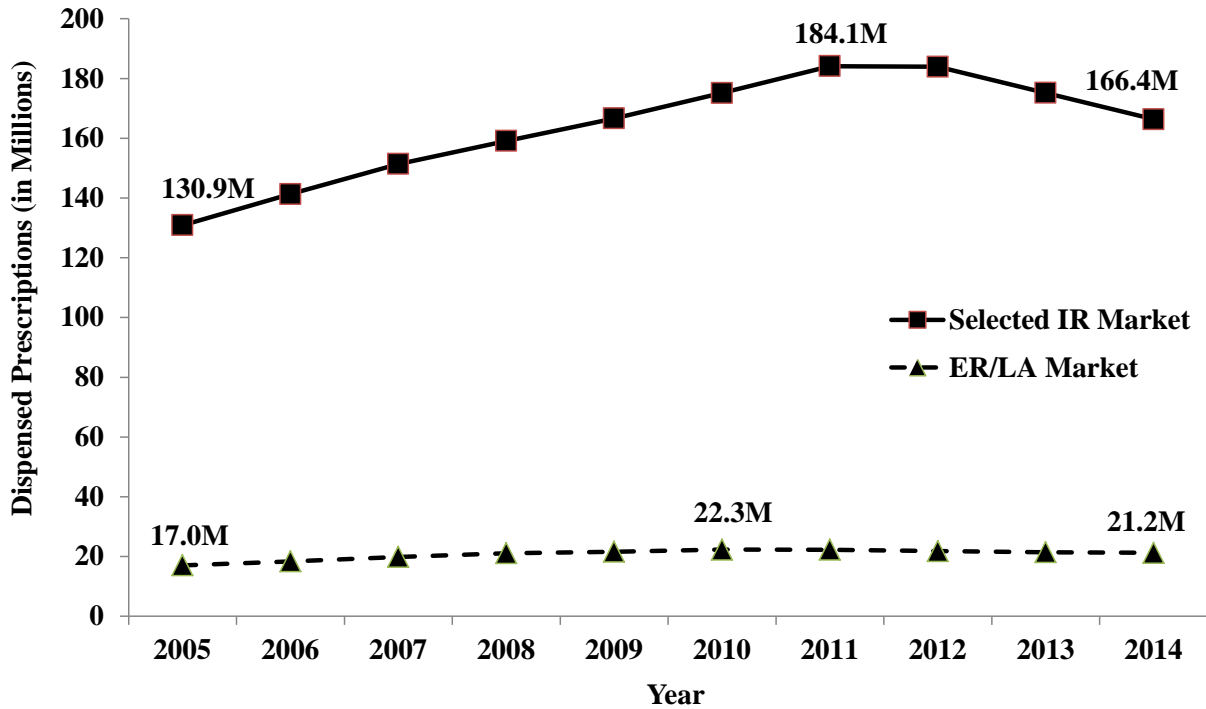
⁵ H.R. 3244, Title VI, Sec. 1603

⁶ Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research, 2011.

⁷ Boudreau D, Von Korff M, Rutter CM et al. Trends in long-term opioid therapy for chronic non-cancer pain. *Pharmacoepidemiol. Drug Saf.* 18(12), 1166–1175 (2009)

⁸ Edlund MJ, Martin BC, Devries A, Fan MY, Braden JB, Sullivan MD. Trends in use of opioids for chronic noncancer pain among individuals with mental health and substance use disorders: the TROUP study. *Clin. J. Pain* 26(1), 1–8 (2010).

Figure 1. Nationally estimated number of prescriptions dispensed for selected* IR and ER/LA opioids analgesic products from U.S. outpatient retail pharmacies



Source: IMS Health, National Prescription Audit™. Extracted May and August 2015

*Selected IR Opioids molecules include the following: Hydrocodone combination analgesics (hydrocodone in combination with acetaminophen, ibuprofen or aspirin), Oxycodone combination analgesics (oxycodone in combination with acetaminophen, ibuprofen or aspirin), oxycodone IR, hydromorphone IR, morphine IR, tapentadol IR, and oxymorphone IR.

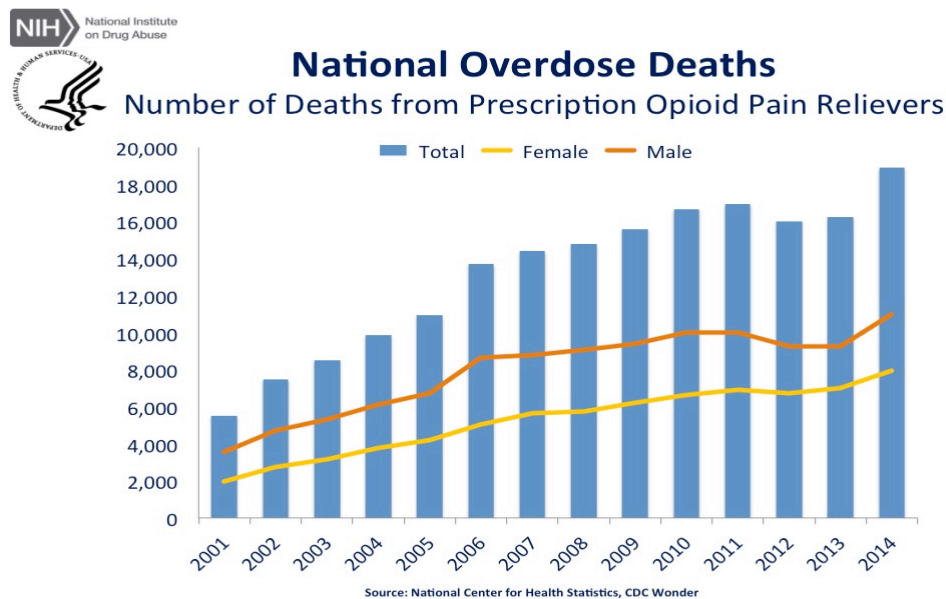
Figure 1 above shows the nationally estimated number of prescriptions dispensed for opioid analgesics from U.S. Outpatient Retail Pharmacies from 2005-2014 with a breakdown between selected IR and ER/LA opioid products. Selected IR opioid prescriptions as shown by the solid line increased from 131M prescriptions to a peak of 184M in 2011 and declined to 166M in 2014. ER/LA opioid prescriptions, shown by the dashed line in Figure 1, increased from 17M in 2005 to a peak of 22M in 2010 and declined to 21M in 2014.

2.2 Prescription Opioid Abuse, Misuse, and Overdose

The opioid analgesics are scheduled under the Controlled Substances Act and all carry a risk of abuse, misuse, addiction, overdose, and death. According to estimates from the Centers for Disease Control and Prevention (CDC), more Americans died from overdoses involving opioid pain relievers in 2014 than in any other year. CDC reports that estimate increased to almost 19,000 deaths in 2014.⁹

⁹ MMWR: Increases in Drug and Opioid Overdose Deaths-United States, 2000-2014: January 1, 2016/64(50); 1378-82.

Figure 2. National Overdose Deaths from Prescription Opioid Pain Relievers¹⁰



Although all opioid formulations have the potential for misuse, abuse, overdose, and death, the ER/LA opioids analgesics have been particularly concerning to the Agency because of the higher amount of opioids contained per tablet, capsule or patch, and the fact that ER/LA opioid analgesics either stay in the body longer or are released into the body over longer periods of time. When the extended-release features of some of these formulations are manipulated, either deliberately or inadvertently, these products deliver high doses of opioid in an immediate-release manner, potentially resulting in overdose. However, given the persistence of opioid-related overdoses and deaths, the Agency is now considering inclusion of the IR opioid analgesics into the ER/LA Opioid Analgesics REMS.

2.3 *Governmental Effort to Address Opioid Crisis*

The FDA efforts to address prescription opioid abuse, misuse, overdose and deaths are part of a larger governmental response to the prescription opioid abuse crisis. In 2011, the White House Office of National Drug Control Policy (ONDCP) launched a plan to combat the growing prescription drug abuse problem in the U.S. The plan focused on four major areas to reduce prescription drug abuse: education, monitoring, proper medication disposal, and

¹⁰ Accessed on April 1, 2016 from the NIH, National Institute on Drug Abuse website at <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>. The supporting data (available on the website) indicates that this includes other opioids, methadone, other synthetic narcotics. Specific products were not listed.

enforcement.¹¹ The Secretary of the Department of Health and Human Services also launched an initiative to combat opioid abuse. This initiative includes improving opioid prescribing practices to reduce opioid use disorders and overdose, expanding use and distribution of naloxone to treat opioid overdoses, and expanding Medication-assisted Treatment (MAT) to reduce opioid use disorders and overdose. More recently, FDA announced in February 2016 a proactive response to address the prescription opioid crisis.¹² This plan is described more fully in Section 2.3.1 below.

There are other critical US Governmental efforts that FDA is supporting. The draft National Pain Strategy, developed by the Interagency Pain Research Coordinating Committee (IPRCC), includes objectives and plans related to key areas of pain and pain care, including professional education and training, public education and communication, service delivery and reimbursement, prevention and care, disparities, and population research.¹³ The IPRCC is also developing the Federal Pain Research Strategy for pain research across federal agencies.¹⁴ Finally, the Centers for Disease Control and Prevention (CDC) published Guidelines for Prescribing Opioids for Chronic Pain. This guideline focuses on topics related to determining when to initiate or continue opioids for chronic pain outside end-of-life care, opioid selection, dosage, duration, follow-up, and discontinuation, and assessing risk and addressing harms of opioid use.¹⁵

2.3.1 FDA Opioid Action Plan¹⁶

The FDA continues to be concerned about the growing epidemic of opioid abuse, addiction, and overdose and in February 2016, the FDA announced a renewed effort that includes a comprehensive action plan to take concrete steps toward reducing the impact of opioid abuse on American families and communities. As part of this plan, the Agency is committing to work more closely with its advisory committees before making critical product and labeling decisions; enhancing safety labeling; requiring new data; and seeking to improve treatment of both addiction and pain. At the same time, the FDA will fundamentally re-examine the risk-benefit paradigm for opioids and ensure that the agency considers the wider public health effects. The FDA is committed to taking all of these steps transparently and in close cooperation with its sister agencies and stakeholders.

The FDA's actions include:

¹¹ Epidemic: Responding to America's Prescription Drug Abuse Crisis available at https://www.whitehouse.gov/sites/default/files/ondcp/policy-and-research/rx_abuse_plan.pdf

¹² Opioid Abuse in the U.S. and HHS Actions to Address Opioid-Drug Related Overdoses and Deaths available at https://aspe.hhs.gov/sites/default/files/pdf/107956/ib_OpioidInitiative.pdf

¹³ National Pain Strategy: A Comprehensive Population Health-Level Strategy for Pain available at <http://iprcc.nih.gov/docs/DraftHHSNationalPainStrategy.pdf>

¹⁴ Information regarding this initiative is available at <http://iprcc.nih.gov/FPRS/FPRS.htm>

¹⁵ Information regarding the CDC Guideline Prescribing Opioids for Chronic Pain can be found at <http://www.cdc.gov/drugoverdose/prescribing/guideline.html>

¹⁶ <http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm>

- **Expand use of advisory committees.** The FDA will convene an expert advisory committee before approving any new drug application for an opioid that does not have abuse-deterrent properties. The Pediatric Advisory Committee will make recommendations regarding a framework for pediatric opioid labeling before any new labeling is approved. The FDA will consult an advisory committee on abuse-deterrent formulation (ADF) opioids when they raise novel issues. Outcome: Review and advice from external experts with opportunity for public input before approval of any new opioid that does not have abuse-deterrent properties and expert advice on pediatric opioid labeling.
- **Develop warnings and safety information for immediate-release (IR) opioid labeling.** On March 22, 2016 the FDA announced required class-wide safety labeling changes for IR opioid pain medications. Among the changes, the FDA is requiring a new boxed warning about the serious risks of misuse, abuse, addiction, overdose, death and neonatal opioid withdrawal syndrome (NOWS). The changes to IR opioid analgesic labeling are similar to ER/LA opioid analgesics labeling update that occurred in 2013. Outcome: Better information for doctors about the risks and how to prescribe safely.
- **Strengthen postmarket requirements.** Because the evidence base to guide the use of opioid medications, particularly in the setting of long-term use, is substantially lacking, the FDA has strengthened the requirements for drug companies to generate postmarket data on the long-term impact of using ER/LA opioid analgesics. Outcome: Better evidence on the serious risks of misuse and abuse associated with long-term use of opioids, predictors of opioid addiction and other important issues.
- **Update Risk Evaluation and Mitigation Strategy (REMS) Program.** ER/LA opioid analgesics are currently subject to a REMS program that requires application holders to fund continuing medical education (CME) providers to offer, at low or no cost, CME courses on the appropriate use of these products. The FDA will update the REMS program requirements for opioids after considering advisory committee recommendations and review of existing requirements. Outcome: Increase the number of prescribers who receive training on pain management and safe prescribing of opioid drugs in order to decrease inappropriate opioid prescribing.
- **Expand access to abuse-deterrent formulations (ADFs) to discourage abuse.** The pharmaceutical industry has shown significant interest in developing ADFs and the technology is progressing rapidly. ADFs hold promise as their abuse-deterrent qualities continue to improve and as they become more widely available. The FDA will issue draft guidance with its recommendations for the approval standards for generic abuse-deterrent formulations. Release of this guidance is a high priority, since the availability of less costly generic products should accelerate prescribers' uptake of ADFs. Outcome: Spur innovation and generic ADF product development.
- **Support better treatment.** The FDA is reviewing options, including over-the-counter availability, to make naloxone more accessible to treat opioid overdose, building on the Agency's recent approval of intranasal naloxone. The agency actively supports the CDC

guidelines for prescribing opioids for the treatment of pain and will facilitate the development of evidence and improved treatments. Outcome: Broader access to overdose treatment, safer prescribing and use of opioids, and ultimately, new classes of pain medicines without the same risks as opioids.

- **Reassess the risk-benefit approval framework for opioid use.** The FDA held a Meeting of the Agency's Science Board on March 1, 2016 to discuss: (1) the role of opioids in pain management; (2) scientific challenges facing FDA in supporting the development of pain medications, including opioids, that have reduced risks of being abused; (3) scientific challenges facing FDA in seeking to understand the real-world use of opioids to treat pain, including the impact of opioids with potentially less risk for abuse; (4) the role that FDA plays as a part of a larger Federal, State and local response to the challenges of providing appropriate pain treatment while reducing opioid abuse; and (5) postmarket surveillance activities related to opioids. FDA is also engaging the National Academy of Medicine on how to take into account our evolving understanding of the risks of opioids, not only to the patient but also the risks of misuse by other persons who obtain them. These reports will be publicly available. Outcome: Formal incorporation of the broader public health impact of opioid abuse in approval decisions.

3 Risk Evaluation and Mitigation Strategy (REMS)

3.1 *REMS Authority*

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), as amended by the Food and Drug Administration Amendments Act of 2007 (FDAAA), authorizes the FDA to require a pharmaceutical application holder to develop and comply with a risk evaluation and mitigation strategy (REMS) for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management program that uses risk minimization strategies beyond the professional labeling. The elements of a REMS may include the following:

A **Medication Guide** provides FDA approved patient-focused labeling and can be required as part of the approved labeling if FDA determines one or more of the following apply:

- Patient labeling could help prevent serious adverse events.
- The product has serious risks that could affect a patient's decision to use or continue to use the drug.
- Patient adherence to directions is crucial to product effectiveness.

FDA has the authority to determine, based on the risks of a drug and public health concern, whether a Medication Guide should be required as part of a REMS (when the standard for requiring a Medication Guide in 21 CFR part 208 is met), and may decide the Medication Guide should be required as labeling but not part of a REMS if FDA determines that a REMS is not necessary to ensure the benefits of the drug outweigh its risks.

A **Communication Plan** consists of FDA approved materials used to aid an application holder's implementation of the REMS and/or inform healthcare providers about serious risk(s) of an

approved product. This can include, for example, “Dear Healthcare Professional” letters, collaboration with professional societies, and education pieces (such as letters, drug fact sheets) to inform prescribers of the risks and the safe use practices for the drug.

Elements to assure safe use (ETASU) are requirements FDA can impose to help ensure safe use of the drug. In some cases these requirements can place restrictions on prescribing or dispensing the drug to the patient. ETASU can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling – and, for drugs initially approved without ETASU, other elements of a REMS are not sufficient to mitigate the serious risk that is the subject of the REMS. Accordingly, section 505-1(f)(2) of the FDCA specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Considering such risk, cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

A REMS may also include an **Implementation System** to enable the application holder to monitor, evaluate, and improve the implementation of the elements.

All REMS approved for drugs or biologics under New Drug Applications (NDA) and Biologics License Applications (BLA) must have a **timetable for submission of assessments** of the REMS. The application holder must conduct assessments on a periodic basis to determine whether the goals of the program are being met and to identify any potential areas for improvement or modification of the REMS. The minimum requirement for REMS assessment submission is 18 months, 3 years and 7 years following approval of the REMS, although the Agency may require more frequent assessments for some programs with ETASU. These assessments are prepared by the application holder and reviewed by FDA.

3.2 History of the ER/LA Opioid Analgesic REMS Development

In 2000, FDA first received reports of significant problems with prescription opioid abuse, especially involving OxyContin (oxycodone extended-release tablets).¹⁷ The problems included crushing of the tablet to defeat the extended-release (ER) properties, misuse by several different routes, and addiction, overdose and death. A Risk Management Plan (RMP)¹⁸ was developed in 2001 for OxyContin. The RMP focused on education, surveillance, and intervention when a signal of misuse or abuse became apparent. The educational component of the RMP targeted healthcare providers using a variety of materials.

As FDA continued to address the problems of prescription opioid abuse and misuse, meetings of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) were held to provide advice and recommendations to FDA. Some examples include:

- January 2002: Medical use of opioid analgesics and concerns about abuse potential and addiction.
- September 2003: RMPs for opioid analgesic drug products with particular attention to modified-release products.
- May 2008, September 2009, October 2010: Joint meeting with the Drug Safety and Risk Management (DSaRM) Advisory Committee to discuss reformulated OxyContin, including its purported abuse-deterrent properties and the design of postmarketing studies intended to assess the effects of abuse-deterrent properties post approval.

Despite adding warnings to product labeling and developing RMPs to prevent inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics, unintentional overdose, addiction, and death resulting from these products continued to increase.

Title IX, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85) gave FDA the authority to require a REMS when it is necessary to ensure the benefits of a drug outweigh the risks (21 U.S.C. 505-1). For products initially marketed without a REMS, FDA may determine, based on new safety information, that a REMS is necessary to ensure that the benefits of the drug outweigh the risks.

- On February 6, 2009, FDA notified the application holders of ER/LA opioid analgesics that a REMS was required for their products to ensure that the benefits of those products continued to outweigh their risks.
- On March 3, 2009 FDA met with the application holders (referred to initially as the Industry Work Group (IWG) and now the REMS Program Committee (RPC)) to discuss

¹⁷ Please refer to the following presentation at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM248776.pdf>

¹⁸ Prior to the passage of the Food and Drug Administration Amendments Act of 2007, the Agency often negotiated Risk Management Plans (RMPs) or Risk Minimization Action Plans (RiskMAPs). Many of these were voluntary; in some cases, the RMPs or RiskMAPs were approved under 21 CFR 314.520 Subpart H, approval with restrictions to assure safe use.

the REMS design to manage the risks while considering the burden on the health care system.

- On December 4, 2009, FDA held a public meeting to hear from the RPC about their views on the specific features of the REMS.
- On July 22 and 23, 2010, a Joint Meeting of the FDA ALSD and DSaRM advisory committees was convened to discuss FDA's proposal for a class-wide REMS for ER/LA opioid analgesics and to solicit feedback from the advisory committees and public on the components of the proposal.

Between February and May 2009, FDA held a series of meetings with stakeholders to collect comments and opinions on how a REMS could be designed to minimize the risks of the ER/LA opioid analgesic drugs while also not overly burdening the healthcare system or reducing legitimate and appropriate access to these medications for patients. FDA also opened a public docket on April 20, 2009 to receive public comments on the proposed REMS.

FDA considered that the REMS require individual prescribers or patients to enroll in a REMS program with real-time verification of prescriber training at the pharmacy level, but decided that the REMS should not include these requirements at that time. FDA heard from stakeholders that a requirement for individual prescriber registration and real-time verification of training at the pharmacy before filling an opioid prescription could cause some prescribers and pharmacies to “opt out” of the program, with potential adverse consequences on patient access to pain medications. FDA noted that mandatory prescriber registration would require the establishment of a new system for registering prescribers of ER/LA opioid analgesics that would duplicate the existing Drug Enforcement Administration (DEA) registration system. More than 1 million prescribers and approximately 66,000 pharmacies were registered with DEA at that time. Instead of creating a potentially burdensome new system that would parallel the existing DEA system, FDA supported a mandatory prescriber training program on responsible opioid prescribing practices that would be linked to DEA registration. Such a program was proposed in the Administration's comprehensive plan to address the epidemic of prescription drug abuse in April 2011. FDA also received numerous comments indicating that a REMS limited to only ER/LA opioids analgesics would simply shift prescribing behavior to immediate-release opioid products. These commenters argued that the REMS should be required for immediate-release products as well to avoid this potential problem. Opponents asserted that such an expansion would exponentially increase the complexity of the REMS. Although immediate-release (IR) opioid analgesics also present serious risks to patients when they are not used properly, at the time the ER/LA opioid analgesic REMS was required, the ER/LA products were determined to have increased risk on a per-tablet basis compared to other opioid products. Since the amount of opioid contained in one tablet or capsule of an ER/LA product is often greater than the amount in a tablet or capsule of an IR product, accidental or purposeful misuse is more likely to result in adverse events, including respiratory depression or death.

In April 2011, the Agency sent REMS notification letters to application holders of ER/LA opioid analgesics. The notification letters specified requirements for

- Prescriber training/education

- Tmetable for submission of assessments of the REMS
- Medication Guide
- Patient Education Materials

The key element of the REMS program is prescriber education, the content of which was described in the REMS notification letter. The prescriber education program includes general information about the use of the class of ER/LA opioid analgesics to aid in patient selection and counseling and specific information about the individual drugs in this class. Prescriber education will inform prescribers about how to recognize the potential for and evidence of addiction, dependence and tolerance. The letter stated that to “assure access to DRUG and minimize the burden on the healthcare delivery system, FDA expects that the training will be conducted by accredited, independent continuing medical education (CME) providers, to the extent practicable.”

In response to the April 2011 REMS notification letter, industry submitted an expanded outline of the potential topics to be covered in the CE. FDA reviewed the industry submission and developed core messages to be communicated to prescribers. The core messages are the “blueprint” to be used by CE providers to develop the actual CE materials.

On November 7, 2011, FDA issued a Federal Register (FR) Notice announcing the availability of a draft document entitled “Blueprint for Prescriber Education for Long-Acting/Extended-Release Opioid Class-Wide REMS.” FDA received comments from about 65 individuals and organizations when the document posted in the FR. In addition to the stakeholder feedback submitted to the docket, FDA also discussed the blueprint at meetings of FDA’s Drug Safety Board, and consulted with National Institute on Drug Abuse (NIDA) and Substance Abuse and Mental Health Services Administration (SAMHSA). Most comments were favorable and offered specific edits. The negative comments focused primarily on the REMS being ineffective in addressing the problem because completion of the REMS training by prescribers is voluntary; industry is involved; and the ER/LA opioid analgesic focus is too narrow.

In development of the “blueprint” FDA worked in association with other federal agencies to ensure the scope of the material was appropriate. FDA then worked with the Accreditation Council for Continuing Medical Education (ACCME) and other accrediting bodies and CE providers to help ensure that accredited CE programs developed to comply with the REMS would be in compliance with ACCME accreditation criteria and standards for commercial support. The ACCME standards of independence require that the content and format of the activity must be free from commercial bias.

FDA considered comments received and on July 9, 2012, approved the ER/LA Opioid Analgesics REMS, which included the final FDA “blueprint.” The blueprint was posted on the FDA website to be used by accredited CE providers to develop training supported by independent educational grants from ER/LA opioid analgesic manufacturers. The content of the FDA “blueprint” focuses on the safe prescribing of ER/LA opioid analgesics and includes information on assessing patients for treatment with ER/LA opioid analgesics, dosing ER/LA opioid analgesics, counseling and managing patients on ER/LA opioid analgesics, and product-specific

information related to ER/LA opioid analgesics. It is directed to prescribers of ER/LA opioid analgesics but may be relevant for other healthcare professionals (e.g. pharmacists).

3.3 Current Approved ER/LA Opioid Analgesics REMS

Below is a brief summary of the approved ER/LA Opioid Analgesics REMS. The approved REMS document is included as Appendix 1.

The **goal of the ER/LA Opioid Analgesics REMS** is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

The ER/LA Opioid Analgesics REMS elements include:

Medication Guide (MG) – an updated one-page Medication Guide that contains consumer-friendly information on the safe use and disposal of the ER/LA opioid analgesics. The product-specific Medication Guides are part of the ER/LA Opioid Analgesics REMS. The MGs are to be dispensed in accordance with 21 CFR § 208.24.

Elements to Assure Safe Use: Training will be made available to healthcare providers who prescribe ER/LA opioid analgesics.

1. **Prescriber Training** – The application holders must ensure that REMS-compliant training, based upon the *FDA Blueprint for Prescriber Education for ER/LA Opioid Analgesics*, is available to prescribers who prescribe the ER/LA opioid analgesics. The training is considered REMS-compliant if: 1) it, for training provided by CE providers, is offered by an accredited provider to licensed prescribers, 2) it includes all elements of the 3) it includes a knowledge assessment of all of the sections of the FDA Blueprint, and 4) it is subject to independent audit to confirm that conditions of the REMS training have been met. The FDA Blueprint is included as Appendix 2.
2. **Prescriber Training Performance Goals:** The application holders were required to ensure the REMS-compliant training was made available by accredited CE providers by March 1, 2013 with the following performance goals:
 - Within 2 years from the time the first REMS-compliant training becomes available, 80,000 prescribers (based on 25% of the 320,000 active prescribers in 2011) will have been trained
 - Within 3 years from the time the first REMS-compliant training becomes available, 160,000 prescribers (based on 50% of the 320,000 active prescribers in 2011) will have been trained
 - Within 4 years from the time the first REMS-compliant training becomes available, 192,000 prescribers (based on 60% of 320,000 active prescribers in 2011) will have been trained
3. **Prescriber Letters** – application holders were required to send three prescriber letters to all DEA-registered prescribers who are registered to prescribe Schedule II and III drugs. The letter notified prescribers about the REMS, the availability and importance of

taking the REMS-compliant training through accredited CE, as well as encouraging the use of the *Patient Counseling Document (PCD)*. The PCD is included as Appendix 3.

4. **Professional Organization/Licensing Board Letters** – application holders were required to send two letters specified state licensing boards, associations of state licensing boards, and professional organizations notifying these organizations about the REMS, the availability and importance of taking the REMS-compliant training through accredited CE, as well as encouraging the use of the PCD.
5. **Patient Counseling Document (PCD)** – this document is provided to prescribers to give to patients, helping prescribers to properly counsel patients on their responsibilities for using these medicines safely.

Timetable for Submission of Assessments: REMS assessments were submitted to the FDA by the application holders at 6 months, 12 months after the initial approval date of the REMS, and annually thereafter.

Appendix 5 includes a table of the ER/LA opioid analgesics that are subject to the ER/LA Opioid Analgesics REMS requirements.

3.4 ER/LA Opioid Analgesics REMS Assessment Plan

The application holders' 36-month REMS Assessment Report for the ER/LA Opioid Analgesics REMS includes the following major assessment plan elements:¹⁹

Assessment Element 1: Assessment of how many prescribers of ER/LA opioids have successfully completed the training. Specify performance goals for the number of prescribers trained by time.

Assessment Element 2: Independent audit of the quality of the content of the educational materials used by the CE Providers to provide the education. The audit should evaluate the quality of the content against the content approved by FDA as part of the REMS, as well as against the ACCME's and other accrediting bodies' standards for commercial support.

Assessment Element 3a: Prescriber Survey-Evaluation of Healthcare Professional (HCP) awareness and understanding of the serious risks associated with these products (e.g., through surveys of HCPs) and specification of measures that would be taken to increase awareness if surveys of HCPs indicate that HCP awareness is not adequate.

Assessment Element 3b: Long-term evaluation (of prescriber knowledge)

Assessment Element 4: Patient Survey-Evaluation of patients' understanding of the serious risks of these products.

Assessment Element 5: Surveillance monitoring for misuse, abuse, overdose, addiction, death and any intervention to be taken resulting from signals of these metrics, including information for different risk groups (e.g., teens, chronic abusers) and different settings

¹⁹ Table 1, 36th month assessment of the ER/LA Opioid Analgesics REMS Assessment Report

(e.g., emergency rooms, addiction treatment centers, poison control call centers). As much as possible, the information should be drug-specific.

Assessment Element 6: Evaluation of drug utilization patterns (IMS data)

Assessment Element 7: Evaluation of changes in prescribing behavior-Evaluation of changes in prescribing behavior of prescribers, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills.

Assessment Element 8: Monitoring patterns of prescribing to identify changes in access to ER/LA opioid analgesics.

The full ER/LA Opioid Analgesics REMS assessment plan as specified in the initial REMS approval letter can be found in Appendix 4.

The timetable for submission of assessments is 6 months, 12 months and annually from initial approval of the ER/LA Opioid Analgesics REMS on July 9, 2012.

4 FDA SUMMARY OF 36th MONTH ASSESSMENT REVIEW

The RPC submitted the 36th Month ER/LA Opioid Analgesics REMS Assessment Report on July 9, 2015. This is the fourth assessment of the ER/LA Opioid Analgesics REMS and it includes data on all assessment elements. Below is a summary of the key findings based on FDA's review of this assessment report.

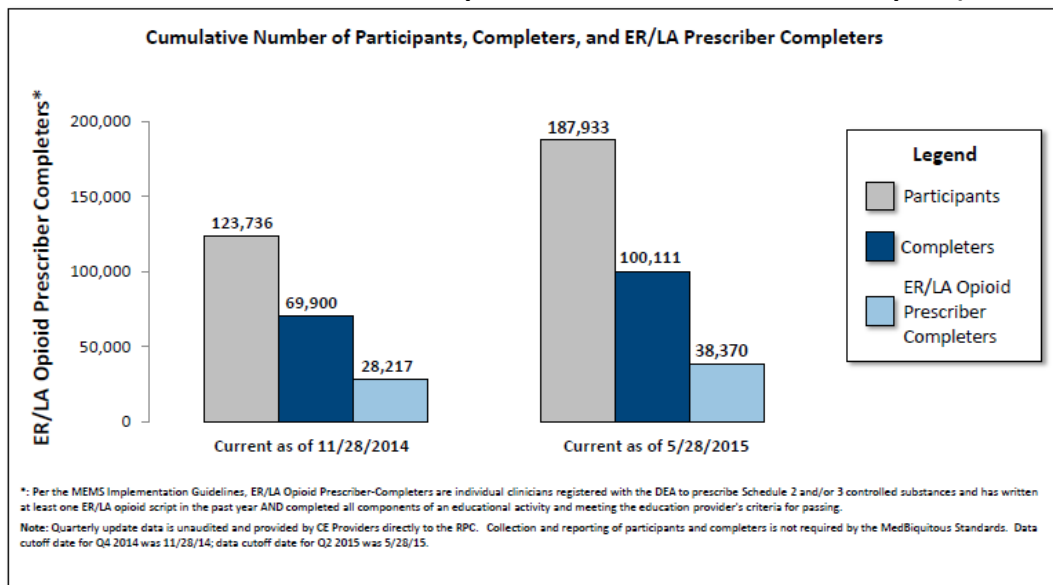
4.1 Assessment Element 1: Prescriber Training and CE Audits

As mentioned above, the primary component of the REMS is the requirement for application holders of ER/LA opioid analgesics to make training available to healthcare providers who prescribe ER/LA opioid analgesics.

As of March 1, 2015, a total of 37,512 ER/LA opioid analgesic prescribers have completed RPC-supported REMS-compliant training which represents 47% of the milestone of 80,000 for this report. There are an approximately 150,000 additional individuals who initiated CE training who either did not complete the training, or completed the training but do not self-identify as ER/LA opioid analgesic prescribers.

Figure 3 below reveals that as of May 28, 2015, 53% of healthcare providers (HCPs) who start a REMS-compliant CE program actually complete the activity. Of these completers, 38% self-identify as ER/LA opioid analgesic prescribers.

Figure 3: Cumulative Number of Participants, Completers, and ER/LA Prescriber Completers Reported Directly from RPC-supported CE Providers (provided by the application holders on 10/26/15 in response to an FDA information request)



Source: October 26, 2015 RPC response to an October 22, 2015 FDA Information Request

There are likely a number of factors as to why the goal of 80,000 ER/LA prescriber-completers has not been achieved. The application holders have identified three predominant challenges in this regard:

1. Lack of awareness of the REMS and the importance of completing ER/LA opioid analgesic REMS-compliant CE. Because completion of training is not linked to prescribing an ER/LA opioid analgesic, a general lack of awareness of the REMS may in part be responsible for lower than targeted training numbers. The application holders confirmed this through a survey of prescribers conducted 8 months after the launch of the first REMS-compliant training, which demonstrated that 41% of prescribers surveyed were unaware of the REMS.
2. Education is not tailored to the adult professional learner: the length of activities and the associated time commitment for completion, coupled with no accommodation for demonstration of prior knowledge or competency impacts prescriber willingness to complete REMS-compliant CE. The RPC has indicated based on feedback from REMS CE providers, accrediting bodies, the CCCE, and from learners that the rigidity and extent of content of the FDA Blueprint is not conducive to the type of education that is engaging to adult learners.
3. There are many non-REMS-compliant CE activities regarding opioids available to clinicians, both online and in live settings that may potentially dilute the audience of ER/LA opioid analgesic prescribers who may complete the REMS-compliant CE activities (such as those that fulfill state-mandated licensure requirements; or endorsed by prominent, non-industry-related organizations such as NIDA, the Office of National Drug Control Policy (ONDCP), the Substance Abuse and Mental Health Services

Administration (SAMHSA), etc.; or cover opioid risk management within the broader context of appropriate pain management).

It is also possible that certain completers were not counted in the definition of ER/LA opioid prescriber-completers for a couple of reasons. The definition of ER/LA opioid prescribers excludes prescribers who, despite being registered to prescribe Schedule II and III medications, indicated that they did not prescribe an ER/LA opioid analgesic in the 12-month period prior to taking the CE training. Prescribers who utilize an institutional DEA registration are also excluded from this definition.

Independent audits of CE training were conducted in 10% of RPC-supported REMS CE activities. The audits evaluate whether the content is factually correct; the training covers all sections of the FDA Blueprint; the post-course knowledge assessment measures knowledge of all sections of the FDA Blueprint; and the training was conducted in accordance with the standards for CE of the ACCME or other accrediting bodies (is independent of the pharmaceutical industry's influence; and the content is free from promotional material). Of the 29 audit reports received, 20 (69%) met the criteria for REMS Compliant CE. Nine CE trainings (of the 29 audited) did not meet the criteria for REMS Compliant CE for reasons of disclosure of financial relationships.

4.2 Assessment Elements 3a, 3b and 4: Prescriber and Patient Surveys

Prescriber and patient surveys were conducted during this assessment period. Prescriber surveys included the Follow-up Prescriber Survey and the Long-Term Evaluation (LTE) Survey.

The objective of the Follow-up Prescriber Survey was to assess ER/LA opioid analgesics prescribers' awareness and understanding of the serious risks associated with ER/LA opioid analgesics and their awareness of appropriate prescribing practices for ER/LA opioid analgesics. The survey compared the awareness and understanding of prescribers who had taken the REMS-compliant training (recruited from CE providers) with those who did not take the training (recruited from IMS Health). Prescribers were eligible if they prescribed an ER/LA opioid analgesic at least once in the year prior to the survey. This survey was a follow-up to the Baseline Prescriber Survey (BPS) which was launched before the implementation of REMS-compliant CE activities and served as the basis for comparing prescribers' knowledge, attitudes, and behavior (KAB) and prescribing practices. Key risk messages were established by the application holders that corresponded to the core areas of the FDA Blueprint. A target knowledge rate of at least 70% was initially set for each key risk message but later raised to 80% per FDA request. Overall, the majority of survey respondents (those that took the CE training and those that did not take the training) were knowledgeable about the assessment, management, and counseling requirements for patients being considered for treatment or currently being treated with an ER/LA opioid analgesic. Survey respondents were less knowledgeable about initiation, modification, and discontinuation of therapy, and general and product specific information for ER/LA opioid analgesics.²⁰ In general, survey respondents who completed a CE activity were more likely to answer questions correctly as compared to those

²⁰ Tables 4-9, 36th month assessment of the ER/LA Opioid Analgesics REMS Assessment Report

that did not complete a CE activity. Survey respondents that reported completion of a CE activity also had higher knowledge scores than respondents that reported not completing a CE activity. Compared to the BPS, overall response rates to 44 items improved, 17 remained the same, and 4 items decreased. Overall, awareness of REMS materials was low for all survey respondents: 60% aware of the Medication Guide, 37% aware of the Dear DEA Prescriber Letter, 43% aware of the Patient Counseling Document, and 30% aware of the REMS website although survey respondents who completed a CE activity had a higher awareness of REMS materials than those that did not.

The objectives of the Long-term Evaluation Survey were to evaluate knowledge about prescribing ER/LA opioid analgesics, completion of the REMS processes, and to assess changes in behavior, prescribing, and patient assessment practices in prescribers who had completed a REMS-compliant CE activity within the 6 to 12 months prior to survey completion. All respondents were recruited directly from CE providers. The LTE survey included a subset of questions included in the Follow-up Prescriber survey along with case-based scenario questions that assessed if prescribers were able to apply information learned from the CE activity to patient scenarios. Key risk messages were established by the RPC that corresponded to the core areas of the FDA Blueprint. A target knowledge rate of at least 70% was initially set by the RPC for each key risk message but later raised to 80% per FDA request. Results of the evaluation of prescriber knowledge were consistent with results of the Follow-up Prescriber Survey²¹. The majority of the lowest scoring items were case-based scenario questions rather than multiple choice or true-false questions from the Follow-up Prescriber Survey. Since participating in a REMS-compliant activity, survey respondents reported more often conducting appropriate prescriber behaviors such as counseling on risks and side effects, instructing patients how to safely dispose of unused ER/LA opioid analgesics, instructing patients to keep ER/LA opioid analgesics medications away from children, informing patients that it is illegal to share, sell, or give-away ER/LA opioid analgesics, using tools to screen patients for risk of misuse or abuse, completing a prescriber-patient agreement (PPA), performing urine drug screens, checking the state prescription monitoring program database, and reassessing the need for opioids. Respondents reported that the main barriers to applying information learned from the REMS-compliant CE activities were insufficient time to address all of the treatment considerations (63%), patient non-compliance (57%), and patients continuing to identify new drug-seeking behaviors that were not addressed in the training activity (48%).

The objective of the patient survey was to assess patient knowledge of the safe use of ER/LA opioid analgesics following implementation of the REMS and to determine possible effects of the REMS, including impact on access to medication and satisfaction with access to pain management. Patients were identified from medical and pharmacy claims in the HealthCore Integrated Research Database (HIRD), a database of all commercially insured patients. Patients were eligible to participate if they were currently active members and adults age 18 or older who filled at least one prescription for an ER/LA opioid analgesic in the year preceding the survey. Key risk messages were established that corresponded to the core areas of the FDA

²¹ Tables 11-16, 36th month assessment of the ER/LA Opioid Analgesics REMS Assessment Report

Blueprint. A target knowledge rate of at least 80% was set for each key risk message. Overall, patient survey respondents had a high understanding of the key risk messages of the REMS, though the survey respondents were not representative of the population of patients prescribed ER/LA opioid analgesics. There was a lower understanding of aspects of safe storage and using the drug safely. The majority of survey respondents received the Medication Guide in the last 12 months (95%) but only 32% of respondents received the Patient Counseling Document (PCD) in the last 12 months. Most survey respondents reported satisfaction with access to ER/LA opioid analgesics (83%)²².

One main concern with the three surveys is generalizing their results to the targeted population of interest. Those choosing to take the CE may differ from the ER/LA opioid analgesic prescriber population in general. The two prescriber surveys are convenience samples of the targeted population of ER/LA opioid analgesic prescribers. The patient survey is also a convenience sample of the targeted patients who were prescribed ER/LA opioid analgesics. The 36-month REMS assessment report did not provide comparisons of the characteristics of the survey respondents to those of the targeted population for each of the surveys. Thus, it is impossible to assess whether or how the results of these surveys can be generalized to the population. The FDA statistical review recommended that future survey analyses: (1) compare characteristics of survey participants to its target population for each survey; and (2) propose methods to standardize the results of each survey to its targeted population.

4.3 Assessment Element 5: Surveillance Studies

The surveillance studies suggest encouraging downward trends in some, but not all, clinical outcomes; rates of calls to poison control centers relating to prescription opioids decreased, the prevalence of self-reported recent abuse of prescription opioids among those entering addiction treatment programs decreased, and deaths involving opioids with an available ER/LA formulation decreased in Washington state. However, a survey of college students found increased non-medical use of opioids, and studies showed that emergency department visits and hospitalizations for prescription opioid overdose did not substantially change in a large commercially insured cohort or in a small subset of Medicaid patients.

Each of the surveillance studies had considerable methodological limitations, as discussed in the epidemiologic and statistical reviews. Further, it is not clear from the study findings whether the REMS itself is contributing to the observed changes, since the decreases noted above generally began prior to implementation of the REMS and were not limited to ER/LA opioids but were seen for IR opioids and selected other controlled substances as well. In interpreting the overall findings, the impact of the REMS itself could not be isolated from the effects of the many other federal, state, local, and health-system level interventions implemented during the study period intended to curb inappropriate prescribing, abuse, and overdose. However, nor can it be concluded that the studies demonstrate that the REMS is failing to achieve its goals.

²² Tables 18-25, 36th month assessment of the ER/LA Opioid Analgesics REMS Assessment Report

The lack of studies that directly examine the impact of participation in REMS training and resulting changes in knowledge, practice, or patient outcomes limits the ability of these studies to evaluate the effectiveness of the REMS and guide specific changes to the program. To assess the impact of the REMS trainings directly, changes in prescriber behavior and/or patient outcomes for a group of providers who have taken the REMS training would need to be compared to those in a group who had not taken the training. Conducting such a study would be challenging and resource intensive, as it would require the identification of individual prescribers who had and had not received the REMS training, and then linkage to prescribing data by each individual prescriber for examination and comparison of changes over time – and finally ascertainment of changes in patient outcomes associated with each prescriber. These types of data linkages are not readily available in existing electronic healthcare databases, but the feasibility of this type of investigation should be explored if more rigorous evaluation of the impact of the ER/LA opioid analgesic REMS is needed.

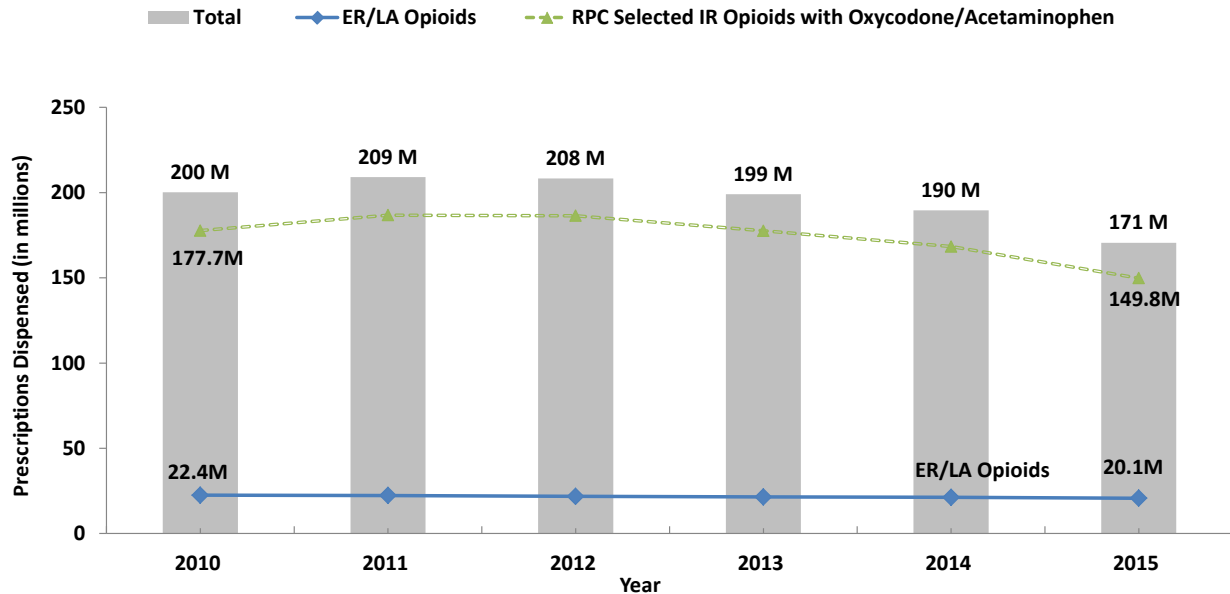
A strength of the surveillance assessment is that it presents results on clinical outcomes (e.g., emergency department visits, hospitalizations, deaths) over time and quantifies change in these clinical outcomes from pre-to post-REMS periods. Another strength of this assessment is that it provides information specific to individual drugs, in addition to the overall class of ER/LA opioid analgesics. One limitation with the design and models of change in this assessment is that the change cannot be causally attributed solely to REMS interventions, since it is known that many interventions occurred in the same time frame as the REMS. Each database is a convenience sample of the targeted population at each time point and the sampling fraction likely varies over time. Therefore, another limitation with the analyses in this REMS assessment report is that results are not easily generalizable to the US population of interest at any given time and may not be comparable over time. Sensitivity analyses using additional information on covariates and external sources could calibrate or standardize these results and test impact of different sampling fractions on measured change. The FDA’s statistical reviews elaborate on some of these limitations and recommendations as well as specific statistical issues in each database.

4.4 Assessment Elements 6 and 7: Drug Use Patterns and Prescribing Behaviors

The application holders reported a significant decrease in ER/LA opioid analgesic utilization with 5.58M prescriptions dispensed in the year prior to REMS implementation (July 2011-June 2012) to 5.34M prescriptions dispensed in the 18 months after REMS implementation (July 2013-December 2014) . However, because these national level estimates represent large numbers of prescriptions, small changes in study metrics could be statistically significant, but lack clinical relevance. We (FDA) also note that the decreasing trend in the total number of ER/LA opioid analgesic prescriptions dispensed appears to have begun before the implementation of the REMS (see Figure 4). The prescription data show only certain ER/LA opioid analgesics decreased utilization (e.g. oxymorphone, oxycodone and methadone); the decrease in total ER/LA opioid analgesic prescriptions appears to be largely due to a decrease in prescriptions dispensed for oxycodone ER. Of note, prescriptions dispensed for morphine ER increased during the same

time period. In addition, there was a decrease in the overall IR opioid market during the examined time, although utilization of oxycodone IR increased.

Figure 4. Nationally estimated number of prescriptions for ER/LA opioids and selected IR opioid products dispensed from U.S. outpatient retail pharmacies



Source: IMS Health, National Prescription Audit™. Extracted January 2016

*RPC Selected IR Opioids assessed as comparators in the ER/LA REMS assessment: fentanyl, fentanyl citrate, hydrocodone/acetaminophen, hydrocodone-ibuprofen, hydromorphone, morphine sulfate, oxycodone, oxycodone HCl, tapentadol

Longitudinal studies that track changes in prescribing behavior before and after REMS-compliant training by prescribers who have undergone ER/LA Opioid Analgesics REMS training vs. prescribers who have not, as well as an assessment of the impact on utilization trends at the patient level should also be considered if a more rigorous assessment of the REMS is desired. Secondly, information on appropriateness of use of drug products cannot be ascertained using typical drug utilization data sources (e.g., pharmacy claims from pharmacy systems or payers). The RPC would need to address this by designing studies that utilize more appropriate data resources.

4.5 Assessment Element 8: Patient Access

Since the ER/LA Opioid Analgesic REMS does not include restricted distribution components, there is no direct impact on patient access to ER/LA opioid analgesics. Any impact on patient access would be indirect – for example, an HCP takes the training and has a new and higher threshold for prescribing ER/LA opioid analgesic, and perhaps chooses not to prescribe an ER/LA opioid analgesic to a patient for whom such a prescription would be appropriate.

Evaluation of the impact of the ER/LA Opioid Analgesics REMS on patient access is challenging. Drug utilization studies and survey questions were selected as proxy measures to inform

whether patient access has been impeded as a result of the ER/LA Opioid Analgesics REMS. Though responses to specific survey questions from the prescriber and patient surveys do not indicate a negative impact on patient access to ER/LA opioid analgesics, these surveys are administered to patients' already dispensed prescriptions for ER/LA opioid analgesics and prescribers continuing to prescribe these products. Therefore, neither the survey questions nor drug utilization studies inform whether the ER/LA Opioid Analgesics REMS negatively impacted appropriate patient access to these products. Novel strategies are needed to better measure patient access.

5 CONSIDERATIONS FOR MODIFYING THE ER/LA OPIOID ANALGESICS REMS

When considering whether modifications to the ER/LA Opioid Analgesics REMS are necessary, it is important to both understand how the addition of elements to the current ER/LA Opioid Analgesics REMS might result in requirements for patients, prescribers, pharmacies, distributors, and application holders, as well as how many stakeholders might be affected by the additional elements. Potential modifications to the current program that could impact stakeholders include broadening the focus of the FDA blueprint to include safe prescribing of the IR opioid analgesics, which would in turn broaden the target of the CE training to include prescribers of both IR and ER/LA opioid analgesics. Modifications could also include the addition of restrictive ETASU, which will be discussed further in this section.

Of the 75 currently approved REMS programs, 40 include ETASU.²³ The majority (33) of the REMS with ETASU require mandatory certification and training of prescribers, pharmacies, and/or healthcare settings in order to prescribe, dispense, or administer the drug (i.e., restricted distribution). Completion of a PPA or patient enrollment is also required under some of these programs with restricted distribution. Additionally, the application holders of the products with approved REMS are required to implement and maintain the program which includes maintaining records for all certified prescribers and pharmacies, as well as enrolled patients. In contrast, seven REMS with ETASU (including the ER/LA Opioid Analgesics REMS), only require that the application holder make training available to likely prescribers of the drug, though this training is not required to prescribe the drug. Under this type of REMS, pharmacies and patients also do not have any requirements in order to dispense or take the drug.

Because the ER/LA opioid analgesics are primarily dispensed in outpatient settings, understanding stakeholder participation in other REMS programs for drugs dispensed for outpatient use, as well as what is required of stakeholders in these programs may be helpful to provide perspective on the potential impact on the healthcare delivery system when considering modifications of the ER/LA Opioid Analgesics REMS. In table 1 below, information is provided on prescriber, pharmacy and patient participation in 13 restrictive REMS with ETASU for drugs that are primarily dispensed for outpatient use. Two of these restrictive REMS

²³ <http://www.accessdata.fda.gov/scripts/cder/remis/index.cfm> (Accessed April 4, 2016)

programs will be highlighted further to provide understanding of how these elements are operationalized in order to ensure safe use of the drugs.

The first of these programs is the Transmucosal Immediate-Release Fentanyl Product (TIRF) REMS. The FDA approved the first TIRF, Actiq, in 1988. Actiq is a lozenge on a plastic stick that patients place between the teeth and lower gum for dissolution. Concerns about accidental pediatric exposure led to approval of Actiq under Subpart H with a Risk Management Program. Additional TIRF medications have been approved including Abstral, Fentora, Lazanda, Onsolis, Subsys, and the generic versions of some of these products. The formulations include a buccal film, buccal tablet, sublingual spray, and nasal spray. All TIRFs are indicated for the treatment of breakthrough pain in cancer patients who are already taking and are tolerant to around-the-clock opioids. The primary safety concern with these products is the potential for life-threatening respiratory depression when used in opioid non-tolerant patients, and these products are contraindicated in the management of acute or postoperative pain, including headache, migraine, or use in the emergency room. Due to this risk and the potential for abuse, misuse, addiction, and serious complications due to medication errors, a REMS for the individual TIRFs was required. Subsequently, the single-shared TIRF REMS program was approved in December 2011 and after a transition period became fully operational in early 2012. The TIRF REMS program was selected for discussion here as it includes elements that restrict distribution of products that also have a risk of abuse, misuse, overdose, and death.²⁴

The second program is the Isotretinoin REMS (also referred to as the iPLEDGE Program). Isotretinoin, first marketed as Accutane (Hoffman LaRoche), was approved in 1982 for the treatment of severe recalcitrant nodular acne. Isotretinoin was labeled as “Pregnancy Category X” based on animal teratogenicity and the expected high likelihood of human teratogenicity. Due to this risk of teratogenicity, a series of risk management efforts have been implemented to mitigate the risk of fetal exposure. The current program, iPLEDGE with restricted distribution, was originally approved in 2005 and became fully operational in March 2006 following a transition period. The iPLEDGE Program is a shared system REMS, and currently includes several generic products and one branded product.²⁵ The iPLEDGE Program was selected for discussion here as it currently has the largest number of stakeholder participants of any approved REMS. Any approved REMS for ER/LA and IR opioid analgesics would far surpass the number of participants in the iPLEDGE program.

Both the iPLEDGE Program and TIRF REMS require certification of all prescribers in order to prescribe these products. To become certified to prescribe a TIRF product, the prescriber must complete the TIRF REMS Access Education Program, including the knowledge assessment and submit the successfully completed knowledge assessment to the TIRF REMS Access Program. The prescriber must enroll in the REMS by completing and submitting the Prescriber Enrollment

²⁴ Detailed REMS program information and stakeholder requirements can be found for the TIRF REMS at <http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=60>

²⁵ Detailed REMS program information and stakeholder requirements can be found for the TIRF REMS at <http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=24>

Form and recertify every two years. To become certified to prescribe isotretinoin, a prescriber must correctly identify and document females of reproductive potential, females not of reproductive potential, or males and enroll in the REMS by completing the Prescriber Enrollment Form and submitting it to the iPLEDGE REMS. Certification has been an effective mechanism to ensure that all prescribers have undergone training and understand the risks and safe use conditions for prescribing these products. However, for the TIRF products, the number of prescribers for all products is less than 10,000 and for isotretinoin, the REMS that affects the largest number of stakeholders, the number is less than 20,000 prescribers. For both of these programs, there are requirements to recertify (every year for isotretinoin and every 2 years for the TIRF REMS). By contrast, certification of ER/LA opioid analgesics prescribers would be at a minimum 320,000 prescribers²⁶ and if expanded to the IR opioids may be as high as 1.5 million prescribers.²⁷

Both the TIRF REMS and the isotretinoin REMS require pharmacy certification to order and dispense the drugs. Both the iPLEDGE and TIRF programs include a relatively large number of certified pharmacies. There are approximately 67,000 retail pharmacies in the U.S. and most likely currently dispense opioid analgesics; so the potential number of pharmacies requiring certification in a restrictive opioid analgesics REMS while large is not orders of magnitude larger than what has been implemented under the TIRF and iPLEDGE program.

Compared to the TIRF and iPLEDGE programs, a modification of the ER/LA Opioid Analgesics REMS to make it a restrictive program would result in a significantly higher number of REMS authorizations by certified pharmacies in order to dispense these drugs to patients. Certified pharmacies ensure that program requirements are met before the drug is dispensed to the patient. For example, with each prescription, pharmacies might verify that the prescription was written by a certified prescriber prior to dispensing the drug to the patient. The mechanisms that the pharmacies use to ensure the REMS requirements are met are different for the TIRF and iPLEDGE programs. In the iPLEDGE program, pharmacists must access a web-based or phone system to obtain authorization to dispense isotretinoin. The TIRF REMS program utilizes innovative technology linked to prescription insurance claims to verify that REMS requirements are met. Utilization of this claims adjudication system ensures REMS requirements are met for prescriber certification, as well as the completion of a PPA prior to authorizing dispensing of the TIRF product. If manual mechanisms are put into place for authorization of outpatient dispensing of opioid analgesics, similar to the iPLEDGE program, this would require a separate verification of REMS requirements with each opioid prescription. Combining the average past 2 years of REMS authorizations for each of these programs yields a total of 1.26 million authorizations for dispensing. Comparing this to the data provided in Figure 1 on page 6 of this memorandum, implementation of a restrictive REMS for the ER/LA opioid analgesics could affect 21 million outpatient prescriptions. Requiring a restrictive REMS that includes both the ER/LA and IR opioid analgesics could affect an additional 166 million outpatient prescriptions.

²⁶ Number of Prescribers of ER/LA opioid based on prescription dispensed from U.S. outpatient retail and long-term care pharmacies for 2014. Source: IMS Health, National Prescription Audit (NPA). Extracted November 2015

²⁷ <http://www.deadiversion.usdoj.gov/> - Accessed on March 24, 2016

Although 79% of the use of opioid analgesics is dispensed in outpatient retail channels, the remainder is used in other settings (e.g., hospitals, long-term care facilities). Under the TIRF program, prescribers ordering TIRFs for inpatient use are exempt from the requirement to certify; however, inpatient pharmacies that dispense TIRFs must certify and ensure that all pharmacists understand the risks of TIRFs and do not dispense TIRFs for outpatient use. If a restrictive REMS were required for the ER/LA or ER/LA and IR opioid analgesics, a mechanism would also need to be put into place to assure access to these products is maintained in those settings.

Finally, the REMS implementation system for each of these programs requires that distributors are also enrolled or registered in the program, and agree to ship product only to enrolled pharmacies or wholesalers.

Legitimate patient access to ER/LA opioid analgesics is likely to be impacted by a restrictive opioid analgesic REMS. When REMS place significant burdens on healthcare systems (e.g., need to enroll in program, take training, or enroll patients) some providers, (e.g., prescribers, pharmacies, or clinics), may choose not to prescribe or dispense the drug because they may be unwilling to participate in the REMS. It may be difficult for a patient to find a participating prescriber or pharmacy in their geographical area, thus impacting the patient's access to the drug. In addition, pharmacy denials or rejections of dispensing authorizations could delay patient access to these products.

Though the FDA has long supported legislative changes that would require mandatory prescriber education on opioid use to obtain and renew DEA registration to prescribe controlled substances, the only tool currently available to the Agency to achieve the goal of mandatory prescriber education is a restrictive REMS similar to either the iPLEDGE or TIRF REMS. Although both of these programs attempt to minimize burden to the healthcare delivery system, as with all REMS programs with ETASU, burden exists for all stakeholders including patients, prescribers, pharmacies, distributors and the application holder groups responsible for maintaining these programs. Comparing data from current programs provides useful information when considering both the magnitude of requiring a restrictive REMS for the ER/LA or ER/LA plus IR opioid analgesics as well as the length of time it may take to build the infrastructure that would support such programs.

REMS program	Active ^b prescribers	Active outpatient/ specialty pharmacies	Active patients
Program 1	84	3	85
Program 2	196	52	75
Program 3	316	3	421
Program 4	784	5	612

Program 5	888	9	2055
Program 6	2075	9	3389
Program 7	2590	10	8533
Program 8	9328	10	13,172
Program 9	9418	292	9121
Program 10	14,710	1011	16,936
Program 11	16,758	297	58,260
TIRF Shared REMS	9096	42,316	8740 ^c
Isotretinoin Shared REMS	18,461	46,726	234,622

a Programs 1-11 each have one application holder; the TIRF and iPLEDGE REMS have 8 and 5 application holders, respectively.

b Active prescribers pharmacies and patients are those that have prescribed, dispensed or received one prescription during the assessment period.

c For the TIRF REMS program only, number of patients provided are those that were newly enrolled during the assessment period

6 CONCLUSIONS

Findings from the 36th Month ER/LA Opioid Analgesics REMS Assessment show mixed results that make it difficult to draw conclusions regarding the success of the program. While a relatively large number of healthcare providers overall have taken the voluntary CE training, the proportion of targeted prescribers who actually took the voluntary training is consistent with participation rates for other REMS with voluntary training. The hope was that CE credits, awarded as part of the training, would incentivize targeted prescribers to take the REMS-compliant CE training, and completion of training would lead to safe and responsible ER/LA opioid prescribing and patient counseling on the risks, safe use, and safe storage of ER/LA opioid analgesics. Though we are encouraged by the uptake of the ER/LA Opioid Analgesics REMS training by both the targeted prescribers as well as other HCPs, it is likely too early to see widespread impact of this training on prescriber behavior and subsequent impact on the adverse events of interest (addiction, unintentional overdose, and death). Also confounding the evaluation of impact of the ER/LA Opioid Analgesics REMS are the multiple competing educational programs offered by other federal agencies and requirements for pain and/or opioid education by individual states. If the ER/LA Opioid Analgesics REMS training is to remain voluntary for prescribers (with or without the addition of the IR products), additional efforts to consolidate the training among federal and state entities may be necessary. Despite these challenges, the Agency is committed to using our authority to address the opioid epidemic. As a strategy to encourage REMS training, the experience gained by the Agency to-date from utilizing accredited CE as a means to train prescribers has been extremely valuable. We look forward to the committees' discussion and advice on the need for modifying the REMS program to include IR opioid analgesics, as well as the need for restrictions on prescribers, pharmacies

and patients, and the impact on the healthcare delivery system if these restrictions are implemented for ER/LA or ER/LA and IR opioid analgesics.

7 DISCUSSION TOPICS

The overarching goal of the ER/LA Opioid Analgesics REMS is to reduce serious adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, misuse and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. The method for achieving this goal is through education of prescribers, patients and their caregivers.

The following points to consider will be discussed by the committee members:

1. Considering the number of participants and completers in the REMS CE programs in the first 3 years of the program, discuss
 - The expectations for the reach of a voluntary education program, and whether the number of completers and participants is satisfactory
 - Whether the goal of training 80,000 prescribers of ER/LA opioid analgesics within 2 years was appropriate. If not, what is a reasonable expectation in light of the many competing programs?
2. Discuss the appropriateness of the data sources and methodologies used to evaluate the ER/LA opioid analgesic REMS, particularly
 - Whether there are more appropriate short and long-term measures of success of the ER/LA Opioid Analgesics REMS
 - Whether the effects of the ER/LA Opioid Analgesics REMS on abuse, misuse, addiction, overdose, and death can be differentiated from the many federal, state, local and health-system activities with similar goals
 - What is the anticipated length of time for an educational intervention to broadly impact prescriber behaviors
3. Discuss the impact of the ER/LA opioid analgesics REMS on patient access; provide examples of how best to evaluate patient access issues for this program.
4. Considering the information provided today regarding the current ER/LA Opioid Analgesics REMS, discuss:
 - a. Whether the REMS assures safe use of ER/LA opioid analgesics,
 - b. Whether the REMS is unduly burdensome to patient access to ER/LA opioid analgesics
 - c. To the extent practicable, whether the REMS is minimizing the burden on the healthcare delivery system
5. Do you recommend that;

- i. The REMS should remain the same?
 - ii. The REMS should be modified? If so, should:
 - 1. The content of the current FDA blueprint should be expanded? Discuss how you believe it should be expanded; provide specifics and rationale (e.g., general pain management, addiction management, treatment of overdose)
 - 2. The prescribers be required to complete training in order to prescribe opioid analgesics? Discuss if a REMS administered by industry, requiring a closed restricted distribution system (involving pharmacy and possibly patient enrollment) is the appropriate mechanism to ensure this training? If not, provide other options and rationale
 - 3. A REMS for the IR opioid analgesics is necessary to ensure the benefits outweigh the risks?
 - 4. Other modifications be made? Specify what modifications are recommended.
 - iii. The REMS should be eliminated? Discuss rationale for elimination (e.g., training needs met by other programs or requirements)
6. If any changes or modifications are recommended, discuss how you would assess the impact of these changes on the safe use of ER/LA Opioid Analgesics (or immediate-release opioid analgesics if addition of these products is recommended); include how the impact of these modifications on patient access and healthcare delivery system burden could be assessed.



**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: April 6, 2016

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

From: **Igor Cerny, PharmD, REMS Assessment Reviewer
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Division of Risk Management (DRISK)
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Subject: **DRISK Review of 36th Month Assessment of the Risk Evaluation and Mitigation Strategy for the Extended Release and Long-Acting Opioid Analgesics: Functional Components, Prescriber Training, CE Audits, Prescriber and Patient Surveys, and Patient Access (Assessment Elements 1, 2, 3a and 3b, 4, and 8)**

Executive Summary

This review evaluates five of the 36-month Extended-Release and Long-Acting (ER/LA) Risk Evaluation and Mitigation Strategy (REMS) assessment (Elements 1, 2, 3a, 3b, 4 and 8 report. These include the prescriber training, audits of continuing education activities, surveys of prescribers and patients, and the evaluation of patient access. This assessment report was submitted by the ER/LA Opioid Analgesic Applicant holders, also known as the REMS Program Committee (RPC), and is the fourth assessment report since approval of the ER/LA REMS on July 9, 2012, and the first assessment report to address a specific numeric goal for REMS-compliant training.

The goal of the ER/LA Opioid Analgesic REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining

patient access to pain medications. Adverse outcomes of interest include addiction, unintentional overdose, and death.

The primary intervention of this REMS is prescriber training made available through accredited continuing education (CE) programs funded by the RPC. The training is based upon the FDA blueprint for Prescriber Education for Extended-Release and Long-Acting Opioids. The goal of this training is to sufficiently inform prescribers such that serious adverse outcomes (such as addiction, unintentional overdose, death) will be reduced by reducing inappropriate prescribing, misuse and abuse. Prescribers are not required to take the training in order to prescribe ER/LA opioid analgesics. A total of 37,512 ER/LA opioid analgesic prescribers have completed RPC-supported REMS-compliant training, which represents 47% of the milestone of 80,000 which was to be achieved by March 1, 2015. While the milestone wasn't met, over 100,000 health professionals have taken the RPC-funded training. Potential factors that may impact on why the goal of 80,000 prescriber-completers has not been achieved include: 1) how "prescribers" are defined, 2) the large number of competing CE programs. To date, the RPC has issued 4 Requests for Applications (RFAs) and has awarded funding for over 500 REMS-compliant CE programs through 19 grants to accredited CE providers. Thus the RPC has made significant strides in making REMS-compliant training available. The RPC should continue to explore other means of increasing awareness of the REMS-compliant trainings.

Two prescriber surveys were included in this evaluation. In the survey conducted as a follow-up to the 2013 baseline prescriber survey conducted in 2013 ("follow-up survey"), across all key risk messages, completing a CE activity significantly increased the likelihood of answering questions correctly. The second survey of prescribers included in this assessment, surveyed prescribers 6-12 months following participation in a REMS training. The results of this survey demonstrated that since participating in a REMS-compliant activity, respondents reported more often conducting appropriate prescriber behaviors (i.e. counseling on risks and side effects, using tools to screen patients for risk or misuse and abuse, completing a Patient-Prescriber Agreement). In addition, findings of surveys of patients submitted in this assessment, show similar knowledge to that found in the 24-month assessment, and respondents showed a good understanding ER/LA opioid analgesics risks. However, across all surveys, respondents were not representative of the general population of prescribers and patients that use ER/LA opioid analgesics.

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1 Introduction

This review evaluates 5 components of the 36-month ER/LA Opioid Analgesic REMS assessment report submitted by the REMS Program Companies (RPC) on July 7-13th, 2015 for ER/LA Opioid Analgesics (referred to in this document as ER/LA REMS to determine if the assessment is complete and if the goals of the REMS are being met. This REMS assessment report covers the period from May 11, 2014 through May 9, 2015. The elements are as follows:

Assessment Element 1: Assessment of how many prescribers of ER/LA opioid analgesics have successfully completed the training. Specify performance goals for the number of prescribers trained by time.

Assessment Element 2: Independent audit of the quality of the content of the educational materials used by the CE Providers to provide the education. The audit should evaluate the quality of the content against the content approved by FDA as part of the REMS, as well as against the ACCME's and other accrediting bodies' standards for commercial support.

Assessment Element 3a: Prescriber Survey (Follow-up Survey)-Evaluation of Healthcare Professional (HCP) awareness and understanding of the serious risks associated with these products (e.g., through surveys of HCPs) and specification of measures that would be taken to increase awareness if surveys of HCPs indicate that HCP awareness is not adequate.

Assessment Element 3b: Prescriber Survey Long-term Evaluation

Assessment Element 4: Patient Survey-Evaluation of patients' understanding of the serious risks of these products.

Assessment Element 8: Evaluation of Patient Access

2 Review Materials

The following is a list of materials informing this review:

- March 28, 2014 DRISK (J. Ju) review of Review of Proposed Methodology and Survey Instruments
- May 13, 2015 response from the RPC to an April 9, 2015 IR from the FDA (regarding patient access)
- July 7 – 13, 2015 36-month REMS Assessment Report from the RPC
- July 23, 2015 36-month REMS Assessment Report Errata from the RPC
- August 4, 2015 response from the RPC to a July 21, 2015 IR from FDA (re: prescriber training completer totals)
- August 14, 2015 response from the RPC to an August 4, 2015 IR from FDA (re: prescriber training completer totals)
- September 21, 2015 response from the RPC to a September 4, 2015 IR from FDA (re: patient survey)
- September 25, 2015 response from the RPC to a September 4, 2015 IR from FDA (re: patient survey)
- September 28, 2015 Amended 36-month REMS Assessment Report from the RPC

- October 26, 2015 response from the RPC to an October 22, 2015 IR from FDA (re: prescriber training completer totals)
- November 13, 2015 response from the RPC to a November 10, 2015 IR from FDA (re: identity of accrediting bodies)
- December 11, 2015 DB7 (J-Y Lee & Y-H Hsueh) Statistical Review and Evaluation of a REMS Assessment
- December 11, 2015 DB7 (Y-H Hsueh) Statistical Review and Evaluation of REMS Knowledge Surveys

3 REVIEW RESULTS

3.1 Assessment Element 1 - Prescriber Training

This assessment element states:

Documentation of the number of prescribers of ER/LA opioids who have completed REMS-compliant training. Performance goals based on the 2011 estimate that 320,000 prescribers are active prescribers of ER/LA opioids (prescribers who have prescribed an ER/LA opioid within the last 12 months), are as follows:

- *Within two years from the time the first REMS-compliant training becomes available, 80,000 prescribers (based on 25% of active prescribers) are to have been trained*

The REMS Supporting Document (SD) states that a secondary outcome measure will be the number of prescribers who have completed some but not all portions of a training activity. The SD also states that an independent non-industry party is to produce the report (compiled from all accredited CE providers) of the number of prescribers who have taken the training by profession type and by other characteristics.

3.1.1 RPC Data for Prescriber Training

REMS compliant-training is characterized as: 1) training offered by an accredited CE provider to licensed prescribers; 2) includes all elements of the FDA Blueprint; 3) includes a knowledge assessment of all of the sections of the Blueprint, and 4) is subject to independent audit.

While the ER/LA REMS was approved on July 9, 2012, the first RPC-supported REMS-compliant CE activity was launched on February 28, 2013. This REMS represents the first time that accredited CE has been used to fulfill a REMS training requirement. “Prescribers” are defined as “*clinicians who are registered with the DEA to prescribe Schedule II and/or III controlled substances and have written at least one ER/LA opioid analgesic prescription in the past year.*” Completion of an activity is defined as “*prescribers that have completed all components of an educational activity including instruction, assessment of learning, and potentially evaluation.*”²⁸

The data cut-off for this current 36-month report was February 28, 2015, which represents the 2-year mark and the first training milestone of 80,000 prescribers completing REMS-compliant training. The previous assessment report indicated that 20,345 ER/LA opioid analgesics prescribers completed RPC-supported REMS-compliant training (February 28, 2013 – February

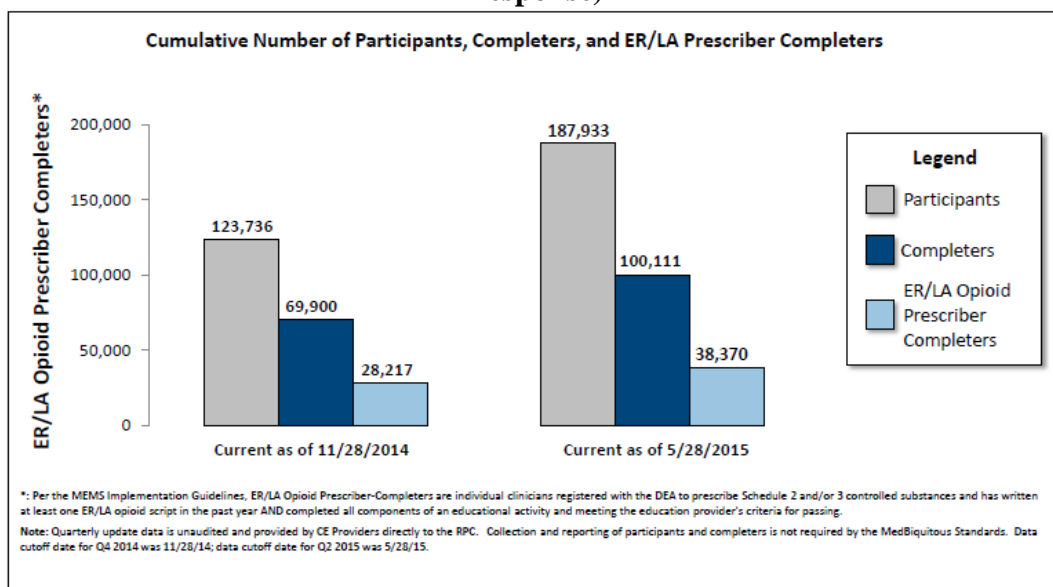
²⁸ These criteria were determined based on prescribers’ self-attestation.

28, 2014). During this reporting period (March 1, 2014- February 28, 2015), data from the RPC’s October 26, 2015 response to an FDA information request) an additional 17,707 prescribers completed the training. The overall total number of ER/LA opioid analgesic prescribers completing REMS-compliant is **37,512**, a total which represents 47% of the 2 –year goal of 80,000. The RPC states that any additional prescriber completer totals which result following resolution will be included in the 48-Month Report.

On October 26th 2015, in response to an FDA information request, the RPC provided updated data regarding the number of CE training participants, completers, and ER/LA prescriber completers current as of 2/28/15. The RPC emphasizes that while CE providers collect these data, the data are not required for reporting to accreditors and thus RPC-funded CE providers provide these data informally. However, the RPC was able to provide these informal, unaudited data in Figure 1 below which displays the cumulative number of participants, completers, and ER/LA prescriber completers. Data presented is based on the definitions below. It should be noted that the completers and ER/LA prescriber completers are subsets of the total number of participants.

- Participant- an individual who at the time of data reporting had only partially completed the CE activity
- Completer- an individual that has completed all components of an educational activity and meets the criteria for passing
- ER/LA prescriber completer- A clinician registered with the DEA to prescribe Schedule II and/or III controlled substances and has written at least one ER/LA prescription in the past year, has completed all components of an educational activity, and meets the criteria for passing

Figure 1: Cumulative Number of Participants, Completers, and ER/LA Prescriber Completers Reported Directly from RPC-supported CE Providers (from 10/26/15 IR response)



Source: October 26, 2015 RPC response to an October 22, 2015 FDA Information Request

Figure 1 reveals that as of May 28, 2015, only 53% of healthcare providers (HCPs) who start a REMS-compliant CE program actually complete the activity. Of these completers, only 38% self-identify as ER/LA prescribers. Additionally, the RPC reports that CE providers indicate that approximately 60% of HCPs completing REMS-compliant CE have stated that they had not written a prescription for an ER/LA opioid analgesic in the past year and thus cannot be counted toward the REMS completer goal.

The majority of ER/LA prescribers completers (N=38,370) were physicians (approximately 67%). The remaining prescribers were advanced practice nurses (approximately 24%), physician assistants (approximately 7%) and “other” (approximately 3%). For those prescribers for whom a practice area was reported (N= 11,184), 66.4% were primary care physicians, 21% were “non-pain specialists” and 12.6% were pain specialists.

Regarding REMS-compliant CE education activities, cumulatively, 507 of these have been launched. Of these, 253 were available during this reporting period. A total of 220 activities were presented as live training, 32 were internet-based enduring programs and one program was in the form of print materials. All activities were accredited by at least 1 of 6 National Accrediting Bodies.²⁹ A description of all REMS-compliant CE activities available March 1, 2014 to February 28, 2015, arranged by grantee, is provided in Table 1 below (reproduced directly from the RPC report’s Table 4):

²⁹ Accreditation Council for Continuing Medical Education (ACCME); American Academy of Family Physicians (AAFP); American Osteopathic Association (AOA); Accreditation Council for Pharmacy Education (ACPE); American Nurses Credentialing Center (ANCC); and American Academy of Physician Assistants (AAPA)

Table 1: RPC-Supported REMS-compliant Continuing Education Activities Available During the Reporting Period (March 1, 2014- February 28, 2015)

GRANTEE ¹	PROGRAM START DATE	PROGRAM FORMAT(S)	NUMBER OF ACTIVITIES
Trustees of Boston University	March 1, 2014	Live Training	46
		Internet-based	1
CO*RE (Collaborative for REMS Education)	March 1, 2014	Live Training	107
		Internet-based	20
Association for Hospital Medical Education	March 1, 2014	Internet-based	6
			1
Temple University	March 1, 2014	Internet-based	1
UMA Foundation	March 1, 2014	Live Training	1
	March 7, 2014	Internet-based	1
University of Cincinnati	March 21, 2014	Internet-based	4
			4
American College of Physicians/Pri-Med	March 31, 2014	Live Training	4
American Academy of Pain Management	April 1, 2014	Internet-based	1
			1
University of Nebraska Board of Regents/UNMC	May 16, 2014	Live Training	39
	November 20, 2014	Internet-based	1
Montefiore Medical Center	January 10, 2015	Live Training	9
			2
University of North Texas Health Science Center/TCOM Foundation	January 30, 2015	Live Training	2
Postgraduate Institute for Medicine	March 1, 2014	Live Training	12
			1
Dannemiller, Inc.	March 1, 2014	Print	1
TOTAL			253

¹The table is organized by start date of the activities; if there were multiple activities, the start date reflects date of first activity.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

There have been 18 non-RPC supported CE activities reported to ACCME (or other accreditors), with 1,747 prescriber completers. These 18 activities were “self-identified” as REMS-compliant by the CE provider. As reported previously by the RPC, the RPC itself cannot directly verify that non-RPC supported activities are REMS-compliant. Thus these prescribers are not included in the total number of prescriber completers reported in assessment element 2. The RPC reports that one non-RPC supported CE (presumably based upon the FDA Blueprint) was evaluated. The CD program, entitled *Safe Prescribing for Pain*, was mapped to the educational items contained within the FDA Blueprint. The evaluation revealed that 39% of the FDA Blueprint educational content was covered by this CE activity.

Each year, the RPC issues a Request for Applications (RFA) to secure, support and make available REMS CE programs that train HCPs on the ER/LA REMS FDA Blueprint. Since 2012, the RPC has issued 4 RFAs and awarded funding to support over 500 REMS-compliant activities through 19 grants to accredited CE providers and their 100+ educational partners. The RPC

receives feedback from the CE Community, including CE providers and the Conjoint Committee for Continuing Education (CCCE) prior to each RFA cycle. On March 10, 2015, the RPC issued two RFAs that were designed to ensure that a broad spectrum of REMS CE activities would be available to HCPs for 2016 and 2017. One of these, RFA 050315, asks proposers to detail novel educational initiatives that will increase the reach, attraction, and engagement of ER/LA opioid analgesic prescribers to increase their participation in and completion of REMS CE. It is hoped that the applicant will propose educational modalities and/or partnerships that are likely to yield more completers that prescribe ER/LA opioid analgesics.

The RPC states that they had expected that the goal of 80,000 ER/LA opioid analgesic prescribers could be exceeded based on their projection of 165,000 prescribers that could be reached by the CE Providers receiving funding. However, the RPC states that CE providers have informed them that it is considerably more challenging than expected to attract ER/LA opioid analgesic prescribers to participate in REMS-compliant activities and to keep them engaged through completion of the full activity and assessment. The RPC has identified three predominant challenges in getting prescribers to complete the trainings:

1. **Lack of awareness of the REMS and the importance of completing ER/LA opioid analgesic REMS-compliant CE:** A survey done by CO*RE in November and December 2013 (8 months after the launch of the first REMS-compliant CE activity) demonstrated that 41% of the 2,629 respondents were unaware of the FDA ER/LA REMS. The RPC has received the following additional information:
 - a. The term “REMS” itself is not meaningful to prescribers;
 - b. There is considerable ambiguity given the variability in clinician-related requirements from one REMS to another;
 - c. Prescribers may find it difficult to distinguish between those that are and are not REMS-compliant;
 - d. Prescribers who complete non-REMS compliant CE (such as those required for state licensure) are unlikely to complete REMS-compliant CE since prescribers may consider it redundant; and
 - e. Prescribers may not complete REMS-compliant CE as they may think they already know the material.
2. **Education is not tailored to the adult professional learner:** the length of activities and the associated time commitment for completion, coupled with no accommodation for demonstration of prior knowledge or competency impacts prescriber willingness to complete REMS-compliant CE.

The RPC has indicated based on feedback from REMS CE providers, accrediting bodies, the CCCE, and from learners that the rigidity and extent of content of the FDA Blueprint is not conducive to the type of education that is engaging to adult learners.

3. **Available opioid education competes with REMS-Compliant CE:** there are many non-REMS-compliant (hence non-RPC funded) CE activities regarding opioid available to clinicians, both online and in live settings that may potentially dilute the audience of ER/LA opioid analgesic prescribers who may complete the REMS-compliant CE activities (such as those that fulfill state-mandated licensure requirements; or endorsed by prominent, non-industry-related organizations such as NIDA, the Office of National Drug Control Policy (ONDCP), the Substance Abuse and Mental Health Services

Administration (SAMHSA), etc.; or cover opioid risk management within the broader context of appropriate pain management). The RPC has conducted a keyword search to determine the number of non-RPC funded CE activities that may be returned if a prescriber attempted to search for CE activities related to opioids, controlled substances, pain management or another similar search term.

A total of 150 non-RPC-funded accredited CE activities related to opioid analgesics were reviewed and categorized. Key findings were:

- a. 87% of the activities were “Non-REMS Opioid-Related CE”
- b. 34% of these “Non-REMS Opioid Related CE” activities were endorsed developed, or funded by federal agencies such as NIDA, ONDCP, SAMHSA, and National Institute of Neurological Disorders and Stroke (NINDS)
- c. 8% of the activities were identified by the CE Provider as “FDA Blueprint-Compliant”
- d. A significant percentage met state-mandated CE requirements for license renewal. These included:
 - 100% (12 out of 12) of those non-RPC funded CE activities identified by the CE Provider as “FDA Blueprint-Compliant”
 - 38% of the “Non-REMS Opioid-Related CE activities”

In response to these identified challenges, the RPC states that they are implementing a REMS awareness campaign and have selected an awareness campaign vendor. This effort is to include ongoing communication with RPC-supported CE Providers to gain insights into challenges encountered in providing REMS-compliant CE and potential ways to increase awareness and prescriber completers. Part of this effort is to assess the desired look and feel for REMS-awareness materials, what the materials should convey, and potential suggestions for how the REMS awareness materials could be used. The RPC is considering a logo and tagline.

3.1.2 Reviewer Comments

1. A total of 37,512 ER/LA opioid analgesic prescribers have completed RPC-supported REMS-compliant training which represents 47% of the 2 year milestone of 80,000 for this report. However as of May 28, 2015, over 100,000 health professionals (this total includes the 37,512 aforementioned prescribers) have taken the RPC-funded training. There are likely a number of factors as to why the goal of 80,000 ER/LA prescriber-completers has not been achieved:
 - The definition of “Prescribers” is “*clinicians who are registered with the DEA to prescribe Schedule II and/or III controlled substances and have written at least one ER/LA opioid analgesic prescription in the past year.*” Thus this definition excludes prescribers who have only recently registered with the DEA.
 - The RPC points out and the FDA is aware that there are a number of competing opioid educational programs (both private and governmental) for prescribers to choose from. In addition, the RPC also points out that 41% of prescribers in a survey done 8 months after the launch of the first REMS-compliant CE activity were unaware of this REMS.
2. The FDA has asked the RPC to continue to explore other means of increasing awareness of the REMS-compliant trainings. To-date, the RPC has issued 4 RFAs and has awarded funding for over 500 REMS-compliant CEs through 19 grants to accredited CE

providers. Thus the RPC has made significant strides in making REMS-compliant training available.

3.2 Assessment Element 2 – Audits of CE Activities

This assessment element states:

The results of an independent audit of the quality of the content of the educational materials used by the CE providers to provide the REMS-compliant training. Audits must be conducted on a random sample of at least 10% of the training funded under the ER/LA Opioid REMS, and a random sample of REMS-compliant training not funded under the ER/LA Opioid REMS that will be counted as REMS-compliant training for purposes of meeting the milestones in item 2 above and must evaluate:

- a. whether the content of the training covers all elements of the FDA “blueprint” approved as part of the REMS;*
- b. whether the post-course knowledge assessment measures knowledge of all sections of the FDA “blueprint”; and*
- c. whether the training was conducted in accordance with the Accreditation Council for Continuing Medication Education (ACCME) standards for CE or appropriate standards for accreditation bodies.*

The REMS SD states that the training should also be assessed as to whether or not the content is free from promotional material and that accreditation bodies of CE providers would be considered independent of the RPC and would be eligible to conduct the audits.

3.2.1 RPC Data for CE Audits

The RPC has audits conducted by parties that are independent of the NDA/ANDA holders and acceptable to various CE accrediting bodies. The audits evaluate whether:

- the content is factually correct;
- the training covers all sections of the FDA Blueprint;
- the post-course knowledge assessment measures knowledge of all sections of the FDA Blueprint; and
- the training was conducted in accordance with the standards for CE of the ACCME or other accrediting bodies; is independent of the pharmaceutical industry’s influence; and the content is free from promotional material.

The CE activity audits are based on a random sample of at least 10% of the RPC-supported, REMS-compliant CE activities (and REMS-compliant training not funded by the RPC but that will be counted towards meeting the REMS performance goals).

Five nationally recognized accrediting bodies that have submitted independent audit reports are shown in Table 2 below (a reproduction of an RPC table).

Table 2: SUMMARY OF INDEPENDENT AUDIT REPORTS

ACCREDITING BODY	NUMBER OF AUDIT REPORTS RECEIVED	AUDIT OBSERVATIONS	NUMBER OF AUDIT REPORTS COMPLETED THAT MEET REMS REQUIREMENTS
AAFP	2	0	2
AANP	3	0	3
ACCME [®]	19	9	10
ANCC	1	0	1
AOA	4	0	4
TOTAL	29	9	20

American Academy of Family Physicians (AAFP); American Association of Nurse Practitioners (AANP); Accreditation Council for Continuing Medical Education (ACCME); American Nurses Credentialing Center (ANCC); and American Osteopathic Association (AOA).

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Of the 29 audit reports received, 20 (69%) met the criteria for REMS-compliant CE. Nine of the 29 audit reports had issues related to disclosure of financial relationships. Of the 9:

- seven did not disclose relevant financial information;
- eight of the nine did not provide evidence that disclosure of either relevant financial information or of no financial relationships was made to learners prior to the beginning of the activity;
- six did not meet either financial disclosure requirement (noted above).

The RPC has reviewed the documentation for these 9 ACCME audit reports and views the issues as important but not impacting content. The RPC is following up with each provider to ensure appropriate remediation in a timely manner.

The RPC states that CE providers are informed that they are now required to submit activities for audit *prior to launch* so that any observations can be remediated prior to the program being available to the public. However, the RPC also admits that this is not possible for programs that were created and launched prior to implementation of the audit process. Regardless, the RPC requires CE providers to provide documentation of remedial actions taken to address any non-compliance observations (i.e., identify why the issue occurred, what procedures have been put in place to safeguard a repeat occurrence, and communicate with the CE provider a ‘demonstration of compliance is a requirement for RPC-supported activities.’”

The 36-month assessment report did not include any information regarding audit results of non-RPC-funded REMS-compliant training. However, audits of these non-RPC-funded programs are required only if these participants are to contribute to the total numbers trained. The RPC has indicated that they have no authority to audit programs that are not funded by them or unless they are requested by the other funder(s) to audit the programs.

3.2.2 Reviewer Comments

The RPC should continue to encourage their grantees to ensure that financial information regarding the authors of the REMS-compliant training is disclosed and done so prior to the beginning of the activity.

3.3 Assessment Element 3: Prescriber Surveys

This assessment element states:

Evaluation of Prescriber Understanding:

- a. *The results of an evaluation of ER/LA opioid prescribers' awareness and understanding of the serious risks associated with these products and their awareness of appropriate prescribing practices for ER/LA opioids, comparing the awareness and understanding of prescribers who have taken the REMS-compliant training with those who have not taken such training. This evaluation may include, for example, surveys of healthcare providers.*
- b. *The results of any long-term evaluation of prescribers of ER/LA opioid analgesics who have taken ER/LA Opioid REMS-funded training to determine these prescribers' knowledge retention and practice changes 6 months to 1 year after they completed the REMS-compliant training.*

3.3.1 Assessment Element 3a – Follow-Up Prescriber Survey

This survey of prescribers is a follow-up to the baseline prescriber survey. The baseline prescriber survey was conducted with 605 prescribers, who prescribed at least one ER/LA opioid analgesic in the last year as identified by the IMS XPoint database and who had not completed the REMS-compliant training, between February 8, 2013 and April 17, 2013. The results of the baseline survey were reported in the 12-month REMS assessment.

This follow-up survey was conducted two years post-launch of the REMS compliant CE in order to compare prescribers that took the REMS complaint CE training with prescribers that did not take the training. The assessment report states "The objectives of the follow-up prescriber survey are to: 1) assess the prescribers' understanding of the serious risks associated with the use of the ER/LA opioid analgesics and how to prescribe ER/LA opioid analgesics appropriately according to the six domains of the FDA Blueprint, 2) assess ER/LA prescribers' opioid prescribing behavior and practice, including questions from the five domains from the FDA Blueprint, where applicable and feasible, and 3) to assess prescribers familiarity with general and product-specific drug information concerning ER/LA opioid analgesics.

The FDA Blueprint includes six core messages for prescribers. Prescribers should:

1. Understand how to assess patients for treatment with ER/LA opioid analgesics
2. Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics

3. Be knowledgeable about how to manage ongoing therapy with ER/LA opioid analgesics
4. Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal
5. Be familiar with general drug information concerning ER/LA opioid analgesics
6. Be familiar with product-specific drug information concerning ER/LA opioid analgesics

The follow-up prescriber survey was pretested in 24 ER/LA opioid analgesic prescribers to assess comprehension and interpretation of the survey questions related to the key risk messages and to identify whether question or response options may be misunderstood. Findings and recommendations were incorporated into the final survey. User acceptance testing (UAT) was also conducted to test that the survey had been developed according to the user requirements and the protocol. Follow-up formal testing then occurred to ensure the system was compliant with the requirements.

Results

The follow-up prescriber survey was conducted between February and April 2015. Prescribers were eligible to participate if they had prescribed an ER/LA opioid analgesic at least once in the year prior to the survey. A total of 993 prescribers responded to the survey invitation. Of those 612 prescribers completed the survey (99% by internet and 1% via paper). Over half of the survey respondents were recruited from IMS data (n=311; 51%) and the remaining participants were invited by CE providers (n=301; 49%). Approximately 60% of respondents reported that they completed a REMS-compliant continuing education (CE). Of the prescribers surveyed, 70% prescribed Oxycontin ER, 69% prescribed fentanyl patch, 68% prescribed MS Contin, 53% prescribed Duragesic, and 51% prescribed morphine sulfate ER. Eight-one percent (81%) of respondents were transdermal patch prescribers, 49% were methadone prescribers, and 96% were oral ER/LA opioid analgesic prescribers. Over half of respondents were male (54%). Almost half of respondents were Doctors of Medicine (MD) (48%), followed by physician assistants (22%) and nurse practitioners (21%). Approximately 34% of MDs and Doctors of Osteopathy (DO) had been practicing medicine for over 15 years.

Survey respondents were more likely to have prescribed ER/LA opioid analgesics in the past month, were more likely to come from the west, and were more likely to have a specialty of pain management (22% survey vs. 1% IMS database) than those in the overall population of ER/LA opioid analgesic prescribers. It should be noted that the population of overall ER/LA opioid analgesic prescribers for this comparison was extracted from IMS in December of 2014, and includes 420,154 prescribers, which is 100,000 more ER/LA opioid analgesic prescribers than the FDA estimates that were used to determine the training targets of 320,000. We are awaiting further description from the RPC of the database used for this analysis (see Table 3 below).

	Baseline (n=605)	36-Month Survey (n=612)
Gender	Male: 407 (67%) Female: 197 (33%)	Male: 333 (54%) Female: 274 (45%) Prefer not to answer: 5 (1%)
Medical Degree	MD: 284 (47%) DO: 18 (3%) Nurse Practitioner: 142 (24%) Advanced Practice Nurse: 1 (1%) Physician Assistant: 154 (26%)	MD: 292 (48%) DO: 36 (6%) Nurse Practitioner: 127 (21%) Advanced Practice Nurse: 23 (4%)

	Baseline (n=605)	36-Month Survey (n=612)
		Physician Assistant: 134 (22%)
Specialty	General Practice: 307 (51%) Pain Medicine: 55 (9%) Internal Medicine: 51 (8%) Orthopedics: 44 (7%) Oncology: 42 (7%) Rheumatology: 23 (4%) Neurology: 18 (3%) Anesthesiology: 9 (2%) Hospice/Palliative Care: 9 (2%) Other: 47 (8%)	General Practice: 307 (51%) Pain Medicine: 55 (9%) Internal Medicine: 51 (8%) Orthopedics: 44 (7%) Oncology: 42 (7%) Rheumatology: 23 (4%) Neurology: 18 (3%) Anesthesiology: 9 (2%) Hospice/Palliative Care: 9 (2%) Other: 47 (8%)

3.3.2 Reviewer’s comments:

1. Respondents that were recruited from IMS data were assumed to not have taken a REMS compliant CE activity. Sixty percent (60%) of all respondents reported completing a REMS-complaint CE activity although only 49% of respondents were recruited from CE providers. There is no way to be certain that respondents categorized as IMS respondents did not take a REMS compliant CE training.
2. Some CE providers did not record how many invitations were sent out so a response rate is not provided. For future assessments, the CE providers should keep track of and report the number of invitations sent.
3. There is no information provided about how many CE providers participated in respondent recruitment and from how many CE providers the current respondents were recruited from. This information should be provided for the current and future assessments.
4. We recognize that there is overlap between some of the messages included in the Blueprint. After reconsideration of the current categorizations, we recommend changes to the key risk message categories.

The survey contained questions addressing six key risk messages: 1) patients should be assessed for treatment with ER/LA opioid analgesic therapy, 2) prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics, 3) management of ongoing therapy with ER/LA opioid analgesics is important, 4) the importance of counseling patients and caregivers about the safe use of ER/LA opioid analgesics, 5) prescribers must be familiar with general drug information concerning ER/LA opioid analgesics, and 6) prescribers must be familiar with product-specific drug information concerning ER/LA opioid analgesics.

Key risk message 1: Patients should be assessed for treatment with ER/LA opioid analgesic therapy

This key risk message included questions about how prescribers assess patients for treatment including understanding risks of overdose, when to refer high-risk patients, and opioid tolerance criteria. (See *Table 4 below*)

- Respondents were aware of some of the important risks to consider when evaluating patients for treatment with ER/LA opioid analgesics including: the patient’s current opioid tolerance level, respiratory depression, interactions with other medications, inadvertent exposure to children, and a personal history of past or current alcohol or drug abuse and knew to refer a patient at high risk for drug abuse to a pain management specialist. Respondents were also aware that a patient with a history of substance abuse can be prescribed an opioid and that a personal history of psychiatric disorders and a family history of illicit drug use or alcohol abuse were risk factors for opioid abuse.
- For all questions, CE provider respondents had a higher knowledge score than IMS data respondents although the differences were not significant.
- Overall, 85% of respondents met or exceed the 80% threshold (5 out of 6 questions correct).

Question	36 Month Survey n (%)		
	CE Providers Respondents (n=301)	IMS Data Respondents (n=311)	Total (N=612)
A patient with a history of substance abuse must not be prescribed an ER/LA opioid analgesic	True: 38 (13%) False: 258 (86%) Don't Know: 5 (2%)	True: 50 (16%) False: 249 (80%) Don't Know: 12 (4%)	True: 88 (14%) False: 507 (83%) Don't Know: 17 (3%)
After thorough clinical evaluation, it is appropriate for prescribers to refer a patient at high risk for drug abuse to a pain management specialist.	True: 289 (96%) False: 10 (3%) Don't Know: 2 (1%)	True: 298 (96%) False: 10 (3%) Don't Know: 3 (1%)	True: 587 (96%) False: 20 (3%) Don't Know: 5 (1%)
When evaluating patients for treatment with ER/LA opioid analgesics, which of the following are important risks to consider?	The patient’s current opioid tolerance: 0 (0%) Respiratory depression, particularly in elderly or debilitated patients: 5 (2%) Interactions with other medications the patient may be taking: 2 (1%) Inadvertent exposure, especially in children present in the home: 1 (<1%) All of the above: 293 (97%) None of the above: 0 (0%) I don't know: 0 (0%)	The patient’s current opioid tolerance: 9 (3%) Respiratory depression, particularly in elderly or debilitated patients: 5 (2%) Interactions with other medications the patient may be taking: 5 (2%) Inadvertent exposure, especially in children present in the home: 1 (<1%) All of the above: 291 (94%) None of the above: 0 (0%) I don't know: 1 (<1%)	The patient’s current opioid tolerance: 9 (1.5%) Respiratory depression, particularly in elderly or debilitated patients: 10 (2%) Interactions with other medications the patient may be taking: 7 (1%) Inadvertent exposure, especially in children present in the home: 2 (<1%) All of the above: 584 (95%) None of the above: 0 (0%) I don't know: 0 (0%)
Which of the following are risk factors for opioid abuse?	A personal history of psychiatric disorders: 257 (85%) A personal history of	A personal history of psychiatric disorders: 263 (85%) A personal history of	A personal history of psychiatric disorders: 520 (85%) A personal history of

Question	36 Month Survey n (%)		
	CE Providers Respondents (n=301)	IMS Data Respondents (n=311)	Total (N=612)
	<p>past or current alcohol or drug abuse: 299 (99%)</p> <p>A family history of illicit drug use or alcohol abuse: 256 (85%)</p> <p>A family history of hypercholesterolemia: 32 (11%)</p> <p>None of the above: 2 (<1%)</p> <p>I don't know: 1 (<1%)</p>	<p>past or current alcohol or drug abuse: 307 (99%)</p> <p>A family history of illicit drug use or alcohol abuse: 269 (86.5%)</p> <p>A family history of hypercholesterolemia: 43 (14%)</p> <p>None of the above: 0 (0%)</p> <p>I don't know: 1 (<1%)</p>	<p>past or current alcohol or drug abuse: 606 (99%)</p> <p>A family history of illicit drug use or alcohol abuse: 525 (86%)</p> <p>A family history of hypercholesterolemia: 75 (12%)</p> <p>None of the above: 2 (<1%)</p> <p>I don't know: 1 (<1%)</p>

Key risk message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA Opioid Analgesics

This key risk message included questions to assess prescriber knowledge about dose selection, individualizing dosage, and the basics of pain management (See *Table 5 below*).

- The majority of respondents were aware of certain factors to consider when selecting an initial dose of an ER/LA opioid analgesic including: the patient’s degree of opioid experience (99%), concurrent medication (99.5%), and general medical status of the patient (100%). Only 65% of respondents correctly answered that the patient’s family history of mental illness did not need to be considered.
- For the question, which should prescribers do when initiating a patient on ER/LA opioid analgesics, 88% correctly answered titrate doses based on efficacy and tolerability while only 75% correctly answered consider a rescue medication for breakthrough pain.
- Eighty-five percent (85.5%) of respondents correctly answered that with methadone, the peak of respiratory depression can occur later and can persist longer than the analgesic effects.
- Most respondents were aware of the correct indication for ER/LA opioid analgesics with 86% correctly identifying chronic non-cancer pain. Twenty-nine percent (29%) of respondents incorrectly chose breakthrough pain from cancer.
- The majority of respondents were aware of federal regulations for writing a prescription for an ER/LA opioid analgesic: 88% were aware that refills are not allowed, 96% aware that refills cannot be phoned in, and 92% aware that prescriptions cannot be faxed.
- Fewer respondents correctly answered questions related to dosing and conversion:
 - 75% of respondents reported that conversion of patients to or from methadone using equianalgesic tables can result in overdose and death (81% CE provider respondents versus 68.5% IMS respondents). High prescribers of oral ER/LA

opioid analgesics had higher knowledge scores than low prescribers (80% vs. 70%).³⁰

- Only 43.5% of respondents identified the recommended way to convert an opioid-tolerant patient safely from a parenteral opioid to an oral ER opioid analgesic by starting with 50% of an equianalgesic dose. High prescribers of transdermal patches and methadone were more knowledgeable (54% and 59%) than low prescribers (38% and 43%). In addition, high prescribers of oral ER/LA opioid analgesics were more likely to get this question correct as compared to low prescribers (51% vs. 39%).
- Only 61% were aware that there are no federal limits on quantities of ER/LA opioid analgesics dispensed via prescription (62% IMS respondents versus 59% CE provider respondents).
- In general, CE provider respondents had higher knowledge scores than IMS respondents.
- Overall, 60% of respondents met or exceed the 80% threshold (12 out of 15 questions correct).

Question	36 Month Survey n (%)		
	CE Providers Respondents (n=301)	IMS Data Respondents (n=311)	Total (N=612)
For methadone, the peak of respiratory depression can occur later and can persist longer than the analgesic effects.	True: 270 (90%) False: 10 (3%) Don't Know: 21 (7%)	True: 253 (81%) False: 13 (4%) Don't Know: 45 (14.5%)	True: 523 (85.5%) False: 23 (4%) Don't Know: 66 (11%)
Conversion of patients to or from methadone using equianalgesic tables can result in overdose and death	True: 244 (81%) False: 31 (10%) Don't Know: 26 (9%)	True: 213 (68.5%) False: 38 (12%) Don't Know: 36 (12%)	True: 457 (75%) False: 69 (11%) Don't Know: 86 (14%)
What is the recommended way to convert safely an opioid-tolerant patient from a parenteral opioid, such as morphine or meperidine, to an oral extended-release opioid, such as oxycodone or oxymorphone?	Start with the lowest available dose: 17 (6%) Start with 25% of an equianalgesic dose: 61 (20%) Start with 50% of an equianalgesic dose: 143 (47.5%) Start with an equianalgesic dose: 54 (18%) I don't know: 26 (9%)	Start with the lowest available dose: 20 (6%) Start with 25% of an equianalgesic dose: 71 (23%) Start with 50% of an equianalgesic dose: 123 (39.5%) Start with an equianalgesic dose: 61 (20%) I don't know: 36 (12%)	Start with the lowest available dose: 37 (6%) Start with 25% of an equianalgesic dose: 132 (22%) Start with 50% of an equianalgesic dose: 266 (43.5%) Start with an equianalgesic dose: 115 (19%) I don't know: 62 (10%)
Which of the following should prescribers do when initiating a	Consider a rescue medication for break-	Consider a rescue medication for break-	Consider a rescue medication for break-

³⁰ High/low prescribers were defined as a response to the question "On average, how many times in the past month have you prescribed ER/LA opioids?" High equals prescribed 11 or more times in the past month. Low equals prescribed 0 to 10 times.

Table 5: Prescribers Understanding of Key Risk Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics

Question	36 Month Survey n (%)		
	CE Providers Respondents (n=301)	IMS Data Respondents (n=311)	Total (N=612)
patient on ER/LA opioid analgesics?	<p>through pain: 228 (76%) Titrate doses based on efficacy and tolerability: 271 (90%) Start with the highest recommended dose of the ER/LA and decrease the dose depending on tolerability: 0 (0%) If switching from another opioid, convert to an equianalgesic dose: 142 (47%) None of the above: 4 (1%) I don't know: 2 (1%)</p>	<p>through pain: 231 (74%) Titrate doses based on efficacy and tolerability: 268 (86%) Start with the highest recommended dose of the ER/LA and decrease the dose depending on tolerability: 2 (1%) If switching from another opioid, convert to an equianalgesic dose: 171 (55%) None of the above: 9 (3%) I don't know: 2 (1%)</p>	<p>through pain: 459 (75%) Titrate doses based on efficacy and tolerability: 539 (88%) Start with the highest recommended dose of the ER/LA and decrease the dose depending on tolerability: 2 (<1%) If switching from another opioid, convert to an equianalgesic dose: 313 (51%) None of the above: 13 (2%) I don't know: 4 (1%)</p>
Which of the following are important factors to consider when selecting an initial dose of an ER/LA opioid analgesic?			
The patient's degree of opioid experience	<p>Yes: 297 (99%) No: 4 (1%) I don't know: 0 (0%)</p>	<p>Yes: 307 (99%) No: 4 (1%) I don't know: 0 (0%)</p>	<p>Yes: 604 (99%) No: 8 (1%) I don't know: 0 (0%)</p>
Concurrent medication	<p>Yes: 299 (99%) No: 1 (<1%) I don't know: 1 (<1%)</p>	<p>Yes: 310 (100%) No: 1 (<1%) I don't know: 0 (0%)</p>	<p>Yes: 609 (99.5%) No: 2 (<1%) I don't know: 1 (<1%)</p>
General medical status of the patient	<p>Yes: 300 (100%) No: 1 (<1%) I don't know: 0 (0%)</p>	<p>Yes: 311 (100%) No: 0 (0%) I don't know: 0 (0%)</p>	<p>Yes: 611 (100%) No: 1 (<1%) I don't know: 0 (0%)</p>
The patient's family history of mental illness	<p>Yes: 197 (65%) No: 88 (29%) I don't know: 16 (5%)</p>	<p>Yes: 199 (64%) No: 92 (30%) I don't know: 20 (6%)</p>	<p>Yes: 396 (65%) No: 180 (29%) I don't know: 36 (6%)</p>
For which of the following conditions are ER/LA opioid analgesics indicated?	<p>Acute or postoperative pain: 43 (14%) As needed for headache or migraine pain: 11 (4%) Dental abscess pain: 14 (5%) Breakthrough pain from cancer: 74 (25%) Chronic non-cancer pain: 260 (86%) None of the above: 28 (9%) I don't know: 0 (0%)</p>	<p>Acute or postoperative pain: 53 (17%) As needed for headache or migraine pain: 14 (4.5%) Dental abscess pain: 17 (5.5%) Breakthrough pain from cancer: 106 (34%) Chronic non-cancer pain: 268 (86%) None of the above: 23 (7%) I don't know: 1 (<1%)</p>	<p>Acute or postoperative pain: 96 (16%) As needed for headache or migraine pain: 25 (4%) Dental abscess pain: 31 (5%) Breakthrough pain from cancer: 180 (29%) Chronic non-cancer pain: 528 (86%) None of the above: 51 (8%) I don't know: 1 (<1%)</p>
Federal regulations stipulate which of the following when writing a prescription for an ER/LA opioid?			

Table 5: Prescribers Understanding of Key Risk Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics			
Question	36 Month Survey n (%)		
	CE Providers Respondents (n=301)	IMS Data Respondents (n=311)	Total (N=612)
Refills are not allowed for Schedule II products	True: 272 (90%) False: 23 (8%) I don't know: 6 (2%)	True: 272 (87.5%) False: 36 (12%) I don't know: 3 (1%)	True: 544 (89%) False: 59 (10%) I don't know: 9 (1.5%)
There are specific federal limits to quantities of ER/LA opioids dispensed via a prescription.	True: 178 (59%) False: 93 (31%) I don't know: 30 (10%)	True: 194 (62%) False: 78 (25%) I don't know: 39 (12.5%)	True: 372 (61%) False: 171 (28%) I don't know: 69 (11%)
Refills for an ER/LA opioid prescription can be phoned into a pharmacy.	True: 8 (3%) False: 291 (97%) I don't know: 2 (1%)	True: 12 (4%) False: 298 (96%) I don't know: 1 (<1%)	True: 20 (3%) False: 589 (96%) I don't know: 3 (<1%)
Any prescription for a Schedule II product can be faxed to the pharmacy.	True: 18 (6%) False: 277 (92%) I don't know: 6 (2%)	True: 14 (4.5%) False: 288 (93%) I don't know: 9 (3%)	True: 32 (5%) False: 565 (92%) I don't know: 15 (2.5%)
Fatal respiratory depression may occur, with the highest risk at initiation and when the dose is increased.	True: 284 (94%) False: 12 (4%) I don't know: 5 (2%)	True: 282 (91%) False: 13 (4%) I don't know: 16 (5%)	True: 566 (92.5%) False: 25 (4%) I don't know: 21 (3%)

Key Risk Message 3: Management of Ongoing Therapy with ER/LA Opioid Analgesics

This key risk message included questions to assess whether prescribers establish goals for therapy and monitor adherence to them, periodically evaluate pain control, outcomes, side effects, and quality of life, and prescriber awareness of the Patient Prescriber Agreements (PPAs) and knowledge about managing adverse events and referral sources (See *Table 6 below*).

- The majority of respondents were aware of the PPA, what it includes, its purpose, and when it should be signed. Twenty-four percent (24%) of respondents incorrectly thought that the PPA was a legal requirement.
- Most respondents correctly chose false to it is unnecessary to re-evaluate a patient's underlying medical condition if the clinical presentation changes over time (96%).
- Respondents were aware that a prescriber should reassess patients on ER/LA opioid analgesics during follow-up visits by periodically assessing the continued need for opioid analgesics (99%), evaluating pain control and functional improvement (99.8%), and evaluating changes in the patient's medical condition (99%). Respondents were less aware that a comprehensive physical exam did not have to be performed at each visit (54%) or that drug screening should not be systematically performed for all patients (20%).
- Most respondents were aware of the appropriate ways to monitor patient adherence in regards to misuse and abuse:
 - Document drug seeking behaviors (97.5%)
 - Utilize state Prescription Drug Monitoring Programs (95%)
 - Use drug testing for both screening and confirmatory tests (94%)
 - Periodically re-evaluate therapy (97%)
 - Perform medication reconciliation by counting leftover drug supplies (87%).

- In general, most CE provider respondents had slightly higher knowledge scores across all questions with the exception of awareness that a comprehensive physical exam did not have to be performed at each visit (51.5% CE provider respondents versus 56% IMS respondents).
- Overall, 91% of respondents met or exceed the 80% threshold (12 out of 15 questions correct).

Question	36 Month Survey n (%)		
	CE Providers Respondents (n=301)	IMS Data Respondents (n=311)	Total (N=612)
It is not necessary to re-evaluate a patient's underlying medical condition if the clinical presentation changes over time.	True: 10 (3%) False: 290 (96%) Don't Know: 1 (<1%)	True: 14 (4.5%) False: 297 (95.5%) Don't Know: 0 (0%)	True: 24 (4%) False: 587 (96%) Don't Know: 1 (<1%)
PPAs are signed by both prescriber and patient at the same time an opioid is initially prescribed.	True: 288 (96%) False: 9 (3%) Don't Know: 4 (1%)	True: 293 (91%) False: 10 (3%) Don't Know: 8 (3%)	True: 581 (95%) False: 19 (3%) Don't Know: 12 (2%)
PPAs can include information about treatment goals, risks, and safe use of the ER/LA opioid.	True: 293 (97%) False: 4 (1%) Don't Know: 4 (1%)	True: 302 (97%) False: 4 (1%) Don't Know: 5 (2%)	True: 595 (97%) False: 8 (1%) Don't Know: 9 (1.5%)
PPAs are a legal requirement.	True: 70 (23%) False: 193 (64%) Don't Know: 38 (13%)	True: 77 (25%) False: 191 (61%) Don't Know: 43 (14%)	True: 147 (14%) False: 384 (63%) Don't Know: 81 (13%)
PPAs may include commitments regarding follow-up visits, monitoring for misuse, and safeguarding the medication.	True: 297 (99%) False: 2 (1%) Don't Know: 2 (1%)	True: 308 (99%) False: 0 (0%) Don't Know: 3 (1%)	True: 605 (99%) False: 2 (<1%) Don't Know: 5 (1%)
How should prescribers reassess patients maintained on ER/LA opioid analgesics during follow-up visits?			
Periodically assess the continued need for opioid analgesics	True: 300 (100%) False: 1 (<1%) Don't Know: 0 (0%)	True: 309 (99%) False: 2 (1%) Don't Know: 0 (0%)	True: 609 (99.5%) False: 3 (<1%) Don't Know: 0 (0%)
Perform a comprehensive physical examination at each visit	True: 155 (51.5%) False: 141 (47%) Don't Know: 5 (2%)	True: 173 (56%) False: 132 (42%) Don't Know: 6 (2%)	True: 328 (54%) False: 273 (45%) Don't Know: 11 (2%)
Evaluate pain control and functional improvement	True: 300 (100%) False: 1 (<1%) Don't Know: 0 (0%)	True: 311 (100%) False: 0 (0%) Don't Know: 0 (0%)	True: 611 (100%) False: 1 (<1%) Don't Know: 0 (0%)
Evaluate for changes in the patient's medical condition	True: 299 (99%) False: 2 (1%) Don't Know: 0 (0%)	True: 309 (99%) False: 2 (1%) Don't Know: 0 (0%)	True: 608 (99%) False: 4 (1%) Don't Know: 0 (0%)
Systematically perform drug screening for all patients	True: 236 (78%) False: 56 (19%) Don't Know: 9 (3%)	True: 234 (75%) False: 67 (21.5%) Don't Know: 10 (3%)	True: 470 (77%) False: 123 (20%) Don't Know: 19 (3%)
How should prescribers monitor patient adherence to the treatment plan, especially with regard to	Document any drug seeking behaviors: 294 (98%)	Document any drug seeking behaviors: 303 (97%)	Document any drug seeking behaviors: 597 (97.5%)

Table 6: Prescribers' Understanding of Key Risk Message 3: Management of Ongoing Therapy with ER/LA Opioid Analgesics is Important			
Question	36 Month Survey n (%)		
	CE Providers Respondents (n=301)	IMS Data Respondents (n=311)	Total (N=612)
misuse and abuse?	Utilize state Prescription Drug Monitoring Program: 291 (97%) Use drug testing for both screening and confirmatory tests: 288 (96%) Perform laboratory testing for serum triglycerides: 46 (15%) Periodically re-evaluate therapy: 292 (97%) Perform medication reconciliation by counting leftover drug supplies: 271 (90%) None of the above: 0 (0%) I don't know: 1 (<1%)	Utilize state Prescription Drug Monitoring Program: 290 (93%) Use drug testing for both screening and confirmatory tests: 285 (92%) Perform laboratory testing for serum triglycerides: 65 (21%) Periodically re-evaluate therapy: 303 (97%) Perform medication reconciliation by counting leftover drug supplies: 264 (85%) None of the above: 0 (0%) I don't know: 1 (<1%)	Utilize state Prescription Drug Monitoring Program: 581 (95%) Use drug testing for both screening and confirmatory tests: 573 (94%) Perform laboratory testing for serum triglycerides: 111 (18%) Periodically re-evaluate therapy: 595 (97%) Perform medication reconciliation by counting leftover drug supplies: 535 (87%) None of the above: 0 (0%) I don't know: 2 (<1%)

Key Risk Message 4: It is Important to Counsel Patients and Caregivers about the Safe Use of ER/LA Opioid Analgesics

This key risk message included questions to assess prescriber knowledge about safe use of the ER/LA opioid analgesics (See *Table 7 below*).

- The majority of respondents were aware of the signs and symptoms of respiratory depression such as reduced urge to breathe (91%), decreased rate of respiration (98%), sighing patterns of breathing (84%), and profound sedation (94%). Respondents were also aware that the most common long-term side effect of ER/LA opioid analgesics was constipation (89%).
- Respondents were aware of medications that could potentiate the risks of serious overdose and death when taken along with ER/LA opioid analgesics including sedative hypnotics (99%) or alcohol (99%).
- Respondents knew that an extended release tablet should not be cut in half to reduce the dose (94%) and that chewing a solid, oral dosage form of an ER/LA opioid analgesic could result in absorption of a fatal dose of opioid (89%). Respondents were less aware that transdermal patches with a matrix formulation should not be cut prior to use (75%).

- The majority of respondents knew that patients should be counseled about the importance of adhering to a dosage regimen as prescribed (99%) and that it is illegal to sell or give away ER/LA opioid analgesics (98.5%).
- CE provider respondent's knowledge scores were slightly higher than IMS respondents for most questions except awareness of constipation as the most common long-term side effect (IMS respondents 89% versus 87% CE provider respondents).
- High prescribers of methadone were more aware that caffeine does not potentiate the risk of overdose and death as compared to low prescribers (78% vs. 60%).
- Overall, 94% of respondents met or exceed the 80% threshold (12 out of 15 questions correct).

Question	36 Month Survey n (%)		
	CE Providers Respondents (n=301)	IMS Data Respondents (n=311)	Total (N=612)
ER/LA opioid analgesic transdermal patches that have a matrix formulation may be cut prior to use.	True: 30 (10%) False: 223 (74%) Don't Know: 48 (16%)	True: 33 (11%) False: 237 (76%) Don't Know: 41 (13%)	True: 63 (10%) False: 460 (75%) Don't Know: 89 (14.5%)
Chewing a solid, oral dosage form of an ER/LA opioid analgesic can result in rapid release and absorption of a potentially fatal dose of opioid.	True: 276 (92%) False: 15 (5%) Don't Know: 10 (3%)	True: 267 (86%) False: 20 (10%) Don't Know: 14 (4.5%)	True: 543 (89%) False: 45 (7%) Don't Know: 24 (4%)
Which of the following are warning signs and symptoms of respiratory depression from ER/LA opioid analgesics?	Reduced urge to breathe: 276 (92%) Decreased rate of respiration: 297 (99%) Signing pattern of breathing: 253 (84%) Profound sedation: 284 (94%)	Reduced urge to breathe: 283 (91%) Decreased rate of respiration: 302 (97%) Signing pattern of breathing: 261 (84%) Profound sedation: 294 (94.5%)	Reduced urge to breathe: 559 (91%) Decreased rate of respiration: 599 (98%) Signing pattern of breathing: 514 (84%) Profound sedation: 578 (94%)
A patient should be told not cut an extended release tablet in half to reduce the dose.	True: 284 (94%) False: 16 (5%) Don't Know: 1 (<1%)	True: 291 (94%) False: 15 (5%) Don't Know: 5 (2%)	True: 575 (94%) False: 31 (5%) Don't Know: 6 (1%)
Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic?			
Sedative hypnotics	Yes: 300 (100%) No: 1 (<1%) I don't know: 0 (0%)	Yes: 304 (98%) No: 2 (1%) I don't know: 5 (2%)	Yes: 604 (99%) No: 3 (<1%) I don't know: 5 (1%)
Anxiolytics	Yes: 286 (95%) No: 5 (2%) I don't know: 10 (3%)	Yes: 283 (91%) No: 10 (3%) I don't know: 18 (6%)	Yes: 569 (93%) No: 15 (2.5%) I don't know: 28 (5%)
Alcohol	Yes: 300 (100%) No: 1 (<1%) I don't know: 1 (<1%)	Yes: 310 (100%) No: 1 (<1%) I don't know: 1 (<1%)	Yes: 610 (100%) No: 1 (<1%) I don't know: 1 (<1%)
Illegal drugs	Yes: 300 (100%)	Yes: 309 (99%)	Yes: 609 (99.5%)

Question	36 Month Survey n (%)		
	CE Providers Respondents (n=301)	IMS Data Respondents (n=311)	Total (N=612)
	No: 0 (0%) I don't know: 1 (<1%)	No: 0 (0%) I don't know: 2 (1%)	No: 0 (0%) I don't know: 3 (<1%)
Caffeine	Yes: 30 (10%) No: 220 (73%) I don't know: 51 (17%)	Yes: 45 (14.5%) No: 197 (63%) I don't know: 69 (22%)	Yes: 75 (12%) No: 417 (68%) I don't know: 120 (20%)
When counseling patients about the safe use of ER/LA opioid analgesics, prescribers should inform patients of the following	The importance of adhering to a dosage regimen as prescribed: 298 (99%) It is illegal to sell or give away ER/LA opioid analgesics: 298 (99%)	The importance of adhering to a dosage regimen as prescribed: 307 (99%) It is illegal to sell or give away ER/LA opioid analgesics: 305 (98%)	The importance of adhering to a dosage regimen as prescribed: 605 (99%) It is illegal to sell or give away ER/LA opioid analgesics: 603 (98.5%)
The most common long-term side effect of ER/LA opioid analgesics is constipation.	True: 261 (87%) False: 30 (10%) I don't know: 10 (3%)	True: 278 (89%) False: 26 (8%) I don't know: 7 (2%)	True: 539 (88%) False: 56 (9%) I don't know: 17 (3%)

Key Risk Message 5: Prescribers Must be Familiar with General Drug Information Concerning ER/LA Opioid Analgesics

This key risk message included questions to assess prescriber knowledge of general characteristics of ER/LA opioid analgesics including side effects, drug-drug interactions, definition of opioid-tolerant patients, and dosing (See *Table 8 below*).

- Eighty-nine percent (89%) of respondents were aware that some opioids can increase QTc interval.
- Most respondents were aware that central nervous system depressants can have a potentiating effect on sedation and respiratory depression caused by opioids (98%), that MAOIs are not the preferred antidepressant for use with ER/LA opioid analgesics (81%), and that concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids (92.5%).
- Most respondents (93%) knew that when starting a patient who is taking a sedative on ER/LA opioid analgesics, that the dose of one or both should be reduced. Respondents were also aware that all ER/LA opioid analgesics do not reach steady plasma concentration at the same time (95%).
- Only 72% of respondents were aware that some ER opioid formulations may rapidly release opioids when exposed to alcohol although awareness of CE provider respondents was significantly higher (82% CE provider respondents versus 63% IMS respondents).
- Similarly, only 78% of respondents correctly answered false to patients that were not opioid tolerant can initiate opioid therapy with any type of ER/LA opioid analgesic although awareness of CE provider respondents was significantly higher (82% CE provider respondents versus 74% IMS respondents).

- Only 55% of respondent were aware that if a patient using a transdermal opioid develops a high fever that the patient should be monitored closely for side effects and the dose of the patch should be reduce if necessary.
- In general, CE provider respondents had statistically significantly higher knowledge scores than IMS respondents across almost all questions.
- Overall, 77.5% of respondents met or exceeded the 80% threshold (answered 9 out of 11 questions correctly).

Question	36 Month Survey n (%)		
	CE Providers Respondents (n=301)	IMS Data Respondents (n=311)	Total (N=612)
Some opioids can increase the QTc interval	True: 491 (81%) False: 19 (1%) Don't Know: 95 (16%)	True: 491 (81%) False: 19 (1%) Don't Know: 95 (16%)	True: 549 (90%) False: 16 (3%) Don't Know: 47 (8%)
Central nervous system depressants can have a potentiating effect on the sedation and respiratory depression caused by opioids	True: 593 (98%) False: 2 (<1%) Don't Know: 10 (2%)	True: 593 (98%) False: 2 (<1%) Don't Know: 10 (2%)	True: 602 (98%) False: 4 (1%) Don't Know: 6 (1%)
Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol.	True: 378 (62%) False: 25 (4%) Don't Know: 202 (33%)	True: 378 (62%) False: 25 (4%) Don't Know: 202 (33%)	True: 441 (72%) False: 27 (4%) Don't Know: 144 (23.5%)
Monoamine oxidase inhibitors (MAOIs) are the preferred antidepressants for use with ER/LA opioid analgesics.	True: 11 (2%) False: 496 (82%) Don't Know: 98 (16%)	True: 11 (2%) False: 496 (82%) Don't Know: 98 (16%)	True: 21 (3%) False: 496 (81%) Don't Know: 95 (15.5%)
Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids.	True: 527 (87%) False: 13 (2%) Don't Know: 65 (11%)	True: 527 (87%) False: 13 (2%) Don't Know: 65 (11%)	True: 566 (92.5%) False: 8 (1%) Don't Know: 38 (6%)
What should be done if a patient treated with a transdermal opioid develops a high fever?	Remove the patch until the fever is below 102: 143 (24%) Switch the patient to another ER/LA: 54 (9%) Monitor the patient closely for opioid side effects and reduce the dose of the patch if necessary: 404 (67%) Move the patch to another location in the body: 4 (<1%) I don't know: 94 (15%)	Remove the patch until the fever is below 102: 143 (24%) Switch the patient to another ER/LA: 54 (9%) Monitor the patient closely for opioid side effects and reduce the dose of the patch if necessary: 404 (67%) Move the patch to another location in the body: 4 (<1%) I don't know: 94	Remove the patch until the fever is below 102: 138 (22.5%) Switch the patient to another ER/LA: 42 (7%) Monitor the patient closely for opioid side effects and reduce the dose of the patch if necessary: 334 (55%) Move the patch to another location in the body: 4 (1%) I don't know: 94

Question	36 Month Survey n (%)		
	CE Providers Respondents (n=301)	IMS Data Respondents (n=311)	Total (N=612)
		(15%)	(15%)
When starting a patient who is currently taking a sedative on an ER/LA opioid analgesic, reduce the dose of one or both.	True: 561 (93%) False: 28 (5%) Don't Know: 16 (3%)	True: 561 (93%) False: 28 (5%) Don't Know: 16 (3%)	True: 568 (93%) False: 18 (3%) Don't Know: 26 (4%)
Patients who are not opioid tolerant can initiate opioid therapy with any type of ER/LA opioid analgesic	True: 194 (32%) False: 354 (59%) Don't Know: 57 (9%)	True: 194 (32%) False: 354 (59%) Don't Know: 57 (9%)	True: 103 (17%) False: 479 (78%) Don't Know: 30 (5%)
All ER/LA opioids reach steady state plasma concentration at the same time.	True: 8 (1%) False: 568 (94%) Don't Know: 29 (5%)	True: 8 (1%) False: 568 (94%) Don't Know: 29 (5%)	True: 11 (2%) False: 583 (95%) Don't Know: 18 (3%)
The Controlled Substance Act includes ER/LA opioids because of the potential risk for abuse.	True: 546 (90%) False: 14 (2%) Don't Know: 45 (7%)	True: 546 (90%) False: 14 (2%) Don't Know: 45 (7%)	True: 558 (91%) False: 17 (3%) Don't Know: 17 (3%)
The underlying pharmacokinetic and pharmacodynamic mechanisms are the same for all ER/LA opioids.	True: 25 (4%) False: 538 (89%) Don't Know: 42 (7%)	True: 25 (4%) False: 538 (89%) Don't Know: 42 (7%)	True: 37 (6%) False: 558 (91%) Don't Know: 17 (3%)

Key Risk Message 6: Prescribers Must be Familiar with Product-Specific Drug Information Concerning ER/LA Opioid Analgesics

This key risk message included questions to assess prescriber knowledge of product-specific characteristics of ER/LA opioid analgesics including side effects, drug-drug interactions, definition of opioid-tolerant patients, and dosing (See *Table 9 below*).

- Respondents were less aware of what patient was considered opioid tolerant with only 36% correctly selecting patients who are taking 25 mcg/hour transdermal fentanyl for at least 7 days as tolerant (IMS respondents 37% versus 35% CE provider respondents) and 69% selecting patients who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer (IMS respondents 67% versus 71% CE provider respondents).
- Seventy-seven percent (77%) of respondents were aware that for some ER/LA opioid analgesic products, patients must be opioid tolerant before using certain strengths or daily doses. Only a little over half (51%) of respondents correctly answered that patients must be opioid tolerant before using any strength of transdermal fentanyl or ER hydromorphone. High prescribers of methadone had higher knowledge scores than low prescribers (60% vs. 43%).
- Only 69% of respondents correctly selected that transdermal opioids should not be disposed of by cutting into small pieces and throwing them in the trash. Only 46% of respondents correctly advised patients experiencing back pain and being treated with a transdermal opioid to not soak in a hot tub since heat can affect absorption of the opioid.

- CE provider respondent's knowledge scores were higher than IMS respondents for most questions except knowledge that patients who are taking 25 mcg/hour transdermal fentanyl for at least 7 days are opioid-tolerant (IMS respondents 37% versus 35% CE provider respondents).
- Overall, only 28% of respondents met or exceeded the 80% threshold (answered 5 out of 6 questions correctly).

Table 9: Prescribers' Understanding of Key Risk Message 6: Prescribers Must be Familiar with Product-Specific Drug Information Concerning ER/LA Opioid Analgesics			
Question	36 Month Survey n (%)		
	CE Providers Respondents (n=301)	IMS Data Respondents (n=311)	Total (N=612)
Patients considered opioid-tolerant are those:	<p>Who are taking 25 mcg/hour transdermal fentanyl for at least 7 days: 106 (35%) Who are not currently taking opioid therapy, but have no known intolerance or hypersensitivity to the drug fentanyl: 23 (8%) Who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer: 215 (71%) None of the above: 66 (22%) I don't know: 14 (5%)</p>	<p>Who are taking 25 mcg/hour transdermal fentanyl for at least 7 days: 114 (37%) Who are not currently taking opioid therapy, but have no known intolerance or hypersensitivity to the drug fentanyl: 41 (13%) Who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer: 207 (67%) None of the above: 71 (23%) I don't know: 22 (7%)</p>	<p>Who are taking 25 mcg/hour transdermal fentanyl for at least 7 days: 220 (36%) Who are not currently taking opioid therapy, but have no known intolerance or hypersensitivity to the drug fentanyl: 64 (10.5%) Who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer: 422 (69%) None of the above: 137 (22%) I don't know: 36 (6%)</p>
Patients must be opioid tolerant before using any strength of transdermal fentanyl or ER hydromorphone.	<p>True: 168 (56%) False: 116 (38.5%) Don't Know: 17 (6%)</p>	<p>True: 142 (46%) False: 150 (48%) Don't Know: 19 (6%)</p>	<p>True: 310 (51%) False: 266 (43.5%) Don't Know: 36 (6%)</p>
For some ER products, patients must be opioid tolerant before using certain strengths or certain daily doses.	<p>True: 237 (79%) False: 48 (16%) Don't Know: 16 (5%)</p>	<p>True: 234 (75%) False: 55 (18%) Don't Know: 22 (7%)</p>	<p>True: 471 (77%) False: 103 (17%) Don't Know: 38 (6%)</p>
Dispose of transdermal patches by cutting into small pieces and throwing in the trash	<p>True: 50 (17%) False: 219 (73%) Don't Know: 32 (11%)</p>	<p>True: 58 (19%) False: 202 (65%) Don't Know: 51 (16%)</p>	<p>True: 108 (18%) False: 421 (69%) Don't Know: 83 (14%)</p>
A patient is experiencing back pain and is being treated with a transdermal opioid product. After a fall at home, he would like to soak in a hot tub to relieve some of the muscle soreness. What is your advice?	<p>It is acceptable to soak in the hot tub for less than half an hour: 9 (3%) He should cover the patch with an occlusive dressing if entering the hot tub: 31 (10%) He must remove the</p>	<p>It is acceptable to soak in the hot tub for less than half an hour: 13 (4%) He should cover the patch with an occlusive dressing if entering the hot tub: 52 (17%) He must remove the patch</p>	<p>It is acceptable to soak in the hot tub for less than half an hour: 22 (4%) He should cover the patch with an occlusive dressing if entering the hot tub: 83 (14%) He must remove the patch</p>

Table 9: Prescribers' Understanding of Key Risk Message 6: Prescribers Must be Familiar with Product-Specific Drug Information Concerning ER/LA Opioid Analgesics			
Question	36 Month Survey n (%)		
	CE Providers Respondents (n=301)	IMS Data Respondents (n=311)	Total (N=612)
	patch while soaking in the hot tub: 79 (26%) Do not soak in the hot tub since heat can affect the absorption of the opioid: 142 (47%) None of the above: 11 (4%) I don't know: 29 (10%)	while soaking in the hot tub: 57 (18%) Do not soak in the hot tub since heat can affect the absorption of the opioid: 138 (44%) None of the above: 11 (3.5%) I don't know: 40 (13%)	while soaking in the hot tub: 136 (22%) Do not soak in the hot tub since heat can affect the absorption of the opioid: 280 (46%) None of the above: 22 (4%) I don't know: 69 (11%)

Educational Materials Questions:

Out of the 612 prescribers:

- 60% were aware of the Medication Guide (67% CE provider respondents; 53% IMS respondents); The main source of awareness for CE provider respondents was conferences (40%) followed by online download (32.5%) and sales representative (28%). The main source of awareness for IMS respondents was sales representatives (60%) followed by mailings (33%) and conferences (32.5%).
- 37% were aware of the Dear DEA Registered Prescriber Letter (44.5% CE provider respondents; 30% IMS respondents); the main source of awareness for both CE provider respondents and IMS respondents was mailing followed by email.
- 43% were aware of the Patient Counseling Document (53.5% CE provider respondents; 33% IMS respondents); the main source of awareness for CE provider respondents was conferences (42%) followed by online download (32.5%). The main source of awareness for IMS respondents was sales representatives (35%) followed by conferences (33%).
- 30% were aware of the ER/LA REMS website (49.5% CE provider respondents; 30% IMS respondents); the main source of awareness for CE provider respondents was email (35%) followed by conferences (34%). The main source of awareness for IMS respondents was sales representatives (32%) followed by email (30%).
- 55% were aware of the availability of REMS-compliant activities (71% CE provider respondents; 39% IMS respondents).

Prescriber Behavior Questions:

These questions assessed prescriber-patient communication related to safe use of ER/LA opioid analgesics, evaluation of potential abuse or misuse of the medications, ease of patient-access to ER/LA opioid analgesics, and impact of the FDA-required REMS on access to ER/LA opioid analgesics (see *Table 10 below*).

- Respondents were asked about obstacles to patient access to prescription opioids for pain control medical needs in the past month. The top obstacles reported were: insurance coverage (74%), insurance authorizations and approvals (72%) and patient's ability to pay (55%).
- Respondents were asked about the current level of access to ER/LA opioid analgesics for patients that are indicated to take them. Over half of respondents (52.5%) though the

ease of access was about right. Twenty-five percent (25%) of respondents thought access was too difficult and 15% reported access as too easy. IMS respondents were more likely to report that access was too difficult as compared to CE provider respondents (29% versus 22%).

- Respondents were asked about the impact of the REMS on patient access to ER/LA opioid analgesics. Overall, 38% of respondents felt that the REMS made access more difficult while 37% of respondents reported that there was no impact. CE provider respondents were more likely to report no impact as compared to IMS respondents (41% versus 33%).
- Respondents were asked how the types of medications they prescribe have changed since the implementation of the REMS in July 2012. Overall, while almost half reported no change (48% overall; 44% CE provider respondents vs. 51% IMS respondents); 23% of respondents reported they have limited which ER/LA opioid analgesic they prescribe, 22.5% reported prescribing more non-opioid medications, and 18% reported prescribing fewer ER/LA opioid analgesics. Twenty-seven percent of CE provider respondents reported prescribing more non-opioid medications since the implementation of the REMS compared to 18% of IMS respondents. In addition, 11% of CE provider respondents reported prescribing more immediate release opioids since the implementation of the REMS compared to 6% of IMS respondents.
- Respondents reported on what activities they do when prescribing an ER/LA opioid analgesic. While most respondents reported warning patients not to break, chew, or crush their oral ER/LA opioid (92.5%), explaining what to do if a dose is missed (85.5%), and advising patient how to safely taper their dose when discontinuing (84%). A smaller percentage of respondents (64%) reported that they use the patient counseling document (PCD) for discussions with patients. CE provider respondents were more likely to report using the PCD than IMS respondents (70% vs. 58%).
- Respondents also reported on how frequently they perform certain activities when prescribing ER/LA opioid analgesics. Respondents self-reported a high frequency of appropriate behaviors reporting that they always or regularly: caution patients about important risks (95.5%) and common side effects (98%), discuss how to safely taper the ER/LA opioid analgesic if it is no longer needed (82%), counsel to keep ER/LA opioid analgesics away from children (89%), and instruct patients that it is illegal to sell, share, or give away ER/LA opioid analgesics (86.5%). Fewer respondents reported always or regularly using the PCD with patients (49.5%; CE provider respondents 54% vs. IMS respondent 44%), instructing patients on how to dispose of unused ER/LA opioid analgesics, and discussed with patients what to do if a dose is missed (76%).
- Respondents also reported on how frequently they perform certain activities when treating patients with ER/LA opioid analgesics. Respondents self-reported that they always or regularly reassess the need for opioid analgesics during treatment (99%). Fewer respondents reported that they always or regularly: use structured interview tools or screening tools to assess patients risk of abuse or misuse (66%), perform urine drug tests (71%), or complete a patient-prescriber agreement (PPA) or patient contract when the ER/LA opioid analgesic is first prescribed (76.5%).

Table 10: Prescriber-Reported Behaviors When Prescribing ER/LA Opioid Analgesics			
Question	36 Month Survey n (%)		
	CE Providers Respondents (n=301)	IMS Data Respondents (n=311)	Total (n=612)
How frequently do you perform the following activities when treating patients with ER/LA opioid analgesics?			
Used the patient counseling document (PCD) on ER/LA opioids for discussions with patients	Always: 73 (24%) Regularly: 91 (30%) Rarely: 53 (18%) Never: 80 (27%) Don't know: 4 (1%)	Always: 60 (19%) Regularly: 77 (25%) Rarely: 64 (21%) Never: 99 (32%) Don't know: 11 (3.5%)	Always: 133 (22%) Regularly: 168 (27.5%) Rarely: 117 (19%) Never: 179 (29%) Don't know: 15 (2.5%)
Cautioned about important risks, including overdose and respiratory depression	Always: 180 (60%) Regularly: 112 (37%) Rarely: 6 (2%) Never: 2 (1%) Don't know: 1 (<1%)	Always: 189 (61%) Regularly: 105 (34%) Rarely: 16 (5%) Never: 0 (0%) Don't know: 1 (<1%)	Always: 369 (60%) Regularly: 217 (35.5%) Rarely: 22 (4%) Never: 2 (<1%) Don't know: 2 (<1%)
Discussed how to safely taper their ER/LA opioid analgesics if it is no longer needed	Always: 101 (34%) Regularly: 142 (47%) Rarely: 49 (16%) Never: 6 (2%) Don't know: 3 (1%)	Always: 118 (38%) Regularly: 138 (44%) Rarely: 48 (15%) Never: 5 (2%) Don't know: 2 (1%)	Always: 219 (36%) Regularly: 280 (46%) Rarely: 97 (16%) Never: 11 (2%) Don't know: 5 (1%)
Counsel patients on the most common side effects from opioid use	Always: 186 (62%) Regularly: 110 (36.5%) Rarely: 3 (1%) Never: 2 (1%) Don't know: 0 (0%)	Always: 175 (56%) Regularly: 128 (41%) Rarely: 7 (2%) Never: 0 (0%) Don't know: 1 (<1%)	Always: 361 (59%) Regularly: 238 (39%) Rarely: 10 (2%) Never: 2 (<1%) Don't know: 1 (<1%)
Instruct patients about the importance and how to safely dispose of their unused opioids	Always: 114 (38%) Regularly: 103 (34%) Rarely: 68 (23%) Never: 15 (5%) Don't know: 1 (<1%)	Always: 116 (37%) Regularly: 108 (35%) Rarely: 71 (23%) Never: 13 (4%) Don't know: 3 (1%)	Always: 230 (38%) Regularly: 211 (34.5%) Rarely: 139 (23%) Never: 28 (5%) Don't know: 4 (1%)
Counsel patients on the importance of keeping ER/LA opioid analgesics safe and away from children.	Always: 173 (57.5%) Regularly: 90 (30%) Rarely: 32 (11%) Never: 5 (2%) Don't know: 1 (<1%)	Always: 182 (58.5%) Regularly: 100 (32%) Rarely: 23 (7%) Never: 4 (1%) Don't know: 2 (1%)	Always: 355 (58%) Regularly: 190 (31%) Rarely: 55 (9%) Never: 9 (1.5%) Don't know: 3 (<1%)
Instruct patients that it is illegal to sell, share, or give away ER/LA opioid analgesics.	Always: 172 (57%) Regularly: 89 (30%) Rarely: 32 (11%) Never: 8 (3%) Don't know: 0 (0%)	Always: 180 (58%) Regularly: 89 (29%) Rarely: 31 (10%) Never: 10 (3%) Don't know: 1 (<1%)	Always: 352 (57.5%) Regularly: 178 (29%) Rarely: 63(10%) Never: 18 (3%) Don't know: 1 (<1%)
Discuss with patients what to do if a dose if missed.	Always: 96 (32%) Regularly: 127 (42%) Rarely: 68 (23%) Never: 8 (3%) Don't know: 2 (1%)	Always: 86 (28%) Regularly: 156 (50%) Rarely: 59 (19%) Never: 8 (3%) Don't know: 2 (1%)	Always: 182 (30%) Regularly: 283 (46%) Rarely: 127 (21%) Never: 16 (3%) Don't know: 4 (1%)
Which of the following do you do with patients when prescribing an ER/LA opioid analgesic?	Use the PCD for discussions with patients: 211 (70%) Advise patients how to safely taper their ER/LA opioid dose when discontinuing: 250 (83%) Explain what patients should do if they miss a dose of their ER/LA opioid	Use the PCD for discussions with patients: 180 (58%) Advise patients how to safely taper their ER/LA opioid dose when discontinuing: 264 (85%) Explain what patients should do if they miss a dose of their ER/LA	Use the PCD for discussions with patients: 391 (64%) Advise patients how to safely taper their ER/LA opioid dose when discontinuing: 514 (84%) Explain what patients should do if they miss a dose of their ER/LA opioid

Table 10: Prescriber-Reported Behaviors When Prescribing ER/LA Opioid Analgesics			
Question	36 Month Survey n (%)		
	CE Providers Respondents (n=301)	IMS Data Respondents (n=311)	Total (n=612)
How frequently do you perform the following activities when treating patients with ER/LA opioid analgesics?			
	analgesic: 261 (87%) Warn patients not to break, chew or crush their oral ER/LA opioid: 281: (93%) None of the above: 12 (4%)	opioid analgesic: 262 (84%) Warn patients not to break, chew or crush their oral ER/LA opioid: 285 (92%) None of the above: 11 (3.5%)	analgesic: 523 (85.5%) Warn patients not to break, chew or crush their oral ER/LA opioid: 566 (92.5%) None of the above: 23 (4%)
Use structured interview tools or other screening tools to assess patients' risk of abuse or misuse of their medications when managing patients using ER/LA opioids	Always: 83 (28%) Regularly: 124 (41%) Rarely: 66 (22%) Never: 27 (9%) Don't know: 1 (<1%)	Always: 88 (28%) Regularly: 107 (34%) Rarely: 73 (23.5%) Never: 39 (12.5%) Don't know: 4 (1%)	Always: 171 (28%) Regularly: 231 (38%) Rarely: 139 (23%) Never: 66 (11%) Don't know: 5 (1%)
Complete a PPA or patient contract at the time an ER/LA opioid is first prescribed.	Always: 151 (50%) Regularly: 79 (26%) Rarely: 34 (11%) Never: 34 (11%) Don't know: 3 (1%)	Always: 166 (53%) Regularly: 71 (23%) Rarely: 38 (12%) Never: 34 (11%) Don't know: 4 (1%)	Always: 317 (52%) Regularly: 150 (24.5%) Rarely: 72 (12%) Never: 68 (11%) Don't know: 5 (1%)
Perform urine drug tests	Always: 55 (18%) Regularly: 157 (52%) Rarely: 65 (22%) Never: 23 (8%) Don't know: 1 (<1%)	Always: 67 (21.5%) Regularly: 154 (49.5%) Rarely: 64 (21%) Never: 24 (8%) Don't know: 2 (1%)	Always: 122 (20%) Regularly: 311 (51%) Rarely: 129 (21%) Never: 47 (8%) Don't know: 3 (<1%)
Reassess the need for opioids	Always: 182 (60.5%) Regularly: 113 (37.5%) Rarely: 5 (2%) Never: 1 (<1%) Don't know: N/A	Always: 190 (61%) Regularly: 119 (38%) Rarely: 2 (1%) Never: 0 (0%) Don't know: N/A	Always: 372 (61%) Regularly: 232 (38%) Rarely: 7 (1%) Never: 1 (<1%) Don't know: N/A
In your opinion, what have the obstacles been to patient access to prescription opioids in the past month?	Insurance coverage: 205 (68%) Insurance authorizations and approvals: 201 (67%) Patients' ability to pay: 159 (53%) Stigma regarding opioids: 98 (33%) Pharmacy authorization: 69 (23%) Pharmacy stocking issues: 102 (34%) Physicians do not want to prescribe ER/LAs because they do not wish to complete REMS training: 63 (21%) Patients are afraid to take ER/LAs because of risk warnings: 71 (24%)	Insurance coverage: 247 (79%) Insurance authorizations and approvals: 238 (76.5%) Patients' ability to pay: 177 (57%) Stigma regarding opioids: 78 (25%) Pharmacy authorization: 90 (29%) Pharmacy stocking issues: 140 (45%) Physicians do not want to prescribe ER/LAs because they do not wish to complete REMS training: 63 (20%) Patients are afraid to take ER/LAs because of risk	Insurance coverage: 452 (74%) Insurance authorizations and approvals: 439 (72%) Patients' ability to pay: 336 (55%) Stigma regarding opioids: 176 (29%) Pharmacy authorization: 159 (26%) Pharmacy stocking issues: 242 (39.5%) Physicians do not want to prescribe ER/LA because they do not wish to complete REMS training: 126 (21%) Patients are afraid to take ER/LAs because of risk warnings: 145 (24%)

Table 10: Prescriber-Reported Behaviors When Prescribing ER/LA Opioid Analgesics			
Question	36 Month Survey n (%)		
	CE Providers Respondents (n=301)	IMS Data Respondents (n=311)	Total (n=612)
How frequently do you perform the following activities when treating patients with ER/LA opioid analgesics?			
	Legal liability or malpractice concerns: 134 (44.5%) Other: 21 (7%) I don't know: 11 (4%)	warnings: 74 (24%) Legal liability or malpractice concerns: 91 (29%) Other: 5 (2%) I don't know: 3 (1%)	Legal liability or malpractice concerns: 225 (37%) Other: 26 (4%) I don't know: 14 (2%)
Do you think the current level of access to ER/LA opioid analgesics for patients who are indicated to take them is:	Too easy: 51 (17%) Too difficult: 65 (22%) About right: 158 (52.5%) I don't know: 27 (9%)	Too easy: 40 (13%) Too difficult: 90 (29%) About right: 163 (52%) I don't know: 18 (6%)	Too easy: 91 (15%) Too difficult: 155 (25%) About right: 321 (52.5%) I don't know: 45 (7%)
What impact does the FDA-required REMS for ER/LA opioid analgesics have on the ability of patients who need opioids to get them?	It makes it more difficult for patients to get opioids: 110 (36.5%) It makes it easier for patients to get opioids: 12 (4%) It doesn't have any impact on patient access to opioids: 124 (41%) I don't know: 55 (18%)	It makes it more difficult for patients to get opioids: 123 (39.5%) It makes it easier for patients to get opioids: 4 (1%) It doesn't have any impact on patient access to opioids: 103 (33%) I don't know: 81 (26%)	It makes it more difficult for patients to get opioids: 233 (38%) It makes it easier for patients to get opioids: 16 (3%) It doesn't have any impact on patient access to opioids: 227 (37%) I don't know: 136 (22%)
Since implementation of the REMS in July 2012, how have the types of medications you prescribed changed?	I have prescribed more ER/LA opioids: 33 (11%) I have prescribed fewer ER/LA opioids: 57 (19%) I have prescribed more immediate release opioids: 34 (11%) I prescribed more non-opioid medications: 81 (27%) I have limited which ER/LA opioid analgesics I prescribe: 70 (23%) Other: 3 (1%) I have not changed the types of medication I prescribe: 133 (44%)	I have prescribed more ER/LA opioids: 31 (10%) I have prescribed fewer ER/LA opioids: 54 (17%) I have prescribed more immediate release opioids: 20 (6%) I prescribed more non-opioid medications: 57 (18%) I have limited which ER/LA opioid analgesics I prescribe: 73 (23.5%) Other: 2 (1%) I have not changed the types of medication I prescribe: 159 (51%)	I have prescribed more ER/LA opioids: 64 (10.5%) I have prescribed fewer ER/LA opioids: 11 (18%) I have prescribed more immediate release opioids: 54 (9%) I prescribed more non-opioid medications: 138 (22.5%) I have limited which ER/LA opioid analgesics I prescribe: 143 (23%) Other: 5 (1%) I have not changed the types of medication I prescribe: 292 (48%)

3.3.3 Overall Reviewer's Comments on Follow-up Prescriber Survey

Overall, respondents were knowledgeable about the assessment, management, and counseling requirements for patients being considered for treatment or currently being treated with an ER/LA opioid analgesic. Respondents were less knowledgeable about initiation, modification, and discontinuation of therapy, and general and product specific information for ER/LA opioid analgesics.

In general, CE provider respondents were more likely to answer questions correctly as compared to IMS respondents. While 60% of all respondents reported that they did complete a CE activity,

there is no way to know if the completed CE activity was REMS compliant. Respondents that reported completion of a CE activity also had higher knowledge scores than respondents that reported not completing a CE activity. High volume prescribers were also more likely to answer questions correctly across almost all key risk messages.

Compared to the baseline survey, overall response rates to 44 items improved, 17 remained the same, and 4 items decreased. Overall, awareness of REMS materials was low: 60% aware of the Medication Guide, 37% aware of the Dear DEA Prescriber Letter, 43% aware of the Patient Counseling Document, and 30% aware of the REMS website. The top sources for REMS materials for CE provider respondents was conferences and online download compared to sales representatives and conferences for IMS respondents. In general, respondents reported a high frequency of appropriate prescriber behaviors such as always or regularly counseling on risks and side effects, instructing patients to keep ER/LA opioid analgesic medications away from children, informing patients that it is illegal to share, sell, or give-away ER/LA opioid analgesics, and reassessing the need for opioid analgesics. Respondents were less likely to always or regularly use the PCD, instruct patients on how to dispose of unused medication, use tools to screen patients for risk of misuse or abuse, perform urine drug tests, and complete Patient Prescriber Agreements.

In terms of access, respondents reported that the main barriers to patient access to prescription opioids analgesics are insurance coverage and insurance authorizations and approvals. While more than half of respondents thought patients' access to ER/LA opioid analgesics were about right, at least 25% thought the current level of access was too difficult. Overall, respondents reported the REMS made it more difficult for patients to get opioid analgesics (38%) followed closely by no impact (37%). IMS respondents were more likely to report that the REMS made access more difficult as compared to CE provider respondents (39.5% vs. 36.5%). While almost half of respondents reported no changes in the types of medications prescribed since implementation of the REMS (48%), 23% reported limiting which ER/LA opioid analgesics they prescribe and prescribing more non-opioid medications.

3.3.4 Assessment Element 4b –Long-Term Evaluation Survey

The purpose of the long-term evaluation (LTE) prescriber survey is to evaluate knowledge about prescribing ER/LA opioid analgesics, completion of the REMS processes, and to assess changes in behavior, prescribing, and patient assessment practices for prescribers who completed a continuing education (CE) activity within the past 6 to 12 months. The specific objectives include: 1) to assess the understanding of ER/LA opioid analgesic prescribers of the serious risks associated with the use of the ER/LA opioid analgesics and how to prescribe ER/LA opioid analgesics appropriately according to the six domains of the FDA Blueprint; 2) to assess understanding of whether the CE activities impacted prescribers' self-reported opioid prescribing behavior and practice; 3) to assess understanding of whether ER/LA opioid analgesic prescribers have encountered any barriers to applying knowledge gained in CE activities; and 4) to assess understanding of whether ER/LA opioid analgesics prescribers found completion of REMS-compliant training to be manageable or experienced obstacles to completion, including the time and/or effort required being overly burdensome.

The survey contained questions about the six core blueprint messages:

- Core Blueprint Message 1: Patients should be assessed for treatment with ER/LA opioid analgesic therapy;

- Core Blueprint Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics;
- Core Blueprint Message 3: Management of ongoing therapy with ER/LA opioid analgesics is important;
- Core Blueprint Message 4: It is important to counsel patients and caregivers about the safe use of ER/LA opioid analgesics.
- Core Blueprint Message 5: Prescribers must be familiar with general drug information concerning ER/LA opioid analgesics.
- Core Blueprint Message 6: Prescribers must be familiar with product-specific drug information concerning ER/LA opioid analgesics.

The LTE survey was qualitatively pre-tested with 16 ER/LA opioid analgesic prescribers that had completed any CE activity within the past year to assess comprehension and interpretation of questions.

Results

The LTE prescriber survey was conducted between February 17, 2015 and April 27, 2015. Prescribers were recruited using a subset of CE providers who sent invitation letters to all prescribers who completed a CE activity in the designated timeframe. Data on the number of invitations sent was not reported. A total of 546 prescribers responded to the invitation, 485 agreed to participate, 361 were eligible, and 328 completed the survey for a completion rate of 60%. Most participants completed the survey by internet (99%) while 1% completed it by paper.

Over half of respondents were male (55.5%), MDs (59.5%), and had been in clinical practice for more than 15 years (60%). The main specialty reported was pain management (28%) followed by other (16%), general practice/family medicine (11.5%), and hospice/palliative care (11.5%). Almost half of prescribers reported prescribing ER/LA opioid analgesics on average between less than 5 to 10 times per month (47.5%). The most commonly prescribed ER/LA were Oxycontin ER (71%), MS Contin (68%), Fentanyl (67%), and Duragesic (55%).

To assess changes in prescribing patterns, respondents were asked how many times, if any, if they considered prescribing an ER/LA opioid analgesic in the past 3 months but decided not to and if so, why. Over half of respondents (55.5%) reported that they considered prescribing on average 2-7 times in the past three months, but ultimately decided not to. The main reasons reported for deciding not to prescribe included I am selecting my patients differently based on assessment (55%) and I changed to prescribing more non-opioid medications (45%).

The survey contained questions about the six blueprint messages: 1) patients should be assessed for treatment with ER/LA opioid analgesics, 2) prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics, 3) management of ongoing therapy with ER/LA opioid analgesics, 4) the importance of counseling patients and caregivers about the safe use of ER/LA opioid analgesics, 5) prescribers must be familiar with general drug information concerning ER/LA opioid analgesics, and 6) prescribers must be familiar with product-specific drug information concerning ER/LA opioid analgesics.

3.3.5 Reviewers Comments

1. There is no information provided about how many CE providers participated in respondent recruitment and from how many CE providers the current respondents were recruited from. This information should be provided for the current and future assessments.
2. We recognize that there is overlap between some of the messages included in the Blueprint. After reconsideration of the current categorizations, we recommend changes to the key risk message categories.

Blueprint Message 1: Patients should be assessed for treatment with ER/LA opioid analgesic therapy

This domain included questions about how prescribers assess patients when they are considering treatment with ER/LA opioid analgesics including considering the risks of overdose and abuse, knowing when to appropriately refer high-risk patients to pain management specialists, and understanding opioid tolerance criteria (*see Table 11*).

- Respondents were aware of the risk factors for opioid abuse and were aware that prescribers should refer patients at high risk for drug abuse to a pain management specialist.
- Respondents were less aware of risk factors for opioid abuse (such as age, gender, and cigarette smoking) when presented with a case. Overall, most respondents were aware of steps to take to further assess possible abuse.
- There were 6 questions in this risk message with 17 correct responses. Overall, 14% of respondents answered all 6 questions correctly, 34% answered 5 correctly, and 30% answered 4 correctly.
- Forty-eight percent (48%) of respondents met or exceeded the 80% threshold (5 out of 6 questions correct).

Table 11: Prescriber Understanding of Blueprint Message 1: Patients Should Be Assessed for Treatment with ER/LA Opioid Analgesics Therapy	
Question	36 Month (n=328) n (%)
A patient with a history of substance abuse must not be prescribed an ER/LA opioid	True: 29 (9%) False: 293 (89%) I don't know: 6 (2%)
After thorough clinical evaluation, it is appropriate for prescribers to refer a patient at high risk for drug abuse to a pain management specialist.	True: 319 (97%) False: 7 (2%) I don't know: 2 (1%)
Which of the following are risk factors for opioid abuse?	A personal history of psychiatric disorders: 280 (85%) A personal history of past or current alcohol or drug abuse: 324 (99%) A family history of hypercholesterolemia: 24 (7%) A family history of illicit drug use or alcohol abuse: 290 (88%) None of the above: 0 (0%) I don't know: 0 (0%)
Case Elliott: Elliot is a thin, anxious 27-year-old man who is new to the area and comes to see you at 3:50	

Table 11: Prescriber Understanding of Blueprint Message 1: Patients Should Be Assessed for Treatment with ER/LA Opioid Analgesics Therapy	
Question	36 Month (n=328) n (%)
PM on Friday with a complaint of chronic left knee pain from a skiing accident 3 years ago. He says he is currently taking Oxycontin® ER 40 mg tablets every 12 hours. He wants only oxycodone ER and oxycodone IR for “rescue”. He has had 3 knee surgeries in the last 4 years and persistent trouble walking since the last surgery 12 months ago. He has had a number of non-medication therapies but says that only oxycodone ER works and that he is allergic to acetaminophen and NSAIDs. On physical examination of the knee, you note no erythema, swelling, or bruising. Surgical scars are present. His left quadriceps has signs of atrophy compared to the right side. There is limited range of motion (flexion less than 90 degrees) and pain on flexion of the left knee. On further questioning, Elliot admits to smoking cigarettes and drinking 1-2 beers every couple of days. He denies seeing other healthcare professionals for pain management. He also denies using therapeutic or recreational marijuana.	
Which of the following factors in Elliot's history raise your assessment of his risk for opioid abuse and misuse?	27 years old: 162 (49%) Male gender: 138 (42%) Chronic left knee pain from skiing accident: 66 (20%) Request for specific drugs: 314 (96%) Cigarette smoking: 177 (54%) I don't know: 1 (<1%)
Which of the following would be useful in further assessing possible abuse?	Ask for contact information for his primary physician: 291 (89%) Ask Elliott to provide a urine sample for drug screen: 298 (91%) Ask Elliott about his family's use of drugs and alcohol: 280 (85%) Check the state prescription monitoring program database for Elliott's prescription history (where available): 324 (99%) Use a risk assessment tool, such as the ORT (Opioid Risk Tool) to find out about mood swings, use of illegal substances, or history of legal problems: 314 (96%) I don't know: 1 (<1%)
Case Warren: Warren is a 67-year-old man with moderately severe degenerative lumbar disc disease, spinal stenosis, chronic back pain, and history of a back injury as a teenager. Up until the last 3 months, Warren has been successful in managing his pain with therapeutic exercises and NSAIDs, but he started having more pain after some vigorous hiking. He has curtailed his activities because of pain on slow walking and standing. He has no history of smoking, excessive alcohol intake, chronic depression, or legal problems.	
Which of the following would be important steps prior to starting Warren on a trial of ER/LA opioid analgesic medication?	Obtain a comprehensive urine drug screen: 235 (72%) Get a full psychiatric evaluation: 53 (16%) Complete a comprehensive pain history and physical examination: 320 (98%) Obtain a signed Patient Prescriber agreement for opioids: 290 (88%) Check for police records: 24 (7%) I don't know: 2 (1%)

Blueprint Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics

This key risk message included questions to assess prescriber knowledge about dose selection, individualizing dosage, and the basics of pain management (See *Table 12 below*).

- Overall, most respondents were aware of the correct indication for ER/LA opioid analgesics; chronic non-cancer pain (85%). Thirty percent of respondents incorrectly selected breakthrough pain from cancer as a possible indication.
- Respondents were less aware of steps prescribers should take when initiating a patient on ER/LA including considering a rescue medication for break-through pain (76.5%) and titrating doses based on efficacy and tolerability (78%).
- There were 7 questions in this risk message with 9 correct responses. Overall, 4% of respondents answered all 7 questions correctly, 25% answered 6 correctly, and 33% answered 5 correctly.
- Twenty-nine percent (29%) of respondents met or exceeded the 80% threshold (6 out of 7 correct responses).

Question	36 Month (n=328) n (%)
For methadone, the peak of respiratory depression can occur later and can persist longer than the analgesic effects.	True: 286 (87%) False: 10 (3%) I don't know: 32 (10%)
Conversion of patients to or from methadone using equianalgesic tables can result in overdose and death.	True: 243 (74%) False: 51 (15.5%) I don't know: 34 (10%)
Which of the following should prescribers do when initiating a patient on ER/LA opioid analgesics?	Start with the highest recommended dose of the ER/LA opioid analgesic and decrease the dose depending on tolerability: 2 (1%) Consider a rescue medication for breakthrough pain: 251 (76.5%) If switching from an immediate-release opioid, convert to an equianalgesic dose: 186 (57%) Titrate doses based on efficacy and tolerability as indicated in the product label: 255 (78%) None of the above: 12 (4%) I don't know: 1 (<1%)
For which of the following conditions are ER/LA opioid analgesics indicated?	Acute or postoperative pain: 64 (19.5%) As needed for headache or migraine pain: 13 (4%) Dental abscess pain: 27 (8%) Breakthrough pain from cancer: 100 (30.5%) Chronic non-cancer pain: 280 (85%) None of the above: 28 (8.5%) I don't know: 0 (0%)
Fatal respiratory depression may occur with the highest risk at initiation and when the dose is increased.	True: 312 (95%) False: 9 (3%) I don't know: 7 (2%)
Case Nancy: Nancy is a 35-year-old woman with chronic back pain from a motor vehicle accident in 2004. She tells you she was recently diagnosed with familial Long QT syndrome after several fainting spells. She has no known allergies and is currently taking NSAIDs for her back pain, but the pain is not well-controlled. She is in your office for help with her pain.	
You decide to give Nancy a 5-day trial of immediate-release oxycodone, 5 mg every 6 hours and 1 extra 5 mg dose at bedtime (25 mg/day total). During that time, her pain was not well controlled and she frequently had breakthrough pain. She says she does	Avinza® (morphine sulfate ER), 45 mg once a day: 92 (28%) Duragesic® (fentanyl transdermal system), one (1) 12 mg patch every 3 days: 176 (54%) Oxycontin® ER (oxycodone hydrochloride), 60

Table 12: Prescribers Understanding of Blueprint Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioids	
Question	36 Month (n=328) n (%)
not like taking a lot of pills. Starting which of the following would be appropriate (select all that apply):	mg once a day: 47 (14%) Nucynta® ER (tapentadol), 50 mg twice a day: 90 (27%) I don't know: 30 (9%)
In managing Nancy's treatment, you decide to rotate her medication to oxymorphone ER. The equianalgesic table indicates that the equianalgesic dose for oral oxycodone 25 mg/per day (current opioid) is 12.5 mg per day oral oxymorphone ER (new opioid). The most prudent course of action is (select the one best response):	Start her on a 24-hour dose of 12.5 mg oxymorphone ER (new opioid) based on the table: 72 (22%) Reduce the starting dose of oxymorphone ER (new opioid) by 25% to 50%: 192 (58.5%) Taper her from the oxycodone before starting oxymorphone ER: 4 (1%) Keep increasing the dose of oxycodone to establish pain control before rotating her to oxymorphone ER: 18 (5.5%) Rotate her medication from immediate release-oxycodone, 5 mg every 6 hours and 1 extra 5 mg dose at bedtime (25 mg/day total), to oxymorphone ER: 31 (9.5%) I don't know: 11 (3%)

Blueprint Message 3: Management of ongoing therapy with ER/LA opioid analgesics is important.

This message included questions to assess whether prescribers establish goals for therapy and monitor adherence to them, periodically evaluate pain control, outcomes, side effects, and quality of life, and prescriber awareness of the Patient Prescriber Agreements (PPAs) and knowledge about managing adverse events and referral sources (See *Table 13*).

- Overall, most respondents were aware of how prescribers should monitor patient adherence.
- There were 6 questions in this risk message with 14 correct responses. Overall, 32% of respondents answered all 6 questions correctly, 36% answered 5 correctly, and 20% answered 4 correctly.
- Sixty-seven percent (67%) of respondents met or exceeded the 80% threshold (5 out of 6 correct responses).

Table 13: Prescribers' Understanding of Blueprint Message 3: Management of Ongoing Therapy with ER/LA Opioid Analgesics is Important	
Question	36 Month (n=328) n (%)
How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Select all that apply.	Document any "drug seeking" behavior: 319 (97%) Utilize state Prescription Drug Monitoring Programs: 322 (98%) Use urine drug testing for both screening and confirmatory tests: 316 (96%) Perform laboratory testing for serum triglycerides: 66 (20%) Periodically re-evaluate therapy: 322 (98%) Perform medication reconciliation by counting

Table 13: Prescribers' Understanding of Blueprint Message 3: Management of Ongoing Therapy with ER/LA Opioid Analgesics is Important	
Question	36 Month (n=328) n (%)
	leftover drug supplies: 305 (93%) None of the above: 0 (0%) I don't know: 2 (1%)
Case Elliott: Elliot is a thin, anxious 27-year-old man who is new to the area and comes to see you at 3:50PM on Friday with a complaint of chronic left knee pain from a skiing accident 3 years ago. He says he is currently taking Oxycontin® ER 40 mg tablets every 12 hours. He wants only oxycodone ER and oxycodone IR for "rescue". He has had 3 knee surgeries in the last 4 years and persistent trouble walking since the last surgery 12 months ago. He has had a number of non-medication therapies but says that only oxycodone ER works and that he is allergic to acetaminophen and NSAIDs. On physical examination of the knee, you note no erythema, swelling, or bruising. Surgical scars are present. His left quadriceps has signs of atrophy compared to the right side. There is limited range of motion (flexion less than 90 degrees) and pain on flexion of the left knee. On further questioning, Elliot admits to smoking cigarettes and drinking 1-2 beers every couple of days. He denies seeing other healthcare professionals for pain management. He also denies using therapeutic or recreational marijuana.	
You find out that Elliot has received 9 prescriptions for opioids from 4 different physicians, using 5 pharmacies in the past 3 months; some insurance paid for, some he paid for with cash. The urine drug screen is positive for THC, hydromorphone, and oxycodone metabolites. The best option would be to (select all that apply):	Write for a 4-day supply of ER and IR oxycodone, to last until you contact his previous prescriber on Monday: 24 (7%) Not write a prescription today, as he lied about prescribers and drug use. His possible untreated addiction or abuse prevents you from addressing his pain. Refer to a pain management physician with addiction expertise: 299 (91%) Write 30-day prescriptions for ER and IR oxycodone while you get his prior medical records, obtain functional testing of his left leg and review test results: 5 (1.5%) Report him to the police as he is obviously diverting drug to pay for marijuana: 14 (4%) I don't know: 3 (1%)
Case Roberta: Roberta is a 71-year-old retired, executive legal secretary. She has osteoarthritis in both knees, with incapacitating pain, but she does not want total knee replacement. She has used hydrocodone/acetaminophen 3 times a day for two years with good pain control and function. She is a non-smoker, no history of excessive alcohol intake or driving while intoxicated or of substance misuse. She signed a treatment agreement and consent form for treatment with ER/LA opioid analgesics. Her urine drug screen is consistent with prescribed hydrocodone. On physical exam, you note swelling and tenderness to palpation of her knees bilaterally with decreased range of motion. Your state's Prescription Drug Monitoring Program reports that Roberta received two identical prescriptions from another prescriber during the past 2 months. When shown the report, Roberta admits diverting one of the prescriptions to her son, who also has chronic back pain.	
Which of the following would be the most appropriate step? Select the one best response.	Ask her to bring her son in at her next clinic visit to counsel them both: 86 (26%) Tell her you will not prescribe ER/LA opioid analgesics for her: 204 (62%) Call the other physician to complain: 3 (1%) Report this as a felony for dispensing opioids without a license: 13 (4%) I don't know: 22 (7%)

Table 13: Prescribers' Understanding of Blueprint Message 3: Management of Ongoing Therapy with ER/LA Opioid Analgesics is Important	
Question	36 Month (n=328) n (%)
<p>Case Danielle: Danielle is a 46-year-old woman with history of crush injury to the right foot and ankle after a bookcase fell on her at work about 2 years ago. She developed a subsequent complex regional pain syndrome with pain, numbness, and joint stiffness, but reports good pain control with regular use of hydrocodone 7.5 mg three times a day and occasional NSAIDs. She says she is not using other medications. She also reports symptom relief and increased joint mobility with physical therapy. She has a signed Opiate Treatment Agreement on file and has kept all her quarterly appointments over the past 18 months. She is in the office for a routine check-up and evaluation for continued opioid treatment.</p>	
<p>With this patient without clinical evidence of addictive illness, interim management at each office visit would include (select all that apply):</p>	<p>Assessment of the continued need for ER/LA opioid analgesics: 303 (92%) Comprehensive physical examination and full laboratory work-up at each visit: 90 (27%) Pain control and functional improvement evaluation: 319 (97%) Asking about changes in medications or the patient's medical condition: 316 (96%) Not doing a urine drug screen: 49 (15%) Checking the state Prescription Monitoring Program database for prescription history (where available): 283 (86%) I don't know: 1 (<1%)</p>
<p>Danielle's urine drug screen comes back strongly positive for cocaine metabolites and negative for hydrocodone metabolites. When confronted, she admits to using cocaine, but says it was several weeks ago and requests another screen on the spot, which gives the same results. Finding only cocaine metabolites in the urine drug screen of two separate samples, without metabolites of the prescribed opioid suggests which of the following? Select the one best response.</p>	<p>Lab error: 3 (1%) Infrequent "recreational use" of cocaine: 10 (3%) Diversion of prescribed opioid: 281 (86%) Need for in-depth psychodynamic in-office counseling sessions: 25 (8%) I don't know: 9 (3%)</p>
<p>Case Lynette: Lynette is a married 58-year-old woman with ovarian cancer, who lives with her husband and two cats. Her disease is stable based on recent imaging and CA 125 assay results. She has had stable pain control for 9 months with hydromorphone ER (EXALGO®) 12 mg QD. She comes to the office each month for renewal of her EXALGO® prescription; however, for the past 2 months, she has asked for renewal 5 days early, as she ran out of medication. When questioned at her office visit, she says she did not realize that she was requesting refills early and does not recall using more medication than prescribed. She reports no change in her pain control and says her current regimen is still effective. She is alert, oriented to person, place and time, and behaves appropriately. When you query your state's Prescription Monitoring Program, you do not find evidence that she has seen other doctors or filled multiple prescriptions for opioids.</p>	
<p>Which of the following steps are most appropriate? (select all that apply):</p>	<p>Collect a sample for urine drug screen: 262 (80%) Refuse to give her a refill until the date when her prescription would have been used up: 100 (30.5%) Ask where she keeps her medications and how she secures them: 310 (94.5%) Consider rotating her to another opioid: 84 (26%) I don't know: 1 (<1%)</p>

Blueprint Message 4: It is important to counsel patients and caregivers about the safe use of ER/LA opioid analgesics.

This key risk message included questions to assess prescriber knowledge about safe use of the ER/LA opioids (See *Table 14*).

- Most respondents were aware of drugs and other substances that can potentiate the risk of a serious overdose and death. Respondents were also aware of instructions to give patients when starting ER/LA opioid analgesic including not to drink alcohol.
- There were 10 questions in this risk message with 13 correct responses. Overall, 45% of respondents answered all 10 questions correctly, 36% answered 9 correctly, and 13% answered 8 correctly.
- Ninety-four percent (94%) of respondents met or exceeded the 80% threshold (8 out of 10 correct responses).

Table 14: Prescribers’ Understanding of Blueprint Message 4: The Importance of Counseling Patients and Caregivers about Safe Use of ER/LA opioid analgesics.	
Question	36 Month (n=328) n (%)
ER/LA opioid analgesic transdermal patches may be cut prior to use.	True: 18 (5.5%) False: 302 (92%) I don't know: 8 (2%)
A patient should be told not to cut an extended release tablet in half to reduce the dose.	True: 299 (91%) False: 27 (8%) I don't know: 2 (1%)
Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? Select Yes, No, or I don't know for each of the following options.	
Sedative hypnotics	Yes: 327 (99.7%) No: 0 (0%) I don't know: 1 (<1%)
Anxiolytics	Yes: 317 (97%) No: 4 (1%) I don't know: 7 (2%)
Alcohol	Yes: 327 (99.7%) No: 1 (<1%) I don't know: 0 (0%)
Illegal drugs	Yes: 328 (100%) No: 0 (0%) I don't know: 0 (0%)
Caffeine	Yes: 30 (9%) No: 238 (73%) I don't know: 60 (18%)
Case Nancy: Nancy is a 35-year-old woman with chronic back pain from a motor vehicle accident in 2004. She tells you she was recently diagnosed with familial Long QT syndrome after several fainting spells. She has no known allergies and is currently taking NSAIDs for her back pain, but the pain is not well-controlled. She is in your office for help with her pain.	
When you initiate the oxymorphone ER, which of the following instructions do you need to give Nancy? Select all that apply.	Take oxymorphone ER tablets whole with enough water to swallow them: 277 (84.5%) For a smaller dose, cut the tablet in half: 9 (3%) Throw away the leftover oxycodone in the trash: 29 (9%)

Table 14: Prescribers' Understanding of Blueprint Message 4: The Importance of Counseling Patients and Caregivers about Safe Use of ER/LA opioid analgesics.	
Question	36 Month (n=328) n (%)
	<p>Don't drink alcohol while taking the oxymorphone ER: 314 (96%)</p> <p>Store the tablets in the bathroom medicine cabinet: 31 (9.5%)</p> <p>I don't know: 3 (1%)</p>
<p>Case Lynette: Lynette is a married 58-year-old woman with ovarian cancer, who lives with her husband and two cats. Her disease is stable based on recent imaging and CA 125 assay results. She has had stable pain control for 9 months with hydromorphone ER (EXALGO®) 12 mg QD. She comes to the office each month for renewal of her EXALGO® prescription; however, for the past 2 months, she has asked for renewal 5 days early, as she ran out of medication. When questioned at her office visit, she says she did not realize that she was requesting refills early and does not recall using more medication than prescribed. She reports no change in her pain control and says her current regimen is still effective. She is alert, oriented to person, place and time, and behaves appropriately. When you query your state's Prescription Monitoring Program, you do not find evidence that she has seen other doctors or filled multiple prescriptions for opioids.</p>	
<p>Lynette reports that she keeps her medications at home in her purse or desk drawer, which is unlocked. On further questioning about her household, she mentions that her neighbor's teenage son has been helping her with her cat boxes for the last four months. Which of the following would be the most appropriate step(s)? Select all that apply.</p>	<p>Only prescribe 2 weeks of hydromorphone ER at a time and ask her to bring in her prescription bottles for pill counts at each visit: 176 (54%)</p> <p>Stress the safety concerns when ER/LA opioid analgesics are taken by someone for whom they are not prescribed: 312 (95%)</p> <p>Recommend storing medication in a safe and secure place away from children, family members, and visitors: 322 (98%)</p> <p>Tell her that if she cannot safeguard her medications, you will consider an alternative treatment plan and therapy: 244 (74%)</p> <p>I don't know: 1 (<1%)</p>
<p>Case Fred: Fred is an 89-year-old obese man with severe lumbar disc degeneration treated for over 10 years with daily acetaminophen/oxycodone 5/325 mg every 6 hours. He has significantly increased back and leg pain after sliding off his chair onto the floor. The pain keeps him awake at night and now he wants "something that works better." You complete a thorough physical examination and abuse risk evaluation. You decide to start Fred on a trial of a daily ER/LA opioid analgesic.</p>	
<p>Which of the following statements are appropriate patient education and counseling information for you to give him (select all that apply):</p>	<p>What to do for a missed dose: Double up with the missed tablet to keep pain under control: 37 (11%)</p> <p>The treatment goal: Control the pain so he can sleep at night and walk with assistance during the day; evaluate with physical examination and information from wife and family: 309 (94%)</p> <p>Discuss the risks of long-term opioid use</p>

Table 14: Prescribers' Understanding of Blueprint Message 4: The Importance of Counseling Patients and Caregivers about Safe Use of ER/LA opioid analgesics.	
Question	36 Month (n=328) n (%)
	<p>including constipation and Fred or his caregivers should let you know if he has any bowel issues: 311 (95%)</p> <p>Avoid discussing addiction potential, respiratory depression, and death with such an elderly patient or his caregivers: 12 (4%)</p> <p>Discontinuing treatment: Just stopping ER/LA opioid analgesics is OK if you are not addicted: 7 (2%)</p> <p>I don't know: 2 (1%)</p>

Blueprint Message 5: Prescribers must be familiar with general drug information concerning ER/LA opioid analgesics.

This key risk message included questions to assess prescriber knowledge of general characteristics of ER/LA opioid analgesics including side effects, drug-drug interactions, definition of opioid-tolerant patients, and dosing (See *Table 15 below*).

- There were 7 questions in this risk message. Overall, 28% of respondents answered all 7 questions correctly, 39% answered 6 correctly, and 24% answered 5 correctly.
- Sixty-eight percent (68%) of respondents met or exceeded the 80% threshold (6 out of 7 correct responses).

Table 15: Prescribers' Understanding of Blueprint Message Key Risk Message 5: Prescribers must be familiar with general drug information concerning ER/LA opioid analgesics.	
Question	36 Month (n=328) n (%)
Central nervous system depressants, such as benzodiazepines, can have a potentiating effect on the sedation and respiratory depression caused by opioids.	<p>True: 326 (99%)</p> <p>False: 0 (0%)</p> <p>I don't know: 2 (1%)</p>
Some ER opioid formulations may rapidly release opioid (dose dump) when taken with alcohol.	<p>True: 267 (81%)</p> <p>False: 24 (7%)</p> <p>I don't know: 37 (11%)</p>
Monoamine oxidase inhibitors (MAOIs) are the preferred antidepressants for use with ER/LA opioid analgesics.	<p>True: 8 (2%)</p> <p>False: 288 (88%)</p> <p>I don't know: 32 (10%)</p>
Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids.	<p>True: 311 (95%)</p> <p>False: 4 (1%)</p> <p>I don't know: 13 (4%)</p>
What should be done if a patient treated with a transdermal opioid develops a high fever? Select the one best response.	<p>Remove the patch until the fever is below 102F: 76 (23%)</p> <p>Switch the patient to another ER/LA opioid analgesic: 34 (10%)</p> <p>Monitor the patient closely for opioid side effects and reduce the dose of the patch if necessary: 169 (51.5%)</p> <p>Move the patch to another location on the body: 3 (1%)</p> <p>I don't know: 46 (14%)</p>
When initiating an ER/LA opioid analgesic in a	True: 314 (96%)

Table 15: Prescribers' Understanding of Blueprint Message Key Risk Message 5: Prescribers must be familiar with general drug information concerning ER/LA opioid analgesics.	
Question	36 Month (n=328) n (%)
patient who is currently taking a sedative, reduce the dose of the opioid and/or sedative.	False: 10 (3%) I don't know: 4 (1%)
Patients who are not opioid tolerant can initiate opioid therapy with any type of ER/LA opioid analgesic.	True: 72 (22%) False: 245 (75%) I don't know: 11 (3%)

Blueprint Message 6: Prescribers must be familiar with product-specific drug information concerning ER/LA opioid analgesics.

This key risk message included questions to assess prescriber knowledge of product-specific characteristics of ER/LA opioid analgesics including side effects, drug-drug interactions, definition of opioid-tolerant patients, and dosing (See *Table 16 below*).

- Respondents were less aware of product-specific drug information. Respondents were less aware of what patients were considered opioid-tolerant, how to properly dispose of transdermal patches, and which specific opioid to prescribe when presented with a case scenario.
- There were 3 questions in this risk message with 5 correct responses. Overall, 8% of respondents answered all 3 questions correctly, 34.5% answered 2 correctly, and 40% answered 1 correctly.
- Eight percent (8%) of respondents met or exceeded the 80% threshold (3 correct responses).

Table 16: Prescribers' Understanding of Blueprint Message Key Risk Message 6: Prescribers must be familiar with product specific drug information concerning ER/LA opioid analgesics.	
Question	36 Month (n=328) n (%)
Patients considered opioid-tolerant are those (select all that apply):	Who are using 25 mcg/hour transdermal fentanyl for at least 7 days: 132 (40%) Who are not currently taking opioid therapy, but have no known intolerance or hypersensitivity to the drug fentanyl: 27 (8%) Who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer: 240 (73%) None of the above: 69 (21%) I don't know: 11 (3%)
Dispose of transdermal patches by cutting into small pieces and throwing in the trash.	True: 67 (20%) False: 229 (70%) I don't know: 32 (10%)
Case Nancy: Nancy is a 35-year-old woman with chronic back pain from a motor vehicle accident in 2004. She tells you she was recently diagnosed with familial Long QT syndrome after several fainting spells. She has no known allergies and is currently taking NSAIDs for her back pain, but the pain is not well-controlled. She is in your office for help with her pain.	
Which of the following opioids should be avoided for her pain management? Select all that apply.	Butrans® (buprenorphine transdermal system): 112 (34%) Avinza® (morphine sulfate ER): 59 (18%) EXALGO® (hydromorphone hydrochloride): 51 (15.5%) Dolophine® (methadone hydrochloride): 221 (67%)

Table 16: Prescribers' Understanding of Blueprint Message Key Risk Message 6: Prescribers must be familiar with product specific drug information concerning ER/LA opioid analgesics.	
Question	36 Month (n=328) n (%)
	None of the above: 21 (6%) I don't know: 41 (12.5%)

Prescriber Behavior Questions:

- These questions assessed changes in prescribing practices, behaviors, and opinions after participating in a REMS-compliant CE activity (see *Table 17 below*).
- Respondents reported on how frequently they perform certain activities when treating patients with ER/LA opioid analgesics since their participation in the REMS-compliant CE activity. Respondents self-reported that since completion of a CE-activity, they more often caution patients about important risks, including overdose and respiratory depressions (65%), counsel patients on the importance of keeping ER/LA opioid analgesics safe and away from children (56%), instruct patient that it is illegal to sell, share, or give away ER/LA opioid analgesics (53%), counsel patient on the most common side effects from opioid use (50%), instruct patients about the importance of and how to safely dispose of their unused opioids (49%), discuss with patients how to safely taper their ER/LA opioid analgesics if it is no longer needed (45%), discuss with patients what to do if a dose is missed (41%), and use the PCD for discussions with patients (39%). Respondents also reported that they more often reassess the need for opioids (65%), check the state Prescription Monitoring Program database for prescription history (64%), use structured interview tools or screening tools to assess patient's risk of abuse or misuse (50%), perform urine drug tests (49%), or complete a patient-prescriber agreement (PPA) or patient contract when the ER/LA opioid analgesics is first prescribed (48%).
- Respondents were asked about barriers to implementing information learned at the CE activities. The top barriers included: insufficient time during the clinical encounter to address all of the treatment considerations (63%), patient non-compliance with dose reconciliation efforts (57%), and patients continue to identify new ways of drug-seeking behavior not currently addressed in the REMS-compliant CE for ER/LA opioid analgesics (48%).
- Respondents were asked how their prescribing behaviors have changed since participation in a REMS-complaint CE activity. Overall, while over half reported no change (56%); 22% of respondents reported prescribing ER/LA opioid analgesics less often and 19% reported prescribing ER/LA opioid analgesics more often.
- Respondents were asked how the types of medications they prescribe have changed since participation in a REMS-compliant CE activity. Thirty-eight percent (38%) of respondents reported prescribing more non-opioid medications and 23% of respondents reported limiting which ER/LA opioid analgesics they prescribe. Thirty-two percent (32%) of respondents reported no change in the types of medications they prescribe.

Table 17: Prescriber-Reported Behaviors When Prescribing ER/LA Opioid Analgesics	
Question	36 Month (n=328) n (%)
Based on your participation in recent REMS-compliant CE for ER/LA opioid analgesics, indicate if you engage in any of these behaviors more often, less often, or about the same.	
Used the patient counseling document (PCD) on ER/LA opioids for discussions with patients	More often: 129 (39%) About the same: 122 (37%)

Table 17: Prescriber-Reported Behaviors When Prescribing ER/LA Opioid Analgesics	
Question	36 Month (n=328) n (%)
	Less often: 3 (1%) Never: 69 (21%) Don't know: 5 (1.5%)
Cautioned about important risks, including overdose and respiratory depression	More often: 213 (65%) About the same: 114 (35%) Less often: 1 (<1%) Never: 0 (0%) Don't know: 0 (0%)
Discuss with patients how to safely taper their ER/LA opioid analgesic if it is no longer needed	More often: 147 (45%) About the same: 171 (52%) Less often: 7 (2%) Never: 3 (1%) Don't know: 0 (0%)
Counsel patients on the most common side effects from opioid use	More often: 165 (50%) About the same: 160 (49%) Less often: 2 (1%) Never: 0 (0%) Don't know: 1 (<1%)
Instruct patients about the importance of and how to safely dispose of their unused opioids	More often: 162 (49%) About the same: 145 (44%) Less often: 8 (2%) Never: 12 (4%) Don't know: 1 (<1%)
Counsel patients on the importance of keeping ER/LA opioid analgesics safe and away from children.	More often: 183 (56%) About the same: 137 (42%) Less often: 6 (2%) Never: 2 (1%) Don't know: 0 (0%)
Instruct patients that it is illegal to sell, share, or give away ER/LA opioid analgesics.	More often: 173 (53%) About the same: 149 (45%) Less often: 2 (1%) Never: 4 (1%) Don't know: 0 (0%)
Discuss with patients what to do if a dose is missed.	More often: 134 (41%) About the same: 180 (55%) Less often: 9 (3%) Never: 4 (1%) Don't know: 1 (<1%)
Based on your participation in recent REMS-compliant CE for ER/LA opioid analgesics, indicate if you engage in any of these behaviors more often, less often, or about the same.	
Use structured interview tools or other screening tools to assess patients' risk of abuse or misuse of their medications when managing patients using ER/LA opioid analgesics	More often: 163 (50%) About the same: 138 (42%) Less often: 6 (2%) Never: 20 (6%) Don't know: 1 (<1%)
Complete a PPA or patient contract at the time an ER/LA opioid analgesic is first prescribed.	More often: 156 (48%) About the same: 146 (44.5%) Less often: 7 (2%) Never: 18 (5.5%) Don't know: 1 (<1%)
Perform urine drug screens	More often: 161 (49%) About the same: 136 (41.5%) Less often: 5 (1.5%)

Table 17: Prescriber-Reported Behaviors When Prescribing ER/LA Opioid Analgesics	
Question	36 Month (n=328) n (%)
	Never: 26 (8%) Don't know: 0 (0%)
Reassess the need for opioids	More often: 213 (65%) About the same: 114 (35%) Less often: 1 (<1%) Never: 0 (0%) Don't know: 0 (0%)
Check the state Prescription Monitoring Program database for prescription history (where available)	More often: 209 (64%) About the same: 98 (30%) Less often: 3 (1%) Never: 16 (5%) Don't know: 2 (1%)
Select from the list below the barriers that you've encountered in your ability to apply the information that you gained in the REMS-compliant CE for ER/LA opioid analgesics	Insufficient time during the clinical encounter to address all of the treatment considerations: 207 (63%) Patient non-compliance with dose reconciliation efforts: 188 (57%) Patients continue to identify new ways of drug seeking behavior not currently addressed in the REMS-compliant CE for ER/LA opioid analgesics: 156 (48%) Challenges communicating safe storage considerations to patients: 65 (20%) Difficulty getting patients to sign treatment agreement forms: 49 (15%) No barriers were encountered: 44 (13%) Other: 5 (1.5%)
Since you have participated in a REMS-compliant CE for ER/LA opioid analgesics, how have the types of medications you prescribed changed?	I have prescribed more ER/LA opioid analgesics: 58 (18%) I have prescribed fewer ER/LA opioid analgesics: 43 (13%) I have prescribed more immediate release opioids: 27 (8%) I prescribed more non-opioid medications: 126 (38%) I have limited which ER/LA opioid analgesics I prescribe: 77 (23.5%) Other: 7 (2%) I have not changed the types of medication I prescribe: 106 (32%)
Since you have participated in a REMS-compliant CE for ER/LA opioid analgesics, how has your prescribing behavior changed?	I write ER/LA opioid analgesic prescriptions more often: 61 (19%) I write ER/LA opioid analgesic prescriptions less often: 72 (22%) Other: 11 (3%) There has been no change in my prescribing behavior related to ER/LA opioid analgesics: 184 (56%)

3.3.6 Reviewer's comments on Long-term Prescriber Survey

Overall, respondents were knowledgeable about management and counseling requirements for patients being considered for treatment or currently being treated with ER/LA opioid analgesics. Respondents were less knowledgeable about assessment of patients, initiation and modification of treatment, and general and product specific information for ER/LA opioid analgesics. Since participating in a REMS-compliant activity, respondents reported more often conducting

appropriate prescriber behaviors such as counseling on risks and side effects, instructing patients how to safely dispose of unused ER/LA opioid analgesics, instructing patients to keep ER/LA opioid analgesics medications away from children, informing patients that it is illegal to share, sell, or give-away ER/LA opioid analgesics, using tools to screen patients for risk of misuse or abuse, completing a PPA, performing urine drug screens, checking the state prescription monitoring program database, and reassessing the need for opioids. Respondents reported that the main barriers to applying information learned from the REMS-compliant CE activities were insufficient time to address all of the treatment considerations (63%), patient non-compliance (57%), and patients continuing to identify new drug-seeking behaviors that were not addressed in the training activity (48%).

While over half of respondents reported no changes in prescribing behaviors since participating in the CE activity, 22% reported writing prescriptions for ER/LA opioid analgesics less often and 19% reported writing more ER/LA opioid analgesics prescriptions. Thirty-eight percent (38%) of respondents reported prescribing more non-opioid medications since the CE activity while 23% reported limiting which ER/LA opioid analgesics they prescribe. Thirty-two percent (32%) of respondents reported no changes in the types of medications prescribed since the CE activity.

3.4 Assessment Element 4: Patient Survey

This assessment element states:

Evaluation of Patient Understanding: The results of an evaluation of patients' understanding of the serious risks of these products and their understanding of how to use these products safely.

The purpose of the patient surveys was to assess patient knowledge of the safe use of ER/LA opioid analgesics products following implementation of the REMS. The survey also included questions about patient-reported prescriber behaviors including appropriate screening and counseling.

Comments about the 24-month patient survey were sent to the RPC on February 13, 2015. The response was that the comments were sent too late to be incorporated into the 36-month assessment report but would be considered for the next assessment. Comments included using an alternative recruitment source to supplement the database used that includes patients on Medicaid and Medicare; the inclusion of caregivers as survey participants; revisions to the survey questions; the possibility of a sub-study focusing on new users; and making the opioid drug lists consistent across the survey.

The 36-month patient survey was conducted between September 1, 2013 and August 31, 2014. The patient survey was pretested in 21 patients prescribed ER/LA opioid analgesics to identify any limitations with the survey instrument and survey process prior to the 12 month assessment report submission. Patients were identified from medical and pharmacy claims in the HealthCore Integrated Research Database (HIRD). This database contains longitudinal claims data from commercially-insured patients in the US (14 health plans). Patients were eligible to participate if they currently active HIRD members and adults age 18 or older who filled at least one prescription for an ER/LA opioid analgesics between September 1, 2013 and August 31, 2014. Patients were excluded if they were contacted for the 24-month survey, failed to validate date of birth or name; did not fill a prescription in the 12 months prior to the survey; were employed as a physician, employed or family member employed with survey vendor, RPC, or

FDA; or unsure of the opioid or class prescribed. Approximately 11,500 patients were eligible to complete the survey. A total of 2,441 patients were contacted via mail or telephone. Out of those, 272 were excluded during screening leaving 2,169 contacted patients. A total of 423 patients completed the survey for a response rate of 17% among the contacted respondents: 268 users of oral, non-methadone opioids; 101 patch users; 54 methadone users.

According to patient reports, most patients were between the ages of 35-64 (83%); female (60%); used oral drugs that were not methadone only (65%); Caucasian (94%); married (68%); and used ER/LA opioid analgesics for arthritis, arthropathies, osteoarthritis, and musculoskeletal pain (86%). Over half of patients (56%) had an annual income of \$50,000 or more and half were college or community college/technical school graduates or completed graduate school (50%). Most patients had used an ER/LA opioid analgesic before the most recent prescription (83%). Almost half were prescribed the ER/LA opioid analgesic by a pain specialist (42%) other specialists (30%), and primary care providers (25%). The most commonly used drugs as reported by survey respondents were: Oxycodone (39%) and Morphine (15%). Only 16% of respondents were new users and 56% of respondents reported 12 months or more since they were first prescribed the ER/LA opioid analgesics.

The survey contained questions about four key domains of interest: 1) patients’ understanding of the serious risks of ER/LA opioid analgesics, 2) receipt and comprehension of the Medication Guide (MG) and patient counseling document (PCD), 3) perceived access and satisfaction of access to pain medications, and 4) patient-reported frequency of appropriate prescriber behaviors, including appropriate screening and counseling about ER/LA opioid analgesics.

Domain 1: Patients’ understanding of the serious risks of ER/LA opioid analgesics.

This domain included questions about the five key risk messages: 1) The patient understands the serious risks associated with the use of their ER/LA opioid analgesics; 2) The patient knows what to do if they take too much drug; 3) The patient understands the need to store the drug in a safe place, 4) The patient knows they should not share the drug with anyone; and 5) The patient understands how to use the drug safely.

Key risk message 1: The patient understands the serious risks associated with the use of their ER/LA opioid analgesic. This key risk message included questions about the risks and side effects associated with the use of ER/LA opioid analgesics. (See *Table 18 below*)

- Respondents’ understanding of this key risk message was high. Eighty-one percent of participants were aware that ER/LA opioid analgesics can cause dizziness, lightheadedness, and sleepiness. Ninety-three percent of participants were aware of the problems that overdoses can cause (i.e. breathing problems, slow breathing that can lead to death).
- Overall, 77% of respondents answered both questions correctly for this risk message; 21% answered 1 of 2 correctly and 3% answered both incorrectly.

Table 18: Patients’ Understanding of the Serious Risks of ER/LA Opioid Analgesics		
Key Risk Message 1: The patient understands the serious risks associated with the use of their ER/LA opioid analgesic		
Question	24-Month (n=413) N (%)	36-Month (n=423) N (%)
Overdose may cause life-threatening breathing problems, respiratory depression, or	Correct: 386 (94%) Incorrect: 10 (2%)	Correct: 394 (93%) Incorrect: 13(3%)

abnormally slow breathing that can lead to death.	Don't Know: 16 (4%)	Don't Know: 15 (4%) No Response: 1 (<1%)
ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy.	Correct: 345 (84%) Incorrect: 46 (11%) Don't Know: 21 (5%)	Correct: 342 (81%) Incorrect: 49 (12%) Don't Know: 32 (8%)

Key risk message 2: The patient knows what to do if they too much drug (See *Table 19 below*).

- Respondent's understanding was high. The majority of respondents (88%) knew to seek emergency medical help for overdose, even if the patient felt fine and knew to seek emergency help if experienced side effects such as trouble breathing, chest pain, or swelling of their face, tongue, or throat (97%).
- Overall, 87% of respondents answered both questions correctly for this risk message.

Table 19: Patients' Understanding of the Serious Risks of ER/LA Opioid Analgesics: Key Risk Message 2: The patient knows what to do if they take too much drug.		
Question	24-Month (n=413) N (%)	36-Month (n=423) N (%)
Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fine.	Correct: 363 (88%) Incorrect: 22 (5%) Don't Know: 26 (6%)	Correct: 374 (88%) Incorrect: 38 (9%) Don't Know: 10 (2%) No Response: 1 (<1%)
Seek emergency medical help for side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain or swelling of their face, tongue, or throat after taking or using ER/LA opioid analgesics.	Correct: 400 (97%) Incorrect: 10 (2%) Don't Know: <5 (1%)	Correct: 412 (97%) Incorrect: 8 (2%) Don't Know: 3 (1%)

Key risk message 3: The patient understands the need to store the drug in a safe place (See *Table 20 below*).

- The majority of respondents knew that unused ER/LA opioid analgesics should not be thrown in the trash (93%) and that a child could die if they take or use ER/LA opioid analgesics (93%).
- Only 71% of respondents were aware the ER/LA opioid analgesics should not be stored in the medicine cabinet with other medications in the household.
- Overall, 62% of respondents answered all three questions correctly and 33% answered 2 out of the 3 correctly.

Table 20: Patients' Understanding of the Serious Risks of ER/LA Opioid Analgesics Key Risk Message 3: The patient understands the need to store the drug in a safe place.		
Question	24-Month (n=413) N (%)	36-Month (n=423) N (%)
Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the household.	Correct: 271 (66%) Incorrect: 96 (23%) Don't Know: 46 (11%)	Correct: 300 (71%) Incorrect: 90 (21%) Don't Know: 33 (8%)
Do not throw away any unused ER/LA opioid analgesics in the trash.	Correct: 375 (91%) Incorrect: 22 (5%) Don't Know: 16 (4%)	Correct: 393 (93%) Incorrect: 21 (5%) Don't Know: 9 (2%)
A child could die if they take or use the respondent's ER/LA opioid analgesics.	Correct: 384 (93%) Incorrect: 14 (3%) Don't Know: 15 (4%)	Correct: 393 (93%) Incorrect: 17 (4%) Don't Know: 13 (3%)

Key risk message 4: The patient knows they should not share the drug with anyone (See *Table 21 below*).

- There was a very high understanding of this key risk message. The majority of respondents were aware that ER/LA opioid analgesics should not be given to other people with the same condition (98%) and selling or giving away ER/LA opioid analgesics was against the law (98%).
- Overall, 96% of respondents answered both questions correctly.

Question	24-Month (n=413) N (%)	36-Month (n=423) N (%)
Do not give ER/LA opioid analgesics to other people who have the same condition as you.	Correct: 406 (98%) Incorrect: 6 (1%) Don’t Know: <5 (1%)	Correct: 415 (98%) Incorrect: 6 (1%) Don’t Know: 2 (<1%)
Selling or giving ER/LA opioid analgesics is against the law.	Correct: 402 (97%) Incorrect: 11 (3%) Don’t Know: 0 (0%)	Correct: 413 (98%) Incorrect: 9 (2%) Don’t Know: 1 (<1%)

Key risk message 5: The patient understands how to use the drug safely (See *Table 22 below*).

- There was a high level of understanding for some questions. Most respondents knew that they should talk to their healthcare provider before stopping ER/LA opioid analgesics (84%), they should talk to their healthcare provider if the current dose doesn’t control their pain (96%), they should inform their healthcare provider about all other medications being used (93%), that it is not okay to drink alcohol while using ER/LA opioid analgesics (93%), they should inform their healthcare provider about a history of drug or alcohol abuse or mental health problems (90%), and they should inform their healthcare provider about over the counter medications and vitamins or supplements (87%).
- There was a lower level of understanding in terms of awareness that patients should read the medication guide every time a prescription is filled (55%) and that it is okay to drink caffeine while using ER/LA opioid analgesics (49%).
- Overall, 16% of respondents answered all eight questions correctly; 40% answered 7 out of 8 correctly, and 26% answered 6 out of 8 correctly.
- The majority of oral non-methadone user respondents (n=268; 93%) were aware that they should not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was missed. Seventy-six percent of oral user respondents (76%) were aware that ER/LA opioid analgesics should not be split or crushed if the respondent is having trouble swallowing.
- Most patch user respondents (n=101; 91%) were aware that the patches should not be cut in half to use less medication. A lower percentage of patch user respondents were aware that they should inform their healthcare provider of any fever (70%) and not to use a hot tub or sauna while using ER/LA opioid analgesics if pain persists (77%)
- Seventy-one percent (71%) of non-methadone oral drug users answered both of the cohort specific questions correctly. Responses were split between patch users with 48%

of respondents answering all three questions correctly and 44% answering 2 out of 3 correctly.

Table 22: Patients' Understanding of the Serious Risks of ER/LA Opioid Analgesics		
Key Risk Message 5: The patient understands how to use the drug safely		
Question	24-Month (n=413) N (%)	36-Month (n=423) N (%)
Talk to a healthcare provider prior to stopping ER/LA opioid analgesics	Correct: 346 (84%) Incorrect: 49 (12%) Don't Know: 18 (4%)	Correct: 357 (84%) Incorrect: 50 (12%) Don't Know: 16 (4%)
Talk to a healthcare provider about taking or using more ER/LA opioid analgesics if the current dose doesn't control your pain.	Correct: 389 (94%) Incorrect: 18 (4%) Don't Know: 6 (1%)	Correct: 405 (96%) Incorrect: 10 (2%) Don't Know: 7 (<1%) No Response: 1 (<1%)
It is not okay to drink alcohol while taking or using ER/LA opioid analgesics.	Correct: 385 (93%) Incorrect: 12 (3%) Don't Know: 16 (4%)	Correct: 394 (93%) Incorrect: 16 (4%) Don't Know: 12 (3%) No Response: 1 (<1%)
Read the attached MG every time an ER/LA opioid analgesic prescription is filled.	Correct: 231 (56%) Incorrect: 145 (35%) Don't Know: 37 (9%)	Correct: 232 (55%) Incorrect: 136 (32%) Don't Know: 55 (13%)
Inform healthcare providers about all the other medications being used.	Correct: 398 (96%) Incorrect: 13 (3%) Don't Know: <5 (1%)	Correct: 394 (93%) Incorrect: 26 (6%) Don't Know: 3 (1%)
Inform healthcare providers about any history of abuse of street or prescription drugs, alcohol addiction, or mental health problems.	Correct: 375 (91%) Incorrect: 28 (7%) Don't Know: 10 (2%)	Correct: 382 (90%) Incorrect: 30 (7%) Don't Know: 10 (2%) No Response: 1 (<1%)
Inform healthcare providers about over the counter medicines, vitamins, and dietary supplements.	Correct: 368 (89%) Incorrect: 38 (9%) Don't Know: 7 (2%)	Correct: 369 (87%) Incorrect: 42 (10%) Don't Know: 10 (2%) No Response: 2 (<1%)
It is okay to drink caffeine while using ER/LA opioid analgesics.	Correct: 202 (49%) Incorrect: 60 (15%) Don't Know: 148 (36%)	Correct: 207 (49%) Incorrect: 85 (20%) Don't Know: 131 (31%)
ER/LA opioid analgesics should not be split or crushed if the respondent is having trouble swallowing their medication. (*only for non-methadone oral drug users)	Correct: 206 (77%) Incorrect: 23 (9%) Don't Know: 37 (14%)	Correct: 204 (76%) Incorrect: 34 (13%) Don't Know: 30 (11%)
Do not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was missed. (only for non-methadone oral drug users)	Correct: 244 (92%) Incorrect: 15 (6%) Don't Know: 5 (2%)	Correct: 248 (93%) Incorrect: 14 (5%) Don't Know: 6 (2%)
Inform healthcare providers of any fever (*only for patch and no methadone users)	Correct: 74 (73%) Incorrect: 14 (14%) Don't Know: 14 (14%)	Correct: 71 (70%) Incorrect: 20 (20%) Don't Know: 10 (10%)
Do not use a hot tub or sauna while using ER/LA opioid analgesics is pain persists (*only for patch and no methadone users)	Correct: 84 (82%) Incorrect: 8 (8%) Don't Know: 10 (10%)	Correct: 78 (77%) Incorrect: 10 (10%) Don't Know: 12 (12%)
Do not cut ER/LA opioid analgesics patches in half to use less medicine. (only for patch and no methadone users)	Correct: 84 (82%) Incorrect: 7 (7%) Don't Know: 11 (11%)	Correct: 91 (90%) Incorrect: 6 (6%) Don't Know: 4 (4%)

Domain 2: Receipt and comprehension of the Medication Guide (MG) and Patient Counseling Document (PCD)

There were 14 questions that accessed patient receipt and comprehension of the Medication Guide and PCD (See *Table 23 below*). Most respondents reported receiving the Medication Guide from their pharmacists with their last fill (94%) while 95% of respondents received the Medication Guide from their pharmacist in the last 12 months. Of the respondents that received the Medication Guide, 89% read all with each pharmacy fill (14%) or read all (65%) of the Medication Guide at least once. The majority of respondents that read the Medication Guide (94%) understood all or most of the information. Respondents that received the Medication Guide were less likely to be first-time users (29% vs 16%). The main source of the Medication Guide was the pharmacist (95%). For respondents that reported receiving the Medication Guide from a source other than a pharmacist, these sources included their HCP, the internet, another HCP, and somewhere else.

Only 38% of respondents reported receiving the PCD from their healthcare provider when the ER/LA opioid analgesic was first prescribed and only 32% of respondents reported receiving the patient counseling document in the last 12 months. Only 26% reported that their HCP referenced the PCD in the past 12 months. Of the respondents that received the PCD, 75% understood all or most of the information.

Question	24-Month (n=413) N (%)	36-Month (n=423) N (%)
Medication Guide (MG) Questions		
Received MG from pharmacist with the last ER/LA opioid analgesic prescription fill	Yes: 373 (90%) No: 21 (5%) Not sure: 19 (5%) Refused: 0 (0%)	Yes: 396 (94%) No: 8 (2%) Not sure: 19 (4%) Refused: 0 (0%)
Received MG from pharmacist in the last 12 months	Yes: 374 (91%) No: 23 (6%) Not sure: 16 (4%) Refused: 0 (0%)	Yes: 400 (95%) No: 9 (2%) Not sure: 14 (3%) Refused: 0 (0%)
Received MG from non-pharmacist in the last 12 months	Yes: 53 (13%) No: 337 (82%) Not sure: 23 (6%) Refused: 0 (0%)	Yes: 48 (11%) No: 359 (85%) Not sure: 16 (4%) Refused: 0 (0%)
Read MG	Never read any: 14 (3%) Read some, at least once: 64 (16%) Read all, at least once: 274 (66%) Read all, with each pharmacy fill: 61 (15%) Refused: 0 (0%)	Never read any: 13 (3%) Read some, at least once: 75 (18%) Read all, at least once: 274 (65%) Read all, with each pharmacy fill: 61 (14%) Refused: 0 (0%)
Offer to explain MG	Yes: 267 (65%) No: 128 (31%) Not sure: 18 (4%) Refused: 0 (0%)	Yes: 269 (64%) No: 140 (33%) Not sure: 14 (3%) Refused: 0 (0%)
Accepted offer to explain MG	Yes: 147 (55%)	Yes: 137 (51%)

Table 23: Patient-Reported Receipt and Comprehension of the Medication Guide and Patient-Counseling Document		
Question	24-Month (n=413) N (%)	36-Month (n=423) N (%)
	No: 119 (45%) Not sure: 1 (<1%) Refused: 0 (0%)	No: 131 (49%) Not sure: <5 (<1%) Refused: 0 (0%)
Usefulness of the information in the MG	Not useful at all: 6 (1%) Not very useful: 15 (4%) Somewhat useful: 164 (40%) Very useful: 224 (55%) Refused: 0 (0%)	Not useful at all: 6 (1%) Not very useful: 9 (2%) Somewhat useful: 164 (39%) Very useful: 243 (58%) Refused: 0 (0%)
Understanding of the information in the MG	Did not understand it at all: <5 (1%) Understood some of the information: 6 (1%) Understood about half of the information: 11 (3%) Understood most of the information: 137 (33%) Understood all of the information: 251 (61%) Refused: <5 (1%)	Did not understand it at all: <5 (<1%) Understood some of the information: <5 (<1%) Understood about half of the information: 18 (4%) Understood most of the information: 163 (39%) Understood all of the information: 234 (55%) Refused: 0 (0%)
Patient Counseling Document (PCD) Questions		
Received PCD from healthcare provider when first prescribed the current ER/LA opioid analgesic	Yes: 155 (38%) No: 135 (33%) Not sure: 123 (30%) Refused: 0 (0%)	Yes: 160 (38%) No: 138 (33%) Not sure: 125 (30%) Refused: 0 (0%)
Received PCD from healthcare provider when prescribed the current ER/LA opioid analgesic in the last 12 months	Yes: 111 (27%) No: 207 (50%) Not sure: 95(23%) Refused: 0 (0%)	Yes: 135 (32%) No: 200 (47%) Not sure: 88 (21%) Refused: 0 (0%)
Healthcare provider referred to or discussed PCD when prescribing the current ER/LA opioid analgesic in the last 12 months	Yes: 109 (26%) No: 206 (50%) Not sure: 98 (24%) Refused: 0 (0%)	Yes: 111 (26%) No: 212 (50%) Not sure: 100 (24%) Refused: 0 (0%)
Understanding of the information discussed from the PCD	Did not understand it at all: 23 (8%) Understood some of the information: 5 (2%) Understood about half of the information: 11 (4%) Understood most of the information: 64 (21%) Understood all of the information: 169 (56%) Refused: 32 (11%)	Did not understand it at all: 33 (10%) Understood some of the information: <5 (<1%) Understood about half of the information: 16 (5%) Understood most of the information: 90 (28%) Understood all of the information: 150 (47%) Refused: 24 (8%)

Domain 3: Perceived access and satisfaction with access to pain medications

Five survey items assessed patient’s perceived access to treatment and satisfaction with access to pain medications (See *Table 24*). In terms of perceived access, 71% agreed they were able to get

a prescription when needed. Thirty-five percent (35%) of respondents felt they had to go to their HCP too often when ER/LA opioid analgesics were needed.

Most respondents reported satisfaction with their access to ER/LA opioid analgesics. The majority were satisfied with their ability to get a prescription (83%), with their access to ER/LA opioid analgesics (78%), and with their ability to get ER/LA opioid analgesics from the pharmacy (80%).

Question	24-Month (n=413) N (%)	36-Month (n=423) N (%)
Able to get a prescription for ER/LA opioid analgesics through my healthcare provider when needed for pain	Agreed: 302 (73%) Disagreed: 62 (15%) Neither agreed not disagreed: 49 (12%)	Agreed: 300 (71%) Disagreed: 79 (19%) Neither agreed not disagreed: 44 (10%)
Satisfied with ability to get a prescription for ER/LA opioid analgesics	Agreed: 329 (80%) Disagreed: 46 (11%) Neither agreed not disagreed: 37 (9%) No response: 1 (<1%)	Agreed: 349 (83%) Disagreed: 41 (10%) Neither agreed not disagreed: 33 (8%)
Satisfied with access to ER/LA opioid analgesics	Agreed: 336 (81%) Disagreed: 38 (9%) Neither agreed not disagreed: 38 (9%) No response: 1 (1%)	Agreed: 329 (78%) Disagreed: 54 (13%) Neither agreed not disagreed: 40 (9%)
Does not have to go to healthcare provider too often when more ER/LA opioid analgesics are needed	Agreed: 223 (54%) Disagreed: 122 (30%) Neither agreed not disagreed: 68 (16%)	Agreed: 227 (54%) Disagreed: 147 (35%) Neither agreed not disagreed: 48 (11%) No response: 1 (<1%)
Satisfied with ability to get ER/LA opioid analgesics from a pharmacy	Agreed: 326 (79%) Disagreed: 52 (13%) Neither agreed not disagreed: 35 (8%)	Agreed: 337 (80%) Disagreed: 61 (14%) Neither agreed not disagreed: 25 (6%)

Domain 4: Patient-reported frequency of appropriate prescriber behaviors, including appropriate screening and counseling about ER/LA opioid analgesics

Survey items assessed patient-reported frequency of appropriate prescriber behaviors (see *Table 25*). The majority of respondents agreed that their HCP asked about medical history when prescribing (93%), talked about how much medication to take or use when prescribing (92%), and discussed opioid choice including the benefits and risks associated with opioid therapy and important safety information (76%). Patient-reported responses were low for other appropriate prescriber behaviors. Sixty-four percent (64%) of respondents reported that their HCP discussed what to do if a dose was missed. A little over half of respondents reported that their HCP talked about what to do with extra medication when prescribing (56%) and discussed how to safely discontinue the current ER/LA opioid analgesics (57%). Respondents reported that their HCP always or regularly used the PCD for discussion (26%), cautioned about the risks associated with use (54%), discussed how to safely discontinue (39%), counseled on common side effects (50%), instructed about the importance of and how to safely dispose of unused medication (38%), instructed to keep medication away from children (52%), and instructed not to share medication

(60%). Respondents reported that their HCP never used the PCD for discussion (29%), discussed how to safely discontinue (27%), instructed about the importance and how to safely dispose of any unused ER/LA opioid analgesics (29%), instructed to keep medication away from children (22%), and instructed not to share medication (20%).

Question	24-Month (n=413) N (%)	36-Month (n=423) N (%)
Used the patient counseling document (PCD) on ER/LA opioid analgesics for discussion	Always: 64 (15%) Regularly: 33 (8%) Sometimes: 68 (16%) Rarely: 44 (11%) Never: 129 (31%) Don't know: 74 (18%) No response: 1 (1%)	Always: 59 (14%) Regularly: 52 (12%) Sometimes: 72 (17%) Rarely: 45 (11%) Never: 122 (29%) Don't know: 72 (17%) No response: 1 (<1%)
Cautioned about important risks associated with ER/LA opioid analgesics, including overdose or taking too much	Always: 131 (32%) Regularly: 83 (20%) Sometimes: 72 (17%) Rarely: 43 (10%) Never: 63 (15%) Don't know: 20 (5%) No response: 1 (1%)	Always: 138 (33%) Regularly: 88 (21%) Sometimes: 86 (20%) Rarely: 41 (10%) Never: 64 (15%) Don't know: 6 (1%)
Discussed how to safely discontinue ER/LA opioid analgesics if they are no longer needed	Always: 97 (23%) Regularly: 60 (15%) Sometimes: 72 (17%) Rarely: 43 (10%) Never: 111 (27%) Don't know: 29 (7%) No response: 1 (1%)	Always: 91 (22%) Regularly: 73 (17%) Sometimes: 82 (19%) Rarely: 43 (10%) Never: 115 (27%) Don't know: 17 (4%) No response: 2 (<1%)
Counseled on the most common side effects from using ER/LA opioid analgesics	Always: 120 (29%) Regularly: 87 (21%) Sometimes: 96 (23%) Rarely: 46 (11%) Never: 48 (12%) Don't know: 16 (4%)	Always: 109 (26%) Regularly: 103 (24%) Sometimes: 105 (25%) Rarely: 45 (11%) Never: 55 (13%) Don't know: 6 (1%)
Instructed about the importance and how to safely dispose of any unused ER/LA opioid analgesics	Always: 87 (21%) Regularly: 52 (13%) Sometimes: 60 (15%) Rarely: 35 (8%) Never: 144 (35%) Don't know: 35 (8%)	Always: 95 (22%) Regularly: 69 (16%) Sometimes: 70 (17%) Rarely: 49 (12%) Never: 123 (29%) Don't know: 15 (4%) No response: 2 (<1%)
Instructed about keeping ER/LA opioid analgesics safe and away from children	Always: 140 (34%) Regularly: 61 (15%) Sometimes: 52 (12%) Rarely: 41 (10%) Never: 98 (24%) Don't know: 20 (5%) No response: 1 (<1%)	Always: 156 (37%) Regularly: 64 (15%) Sometimes: 59 (14%) Rarely: 43 (10%) Never: 94 (22%) Don't know: 7 (2%)
Instructed not to share ER/LA opioid analgesics with anyone else	Always: 166 (40%) Regularly: 59 (14%) Sometimes: 39 (9%) Rarely: 32 (8%) Never: 99 (24%)	Always: 173 (41%) Regularly: 82 (19%) Sometimes: 49 (12%) Rarely: 31 (7%) Never: 84 (20%)

Question	24-Month (n=413) N (%)	36-Month (n=423) N (%)
	Don't know: 18 (4%)	Don't know: 4 (1%)
Healthcare provider asked about medical history when prescribing ER/LA opioid analgesics*	Agreed: 385 (93%) Disagreed: 14 (3%) Neither agreed not disagreed: 14 (3%)	Agreed: 392 (93%) Disagreed: 25 (6%) Neither agreed not disagreed: 6 (1%)
Healthcare provider talked about how much medication to take or use when ER/LA opioid analgesics were prescribed*	Agreed: 393 (95%) Disagreed: 13 (3%) Neither agreed not disagreed: 7 (2%)	Agreed: 391 (92%) Disagreed: 20 (5%) Neither agreed not disagreed: 12 (3%)
Healthcare provider talked about what to do with extra medication when ER/LA opioid analgesics were prescribed*	Agreed: 218 (53%) Disagreed: 143 (35%) Neither agreed not disagreed: 49 (12%) No response: 1 (<1%)	Agreed: 238 (56%) Disagreed: 136 (32%) Neither agreed not disagreed: 48 (11%) No response: 1 (<1%)
Healthcare provider discussed opioid choice, including the benefits and risks associated with opioid therapy, and important safety information when prescribing the current ER/LA opioid analgesic in the last 12 months*	Yes: 321 (78%) No: 78 (19%) Not sure: 14 (3%) Refused: 0 (0%)	Yes: 321 (76%) No: 86 (20%) Not sure: 16 (4%) Refused: 0 (0%)
Healthcare provider discussed how to safely discontinue the current ER/LA opioid analgesic when it was prescribed in the last 12 months*	Yes: 221 (54%) No: 176 (43%) Not sure: 16 (4%) Refused: 0 (0%)	Yes: 243 (57%) No: 161 (38%) Not sure: 19 (4%) Refused: 0 (0%)
Healthcare provider discussed what to do if a dose was missed of the current ER/LA opioid analgesic when it was prescribed in the last 12 months*	Yes: 252 (61%) No: 138 (33%) Not sure: 23 (6%) Refused: 0 (0%)	Yes: 269 (64%) No: 135 (32%) Not sure: 19 (4%) Refused: 0 (0%)
Healthcare provider completed a Patient Prescriber Agreement (PPA) or patient contract when the current ER/LA opioid analgesic was prescribed in the last 12 months*	Yes: 191 (46%) No: 149 (36%) Not sure: 73 (18%) Refused: 0 (0%)	Yes: 225 (53%) No: 133 (31%) Not sure: 65 (15%) Refused: 0 (0%)

*Different response options across survey questions

3.4.1 Reviewer's Comments on Patient Survey

Overall, respondents had a high understanding of the key risk messages, though the survey respondents were not representative of the drug use population. There was a lower understanding of aspects of safe storage and using the drug safely. The majority of respondents received the Medication Guide in the last 12 months (95%) but only 32% of respondents received the PCD in the last 12 months. Most respondents reported satisfaction with access to ER/LA opioid analgesics (83%). Patient-reported frequency of appropriate prescriber behaviors was low.

Survey results were similar to the survey results from the 24-month assessment. As in the previous survey, the survey respondents were not representative of the drug use population. The RPC reported that for subsequent surveys they will use the HealthCore Integrated Research Database for Medicare patients and a vendor that specializes in panel building for survey research to identify Medicaid patients.

FDA recommended the inclusion of caregivers in subsequent surveys. The RPC responded that the HIRD database does not allow for the inclusion of caregivers. For subsequent surveys, the RPC should use a database that will allow parents, caregivers, or legal guardians to be included.

3.5 Assessment Element 8: Changes in Access

This Assessment Element states:

Monitoring patterns of prescribing to identify changes in access to ER/LA opioid analgesics

As per the REMS SD, this element consists of two components:

- Changes in prescribing comparing prescribers from specialties whose prescribing is hypothesized to be relatively unaffected by the REMS (such as oncologists and hospice providers) versus those for whom the REMS could have greater impact on prescribing (e.g., dentists) using drug utilization data.
- A set of questions added to the REMS prescriber survey to assess whether prescribers perceive an impact of the ER/LA opioid analgesic REMS on access to treatment. For prescribers, survey items assess whether the REMS implementation has led to a switch in medications that they prescribe and their perception of a change in access to ER/LA opioid analgesics for patients who the prescriber judges to have a medical need. For patients, survey items assess whether patients perceive a change following implementation of the REMS in: 1) physicians' prescribing of pain medication; 2) access to medications to treat pain; and 3) satisfaction with pain treatment.

Results

Based on the Applicant holder's analysis of drug use data, the ER/LA opioid analgesics (as well as the IR opioids, and celecoxib) demonstrated statistically significant decreases in 3-month prescription volume from the pre-REMS to post-REMS period. In addition, most of the specialties assessed demonstrated statistically significant decreases in prescriptions from the Pre- to Post-REMS periods with the exception of Anesthesiologists, Nurse Practitioners, and Physicians Assistants, who demonstrated statistically significant increases.

Regarding prescribers' perceptions of patients' ability to access ER/LA opioid analgesics, the prescriber surveys revealed the following:

- Most prescribers perceived access to ER/LA opioid analgesics to be moderately easy to easy (n=383 or 62.6% of respondents chose 5 to 8 on a scale of 1 to 10);
- The perceived primary obstacles to patient access to ER/LA opioid analgesics were insurance coverage (74%) and insurance authorizations and approvals (72%);
- Both prescribers who reported taking a CE training and those who had not taken such a training thought that ease of access was "about right" for patients for whom ER/LA opioid analgesics are indicated (52.5% and 52.4%, respectively); however 38% of all respondents felt that the REMS added to the difficulty to access opioids;
- 27% of CE respondents reported prescribing more non-opioid medications since the implementation of the REMS compared to 18% of non-CE-trained respondents; 23% of all respondents also reported limiting which ER/LA they did prescribe;
- Overall, 38% of respondents felt that the REMS made access more difficult while 37% of respondents reported that there was no impact.

- 11% of prescribers who reported taking a CE training reported prescribing more IR opioids versus 6% for those who had not taken such a training.

Regarding patients' perceptions of their ability to access ER/LAs, the patient survey revealed the following:

- 71% agreed that they were able to get a prescription for an ER/LA when needed
 - However, this varied across medication types with fewer patch users (67%) and more methadone users (74%) reporting satisfaction
 - Respondents who did not understand the Medication Guide or PCD, or had only one recorded ER/LA opioid analgesic dispensing less often confirmed their access to obtain a prescription.
- Most respondents (83%) reported satisfaction with access to ER/LA opioid analgesics
 - However, only 60% of single dispensing users and 65% of respondents with a KAS (i.e., proportion of knowledge questions that a respondent answered correctly) <80% stated that they were satisfied with their ability to get a prescription when needed for ER/LAs from a healthcare provider when needed for pain.
 - Satisfaction with their ability to get a prescription was reported by 83% of respondents, and was slightly higher for methadone users (87%)
- Only 54% agreed that they did not have to go to their HCP too often when ER/LA opioid analgesics were needed

We refer to you the Division of Epidemiology II: Drug Utilization Review of Prescribing Patterns, Prescribing Behavior Changes, and Patient Access for more details regarding the methodology and results of this analysis of this assessment element.

3.5.1 Reviewers Comments

The utilization data provided by the RPC do not provide specific information that informs whether or not patient access has been an issue since the implementation of the ER/LA opioid REMS. Responses to specific questions from the prescriber and patients surveys are somewhat reassuring regarding patient access. Overall, however, surveys alone are not a precise tool that can quantify the extent of patient access issues or identify root causes of any access issues identified.

4 Conclusions

The goal of the ER/LA Opioid Analgesic REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

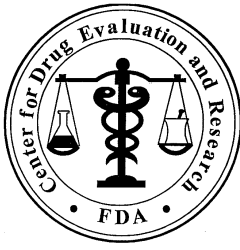
The primary intervention of the REMS is a voluntary training program for prescribers. It is hoped that prescribers who take this training will be sufficiently informed so that serious adverse outcomes (such as addiction, unintentional overdose, death) will be reduced by reducing inappropriate prescribing, misuse and abuse. As of March 1, 2015, a total of 37,512 ER/LA prescribers have completed RPC-supported REMS-compliant training which represents 47% of the milestone of 80,000 for this report. Though this number is less than the target, we are

encouraged by the prescribers and other healthcare providers who have taken the training despite not meeting the definition of an “ER/LA opioid prescriber”. There are also likely a number of factors as to why the goal of 80,000 prescriber-completers has not been achieved. The definition of “ER/LA opioid prescribers”³¹ is sufficiently narrow and thus excludes prescribers who, despite being registered to prescribe Schedule II and III medications, have not prescribed an ER/LA opioid analgesic in the past 12 months. Prescribers who utilize an institutional DEA registration are also excluded from this definition. Because completion of training is not linked to prescribing ER/LA opioid analgesics, a general lack of awareness of the REMS may also be responsible for lower than targeted training numbers. The RPC has confirmed this through a survey of prescribers conducted 8 months after the launch of the first REMS-compliant training, which demonstrated 41% of prescribers were unaware of the REMS. Possibly one of the largest factors that may limit the uptake of the REMS training is the number of competing opioid and/or pain management educational programs, some of which are required for maintenance of state medical licenses. Despite these factors, it is encouraging that over 100,000 healthcare professionals have participated in a REMS training. As the REMS assessment focuses on actual prescribers, it is unknown what the impact of this training has been on these participants, though one would expect this training to also have a positive effect on other members of the healthcare team that care for patients receiving ER/LA opioid analgesics.

Survey results of both prescriber and patient knowledge of the risks and safe use conditions outlined in the REMS also show a positive impact of the REMS training. This is evidenced by the increased likelihood answering survey questions correctly for prescribers who completed a CE activity. Survey respondents also reported conducting appropriate prescriber behaviors such as counseling on risks and side effects, using tools to screen patients for misuse and abuse, and completing a PPA after participating in a REMS-compliant activity. Surveys of patients also showed strong understanding of the risks of ER/LA opioid analgesics. Though these results are encouraging, continued evaluation utilizing a representative sample of the ER/LA opioid analgesic prescribers and patients is warranted to determine whether these initial results are sustained.

Evaluation of the impact of the ER/LA REMS on patient access remains challenging. Drug utilization studies and survey questions initially selected as measures to inform whether patient access has been an impeded as a result of the ER/LA REMS do not adequately inform this concern. Though responses to specific survey questions from the prescriber and patients surveys are somewhat reassuring regarding patient access, surveys alone are not a precise tool that can quantify the extent of patient access issues or identify root causes of any access issues identified.

³¹ The definition of a ER/LA opioid analgesic prescriber includes clinicians who are registered with the DEA to prescribe Schedule II and/or III controlled substances and have written at least one ER/LA opioid analgesic prescription in the past year.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics**

Date: April 6, 2016

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

From: **Ya-Hui Hsueh, Ph.D., Statistical Reviewer
Rima Izem, Ph.D., Team Leader
Mark Levenson, Ph.D., Acting Director
Division of Biometrics VII (DB7)
Office of Biostatistics**

Subject: **DB7 Review of 36th Month Assessment of the Risk Evaluation and Mitigation Strategy for the Extended Release and Long-Acting Opioid Analgesics: Prescriber and Patient Surveys (Assessment Elements 3a, 3b, and 4)**

Executive Summary

In 2012, FDA approved the Extended-Release and Long-Acting (ER/LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program which consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS. On June 30, 2015, REMS Program Companies (RPC) (the Applicant holder) submitted the fourth assessment report since approved, ER/LA Opioid Analgesics REMS Thirty-Six Month FDA Assessment Report. This report includes eight assessment elements. This statistical review is to provide comments on the survey design aspects and analyses considerations of two prescriber surveys (Follow-up Prescriber Survey and Long-Term Evaluation Survey) and a Patient Survey (assessment elements 3a, 3b, and 4) of the thirty-six month FDA assessment report.

Two prescriber surveys were conducted among a sample of ER/LA opioid analgesics prescribers to evaluate prescribers' knowledge, attitudes, and behavior (KAB), prescribing practices, completion of the REMS processes, and changes in behavior, prescribing, and patient assessment practices. For the follow-up prescriber survey, both ER/LA opioid analgesics prescribers who completed the REMS-compliant continuing education (CE) training and those who didn't complete the CE training were recruited. This survey was a follow-up to the Baseline Prescriber

Survey (BPS) which was launched before the implementation of REMS-compliant CE. Note that these two surveys efforts did not attempt to survey the same individual prescribers or to make respondents of these two surveys comparable. For the long-term evaluation (LTE) survey, only prescribers who had completed the REMS-compliant CE training within the 6 to 12 months prior to survey completion were recruited.

The patient survey was conducted among a sample of patients who were commercially-insured and who had filled at least one prescription for an ER/LA opioid analgesic class product. The general objectives of this survey were to assess patient knowledge of the safe use of ER/LA products following implementation of the REMS and to determine possible effects of the REMS, including impact on access to medication and satisfaction with access to pain management.

Comparability is important when assessing a causal question such as the effectiveness of REMS-compliant CE training on prescriber knowledge. In the analyses of follow-up prescriber survey, the Applicant holder did not present pairwise comparisons of the demographic and clinical characteristics of respondents in the different groups of interest. More specifically, pairwise comparisons of prescribers who have taken the REM-compliant CE training to prescribers who have not taken the CE training, and of all completed respondents in the follow-up prescriber survey to all completed respondents in the BPS. If the two groups in any pairwise comparisons do not have similar characteristics and the results are not adjusted, we cannot attribute any difference in the group scores to REMS-compliant CE training alone.

Generalizability is another concern we have for these three surveys. All these surveys were convenience samples (respondents were self-selected and therefore may differ with the general population of interest or target population) and had high non-response rates. In addition, the LTE survey had smaller sample size than planned.). The results may be biased and cannot be generalized to all ER/LA opioid analgesic prescribers or to the general population of patients who were prescribed ER/LA opioid analgesics.

In this review, we proposed alternative designs to evaluate the impact of REMS-compliant CE training on knowledge (such as self-control or randomized assignment), to evaluate prescriber behavior rather than self-assessed behavior, and to generalize results from surveys to ER/LA prescribers or the general population of patient who were prescribed ER/LA opioid analgesics (such as probability random sample). Please see Section 2.3 of this review for detailed comments.

In conclusion, the results of these three surveys may be biased due to the issues of comparability and generalizability. We recommended the Applicant holder to conduct the following analyses: (1) compare characteristics of respondents to characteristics of non-respondents to assess potential non-response bias, (2) compare demographic and clinical characteristics of respondents in each pairwise comparisons of the follow-up prescriber survey, (3) compare demographic and clinical characteristics of each prescriber survey to its' target population (all ER/LA prescribers for follow-up prescriber survey or all ER/LA prescribers who took CE training for LTE survey) and patient survey respondents to the general population of patients who are prescribed ER/LA opioid analgesics, and (4) propose methods to standardize the results of the survey samples to the general ER/LA prescribers or to the general population of patients who were prescribed ER/LA opioid analgesics. Although these procedures will add to the understanding of the results, they do not account for unmeasured differences among the survey population, which good design approaches could address.

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1 Introduction

1.1 Background

On July 9, 2012, FDA approved the ER/LA Opioid Analgesic REMS which consists of a Medication Guide, elements to assure safe use (training will be made available to healthcare providers who prescribe ER/LA opioid analgesics), and a timetable for submission of assessments of the REMS. A critical ER/LA Opioid Analgesics REMS component is the “REMS-compliant training” which is provided by accredited continuing education (CE) providers. This training includes all elements of the FDA Blueprint for Prescriber Education for ER/LA Opioid Analgesics. The FDA Blueprint describes the knowledge and practice domains that need to be covered by REMS-compliant CE activities.

As part of the ER/LA opioid analgesics REMS assessment, FDA has required the Applicant holder to conduct two evaluation assessments. The first assessment is to evaluate healthcare providers’ awareness and understanding of the serious risks associated with the ER/LA opioid analgesics and specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate. The second assessment is to evaluate patients’ understanding of the serious risks of the ER/LA opioid analgesics. For these two evaluations, the Applicant holder conducted 2 prescriber surveys (Follow-up Prescriber survey and Long-Term Evaluation Survey) and a patient survey. The details and results of these surveys were included in the Assessment Elements 3(3a and 3b) and 4 of the ER/LA Opioid Analgesics REMS Thirty-Six Month FDA Assessment Report. The following describes the goal for each assessment element in the REMS requirement.

3a. Follow-up Prescriber survey:

The goal was to evaluate ER/LA opioid prescribers’ awareness and understanding of the serious risks associated with these products and their awareness of appropriate prescribing practices for ER/LA opioids, comparing the awareness and understanding of prescribers who have taken the REMS-compliant training with those who have not taken such training.

3b. Long-Term Evaluation Survey:

The goal was to determine prescribers’ knowledge retention and practice changes 6 months to 1 year after they completed the REMS-compliant training.

4. Patient Survey:

The goal was to assess patients’ understanding of the serious risks of these products and their understanding of how to use these products safely.

The purpose of this review is to provide comments on the survey design aspects of Assessment Elements 3a, 3b and 4 of the thirty-six month ER/LA REMS assessment report. We defer to the review of Division of Risk Management Review for specific comments about risk messages and results of the survey for each risk message.

1.2 Material Reviewed

Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report (dated June 30, 2015)

- Appendix 8 UBC- Follow-Up Prescriber Survey Full Report
- Appendix 10 UBC- Long-Term Evaluation Survey Full Report
- Appendix 11 Healthcare- Patient Survey Full Report

2 Survey Methodological Evaluation

2.1 Assessment Element 3a – Follow-up Prescriber Survey

Based on the assessment report, the Applicant holder stated that the general objective of the Follow-up Prescriber Survey was to assess the prescribing behavior and practice of ER/LA Opioid Analgesics prescribers after implementation of REMS-compliant CE activities. This survey was a follow-up to the Baseline Prescriber Survey (BPS) which was launched before the implementation of REMS-compliant CE and served as the basis for comparing prescribers' knowledge, attitudes, and behavior (KAB) and prescribing practices. The detail of BPS can be found in the 12-Month FDA Assessment Report. This follow-up prescriber survey was launched approximately two years after the launch of the REMS-compliant CE training. A targeted effort was to compare the awareness and understanding of prescribers who have taken the REMS-compliant CE training with those who have not taken such training. Note that these two surveys efforts did not attempt to survey the same individual prescribers or to make respondents of these two surveys comparable.

This cross-sectional survey was conducted among a sample of prescribers of ER/LA Opioid Analgesics from February 18, 2015 to April 18, 2015. Prescribers who completed the CE training and those who didn't complete the CE training were both recruited through CE completer database and IMS database. A total of 612 prescribers completed the follow-up prescriber survey, including 301 respondents who had completed CE training (from CE completer data) and 311 respondents who had not (from IMS data). Respondents were self-administering on paper or online through a secure website.

A total of 68 key risk message questions, 8 demographic questions, and 24 questions related to the requirements of the REMS and receipt of the educational materials were included in the survey. Descriptive statistics (such as counts and percentages) were presented to describe the characteristics of survey completers in terms of survey administration, demographic characteristics, and survey responses to key risk messages.

Primary analyses were response rates to Key Risk Message questions with an exact binomial 95% confidence interval (CI). Secondary analyses were counts and percentages of number of correct responses for each question.

Subgroup analyses by prescribers' gender, medical specialty, region, and past month volume of prescribing (rate and 95% CI) were performed to the responses to questions linked with Key Risk Messages. Multiple linear regression analyses were performed to assess prescriber characteristics that could affect prescriber knowledge regarding safe opioid prescribing. Each

variable above (prescribers' gender, medical specialty, region, and past month volume of prescribing) was a significant predictor of knowledge for at least one key risk message. Chi-square tests and univariate linear regression were used to compare the correct response rates to each individual item of the key risk messages between BPS and Follow-up Prescriber survey. These latter comparison did not control for any covariate or unbalance in respondents between BPS and Follow-up Prescriber survey. The comparability of respondents between these two surveys should be taken into account for causal inference (please refer to comments about comparability in Section 2.3 of this review).

2.2 Assessment Element 3b – Long-Term Evaluation Survey

The general objectives of the Long-Term Evaluation (LTE) Survey were to evaluate knowledge about prescribing ER/LA opioid analgesics, completion of the REMS processes, and to assess changes in behavior, prescribing, and patient assessment practices in prescribers who have completed a REMS-compliant CE activity within the 6 to 12 months prior to survey completion.

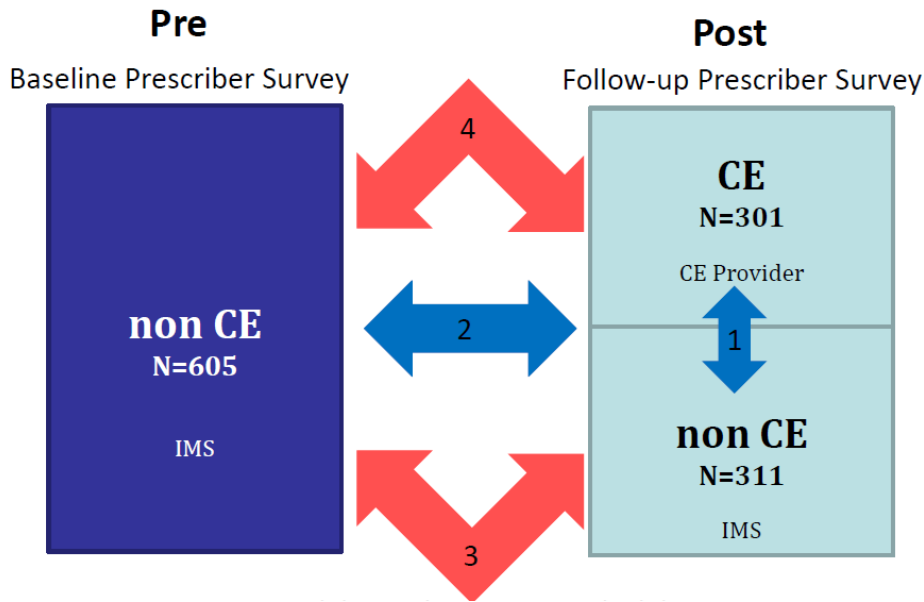
This cross-sectional survey was conducted among a sample of prescribers who had completed a REMS-compliant CE training 6 to 12 months prior to survey completion through CE completer data from February 17, 2015 to April 27, 2015. A total of 328 prescribers out of the targeted 600 prescribers completed the survey. Respondents were self-administering on paper or online through a secure website.

This survey included questions from the Follow-up Prescriber Survey and case scenarios requiring that prescribers apply the knowledge they obtained through the REMS-compliant CE activity. The survey focused on prescriber knowledge and behavior as outlined in the FDA Blueprint and included a total of 65 key risk message items.

Descriptive statistics (such as counts and percentages) were presented to describe the characteristics of survey completers in terms of survey administration, demographic characteristics, and survey responses to key risk messages. Primary analyses were correct response rates to Key Risk Messages with exact binomial 95% CI. Secondary analyses presented counts and percentages of number of correct responses. Subgroup analyses by prescribers' gender, medical specialty, professional degree, region, and past month volume of prescribing (rate and 95% CI) were also performed. Multiple linear regression analyses were performed to assess prescriber characteristics that could affect prescriber knowledge of safe opioid prescribing. Each variable above (prescribers' gender, professional degree, region, and past month volume of prescribing) was a significant predictor of knowledge for at least one key risk message.

2.3 Reviewer's comments on Prescriber Surveys (Assessment Elements 3a and 3b)

Please see the figure below for the notations described in the following comments (1 and 2). CE is for prescribers who completed the CE training. Non-CE is for prescribers who did not complete the CE training. Pre is for baseline prescriber survey and post is for follow-up prescriber survey.



1. Follow-up Prescriber Survey (3a).

- (a) *The Applicant holder compared the results (1) between CE (post) and non-CE (post), and (2) between baseline prescriber survey (non-CE (pre)) and follow-up prescriber survey (non-CE (post) and CE (post)). Based on the current design of the survey, the 1st pairwise comparison is reasonable to assess the change in knowledge of prescribers due to REMS CE training. However, for the 2nd comparison, statistical reviewers do not agree to use all completed respondents (CE (post) and non-CE (post)) from the Follow-up Prescriber Survey as a comparator to assess the effectiveness of the REMS CE training. The appropriate comparator to BPS (non-CE (pre)) should be (CE (post) from the Follow-up Prescriber Survey.*

Statistical reviewers recommend the applicant holder add two more comparisons to the survey 3a: (3) non-CE (pre vs. post) and (4) non-CE (pre) vs. CE (post). The proposed comparison (3) would give us an idea of whether a change in knowledge happened during that time frame that is not due to REMS CE training. The comparison (4) is proposed to replace the comparison (2) to assess the impact of CE in a similar way as comparison (1). Please note that the comparability of respondents in each pairwise comparison should hold to make valid causal inference (see next comment).

- (b) *Comparability is important when assessing a causal question such as the effectiveness of REMS CE training on prescriber knowledge. In the Follow-up prescriber survey report, the Applicant holder only presented the characteristics of all completed respondents (N=612), and all prescribers of ER/LA opioid analgesics as recorded in the IMS database (N=420,154). We recommend that the Applicant holder a) provides the demographic and clinical characteristics of each of the groups in the following pairwise comparisons: (1) CE (post) vs. non-CE (post), (3) non-CE*

(pre vs. post), and (4) non-CE (pre) vs. CE (post), and b) compare response rates for each key risk message and for each pair from (1) to (4) and show the adjusted and unadjusted pairwise difference in response rates if the baseline characteristics in the pairwise comparisons are not similar.

If the two groups in any pairwise comparison do not have similar characteristics and the results are not adjusted, then we cannot attribute any difference in the group scores to CE alone. For example, if CE (post) has more pain prescribers than non-CE (pre), then higher scores in CE (post) compared to CE (pre) could be due to pain prescribers having higher scores than non-prescribers (regardless of training) rather than CE training being effective. Thus, we recommend the applicant holder corrects for confounding in pairwise comparisons if there are any observed differences in characteristics. This could be done using regression or propensity score methods. However, note that given the study design of these surveys, any control for confounding is only possible for observed characteristics. We have proposals for alternate designs (see last comment) that would adjust for both observed and unobserved characteristics.

2. Long-Term Evaluation Survey (3b).

- (a) The target number of 600 prescribers who had completed a REMS CE activity within 6 to 12 months prior to survey completion is not met. We recommend the applicant holder either justifies why the sample size they have is sufficient or describe any needed adjustments to study design to increase sample size.*
- (b) One of the specific objectives was to evaluate whether the CE activities impact prescribers' opioid prescribing behavior and practice. Because this evaluation was based on self-reported measures, the measures can't be validated and the results may not accurately reflect actual behavior and practice. We propose alternate design in the comment 3 below.*

3. All Prescriber Surveys (3a and 3b)

- (a) Generalizability. Because both prescriber surveys were convenience samples (respondents were self-selected), had high non-response rates, and had smaller sample size than planned (3b), the results may be biased and cannot be generalized to all ER/LA opioid prescribers if respondents differ with non-respondents. We recommend the Applicant holder*
 - i. Compare characteristics of respondents to characteristics of non-respondents to assess potential non-response bias*
 - ii. Compare characteristics of respondents in sample to target population*
 - iii. Propose methods to standardize the results of the survey samples to the general ERLA prescribers for the follow-up prescriber survey and to the general population of ER/LA prescribers who had completed REMS-compliant CE training 6 to 12 months prior to the date of survey completion for the LTE survey.*

(b) Alternate designs:

- i. To evaluate the impact of REMS CE training on knowledge, other designs such as self-control or randomized assignment could have been used. In self-control designs, the same prescriber serves as their control and takes two tests, one before the CE training and another after the CE training. Thus, this design controls for measured and unmeasured prescriber characteristics. However, it would not control for learning due to re-taking the same test. The randomized assignment would randomize prescribers to a group taking the CE training and another not taking the training (or taking it later). Randomization would insure that prescriber characteristics (measured and unmeasured) are on average similar in the two groups. Thus, any difference in knowledge can be attributed to the CE training.*
- ii. To evaluate prescriber behavior rather than self-assessed behavior, statistical analyses could use a database that has information on whether the prescriber took the CE training and when, and information on prescribing behavior before and after the CE training.*
- iii. To generalize results from surveys to ERLA prescribers, surveys on probability random samples could have been used. Probability random samples are not only representative of the target population on measurable characteristics; they are also representative of the target population on unmeasured characteristics. Probability sample surveys can also control for non-response and missing values in their estimates of response rates and confidence intervals.*

2.4 Assessment Element 4 – Patient Survey

The general objectives of Assessment Element 4 study were to assess patient knowledge of the safe use of ER/LA products following implementation of the REMS and to determine possible effects of the REMS, including impact on access to medication and satisfaction with access to pain management.

This cross-sectional survey was conducted among a sample of patients who were commercially-insured and who had filled at least one prescription for an ER/LA opioid analgesic class product. Eligible patients were identified from medical and pharmacy claims in the HealthCore Integrated Research Database (HIRD). A total of 423 patients completed the survey from September 1, 2013 to August 31, 2014. Respondents completed the survey either by telephone or online. This survey was in the Year 2 assessment.

The primary objectives of the patient survey were to:

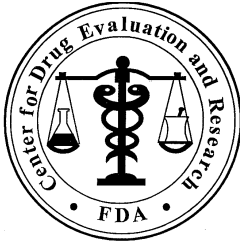
1. Determine whether respondents received the Medication Guide and/or Patient Counseling Document (PCD) and from whom;
2. Determine whether respondents read the Medication Guide and/or PCD;
3. Assess whether respondents understood the serious risks associated with the use of their ER/LA opioid analgesic;
4. Assess whether respondents knew what to do if they took too much drug;
5. Assess whether respondents understood the need to store the drug in a safe place;

6. Assess whether respondents knew they should not share the drug with anyone;
7. Assess whether respondents understood how to use the drug safely; and
8. Assess the impact of the ER/LA REMS on access to treatment.
 - Compared to before REMS, did patients perceive a change following REMS in physicians' prescribing of pain medication;
 - Compared to before REMS, did patients perceive a change following REMS in access to medications to treat pain; and
 - Compared to before REMS, did patients perceive a change following REMS in satisfaction with access to pain treatment.

Outcomes (listed above) identified through the survey were intended to evaluate the effectiveness of the REMS in conveying important information about risks and safe use of ER/LA opioid analgesics and whether patients perceived an impact of the REMS on access to treatment.

2.5 Reviewer's Comments on Patient Survey (Assessment Element 4):

1. *The response rate was 17% in Year 2 and has declined since Year 1 (24%).*
2. *The Applicant holder stated that "the general objectives of this study were to assess patient knowledge of the safe use of ER/LA products following implementation of the REMS and to determine possible effects of the REMS, including impact on access to medication and satisfaction with access to pain management". However, this patient survey assessed patient knowledge once **after the implementation of the REMS** and not before the REMS was implemented. Therefore, this survey was not able to measure change from the pre to post REMS in knowledge as well as the impact on access to medication and satisfaction with access to pain management.*
3. *For objective #8, results from the sub-bullets were missing.*
4. *The Applicant holder didn't provide responses to DRISK's previous comments regarding the patient survey on the 24-Month FDA Assessment Report. Therefore, DRISK's comments were not incorporated into the 36-Month FDA report. We support the previous DRISK recommendation about surveying patients on Medicaid and Medicare.*
5. *The same comments about generalizability and preference for probability sample detailed in comments 3a and 3b (iii) in Section 2.3 holds here as well.*
6. *We recommend the Applicant holder*
 - i. *Provide the result for the sub-bullets of objective #8*
 - ii. *Compare characteristics of respondents in sample to target population*
 - iii. *Propose method to standardize the results of your surveys (from HIRD or requested Medicaid and Medicare sources) to the general population of ER/LA patients*



**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: April 6, 2016

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

From: **Jana McAninch, MD MPH MS, Primary Reviewer
Alex Secora, MPH, Primary Reviewer
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**Judy Staffa, PhD, RPh, Associate Director for Public Health Initiatives (Acting)
Office of Surveillance and Epidemiology (OSE)**

Subject: **DEPI II Review of 36th Month Assessment of the Risk Evaluation and Mitigation Strategy for the Extended Release and Long-Acting Opioid Analgesics: Surveillance Studies (Assessment Element 5)**

EXECUTIVE SUMMARY

Background and Purpose of Review

The REMS Program Companies (RPC) are required to submit annual assessment reports containing specified elements to evaluate the implementation and effectiveness of the REMS, and in June 2015, the RPC submitted the 36-month assessment report.

The Division of Epidemiology II (DEPI) was consulted by the Division of Risk Management (DRISK) to evaluate the studies submitted to fulfill Element 5. Assessment Element 5 is as follows: *Surveillance monitoring for misuse, abuse, overdose, addiction, death and any intervention to be taken resulting from signals of these metrics, including information for different risk groups (e.g., teens, chronic abusers) and different settings (e.g., emergency rooms, addiction treatment centers, poison control call centers). As much as possible, the information should be drug-specific.*

The purpose of this review is to critically evaluate the submitted studies and to determine whether the results indicate that the ER/LA opioid analgesic REMS is making progress toward its goals of reducing adverse outcomes related to inappropriate prescribing, abuse, and misuse.

Review Methods and Materials

DEPI reviewed the following studies included in the “*Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report*.”

1. Emergency department visits related to opioid poisoning/overdose
 - a. HealthCore Integrated Research Database (HIRD)
 - b. Medicaid cohort
2. Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System
 - a. Poison Center Program
 - b. Treatment Center Program
 - c. College Survey Program
3. National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO)
 - a. Addiction Severity Index – Multimedia version (ASI-MV) treatment center study
 - b. Comprehensive Health Assessment for Teens (CHAT)
4. Washington state medical examiner study

Review Results

Overall, the studies suggest that significant decreases in some, but not all, safety outcomes of interest have occurred. However, the studies also suggest that, in general, these decreases 1) began prior to implementation of the REMS and 2) were not limited to products covered by the REMS. In addition, all of the studies have considerable methodological limitations that must be considered in interpreting trends in abuse-related outcomes over time.

In summary,

- Rates of poison center exposure calls involving both ER/LA and IR opioids have decreased significantly, but reductions began during the pre-REMS period and the trajectory of these trends did not change meaningfully with the introduction of the REMS. This pattern was fairly consistent across call types, including abuse, misuse, pediatric unintentional exposure, and calls resulting in major medical outcome, hospitalization, or death. Because of potential changes over time in poison center utilization, it is unknown how well trends in poison center calls reflect trends in actual misuse, abuse, overdose, and death related to prescription opioids.
- The prevalence of self-reported recent abuse of both ER/LA and IR opioids has decreased significantly among those entering treatment for opioid addiction, but downward trends began during the pre-REMS period and the trajectory of these trends did not change meaningfully with the introduction of the REMS. In a broader population of high-risk

individuals being assessed for substance abuse treatment, the reduction in self-reported recent ER/LA opioid abuse was small—less than 5% when a consistent set of assessment sites were analyzed—and not significantly different from reductions seen in IR opioid or benzodiazepine abuse. Reductions in ER/LA opioid abuse were larger among adolescents being assessed for substance abuse. These studies are limited by potential biases created by a shifting study sample and changes in the survey instrument over time.

- Self-reported non-medical use of both ER/LA and IR opioids increased among college students during over REMS study period. It is unknown how well this internet-based convenience sample represents college students nationally or how this has changed over time.
- The incidence of ED visits and hospitalizations for prescription opioid overdose did not change significantly after introduction of the REMS, in either a commercially insured or a Medicaid cohort. The incidence of heroin overdose increased significantly in both populations. These results must be considered exploratory because medical codes for opioid overdose have not been adequately validated and because fatal overdoses are poorly captured in claims data.
- Deaths involving opioids with an available ER/LA formulation have decreased in Washington state, but decreases were not significantly greater than decreases in deaths involving IR hydrocodone. Downward trends appear to have begun prior to full implementation of the REMS, and aggressive state-level efforts to reduce opioid overdose also took place during the study period. In most cases, the study was not able to distinguish between deaths involving ER/LA and those involving IR opioid formulations.

To answer this question, we can turn to some fundamental principles for making causal inferences from observational data, often referred to as the Bradford Hill Criteria.³² Viewed through this lens, the data provide little evidence that REMS itself has resulted in changes in safety outcomes of interest:

- The temporal relationships between the REMS implementation and the observed reductions in some outcomes do not suggest that the REMS was the cause of these changes.
- It is unknown how many providers would need to be trained, and to what extent the training would need to change clinical practice and prescribing behavior, for a measurable effect on these surveillance outcomes to be plausible. Moreover, even if the REMS were to have a widespread impact on prescriber and patient behaviors, the causal pathway from behavior change to changes in the measured surveillance outcomes is often not straightforward.

³² Sir Austin Bradford Hill, "The Environment and Disease: Association or Causation?" *Proc R Soc Med*. 1965.

- There are many alternative explanations for the trends observed in the surveillance studies, and the studies were unable to isolate effects of the REMS from effects of the myriad concurrent efforts to reduce inappropriate prescribing, abuse, and overdose (see Appendix 7). No study directly evaluates the association between participation in REMS trainings and changes in clinical practice, prescribing behaviors, or patient outcomes.
- Although some patterns were seen in multiple studies, overall the results were not consistent with one another.

However, nor do these studies demonstrate that the REMS has been *ineffective* or is failing to make progress toward its goals. Even if the REMS educational messages were having meaningful desired effects on behavior in prescribers and patients receiving the education, it is doubtful that these studies would be capable of detecting the impact of these behavior changes on the measured surveillance outcomes due to:

- considerable individual study limitations
- the complexity of the causal pathways from prescriber and patient behavior changes to changes in measured surveillance outcomes
- the unknown proportion of prescribers that would need to be trained to see a measurable effect on these outcomes, and
- the influence of the many concurrent efforts in this area and the difficulty detecting effects specific to the REMS amidst this “noise”

Conclusions

Despite considerable methodological limitations, the data suggest encouraging downward trends in some, but not all, outcomes; however, they do not indicate whether the REMS itself is contributing to these changes. The submitted surveillance studies may provide some useful contextual information but are unable to show whether the ER/LA opioid analgesic REMS is making progress toward the goal of reducing serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of these drugs. Nor do the studies demonstrate that the REMS is failing to achieve its goals, however.

The lack of studies that directly examine associations between participation in REMS training and changes in clinical practice or patient outcomes limits the ability of these studies to evaluate the effectiveness of the REMS and guide specific changes to the program. To assess the effects of the REMS provider trainings directly, pre-post changes in prescriber behavior and/or patient outcomes for a group of providers who participate in the REMS training would need to be compared to those in a group who do not participate in the training. Conducting such a study would be challenging and resource intensive, but the feasibility of this type of investigation should be explored if more rigorous evaluation of the impact of the ER/LA opioid analgesic REMS is needed.

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1 INTRODUCTION

1.1 *Background and Regulatory History*

Extended-Release and Long-Acting (ER/LA) opioid analgesics are 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. As a class, ER/LA opioid products are generally comprised of two sub-categories:

- opioid analgesics with pharmacologically longer duration of action than most other opioid analgesic substances
- modified-release formulations that are designed to provide a longer duration of action

In 2009, the Food and Drug Administration (FDA) determined that due to the growing public health concern surrounding the risks associated with the misuse and abuse of ER/LA opioid analgesics, a Risk Evaluation and Mitigation Strategy (REMS) was necessary for all approved ER/LA opioid analgesic drug products. On July 9th, 2012, FDA approved a class-wide, shared system REMS for all approved ER/LA opioid analgesics. The goals of the REMS are to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

It was determined that a single shared system should be used to implement a REMS, and that all ER/LA opioid manufacturers would contribute to this effort. The ER/LA opioid manufacturers formed an industry working group called the REMS Program Companies (RPC) to prepare a program proposal for approval by FDA and to operationalize the REMS program once approved. The RPC consists of 24 industry sponsors (16 NDAs/28 ANDAs) who manufacture ER/LA opioid products containing the following opioid substances and formulations:

- Buprenorphine transdermal
- Fentanyl transdermal
- Hydrocodone
- Hydromorphone
- Methadone
- Morphine
- Oxycodone
- Oxymorphone
- Tapentadol

On July 9th, 2012, FDA approved a class-wide, shared system REMS for the ER/LA opioid analgesics. The REMS program consisted of several components directed at reducing serious adverse outcomes associated with ER/LA opioid use and abuse:

1. **Medication Guide**
2. **Elements to Assure Safe Use (ETASU)**

- a. Provide training to ER/LA opioid prescribers: training must include all elements of the “FDA Blueprint” and include a post-course knowledge assessment
- b. Provide prescribers information that can be used to educate patients about the risks of ER/LA opioid analgesics and their safe use, storage, and disposal using the Patient Counseling Document (PCD)
- c. Letters to healthcare professionals and professional organizations
- d. REMS website

3. **Timetable for Submission of Assessments**

For practitioners, participation in these education programs is voluntary. The first REMS Program Companies (RPC)-supported REMS-compliant CE activity was launched in February 2013. As of February 2015, approximately 37, 000 ER/LA opioid analgesic prescribers have completed one of these trainings, with approximately 17,000 of these completing training between March 2014 and February 2015.³³ It is estimated that in 2014, there were approximately 363,000 ER/LA opioid analgesic prescribers in the U.S.³⁴

Between 2012 and 2015, the RPC submitted annual assessment reports evaluating the implementation and effectiveness of the program, describing the progress of the individual REMS components, and monitoring abuse and misuse surveillance data on the ER/LA opioid class. On June 30th, 2015, the RPC submitted the 36-month assessment report, containing information on all the required assessment elements, as described in the table below.

³³ The “*Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report:*”

³⁴ IMS Health, National Prescription Audit (NPA), Extracted by IMS: August, 2015

Table 1. FDA requirements for the ER/LA opioid analgesic REMS assessment

FDA REQUIREMENTS
Evaluation of Functional Components <ul style="list-style-type: none"> • REMS Website • Dear DEA-Registered Prescriber Letter • Dear Professional Organizations, Licensing Boards, and Medical Societies Letter • Call Center (Modified March 19, 2014 to IVRS)
Assessment Element 1: Assessment of how many prescribers of ER/LA opioids have successfully completed the training. Specify performance goals for number of prescribers trained by time.
Assessment Element 2: Independent audit of the quality of the content of the educational materials used by the CE Providers to provide the education. The audit should evaluate the quality of the content against the content approved by the FDA as part of the REMS, as well as against the ACCME [®] 's and other accrediting bodies' standards for commercial support.
Assessment Element 3a: Prescriber survey Evaluation of Healthcare Professional (HCP) awareness and understanding of the serious risks associated with these products (e.g., through surveys of HCPs) and specification of measures that would be taken to increase awareness if surveys of HCPs indicate that HCP awareness is not adequate.
Assessment Element 3b: Long-term evaluation
Assessment Element 4: Patient survey Evaluation of patients' understanding of the serious risks of these products.
Assessment Element 5: Surveillance monitoring for misuse, abuse, overdose, addiction, death and any intervention to be taken resulting from signals of these metrics, including information for different risk groups (e.g., teens, chronic abusers) and different settings (e.g., emergency rooms, addiction treatment centers, poison control call centers). As much as possible, the information should be drug-specific.
Assessment Element 6: Evaluation of drug utilization patterns (IMS data)
Assessment Element 7: Evaluation of changes in prescribing behavior Evaluation of changes in prescribing behavior of prescribers, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills.
Assessment Element 8: Monitoring patterns of prescribing to identify changes in access to ER/LA opioid analgesics

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

The Division of Epidemiology II (DEPI) was consulted by the Division of Risk Management (DRISK) to evaluate the studies submitted to fulfill Element 5. Assessment Element 5 is as follows: *Surveillance monitoring for misuse, abuse, overdose, addiction, death and any intervention to be taken resulting from signals of these metrics, including information for different risk groups (e.g., teens, chronic abusers) and different settings (e.g., emergency rooms, addiction treatment centers, poison control call centers). As much as possible, the information should be drug-specific.*

The purpose of this review is to critically evaluate the submitted epidemiologic data and to determine whether the results suggest that the REMS is making progress toward its goals of reducing these adverse outcomes.

2 REVIEW METHODS AND MATERIALS

This review includes summaries and evaluations of the epidemiologic investigations included in the report, “*Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report,*” submitted by the RPC in June 2015, as well as the revised study report from the HealthCore Integrated Research Database (HIRD) and Medicaid claims-based cohort study, submitted September 30, 2015. The studies reviewed include the following:

1. Emergency department visits related to opioid poisoning/overdose

- a. HealthCore Integrated Research Database (HIRD)
 - b. Medicaid cohort
2. Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System
 - a. Poison Control Program
 - b. Treatment Center Program
 - c. College Survey Program
3. National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO)
 - a. Addiction Severity Index – Multimedia version (ASI-MV) treatment center study
 - b. Comprehensive Health Assessment for Teens (CHAT)
4. Washington state medical examiner study

Each of the investigations was evaluated independently on its study design and methodology. The results of each of the studies were considered independently, as well as together, to determine what they contributed to assessing the impact of the REMS on the surveillance outcomes of interest. Descriptions of study methods were abstracted and paraphrased from study reports and protocols submitted as part of the assessment report. Considering the extremely large quantity of the surveillance data submitted and reviewed (more than 4000 pages), only results deemed to be the most relevant to assessing the impact of the REMS are presented and discussed in detail in this review.

Please see additional reviews of the 36-month ER/LA Opioid Analgesic REMS Assessment by the Division of Risk Management (Igor Cerny) and the Division of Biometrics VII (Joo-Yeon Lee).

3 REVIEW RESULTS

3.1 Opioid Poisoning/Overdose in HealthCore Integrated Research Database (HIRD) and Medicaid Claims Databases

3.1.1 Objectives

The primary objectives of these studies were to estimate the incidence of ED visits and hospitalizations for opioid overdose/poisoning among commercially-insured and Medicaid patients, both among those prescribed ER/LA opioid analgesics and among all enrollees, and to compare these incidence rates across the pre-REMS, REMS launch, and continuing REMS study periods. Heroin overdose incidence was also analyzed.

3.1.2 Methods

Data Sources

This study employed a retrospective cohort design using the HealthCore Integrated Research Database (HIRD), a longitudinal medical and pharmacy claims database of commercially-insured members of participating health plans across the U.S., as well as a small subset of U.S.

Medicaid patient data. The exact process by which state Medicaid data was procured and the number of participating state Medicaid programs included in this study was not entirely clear. Claims data were assessed to ascertain ED visits and hospitalizations for opioid overdose/poisoning using ICD-9 codes from July 2010 through August 2014. The main analyses included all eligible individuals with at least one pharmacy dispensing for an ER/LA opioid analgesic during the study period. Crude analyses also examined the incidence of opioid overdose/poisoning among all enrollees, both with and without an opioid dispensing. Linkage to the National Death Index (NDI) is planned for the next assessment but is not included in the current report.

Study Population

The study population was comprised of individuals enrolled in a health plan included in the HIRD or a participating Medicaid plan (Table 2). The main analyses include patients that met the following criteria:

Inclusion Criteria:

- At least one dispensing of an ER/LA opioid after July 1, 2010
- At least six months of continuous health plan eligibility prior to the first recorded dispensing of an opioid that occurs during an included REMS period

Exclusion Criteria:

- Missing or implausible values for age (i.e., >120 years)
- Missing or implausible values for gender.

Table 2. HIRD and Medicaid study ER/LA opioid analgesic user cohort summary, by time-period

	Pre-Implementation Period		Implementation Period		Active Period	
	N	%	N	%	N	%
HIRD						
Patients with ≥1 ER/LA opioid analgesic dispensing during the study period	156,606 (100.0%)					
Excluding those with missing or invalid age at ER/LA opioid dispensing or gender	156,603 (>99.9%)					
≥1 ER/LA opioid analgesic dispensing during the applicable REMS period ¹	101,770	65.0	56,895	36.3	55,659	35.5
Enrolled in health plan 6 months prior to first ER/LA opioid analgesic dispensing during the exposure period	88,209	86.7	48,654	85.5	43,730	78.6
Medicaid						
Patients with ≥1 ER/LA opioid analgesic dispensing during the study period	7,592 (100.0%)					
Excluding those with missing or invalid age at ER/LA opioid dispensing or gender	7,589 (>99.9%)					
≥1 ER/LA opioid analgesic dispensing during the applicable REMS period	4,172	55.0	4,169	55.0	4,132	54.4
Enrolled in health plan 6 months prior to first ER/LA opioid analgesic dispensing during the exposure period	3,488	83.6	3,746	89.9	3,625	87.7

Abbreviations: ER/LA: extended release/long-acting, HIRD: HealthCore Integrated Research DatabaseSM, REMS: Risk Evaluation and Mitigation Strategy.
 1. Pre-Implementation: 01 July 2010 through 30 June 2012, Implementation: 01 July 2012 through 30 June 2013, Active: 01 July 2013 through 31 August 2014. For Year Two, the Active Period will be extended through October 2015.

Source: Revised study report: HealthCore Integrated Research Database (HIRD) and Medicaid claims-based cohort study, September 30, 2015

In the sub-analyses that included all patients enrolled in a HIRD or participating Medicaid plan, patients must have met the following inclusion and exclusion criteria:

Inclusion Criteria:

- At least one day of continuous health plan eligibility during an included REMS period

Exclusion Criteria:

- Missing or implausible values for age (i.e., >120 years)
- Missing or implausible values for gender

Study time frame

The patients included in the main analyses must have received ER/LA opioid analgesics during one or more of the following three REMS periods:

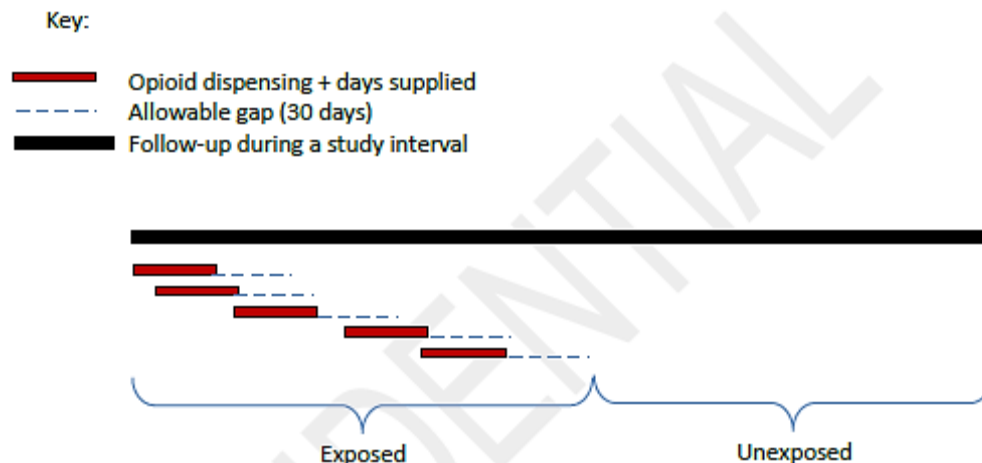
1. Pre-REMS period, July 2010 through June 2012;
2. REMS implementation period, July 2012 through June 2013; and
3. Active REMS period, July 2013 through August 2014

Exposure Categorization

Patients were considered exposed from the time of the first ER/LA oral-dosage form opioid dispensing. Patients were defined as either new users or non-new users upon the start of their follow-up during each REMS period.

- New users were individuals for whom there were no prior recorded dispensings of ER/LA opioid analgesics identified in the administrative claims data at any time prior to the start of follow-up.
- Non-new users include individuals for whom pharmacy dispensings were identified within the pre-REMS period. Patients were considered new users only in the specific REMS period during which they first started follow-up. For example, a patient that initiates treatment during the pre-REMS period and continues to obtain dispensings during the REMS launch period is considered a new user during the pre-REMS period and a non-new user during the REMS implementation period and active REMS period.
- A treatment episode was identified as the date when medication was dispensed plus days supplied, and an additional 30 days (to account for intermittent use or use of medication still on hand from a prior dispensing). Investigators assumed that concurrent or overlapping medication dispensings were used concurrently.

Figure 1. Exposure categorization, HIRD and Medicaid claims studies



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Within a given REMS period, patients were followed from their first opioid dispensing during that REMS period until (1) the end of the patient’s health plan eligibility, (2) the end of the REMS period, or (3) the first occurrence of a study outcome within the REMS period, whichever came first. The first occurrence of an opioid overdose/poisoning event censors follow-up for that outcome only (i.e., patients who experience an opioid overdose are still under follow-up for mortality outcomes). Patients who were censored during a prior REMS period remain eligible for inclusion in subsequent REMS periods as non-new users if they meet study criteria.

Outcome Ascertainment

Outcomes of interest included ED visits and hospitalizations for opioid overdose/poisoning, identified through ICD-9-CM diagnosis codes:

- 965.00: Poisoning by opium (alkaloids), unspecified
- 965.02: Poisoning by methadone
- 965.09: Poisoning by codeine (methyldormine), meperidine (pethidine), morphine
- E850.1: Accidental poisoning by methadone
- E850.2: Accidental poisoning by other opiates and related narcotics, codeine (methyldormine), meperidine (pethidine), morphine, opium (alkaloids).

Outcomes were also stratified based on reasons for the opioid overdose/poisoning (e.g. suicide attempt, poisoning related to administration of anesthetics, other reasons), and inpatient and ED outcomes are presented separately and combined. ED visits and hospitalizations for heroin overdose/poisoning were also included as a secondary outcome.

Statistical Analysis

Separate analyses were performed for the following groups of HIRD commercially-insured patients:

- New ER/LA opioid users

- During continuous ER/LA opioid treatment episodes (exposed person-time);
- Outside of continuous ER/LA opioid treatment episodes (unexposed person-time)
- Non-new ER/LA opioid users
 - During continuous ER/LA opioid treatment episodes (exposed person-time);
 - Outside of continuous ER/LA opioid treatment episodes (unexposed person-time)

Exposed person-time analyses were considered primary.

The number of events observed during each REMS period was divided by the total person-time at risk within that REMS period and presented as an incidence rate per 10,000 or 100,000 person-years as appropriate. Incidence rate ratios (IRRs) are presented comparing (1) the pre-REMS period to the REMS implementation period and (2) the pre-REMS period to the active REMS period. These estimates are presented as both crude and adjusted for patient and treatment characteristics using Poisson regression. Given that there is variation in the total length of the pre-REMS, REMS implementation and active REMS periods, incidence rates were estimated using person-time denominators that take into account duration of follow-up and time since last exposure. Because duration of exposure may vary between REMS periods and may also be related to risk of overdose, adjustments include conditioning analyses on duration of exposure. Estimates were also computed during periods of non-exposure to account for use of opioids outside of the estimated treatment episodes.

As a sensitivity analysis, incidence rates and IRR were computed for outcomes of interest after excluding patients that received any product that was available with abuse-deterrent properties at any time during the study period.

3.1.3 Key Results

3.1.3.1 HIRD Commercially-insured Cohort Study

Clinical characteristics of ER/LA opioid analgesic users:

Some changes are observed in the clinical characteristics of the ER/LA user cohort across study periods. Most notable is the increasing proportion of patients with specific pain diagnoses and psychiatric comorbidities, including substance use disorders. For example, the proportion of ER/LA users with a diagnosis of chronic pain at the beginning of follow-up increased across the study periods, from 25.5% in the pre-period to 43.4% in the active period, and the proportion with an anxiety disorder increased from 29.7% to 39.5% (Table 3). These increases appear to be partly due to the decreasing proportion of new, or incident, ER/LA opioid users across the study periods (from 61.0% to 39.3% to 41.7% in the three REMS study periods, respectively). This decrease appears to be due to the shorter duration of the implementation and active periods compared to the pre-REMS period, resulting in less time to accumulate new users during the later time periods. This decrease in new users, in conjunction with the higher prevalence of many coded diagnoses among non-new ER/LA opioid users (Table 4), appears to partially explain the increasing prevalence of these disorders among ER/LA opioid users across study

periods. Looking at clinical characteristics of new and non-new users separately, however, one still sees increases across study periods in codes for important psychiatric comorbidities such as anxiety, depressive, sleep, and substance use disorders, among *both* new and non-new users.

Among ER/LA opioid users, more than 80% were also dispensed IR opioids during the follow-up period. Baseline dispensing of non-opioid drugs with abuse potential, particularly benzodiazepines, was consistently higher among non-new ER/LA opioid users than among new users, ranging from 57-59% across study periods (data not shown), compared to 40-41%, respectively. Follow-up dispensing of benzodiazepines decreased across study periods, particularly among non-new ER/LA opioid users; however, this may, at least in part, be due to the shorter duration of the implementation and active study periods.

Table 3. Pain diagnoses and comorbidities (based on ICD-9 codes) among ER/LA opioid analgesic users across study periods,¹ HIRD Commercially-insured cohort

	All Patients:						Patients with an Opioid Overdose or Poisoning Event					
	Pre-Implementation Period		Implementation Period		Active Period		Pre-Implementation Period		Implementation Period		Active Period	
	N = 80,209		N = 48,654		N = 43,730		N = 483		N = 225		N = 220	
	N	%	N	%	N	%	N	%	N	%	N	%
Pain diagnosis:												
Abdominal pain	38,428	47.9	24,412	50.2	22,897	52.4	320	66.3	141	62.7	143	65.0
Amputation	5,484	6.8	4,031	8.3	4,022	9.2	34	7.0	34	15.1	33	15.0
Arthritis, arthropathies, osteoarthritis and musculoskeletal pain	46,537	58.0	29,745	61.1	27,896	63.8	331	68.5	162	72.0	151	68.6
Back pain	61,899	77.2	39,957	82.1	36,449	83.4	432	89.4	207	92.0	204	92.7
Chronic pain	20,429	25.5	18,969	39.0	18,926	43.3	271	56.1	146	64.9	157	71.4
Fibromyalgia	21,798	27.2	16,100	33.1	15,157	34.7	208	43.1	103	45.8	103	46.8
Headache	26,098	32.5	17,500	36.0	16,611	38.0	242	50.1	116	51.6	104	47.3
Malignancy	21,784	27.2	13,084	26.9	12,527	28.7	120	24.8	74	32.9	67	30.5
Multiple sclerosis	1,139	1.4	826	1.7	752	1.7	7	1.5	2	0.9	10	4.6
Neuropathic pain	6,239	7.8	4,485	9.2	4,373	10.0	50	10.4	37	16.4	30	13.6
extremity pain and/or skin ulcers	18,393	22.9	12,253	25.2	11,705	26.8	157	32.5	82	36.4	78	35.5
Stroke	8,627	10.8	5,666	11.7	5,496	12.6	85	17.6	61	27.1	39	17.7
None of the above	3,716	4.6	1,507	3.1	1,145	2.6	6	1.2	2	0.9	1	0.5
Psychiatric comorbidities:												
Alcoholism ²	3,988	5.0	2,714	5.6	2,692	6.2	67	13.9	40	17.8	39	17.7
Anxiety disorder	23,835	29.7	17,378	35.7	17,252	39.5	269	55.7	151	67.1	139	63.2
Bipolar disorder	3,651	4.6	2,689	5.5	2,467	5.6	89	18.4	41	18.2	38	17.3
Depressive disorder	22,590	28.2	16,344	33.6	15,655	35.8	269	55.7	131	58.2	125	56.8
History of suicide attempt ²	629	0.8	424	0.9	461	1.1	29	6.0	18	8.0	11	5.0
Post-traumatic stress disorder	1,406	1.8	1,172	2.4	1,173	2.7	17	3.5	16	7.1	11	5.0
Sleep disorder	24,299	30.3	17,186	35.3	16,535	37.8	231	47.8	114	50.7	124	56.4
Somatiform disorder	157	0.2	120	0.3	119	0.3	4	0.8	0	0.0	0	0.0
Drug dependence²												
Opioid type dependence	4,651	5.8	4,236	8.7	4,615	10.6	106	22.0	66	29.3	60	27.3
Other drug dependence	5,233	6.5	4,259	8.8	4,325	9.9	124	25.7	58	25.8	59	26.8

1. Pre-implementation: 7/1/10-6/30/12; Implementation: 7/1/12-6/30/13; Active: 7/1/13-8/31/14

2. Limited ability to capture these variables from automated claims codes

Source: Revised study report: HealthCore Integrated Research Database (HIRD) and Medicaid claims-based cohort study, September 30, 2015

Table 4. Comorbidities (based on ICD-9 codes)among new (incident) and non-new (prevalent) ER/LA opioid analgesic users across study periods,¹ HIRD Commercially-insured cohort

	New Users						Non-New Users					
	Pre-Implementation Period		Implementation Period		Active Period		Pre-Implementation Period		Implementation Period		Active Period	
	N = 48,944		N = 19,116		N = 17,795		N = 31,265		N = 29,538		N = 25,935	
	N	%	N	%	N	%	N	%	N	%	N	%
Pain diagnosis:												
Abdominal pain	22,293	45.6	8,934	46.7	8,573	48.2	16,135	51.6	15,478	52.4	14,324	55.2
Amputation	3,312	6.8	1,493	7.8	1,532	8.7	2,172	7.0	2,538	8.6	2,470	9.5
pain	26,982	55.1	10,788	56.4	10,560	59.3	19,555	62.6	18,957	64.2	17,336	66.8
Back pain	34,391	70.3	13,661	71.5	12,980	72.9	27,508	88.0	26,296	89.0	23,469	90.5
Chronic pain	7,233	14.8	3,536	18.5	3,914	22.0	13,196	42.2	15,433	52.3	15,012	57.9
Fibromyalgia	10,260	21.0	4,258	22.3	4,070	22.9	11,538	36.9	11,842	40.1	11,087	42.8
Headache	14,286	29.2	5,811	30.4	5,578	31.4	11,812	37.8	11,689	39.6	11,033	42.5
Malignancy	14,295	29.2	6,002	31.4	5,898	33.1	7,489	24.0	7,082	24.0	6,629	25.6
Multiple sclerosis	517	1.1	181	1.0	180	1.0	622	2.0	645	2.2	572	2.2
Neuropathic pain	3,177	6.5	1,279	6.7	1,326	7.5	3,062	9.8	3,206	10.9	3,047	11.8
extremity pain and/or skin ulcers	10,388	21.2	4,246	22.2	4,219	23.7	8,005	25.6	8,007	27.1	7,486	28.9
Stroke	5,021	10.3	2,022	10.6	2,074	11.7	3,606	11.5	3,644	12.3	3,422	13.2
None of the above	3,124	6.4	1,031	5.4	864	4.9	592	1.9	476	1.6	281	1.1
Psychiatric comorbidities:												
Alcoholism ²	2,314	4.7	1,048	5.5	1,019	5.7	1,674	5.4	1,666	5.6	1,673	6.5
Anxiety disorder	12,726	26.0	5,609	29.3	5,720	32.1	11,109	35.5	11,769	39.8	11,532	44.5
Bipolar disorder	1,737	3.6	726	3.8	680	3.8	1,914	6.1	1,963	6.7	1,787	6.9
Depressive disorder	11,060	22.6	4,667	24.4	4,687	26.3	11,530	36.9	11,677	39.5	10,968	42.3
History of suicide attempt ²	254	0.5	118	0.6	132	0.7	375	1.2	306	1.0	329	1.3
Post-traumatic stress disorder	665	1.4	291	1.5	319	1.8	741	2.4	881	3.0	854	3.3
Sleep disorder	12,920	26.4	5,408	28.3	5,279	29.7	11,379	36.4	11,778	39.9	11,256	43.4
Somatiform disorder	52	0.1	22	0.1	19	0.1	105	0.3	98	0.3	100	0.4
Drug dependence ²												
Opioid type dependence	1,349	2.8	610	3.2	737	4.1	3,302	10.6	3,626	12.3	3,878	15.0
Other drug dependence	1,889	3.9	844	4.4	879	4.9	3,344	10.7	3,415	11.6	3,446	13.3

1. Pre-implementation: 7/1/10-6/30/12; Implementation: 7/1/12-6/30/13; Active: 7/1/13-8/31/14

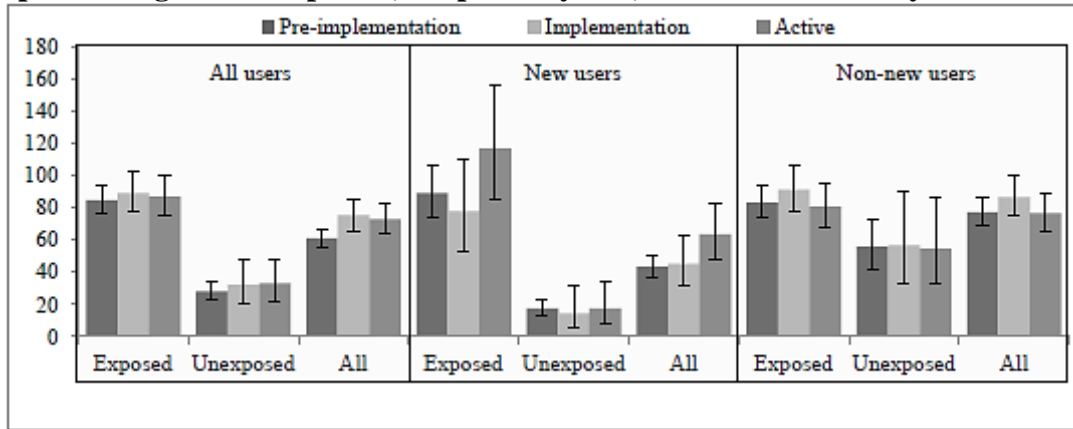
2. Limited ability to capture these variables from automated claims codes

Source: Revised study report: HealthCore Integrated Research Database (HIRD) and Medicaid claims-based cohort study, September 30, 2015

Incidence of opioid and heroin overdose among ER/LA opioid analgesic users:

The unadjusted incidence of prescription opioid overdose or poisoning ED visits or hospitalization (hereafter referred to as *opioid overdose*) among all ER/LA opioid users, new users, and non-new users by person-years (“exposed,” “unexposed,” and “all,” with “all” person-years representing exposed and unexposed person-years combined) is shown in Figure 2. The incidence of opioid overdose did not differ significantly across the three study periods among all ER/LA opioid users, new users, or non-new users during exposed or unexposed person time. The highest incidence was among new users during exposed person-time and the lowest incidence was among new users during unexposed person-time.

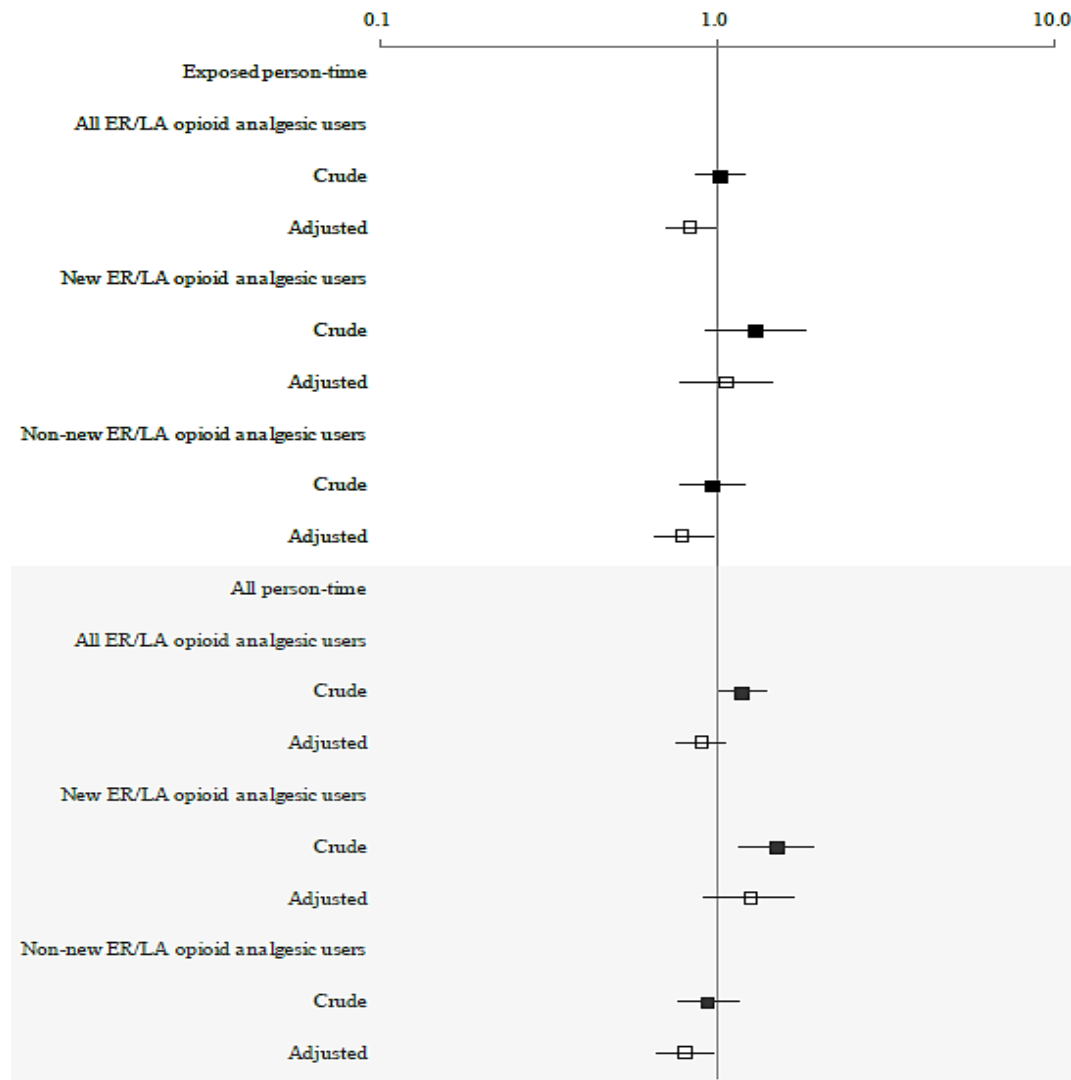
Figure 2. Unadjusted incidence of opioid overdose (based on ICD-9 codes) among ER/LA opioid analgesic users per 10,000 person-years, HIRD commercially-insured cohort



Source: Revised study report: HealthCore Integrated Research Database (HIRD) and Medicaid claims-based cohort study, September 30, 2015

Figure 3 shows the incidence rate ratio (IRR) for opioid overdose among ER/LA opioid users comparing the active to pre-REMS periods, both unadjusted (crude) and adjusted for selected covariables. The results varied considerably in both magnitude and direction, depending on the subgroup (new vs. non-new ER/LA users) and the analysis (crude vs. adjusted). Looking at all person-time, the crude incidence of opioid overdose increased significantly among new ER/LA opioid users. However, opioid overdose incidence rates decreased significantly for non-new users (adjusted IRR using exposed person-time 0.79, 95% CI 0.65-0.97 and adjusted IRR using all person-time 0.80, 95% CI 0.66-0.97) after adjusting for region, Deyo-Charlson comorbidity index, benzodiazepine use, sleep medication use, chronic pain, alcohol abuse, anxiety disorder, depressive disorder, bipolar disorder, history of overdose, drug abuse, and time since most recent ER/LA opioid exposure. Unlike in the non-new user subgroup, the adjusted analysis (including all of the above covariables except region, comorbidity index, and benzodiazepine use) did not show a significant reduction in opioid overdose incidence in the new user subgroup. The decrease in incidence was borderline statistically significant if new and non-new users were combined, after adjusting for covariables. After excluding opioids with abuse-deterrent properties, there were no significant reductions in the incidence of opioid overdose among ER/LA opioid recipients (data not shown).

Figure 3. IRR* of opioid overdose events (based on ICD-9 codes) among ER/LA opioid analgesic users, active versus pre-implementation period, HIRD commercially-insured



*IRRs to the left of the null (1.0) indicate a lower risk of opioid overdose in the REMS active period compared to the pre-period.

Source: Revised study report: HealthCore Integrated Research Database (HIRD) and Medicaid claims-based cohort study, September 30, 2015

Among ER/LA opioid users, the incidence of heroin overdose increased from 0.7 (95% CI 0.1-1.9) to 2.7 ((5% CI 1.0—5.8) per 10,000 person-years across the study periods. The IRR for heroin overdose during periods of ER/LA opioid exposure was 4.12 (95% CI 1.03-16.49), indicating a significant increase in heroin overdoses in this group between the active and pre-REMS period (data not shown).

Incidence of opioid and heroin overdose among all enrollees:

Among all HIRD commercially-insured enrollees, the incidence of opioid overdose did not change significantly across the study periods. Incidence rates were 1.8-1.9 per 10,000 person years for all three periods (IRR 1.0, 95% CI 1.0-1.1 comparing active to pre-implementation

periods). Among patients with an opioid overdose identified, 20-24% had at least one ER/LA opioid dispensing and 40-44% had at least one IR opioid dispensing prior to the event. The incidence of heroin overdose increased significantly in HIRD enrollees across the study period, from 0.4 to 0.7 per 10,000 person-years (IRR 2.0, 95% CI 1.7-2.2 comparing active to pre-implementation periods).

3.1.3.2 Medicaid Cohort

Clinical characteristics of ER/LA opioid analgesic users:

Similar to the commercially-insured cohort, the proportion of new ER/LA opioid users in the Medicaid cohort decreased across the REMS study periods, accounting for 66.6% of users in the pre-implementation period, 46.2% in the implementation, and 27.5% in the active period. The prevalence of coded chronic pain diagnoses as well as psychiatric comorbidities at baseline was higher than in the commercially-insured cohort. In particular, more than 90% of ER/LA opioid users in the Medicaid cohort had a coded diagnosis of back pain. The prevalence of coded substance use disorders was also notably high, with 28.4-35.4% having a diagnosis of opioid drug dependence and 33.2-37.9% having other drug dependence disorders (Table 5). Again, the prevalence of coded baseline pain diagnoses and comorbidities increased across the study periods. The Medicaid cohort was much smaller than the commercially-insured cohort, however, and therefore new and non-new ER/LA users were not analyzed separately. More than half of ER/LA opioid users in the Medicaid cohort had been dispensed benzodiazepines prior to initiating use of ER/LA opioids (data not shown).

Table 5. Comorbidities (based on ICD-9 codes) among ER/LA opioid analgesic users, Medicaid cohort

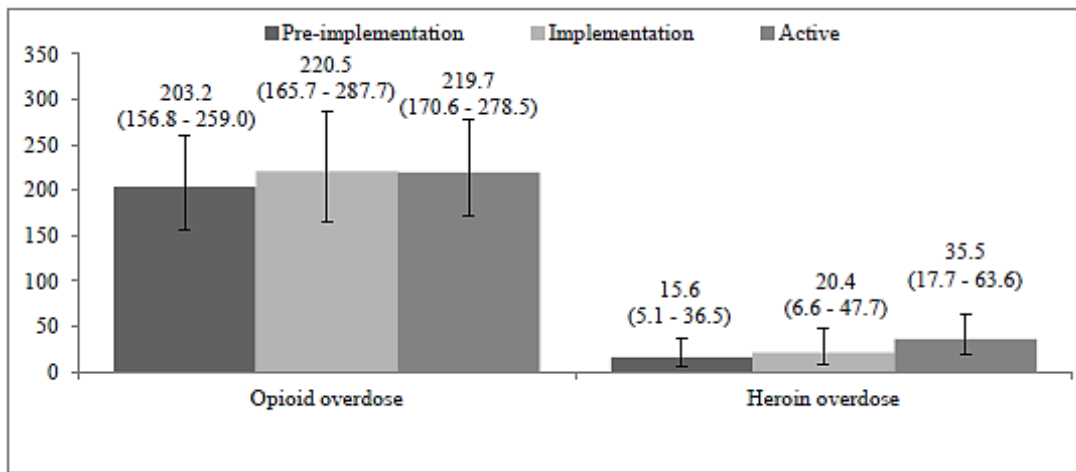
	All Patients					
	Pre-Implementation Period		Implementation Period		Active Period	
	N = 3,488		N = 3,746		N = 3,625	
	N	%	N	%	N	%
Pain diagnosis:						
Abdominal pain	1,845	52.9	2,207	58.9	2,193	60.5
Amputation pain	138	4.0	170	4.5	178	4.9
Back pain	1,939	55.6	2,429	64.8	2,474	68.3
Chronic pain	3,208	92.0	3,549	94.7	3,433	94.7
Fibromyalgia	1,935	55.5	2,324	62.0	2,416	66.7
Headache	996	28.6	1,375	36.7	1,428	39.4
Malignancy	1,649	47.3	1,927	51.4	1,972	54.4
Multiple sclerosis	415	11.9	526	14.0	582	16.1
Neuropathic pain	39	1.1	57	1.5	57	1.6
Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers	242	6.9	373	10.0	397	11.0
Stroke	641	18.4	862	23.0	940	25.9
None of the above	211	6.1	282	7.5	309	8.5
	24	0.7	17	0.5	22	0.6
Psychiatric comorbidities:						
Alcoholism ²	512	14.7	647	17.3	700	19.3
Anxiety disorder	1,661	47.6	2,132	56.9	2,189	60.4
Bipolar disorder	687	19.7	823	22.0	897	24.7
Depressive disorder	1,597	45.8	2,032	54.2	2,031	56.0
History of suicide attempt ²	158	4.5	181	4.8	181	5.0
Post-traumatic stress disorder	215	6.2	313	8.4	358	9.9
Sleep disorder	1,343	38.5	1,783	47.6	1,837	50.7
Somatiform disorder	6	0.2	15	0.4	17	0.5
Drug dependence²						
Opioid type dependence	989	28.4	1,116	29.8	1,284	35.4
Other drug dependence	1,158	33.2	1,347	36.0	1,372	37.9

Source: Revised study report: HealthCore Integrated Research Database (HIRD) and Medicaid claims-based cohort study, September 30, 2015

Incidence of opioid and heroin overdose among ER/LA opioid analgesic users:

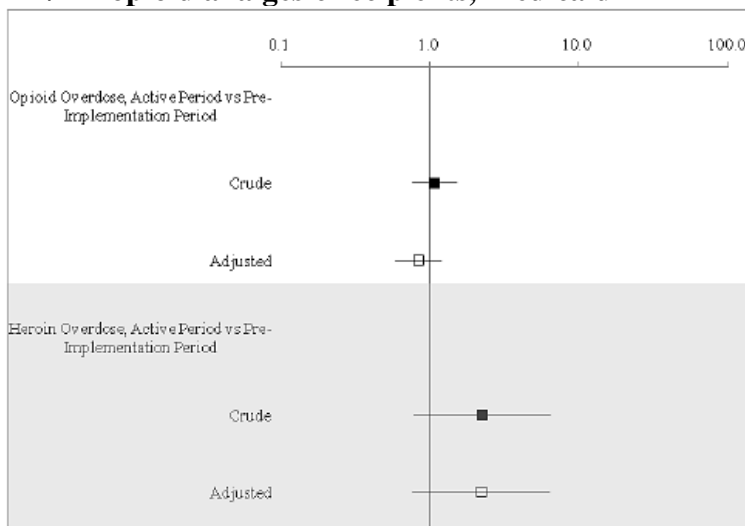
The incidence of opioid overdose among ER/LA users in the Medicaid cohort was more than twice that in the commercially-insured cohort (Figures 2,4), while the incidence of heroin overdose was many times higher in the Medicaid user cohort. The incidence of opioid overdose did not change significantly across study periods, either unadjusted or after adjusting for sleep medications, alcohol abuse, bipolar disorder, depressive disorder, and history of overdose (Figure 5). The incidence of heroin overdose increased in the Medicaid ER/LA opioid user group, but not significantly (Figures 4,5).

Figure 4. Incidence of opioid and heroin overdose (based on ICD-9 codes) during opioid exposure among ER/LA opioid analgesic users, per 10,000 person-years, Medicaid



Source: Revised study report: HealthCore Integrated Research Database (HIRD) and Medicaid claims-based cohort study, September 30, 2015

Figure 5. IRR of opioid and heroin overdose outcomes (based on ICD-9 codes) among ER/LA opioid analgesic recipients, Medicaid



Source: Revised study report: HealthCore Integrated Research Database (HIRD) and Medicaid claims-based cohort study, September 30, 2015

Incidence of opioid and heroin overdose among all enrollees:

Among all Medicaid enrollees in the cohort, the incidence of opioid overdose increased across REMS study periods, from 12.5 to 13.8 events per 10,000 person years, and this increase was of borderline statistical significance (IRR 1.1, 95% CI 1.0-1.3). The incidence of heroin overdose increased significantly, from 3.2 to 11.3 events per 10,000 person-years (IRR 3.6, 95% CI 2.9-4.5). Again, these incidence rates were much higher than those observed in the commercially-insured cohort.

3.1.4 Discussion of HIRD Commercially Insured and Medicaid Cohort Studies

Overall, the HIRD commercially-insured and Medicaid claims-based studies do not suggest a decrease in the incidence of coded opioid overdose events after implementation of the REMS, either in ER/LA opioid analgesic users or in plan enrollees overall. None of the crude analyses demonstrated significant reductions in overdose among ER/LA users or among all enrollees in either the commercially-insured or Medicaid cohorts, and several analyses suggested possible increases.

Significant reductions of approximately 20% were seen among prevalent ER/LA opioid users only after adjusting for multiple covariables. The multivariate adjustments appear to result in lower IRRs because the prevalence of most of these coded overdose risk factors (e.g. history of substance use disorders and psychiatric comorbidities) increased across study periods. However, it is not clear why the prevalence of these factors increased, and it may not be appropriate to control for these changes in assessing the impact of the REMS. The REMS includes messages about appropriate patient selection and assessing for risk factors that may make some patients unsuitable candidates for ER/LA opioid therapy. If the REMS were to have an impact on patient selection, this effect could be reflected as a shift in the clinical and risk factor profile of an ER/LA opioid user cohort. In an analysis intended to measure the impact of a REMS on the incidence of overdose, controlling for these changes in clinical risk profile of the ER/LA opioid user population may not be the best approach.

A strength of this study was the ability to look at demographic and clinical characteristics, including coded pain and comorbid diagnoses, as well as detailed dispensing histories for opioids and other relevant prescription drugs. Another strength, like other studies using administrative claims data, is the accurate classification of the products dispensed. Furthermore, the healthcare environment—including enrollees of both private and public insurance plans—seems an appropriate setting in which to try to examine the effects of an intervention targeting prescribers and patients.

The study has multiple limitations, however. First, the proportion of ER/LA opioid prescribers within these databases who participated in REMS-accredited CME and/or utilized other REMS materials such as patient counseling documents or Medication Guides is unknown. Furthermore, we do not know whether the change in overdose rates was different among patients of prescribers who received training and those who did not. The lack of individual prescriber-level

information makes it exceedingly difficult to attribute any change in overdose outcomes, or lack thereof, to the REMS itself.

Another overarching issue in the HIRD and Medicaid studies is that overdose outcomes have not yet been validated, and the predictive value of the administrative codes for these outcomes, as well as many of the covariables and presumed indications, are unknown. However, work is currently underway to develop and validate an algorithm for identifying opioid overdose using administrative claims codes, and the RPC has indicated that this work will be incorporated into future ER/LA opioid REMS assessments. In addition, without linkage to overdose death data, the study is missing what is arguably the most important outcome associated with opioid use. The RPC indicates that National Death Index linkage is planned as part of next year's assessment. Both of these additions would be essential improvements to the HIRD commercially-insured and Medicaid cohort studies.

Two additional limitations are that exposure data reflect only dispensing and not actual use of dispensed drugs. Opioids obtained through other means, including cash transactions and non-prescribed sources such as friends or dealers are also not captured. This study suggests that these non-captured opioid exposures may contribute to a large proportion of opioid overdose cases, with only 20-24% having had an ER/LA opioid dispensing and 40-44% having had IR opioid dispensing documented in the database prior to the event.

In the study report, the RPC suggests that after the many years of increasing national trends in opioid overdose incidence, no change in trend might represent a successful REMS outcome. However, pre-REMS overdose trends are not assessed in this study, and other studies in this assessment (e.g. RADARS Poison Center and Treatment Center, discussed in next section) suggest downward trends in ER/LA-associated adverse outcomes predating the REMS. Other national data also suggest a plateauing of prescription-opioid diversion, adverse outcomes, and overdose deaths nationally prior to REMS implementation.³⁵ It is therefore difficult to attribute a lack of change in overdose incidence in this study to a successful REMS program. Furthermore, changes in opioid overdose rates may reflect the effects of myriad efforts at the institution, community, state, and federal level to prevent prescription opioid abuse and overdose. The increases in heroin overdose seen in this study are troubling, although they are consistent with national trends from other sources.³⁶ The utility of heroin as a comparator in this study is limited, however, given the many factors—for example changes in street price, purity, and availability—that can influence regional and national trends in heroin abuse.

³⁵ Dart RC, Surratt HL, Cicero TJ et al. Trends in Opioid Analgesic Abuse and Mortality in the United States. *N Engl J Med* 2015;372:241-248. <http://www.nejm.org/doi/full/10.1056/NEJMsa1406143>; <http://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>

³⁶ Compton WM, Jones CM, Baldwin GT. Relationship between nonmedical prescription opioid use and heroin use. *N Engl J Med* 2016; 374:154-63. <http://www.nejm.org/doi/full/10.1056/NEJMra1508490>

3.2 RADARS Prescription Opioid Surveillance Program: Poison Centers, Treatment Centers, and College Survey

3.2.1 Objectives

The primary objectives of the REMS assessment are to conduct surveillance for ER/LA opioid abuse, misuse, overdose, addiction, and death for different risk groups and settings, and to evaluate trends before and after the shared REMS was implemented. To help achieve this objective, this investigation compiles and analyzes abuse-related data from several different risk groups that make up three separate Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System databases:

- Poison Center Program (PCP) collects data on the general population
- Treatment Center Program (TCP) collects data on those entering treatment for opioids and other drugs of abuse
- College Survey Program (CSP) collects data on a college-aged population

3.2.2 Methods

Data Sources

The RADARS System is comprised of multiple programs which gather data from several unique populations along the spectrum of drug abuse. The three programs that are included in this assessment are briefly described below:

- The Poison Center Program (PCP) obtains data from poison control centers (PCCs) on individuals and healthcare providers who seek advice regarding potentially toxic exposures to prescription opioids and prescription stimulants. The objectives of the PCP are to detect product-specific prescription drug abuse and misuse in near real-time and to identify geographic sites with disproportionately high rates of abuse and misuse. Poison center data collected through the RADARS System can be used to estimate the change in intentional abuse, misuse, and deaths associated with these drugs. The PCP gathers data from 48 regional US Poison Centers in 46 states, including urban, suburban, and rural regions (over 90% of the US population). Trained personnel at each participating poison center collect data using a nationally standardized electronic health record. In addition to obtaining exposure and substance data, the PCP collects demographic, clinical effects, treatment, and medical outcomes information. Exposure cases are composed of two main categories: unintentional/other (resulting from unforeseen or unplanned events, adverse reactions, other, and unknown reasons), and intentional exposures (which include suicide, intentional misuse, abuse, intentional unknown, and withdrawal cases).
- The Treatment Center Program (TCP) provides data from two distinct RADARS System programs: the Opioid Treatment Program (OTP) and the Survey of Key Informants' Patients Program (SKIP). These two programs use the same core data collection form and complement each other by providing information from patients entering both private and

public opioid addiction treatment programs. Patients enrolling in the study are voluntarily recruited and complete a self-administered anonymous questionnaire within the first week of admission. The objectives of these programs are to estimate 1-month prevalence of the abuse of opioids and other drugs among patients admitted to selected substance abuse treatment programs. In addition, they seek to determine the patient's drug of choice and the source of the primary drug. The OTP includes 72 methadone maintenance treatment programs in both urban and rural areas across 42 states. The Survey of Key Informants' Patients Program (SKIP) involves 135 substance abuse treatment programs covering 47 states. These are primarily private treatment centers and are balanced geographically with representation from urban, suburban, and rural centers.

- The College Survey Program (CSP) is an online questionnaire that collects data from self-identified students attending a 2- or 4-year college, university, or technical school at least part-time during the specified sampling period. Data on non-medical use (abuse/misuse) of specific prescription drugs are collected at the completion of the fall and spring academic semesters/quarters and at the end of the summer. The objectives of the CSP are to estimate the scope of non-medical prescription drug use among US college students, determine the drug source, and determine the route of drug administration among these students. A target of 2000 surveys is completed three times per year with enrollment stratified into the four US Census-regions to ensure nationwide distribution of respondents. A nationwide panel company is utilized to identify and target ideal responders. Students are sent an invitation to participate in the study and they receive credits upon completion of the survey.

ER/LA opioid utilization estimates were obtained from IMS Health for total prescriptions dispensed and total dosing units dispensed at the 3-digit ZIP code level for all ER/LA REMS opioids and comparator groups. For a given year-quarter, the totals of prescriptions and dosing units in the 3-digit ZIP codes covered by the RADARS System Programs were computed and these estimates were used as the denominators to contextualize rates of abuse. US Census 3-digit ZIP code population data from the 2000 and 2010 US decennial Censuses were utilized to compute population rates of abuse, misuse, and death.

Outcome Ascertainment

Outcome variables included measures of abuse, misuse, serious adverse events, death, unintentional therapeutic errors, pediatric unintentional general exposures, and adolescent abuse:

1. Abuse (PCP, TCP, CSP) - In the PCP, an intentional abuse case was defined as: "An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high euphoric effect or some other psychotropic effect." In the TCP, abuse was measured as survey respondent endorsing the use of an ER/LA opioid "to get high" in the past 30 days. In the CSP, abuse was defined as the endorsement of the non-medical use of a drug in the past 90 days.

2. Misuse (PCP) – The RADARS working definition of misuse is: the intentional use of a prescription drug in a way other than prescribed or directed by a healthcare provider or the use of an over-the-counter drug in other ways than directed, including: patients intentionally using an over-the-counter or a prescription drug for a different condition than the drug is directed or prescribed for, patients intentionally taking more drug or at a different dosing interval than prescribed, and individuals intentionally using a drug not prescribed for them, though for therapeutic purposes. Misuse is captured in the PCP and is defined as those cases with a reason for exposure of intentional misuse, unintentional general and unintentional therapeutic error. In the PCP, intentional misuse is defined as: “an exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of psychotropic effect.”
3. Major Medical Outcome, Hospitalization or Death (PCP) - Any exposure resulting in a major medical outcome or death is included. Death is recorded in the PCP medical outcome field and is based upon case follow-up, as well as any exposures with a level of healthcare coded as treated/evaluated and released.
4. Unintentional Therapeutic Errors (PCP) - Defined as: “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.”
5. Pediatric Unintentional General Exposures (PCP) – Defined as those cases in children under 6 years of age with a reason code of unintentional general, which consists primarily of accidental unsupervised ingestions such as a toddler getting into a grandparent’s prescription medicine.
6. Pediatric Unintentional General Exposures Resulting in a Major Medical Outcome, Hospitalization or Death (PCP) - Defined as those cases in children under 6 years of age with a reason code of unintentional general and an exposure resulting in a major medical outcome or death is defined as a Major Medical Outcome, Hospitalization or Death. In addition those with a level of healthcare coded as: admitted to critical care, admitted to non-critical care, or admitted to psychiatric care facility are included.
7. Pediatric Unintentional General Exposures Treated/Evaluated and Released (PCP) – Defined as those cases in children under 6 years of age with a reason code of unintentional general and level of healthcare coded as treated/evaluated and released.
8. Adolescent Abuse (PCP) - Defined as cases 13-19 years old or with an age code of teen that have a reason for exposure of intentional abuse. This is a subset of all intentional abuse cases noted above.

Comparators

Two comparator groups were utilized for analyses: immediate release prescription opioids and prescription stimulants:

- Immediate Release (IR) Prescription Opioids - Rates of abuse, misuse, and death for ER/LA opioids are compared to corresponding rates for selected prescription IR opioids. This control group includes IR formulations of fentanyl, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, and tapentadol. IR formulations for injection are excluded.
- Prescription Stimulants – For the PCP and CSP programs, ER/LA opioid abuse rates are also compared to rates for prescription methylphenidate and amphetamine products. Although the ER/LA REMS is specifically targeted to ER/LA opioids, some overlap of the education effect may be realized for IR opioids as well, so stimulants were also included as a comparator.

Denominators

The three denominators used were population, number of prescriptions dispensed, and number of dosing units dispensed. The population denominator is considered primary.

- Population - Estimates were obtained by extrapolating data from the 2000 and 2010 US censuses at the 3-digit ZIP code level for each quarter. Data were summed across those 3-digit ZIP codes in areas covered by a particular RADARS System Program.
- Prescriptions Dispensed - Detailed data on projected number of prescriptions dispensed by drug, formulation, and 3-digit ZIP code were purchased from IMS Health. Data were then summed to determine the total number of prescriptions dispensed separately for ER/LA REMS products, IR prescription opioids, and prescription stimulants across 3-digit ZIP codes covered by a particular RADARS System Program.
- Dosing Units Dispensed – The projected number of dosing units dispensed by drug, formulation, and 3-digit ZIP code were also purchased from IMS Health. Data were then summed to determine the total number of units dispensed for all ER/LA REMS products, IR prescription opioids, and prescription stimulants across 3-digit ZIP codes covered by the RADARS System Program.

Statistical Analysis

Poisson regression was used to compare changes in rates of abuse, misuse, overdose, and death and other outcomes over time within the ER/LA opioid group to changes in rates among the comparator groups. Time was divided into three periods: Pre-Implementation (third quarter 2010 through second quarter 2012), Transition (third quarter 2012 through second quarter 2013), and Active Period (third quarter 2013 forward). The Transition Period corresponds to the release of the class-wide medication guide, while the Active Period corresponds to the time period when both the medication guide and prescriber education were implemented. The different methods of analysis include a means model, a piecewise linear model, and a bootstrap method, all described in detail in the Statistical Analysis Plan (SAP). In brief, in the means model, mean outcome rates are compared across the three periods. Progressive changes in the trends over time are compared using a piecewise linear model. For both the mean and piecewise linear models, drug product was categorized as an ER/LA REMS opioid or comparators: IR opioids or stimulants. The total

number of cases mentioning one or more ER/LA REMS opioid or comparator in the 3-digit ZIP codes covered by the RADARS System each quarter was computed and used as the dependent variable in the Poisson regression models. The denominator of the rates was included in the Poisson model as an offset variable. A drug group specific variance structure was fit to allow for different variances in the ER/LA REMS opioid group versus the comparators. A secondary analysis was conducted to determine if the mean number of dosing units per prescriptions dispensed differs across time for the ER/LA REMS drug group.

3.2.3 Key Results

Table 6 shows the event counts in the three RADARS studies during the pre-implementation and active REMS periods. Note that the length of the pre-period was longer than the length of the active REMS period.

Table 6. Event Counts in the RADARS Poison Center, Treatment Center, and College Survey Programs, Pre-implementation and Active REMS Periods

RADARS Program Counts		Pre- Period (Q3 2010 to Q2 2012)	Active REMS Period (Q3 2013 to Q4 2014)
Poison Center Program (Mean exposure calls per quarter)			
Abuse	ER/LA Opioids	337	205
	IR Opioids	757	568
Misuse	ER/LA Opioids	645	543
	IR Opioids	3,360	2994
Unintentional Therapeutic Errors	ER/LA Opioids	367	333
	IR Opioids	1,561	1495
Treatment Center Program (Total mentions)			
Mentions of abuse in past 30 days	ER/LA Opioids	22,890	10,294
	IR Opioids	24,567	18,332
College Survey Program (Total mentions)			
Mentions of non-medical use in past 90 days	ER/LA Opioids	790	1227
	IR Opioids	1828	2633

Source: Table generated by reviewer, based on data provided in the Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

3.2.3.1 RADARS Poison Center Program

3.2.3.1.1 Intentional abuse

Means analyses

The mean number of intentional abuse exposure calls for both ER/LA and IR opioids decreased significantly across the REMS study periods, although reductions were significantly larger for

the ER/LA opioids than for the IR opioids, comparing the pre- to transition and pre- to active periods (Table 7). For the ER/LA opioid group, the largest portion of the decrease occurred between the pre- and transition periods, with much smaller reductions comparing the transition to active periods. Small but significant reductions were also seen for prescription stimulants. Adjusting for utilization slightly attenuated the reductions for the ER/LA and IR opioid groups and increased the reductions in prescription stimulants (data not shown).

Table 7. Mean Intentional Abuse Exposure Population-adjusted Rates, RADARS Poison Control, Q3 2010 to Q4 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.123	Pre versus Transition	-31.19%(-39.84%,-21.29%)	<.001	.
	Transition	0.085	Transition versus Active	-18.67%(-30.31%,-5.10%)	0.009	.
	Active	0.069	Pre versus Active	-44.04%(-50.57%,-36.64%)	<.001	.
IR Prescription Opioids	Pre	0.276	Pre versus Transition	-17.77%(-24.88%,-9.98%)	<.001	0.031
	Transition	0.227	Transition versus Active	-15.96%(-24.00%,-7.06%)	<.001	0.727
	Active	0.191	Pre versus Active	-30.89%(-36.40%,-24.90%)	<.001	0.006
Prescription Stimulants	Pre	0.148	Pre versus Transition	-4.92%(-12.21%,2.98%)	0.215	<.001
	Transition	0.141	Transition versus Active	-8.87%(-16.31%,-0.76%)	0.033	0.205
	Active	0.129	Pre versus Active	-13.35%(-19.35%,-6.90%)	<.001	<.001

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

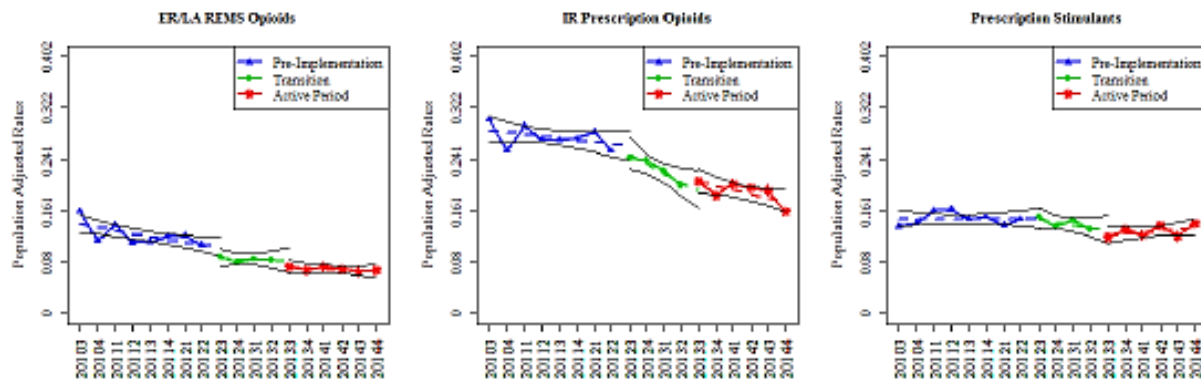
Means analyses for adolescent intentional abuse calls demonstrated even larger reductions for ER/LA opioids (-61.8%; 95% CI -69.5% to -52.3%), with the reduction slightly attenuated after adjustment for dosing units dispensed. Significant reductions were observed for both IR opioids and stimulants; however reductions for ER/LA opioids were significantly larger than for either of these drug classes.

For the individual ER/LA opioids with relatively high utilization—ER morphine, ER oxycodone, fentanyl TDS, and methadone—the patterns were generally similar to the ER/LA opioid class overall. For ER morphine and ER oxycodone, the reductions in intentional abuse calls were slightly greater than for ER/LA opioids overall when comparing the transition to active periods. Results for ER oxymorphone showed large and significant reductions comparing the pre- to transitions periods, with small, non-significant reductions between the transition and active periods. Analyses for some products (ER hydrocodone, ER hydromorphone, ER tapentadol, buprenorphine TDS) were not meaningful because of low market share and small case numbers, yielding extremely wide confidence intervals.

Trend analyses

The piecewise linear model results indicate that there was a significant downward trend in intentional abuse calls involving ER/LA opioids during the pre-implementation period but not during the transition or active periods (Figure 6, Table 8). The differences in slope between the three periods were not statistically significant. The abuse rates for ER/LA opioids at the beginning of the transition period and the active periods were also not significantly different from the expected rates were the trends from the previous periods to continue. Patterns were similar for utilization-adjusted analyses and for most of the individual ER/LA opioids with relatively large market share (data not shown); however, pre-period trends for ER oxymorphone were upward-sloping and suggested a non-linear pattern during this REMS period.

Figure 6. Piecewise Linear Regression Visual Trend Analyses, Intentional Abuse Exposure Calls, Population-adjusted Rates, RADARS Poison Center, Q3 2010 to Q4 2014



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Table 8. Piecewise Linear Regression Analyses, Intentional Abuse Exposure Calls, Population-adjusted Rates, RADARS Poison Center, Q3 2010 to Q4 2014

Drug Group	Time Period	Estimated Rate in 20123	P-value for Difference at 20123	Estimated Rate in 20133	P-value for Difference at 20133	Slope (95% CI)	Comparison	Within Drug Contrast p-values	Between Drug Interaction p-values
ER/LA REMS Opioids	Pre	0.104		.		-3.61%(-6.00%,-1.16%)	Pre versus Transition	0.619 ^a	
	Transition	0.087	0.077 ^a	0.082		-1.41%(-9.47%,7.38%)	Transition versus Active	0.960 ^d	
	Active	.		0.072	0.359 ^b	-1.66%(-6.45%,3.38%)	Pre versus Active	0.482 ^a	
IR Prescription Opioids	Pre	0.263		.		-1.11%(-2.84%,0.65%)	Pre versus Transition	0.061 ^c	0.151 ^f
	Transition	0.250	0.479 ^a	0.192		-6.40%(-11.40%,-1.12%)	Transition versus Active	0.288 ^d	0.538 ^e
	Active	.		0.206	0.436 ^b	-3.13%(-6.14%,-0.02%)	Pre versus Active	0.263 ^a	0.231 ^b
Prescription Stimulants	Pre	0.149		.		0.06%(-1.97%,2.13%)	Pre versus Transition	0.307 ^c	0.320 ^f
	Transition	0.148	0.946 ^a	0.130		-3.15%(-8.71%,2.74%)	Transition versus Active	0.135 ^d	0.376 ^e
	Active	.		0.122	0.525 ^b	1.97%(-1.31%,5.36%)	Pre versus Active	0.336 ^a	0.973 ^b

^ap-value comparing the rate estimated by the Pre-Implementation period regression line at 3Q2012 versus the rate estimated by the Transition period regression line at 3Q2012 within drug group.
^bp-value comparing the rate estimated by the Transition period regression line at 3Q2013 versus the rate estimated by the Active Period regression line at 3Q2013 within drug group.
^cp-value comparing the slope of the Pre-Implementation period regression line to the slope of the Transition period regression line within drug group.
^dp-value comparing the slope of the Transition period regression line to the slope of the Active Period regression line within drug group.
^ep-value comparing the slope of the Pre-Implementation period regression line to the slope of the Active Period regression line within drug group.
^fp-value comparing the difference in slopes for the Pre-Implementation and Transition period regression lines for the ER/LA REMS opioids to the difference in slopes for the Pre-Implementation and Transition period regression lines for IR prescription opioids.
^gp-value comparing the difference in slopes for the Transition and Active Period regression lines for the ER/LA REMS opioids to the difference in slopes for the Transition and Active Period regression lines for IR prescription opioids.
^hp-value comparing the difference in slopes for the Pre-Implementation and Active Period regression lines for the ER/LA REMS opioids to the difference in slopes for the Pre-Implementation and Active Period regression lines for IR prescription opioids.
ⁱp-value comparing the difference in slopes for the Pre-Implementation and Transition period regression lines for the ER/LA REMS opioids to the difference in slopes for the Pre-Implementation and Transition period regression lines for prescription stimulants.
^jp-value comparing the difference in slopes for the Transition and Active Period regression lines for the ER/LA REMS opioids to the difference in slopes for the Transition and Active Period regression lines for prescription stimulants.
^kp-value comparing the difference in slopes for the Pre-Implementation and Active Period regression lines for the ER/LA REMS opioids to the difference in slopes for the Pre-Implementation and Active Period regression lines for prescription stimulants.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Trends in adolescent intentional abuse calls showed similar trends, with significant negative slopes during the pre-REMS period and non-significant slopes for the transition and active periods that were not significantly different from pre-period slopes. In this group, trends for IR opioids and stimulants were not statistically significant during any REMS period.

3.2.3.1.2 Misuse

Means analyses

Reductions in misuse calls involving ER/LA opioids were smaller than for intentional abuse calls and were similar to reductions observed for IR opioid misuse calls, as shown in Table 9. Misuse of prescription stimulants did not change across the study period. Adjusting for prescriptions or for dosage units dispensed slightly attenuated the relative reductions observed in ER/LA opioid misuse call rates but did not appreciably change the overall patterns (data not shown).

Table 9. Mean Misuse Exposure Calls Population-adjusted Rates, RADARS Poison Center Program, Q3 2010 to Q4 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values ^a	Between Drug Interaction p-values ^b
ER/LA REMS Opioids	Pre	0.236	Pre versus Transition	-11.17%(-19.73%,-1.69%)	0.022	.
	Transition	0.209	Transition versus Active	-12.75%(-21.87%,-2.57%)	0.015	.
	Active	0.183	Pre versus Active	-22.49%(-29.32%,-15.01%)	<.001	.
IR Prescription Opioids	Pre	1.226	Pre versus Transition	-8.32%(-12.76%,-3.66%)	<.001	0.584
	Transition	1.124	Transition versus Active	-10.49%(-15.15%,-5.58%)	<.001	0.683
	Active	1.006	Pre versus Active	-17.94%(-21.54%,-14.19%)	<.001	0.275
Prescription Stimulants	Pre	1.195	Pre versus Transition	-0.71%(-6.54%,5.49%)	0.818	0.065
	Transition	1.186	Transition versus Active	-0.75%(-6.82%,5.71%)	0.815	0.047
	Active	1.177	Pre versus Active	-1.46%(-6.57%,3.94%)	0.589	<.001

^aThe within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
^bThe between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Percent reductions in misuse calls varied somewhat across the individual ER/LA opioids, but the overall patterns were similar among those with large enough event counts to yield meaningful results, including ER morphine, ER oxycodone, fentanyl TDS, methadone, and ER oxymorphone (data not shown).

Trend analyses

Similar to the intentional abuse call trend analyses, the misuse piecewise linear regression analyses indicate that there was a significant downward trend in misuse calls for ER/LA opioids during the pre-implementation period but not during the transition or active periods. (Attachment A: Figure 1, Table 1). The differences in slope between the three periods were not statistically significant.

3.2.3.1.3 Major medical outcome, hospitalization, or death

Means analyses

The mean number of exposure calls resulting in a major medical outcome, hospitalization, or death decreased significantly across REMS study periods for both ER/LA and IR opioids, although reductions were significantly larger for the ER/LA opioids than for the IR opioids for all but the transition to active period comparisons (Table 10). Rates for prescription stimulants showed a small but significant increase across the study period. Reductions for the ER/LA opioid group were attenuated slightly after adjusting for utilization.

Table 10. Mean Major Medical Outcome, Hospitalization, or Death Exposure Call Population-adjusted Rates, RADARS Poison Center Program, Q3 2010 to Q4 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values ^a	Between Drug Interaction p-values ^b
ER/LA REMS Opioids	Pre	0.250	Pre versus Transition	-12.08%(-17.76%,-6.02%)	<.001	.
	Transition	0.220	Transition versus Active	-14.56%(-20.58%,-8.07%)	<.001	.
	Active	0.188	Pre versus Active	-24.88%(-29.33%,-20.15%)	<.001	.
IR Prescription Opioids	Pre	1.220	Pre versus Transition	-5.06%(-8.13%,-1.88%)	0.002	0.043
	Transition	1.158	Transition versus Active	-7.81%(-10.99%,-4.52%)	<.001	0.066
	Active	1.068	Pre versus Active	-12.47%(-15.02%,-9.85%)	<.001	<.001
Prescription Stimulants	Pre	0.387	Pre versus Transition	9.71%(1.78%,18.27%)	0.016	<.001
	Transition	0.424	Transition versus Active	3.36%(-4.23%,11.54%)	0.396	<.001
	Active	0.438	Pre versus Active	13.39%(6.19%,21.09%)	<.001	<.001

^aThe within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
^bThe between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Relative percent reductions varied somewhat across the individual ER/LA opioid molecules, but the overall patterns were fairly similar among those with large enough market shares and event counts to yield meaningful results, including ER morphine, ER oxycodone, fentanyl TDS, methadone, and ER oxymorphone (data not shown).

Trend analyses

Similar to the intentional abuse and misuse call trend analyses, the piecewise linear regression analyses for exposure calls resulting in major medical outcome, hospitalization, or death indicate that there was a significant downward trend in these calls for ER/LA opioids during the pre-implementation period but not during the transition or active periods (Attachment A: Figure 2, Table 2). The between-period difference in slope was only significant when comparing the significant negative slope in the pre-period to the non-significant positive slope in the active period.

Analyses of calls resulting in an outcome of death are provided in Attachment A, Figure 3, Tables 3 and 4.

3.2.3.1.4 Pediatric Unintentional Exposures

Means analyses

Because REMS messages, particularly those regarding safe storage and disposal, could affect the risk of pediatric unintentional exposure to prescription opioids, an analysis of this poison center call category was included as part of the assessment. Pediatric unintentional exposure calls (occurring in children under six years of age) decreased significantly for ER/LA opioids across the REMS study period, although the reduction was not significantly different from that observed

for IR opioids (Table 11). Unintentional pediatric exposure calls did not change significantly for prescription stimulants.

Table 11. Mean Pediatric Unintentional Exposure Calls, Population-adjusted Rates, RADARS Poison Center Program, Q3 2010 to Q4 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values ^a	Between Drug Interaction p-values ^b
ER/LA REMS Opioids	Pre	0.530	Pre versus Transition	-6.90%(-21.65%,10.61%)	0.416	.
	Transition	0.494	Transition versus Active	-14.88%(-29.46%,2.71%)	0.093	.
	Active	0.420	Pre versus Active	-20.76%(-32.37%,-7.16%)	0.004	.
IR Prescription Opioids	Pre	3.895	Pre versus Transition	-8.16%(-14.98%,-0.78%)	0.031	0.888
	Transition	3.578	Transition versus Active	-8.42%(-15.71%,-0.49%)	0.038	0.485
	Active	3.276	Pre versus Active	-15.89%(-21.52%,-9.84%)	<.001	0.499
Prescription Stimulants	Pre	5.511	Pre versus Transition	0.58%(-4.05%,5.43%)	0.810	0.397
	Transition	5.543	Transition versus Active	-1.62%(-6.34%,3.34%)	0.515	0.144
	Active	5.453	Pre versus Active	-1.05%(-5.09%,3.16%)	0.619	0.008

^aThe within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
^bThe between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Some of the individual ER/LA opioid analyses showed significant reductions in pediatric unintentional exposures across the study periods, but confidence intervals for the relative percent reductions were generally wide and included zero.

Trend analyses

Similar to the intentional abuse and misuse call trend analyses, the pediatric unintentional exposure piecewise linear regression analyses indicate that there was a significant downward trend in calls involving ER/LA opioids during the pre-implementation period and non-significant downward trending slopes during the transition and active periods (Attachment B: Figure 4, Table 5). The differences in slope between the three periods were not statistically significant.

3.2.3.2 RADARS Treatment Center Program

Means analyses

The mean population-adjusted abuse prevalence for ER/LA opioids decreased significantly from the pre- to active periods, although most of this reduction occurred between the pre- and transition periods (Table 12). The magnitude of change decreased slightly after adjusting for either prescriptions or dosage units dispensed; and the overall pattern for ER/LA opioids as a class was similar to that seen for ER morphine, ER oxycodone, fentanyl TDS, methadone, and ER oxymorphone (data not shown). Observed reductions for IR opioids were smaller and were not statistically significant. The decrease in ER/LA opioid abuse prevalence was significantly greater than for IR opioids, comparing the pre- to active REMS periods.

Table 12: Mean Past 30-day Abuse, Population Rates for ER/LA and IR Opioids, RADARS Treatment Center Programs, Q3 2010 to Q4 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values [*]	Between Drug Interaction p-values [#]
ER/LA REMS Opioids	Pre	1.987	Pre versus Transition	-40.02%(-56.09%,-18.06%)	0.001	.
	Transition	1.192	Transition versus Active	-11.67%(-38.18%,26.21%)	0.496	.
	Active	1.053	Pre versus Active	-47.02%(-60.00%,-29.81%)	<.001	.
IR Prescription Opioids	Pre	2.133	Pre versus Transition	-13.01%(-29.97%,8.06%)	0.208	0.055
	Transition	1.855	Transition versus Active	1.07%(-19.60%,27.03%)	0.928	0.533
	Active	1.875	Pre versus Active	-12.09%(-27.31%,6.32%)	0.184	0.003

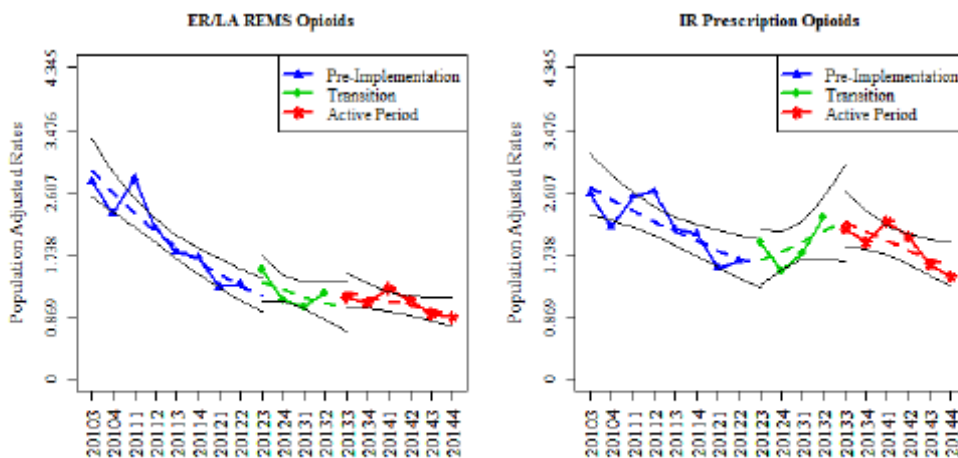
^{*}The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
[#]The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Trend analyses

The piecewise linear model analyses for past 30-day abuse of ER/LA and IR opioids are depicted in Figure 11, with quantitative results in Table 13. The trend analyses demonstrate significant downward trends in both ER/LA and IR opioid abuse prevalence during the pre-REMS period. For the ER/LA opioid group, the slopes for the transition and active periods are also negative but not statistically significant. The differences in slope between the three periods were not statistically significant. The abuse rates for ER/LA opioids at the beginning of the transition period and the active periods were also not significantly different from the expected rates were the trends from the previous periods to continue. Results were similar for ER morphine, ER oxycodone, fentanyl TDS, and methadone (data not shown). Results were similar after adjusting for utilization, either prescriptions or dosage units dispensed (data not shown).

Figure 11. Trends in past 30-day Abuse, Population-adjusted Prevalence for ER/LA and IR Opioids, RADARS Treatment Center Programs, Q3 2010 to Q4 2014



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Table 13. Piecewise Linear Model Results for Past 30-day Population-adjusted Abuse Prevalence for ER/LA and IR Opioids, RADARS Treatment Center Programs, Q3 2010 to Q4 2014

Drug Group	Time Period	Estimated Rate in 20123	P-value for Difference at 20123	Estimated Rate in 20133	P-value for Difference at 20133	Slope (95% CI)	Comparison	Within Drug Contrast p-values	Between Drug Interaction p-values
ER/LA REMS Opioids	Pre	1.152		.		-10.95%(-14.15%,-7.63%)	Pre versus Transition	0.632 ^c	
	Transition	1.352	0.306 ^a	0.967		-8.03%(-18.97%,4.38%)	Transition versus Active	0.707 ^d	
	Active	.		1.203	0.295 ^b	-5.43%(-12.00%,1.63%)	Pre versus Active	0.145 ^e	
IR Prescription Opioids	Pre	1.571		.		-6.46%(-10.12%,-2.65%)	Pre versus Transition	0.028 ^c	0.247 ^f
	Transition	1.653	0.750 ^a	2.205		7.47%(-4.38%,20.78%)	Transition versus Active	0.038 ^d	0.094 ^g
	Active	.		2.203	0.995 ^b	-6.58%(-12.18%,-0.62%)	Pre versus Active	0.973 ^e	0.271 ^h

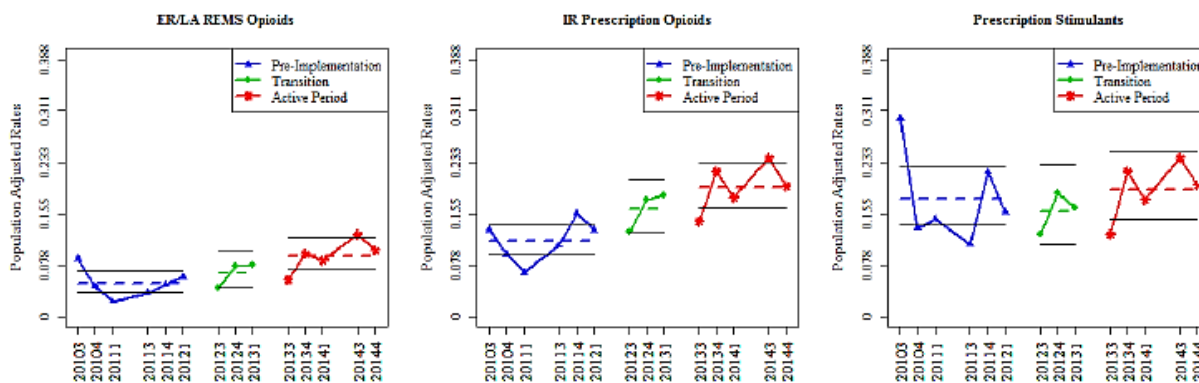
^ap-value comparing the rate estimated by the Pre-Implementation period regression line at 3Q2012 versus the rate estimated by the Transition period regression line at 3Q2012 within drug group.
^bp-value comparing the rate estimated by the Transition period regression line at 3Q2013 versus the rate estimated by the Active Period regression line at 3Q2013 within drug group.
^cp-value comparing the slope of the Pre-Implementation period regression line to the slope of the Transition period regression line within drug group.
^dp-value comparing the slope of the Transition period regression line to the slope of the Active Period regression line within drug group.
^ep-value comparing the slope of the Pre-Implementation period regression line to the slope of the Active Period regression line within drug group.
^fp-value comparing the difference in slopes for the Pre-Implementation and Transition period regression lines for the ERLA REMS opioids to the difference in slopes for the Pre-Implementation and Transition period regression lines for IR prescription opioids.
^gp-value comparing the difference in slopes for the Transition and Active Period regression lines for the ERLA REMS opioids to the difference in slopes for the Transition and Active Period regression lines for IR prescription opioids.
^hp-value comparing the difference in slopes for the Pre-Implementation and Active Period regression lines for the ERLA REMS opioids to the difference in slopes for the Pre-Implementation and Active Period regression lines for IR prescription opioids.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

3.2.3.3 RADARS College Survey Program

Figure 12 and Table 14 show the results of means analyses for the RADARS College Survey Program, indicating a significant increase in past 90-day drug mention rates for non-medical use of both ER/LA and IR opioids in this population. Mentions of stimulants remained fairly stable throughout the REMS study periods, although confidence intervals were quite wide.

Figure 12. RADARS College Survey Program mean past 90-day mention rates per 100,000 population for ER/LA REMS opioids and comparators, Q3 2010 to Q 4 2014



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Table 14. RADARS College Survey Program mean past 90-day mention rates per 100,000 population for ER/LA REMS opioids and comparators, Q3 2010 to Q4 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
ER/LA REMS Opioids	Pre	0.049	Pre versus Transition	33.51%(-19.68%,121.94%)	0.265	.
	Transition	0.066	Transition versus Active	38.45%(-13.47%,121.54%)	0.175	.
	Active	0.091	Pre versus Active	84.85%(22.07%,179.93%)	0.004	.
IR Prescription Opioids	Pre	0.114	Pre versus Transition	42.70%(3.69%,96.37%)	0.029	0.828
	Transition	0.162	Transition versus Active	20.13%(-10.82%,61.84%)	0.228	0.617
	Active	0.195	Pre versus Active	71.43%(30.88%,124.54%)	<.001	0.765
Prescription Stimulants	Pre	0.177	Pre versus Transition	-10.55%(-42.95%,40.23%)	0.627	0.247
	Transition	0.158	Transition versus Active	20.42%(-23.75%,90.19%)	0.425	0.677
	Active	0.191	Pre versus Active	7.72%(-25.25%,55.23%)	0.690	0.056

*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Patterns were similar after adjustment for utilization but varied somewhat across individual ER/LA opioid compounds (data not shown). Trend analyses indicate that the slopes for ER/LA opioids, IR opioids, and stimulants were not statistically significant, with 95% confidence intervals including a slope of zero in all three time periods. There were no significant differences in slope across the three periods.

3.2.4 Discussion of RADARS Program Studies

3.2.4.1 Poison Center Study

The RADARS Poison Center study found significant reductions in the mean number of ER/LA and IR opioid exposure calls classified as intentional abuse (all and adolescent only), misuse, pediatric unintentional exposure, and calls resulting in a major medical outcome, hospitalization or death. In general, relative percent reductions in mean exposure calls for the outcomes of interest were significantly greater for calls involving ER/LA opioids than for calls involving IR opioids or prescription stimulants; however, large and significant reductions were seen for the IR opioids in many analyses. Means analyses can be misleading, however, if rates are changing substantially during the pre-intervention period, indicating pre-existing secular trends that may continue through the study period. In this study, trend analyses indicate significant downward trends in the pre-REMS period across all the major exposure call types of interest involving both ER/LA and IR opioids. In attempting to assess the effect of an intervention, one must account for these pre-existing secular trends. Here, this was done using piecewise linear models—first, to look for a significant change in slope, which might indicate that the intervention was somehow “bending the curve,” or affecting the trajectory of the trend. Second, the analyses tested whether there was a significant break, or drop, in the trend at the beginning of a new period. These

analyses did not indicate either a significant change (decrease) in trajectory or a break in the trend at the beginning of either the transition or active periods for any of the major outcomes of interest.

Adjusting for utilization, either dispensed prescriptions or dosage units, did not meaningfully change the overall findings, and in general, patterns for individual ER/LA drugs were similar among those with relatively large market share and consistent with patterns seen for the class overall. Trends for ER oxymorphone were often quite different from the other drugs, however. This was particularly true during the pre-period, during which time ER oxymorphone was reformulated. Results for ER/LA opioids with very low market share were uninterpretable due to low event counts and unstable estimates.

As with the claims-based studies, a major limitation of this study is that the time periods serve only as proxy measures of exposure to REMS interventions. The study is unable to determine whether having a prescriber who took a REMS-compliant CE course or exposure to REMS patient education materials confers a lower risk of having an abuse, misuse, or overdose event captured in the poison center data system. A comparison of event rates and slopes across time periods measures the combined effects of many different efforts occurring in the U.S. to curb inappropriate prescribing, diversion, abuse, and overdose related to prescription drugs and particularly opioids. The downward trends seen during the pre-REMS period coupled with the lack of change in the trajectory in these trends after the start of the REMS suggests that factors other than the REMS may largely be driving the observed decreases.

Strengths of the poison center study are that it captures clinically meaningful events, represents a large, nearly national geographic region, and allows product-specific analyses. However, DEPI has concerns with the use of poison control call data to estimate changes in abuse of specific prescription opioid products and classes. First, it is unknown how well trends and patterns in poison center calls reflect trends and patterns in actual misuse and abuse of prescription opioids nationally, given the many factors that may influence whether an exposed individual, caregiver, or healthcare provider uses this service. Although there is some evidence that, over time, trends in rates of poison center calls involving misuse and abuse are correlated with trends in rates of emergency department visits involving abuse and misuse use of prescription opioids,³⁷ there is also evidence suggesting that use of poison control call centers has been changing in recent years.³⁸ In addition, it is unclear how accurately the poison centers are able to classify 1) specific products, especially when there are various formulations and generic products, and 2) exposure categories (e.g. intentional abuse, misuse, suicide attempt, adverse reaction) in various abuse and overdose-related situations. Finally, poison control calls will not capture severe overdoses that

³⁷ Davis JM, Severtson SG, Bucher-Bartelson B, Dart RD. Using poison center exposure calls to predict prescription opioid abuse and misuse-related emergency department visits. *Pharmacoepidemiology and Drug Safety* 2014; 23: 18-25.

³⁸ https://aapcc.s3.amazonaws.com/pdfs/annual_reports/2014_AAPCC_NPDS_Annual_Report.pdf

result in death before a call to a poison control center can be made. The fraction of overdose death cases captured in this data system may therefore vary across products and over time, depending on the likelihood of a lethal overdose that never generates a poison center call. For this reason, DEPI does not consider poison center calls to be an appropriate data source for comparing the incidence of overdose death across drug products, classes, or time periods.

3.2.4.2 Treatment Center Study

Similar to the Poison Center study, the RADARS Treatment Center study suggests significant reductions in ER/LA opioid abuse that are greater than those seen for IR opioids. Again, however, trend analyses show downward trends that pre-dated REMS implementation and did not accelerate with the introduction of the REMS. Therefore, as with the poison center data, the treatment center data suggest that the observed reductions in abuse-related outcomes across REMS periods may have been due, in whole or part, to factors other than the REMS interventions.

Surveys of patients entering substance abuse treatment are important sources of product-specific abuse surveillance; however, there are a number of limitations that influence the interpretation of results. RADARS Treatment Center program is a convenience sample, and sites are added to and drop out of the program over time. If abuse patterns vary considerably across treatment centers or geographic regions, these shifts in the study sample could bias trends or relative estimates of abuse for various products. Or, if abuse patterns in sampled treatment centers change over time due to external factors—for example due to increasing availability of office-based buprenorphine treatment for prescription opioid addiction—trends seen in the sampled treatment centers may not accurately reflect trends in the population. Also, because the survey instrument is amended periodically to add newly marketed products and improve the surveillance system, abuse prevalence estimates can change over time due to these adjustments in the survey instrument.

Relating trends observed in this population to REMS interventions is difficult. The RADARS Treatment Center study population is limited to those entering treatment for addiction, including addiction to prescription opioids or heroin. It is unclear in what ways educating providers and patients about safe use of ER/LA opioids would be expected to impact abuse patterns among those with opioid addiction entering treatment. If the REMS were to reduce the amount of ER/LA opioids diverted from legitimate pain management prescriptions through theft, sharing, or selling, it is possible that the availability of ER/LA opioids to opioid addicts could decrease relative to the availability of other drugs. However, it is also conceivable that REMS provider training could improve identification of patients with opioid use disorders and increase referrals to treatment. In addition, many other factors such as law enforcement and judicial practices, funding and access to treatment, and trends in the availability and price of other drugs such as heroin may have a particularly large impact on the relative abuse of different opioids in this highly selected population of individuals with advanced opioid addiction.

3.2.4.3 College Survey

The RADARS college survey study suggests increases in non-medical use of both ER/LA and IR opioids in this population, with no significant change in the non-medical use of stimulants. These results were discordant with the pattern seen in the other studies, including other analyses of adolescent populations (the RADARS Poison Center Study adolescent abuse, and the CHAT study, discussed in the next section). It is not clear how well the population of students participating in this internet-based survey represents college students in the U.S. or how the study sample might have changed over time.

As with the other RADARS studies, it is difficult to link the trends in self-reported non-medical use of ER/LA opioids directly to the REMS interventions. In theory, the REMS could lead to more cautious prescribing in this age group. In addition increased awareness of the need for secure storage of opioids and better provider recognition of abuse and diversion could reduce availability of diverted drugs to college students. However, these data do not suggest such an effect. The suggestion of increasing trends in non-medical use of opioids in this population is troubling, and more focused studies to better understand this phenomenon should be considered.

3.3 *NAVIPPRO System: ASI-MV and CHAT*

3.3.1 Objectives

The objective of this study is to estimate changes in the prevalence of past 30-day abuse of ER/LA opioid products across the three REMS periods. Additional objectives include comparing these changes with those observed for IR opioids and benzodiazepines, examining quarterly trends in ER/LA opioid abuse, and examining changes in the distribution of the source of ER/LA opioids in this population.

3.3.2 Methods

Data Sources

The National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) is a cross-sectional surveillance system that measures patterns of abuse of ER/LA opioid analgesics and comparators over time. The ASI-MV is a proprietary data collection instrument used in the NAVIPPRO system to collect information on substances used and abused from adults within a network of substance abuse treatment centers and other assessment settings using a self-administered, structured, computerized interview. In addition, the ASI-MV collects individual-level data across a series of domain areas, including medical, employment/support status, alcohol/drug use, legal, family/social status, and psychiatric status. The ASI-MV assessment captures product-specific data related to past 30-day use and abuse for over 60 brand and generic prescription opioid products, including information on routes of administration used and sources of procurement for each product.

The Comprehensive Health Assessment for Teens (CHAT) is a computerized behavioral health assessment targeted to adolescents age 18 years and younger entering treatment for drug or alcohol abuse. Similar to the ASI-MV, CHAT collects data on the use and abuse of opioids, as well as factors related to substance abuse that are specific to this younger population. Also like the ASI-MV, data related to route(s) of administration, source for obtaining the products and geographic location are collected. Questions unique to CHAT are focused on adolescent experiences in five domain areas: self and personality factors, family and peer relations, physical and emotional health, psychological issues, and drug use experiences. The CHAT network of participating sites comprises treatment centers and other facilities, such as alternative schools and mental health programs. CHAT monitors the same prescription medications tracked by ASI-MV and began data collection and surveillance in June 2009.

Study Time Frame

The following timeframe definitions were used in this investigation to evaluate changes in patterns of abuse:

- Pre-REMS implementation period: July 2010 – June 2012
- REMS implementation period: July 2012 – June 2013
- Active REMS Period: July 2013 – December 2014

The primary and secondary objective analyses both use the pre-REMS implementation period as the referent category.

Study Population

For the timeframe of July 1, 2010 through December 31, 2014, the ASI-MV database contained a total of 263,485 assessments of patients aged 18 and older (prior to removal of excluded cases). The ASI-MV population includes male and female adults entering or being assessed for substance abuse treatment within a network of participating sites located in 40 states. The ASI-MV population is composed of approximately 65% males and 35% females. Over half of the patient population is Caucasian (60%), approximately 15% is Hispanic/Latino, and 19% is African-American. Of all patients in this ASI-MV dataset, 22% (n = 57,666) reported past 30-day abuse of any prescription opioid.

A preliminary cut of the CHAT dataset yielded 12,510 adolescents who have taken a CHAT assessment. The majority of adolescent respondents were 15 to 18 years of age (79.8%), male (68.1%), and Caucasian (67.8%). Approximately 31% of adolescent respondents reported that they were currently taking a prescribed medication for an emotional, behavioral, or learning problem, and 19.2% reported a pain problem. During the study timeframe, 1,065 (8.5% of all adolescents assessed by CHAT) indicated having abused a prescription opioid within the past 30-days. Prescription opioid abusers within the CHAT network more frequently indicated a self-reported pain problem (30.7%) as compared to all adolescents assessed by the CHAT (19.2%). For all analyses, the target REMS category includes extended-release, oral-dosage forms containing: hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, tapentadol,

methadone tablets that are indicated for use as analgesics, and a combination of fentanyl and buprenorphine-containing transdermal delivery systems.

Data Aggregation

Duplicate cases (individuals taking the ASI more than once during a period) and those who indicate use of the “fake” drug selection in the ASI-MV were removed from all analyses. In addition, for analyses at the patient home 3-digit ZIP code level individuals who meet one of the following criteria were removed: (1) ZIP code data were missing, (2) a ZIP code data could not be recorded due to HIPAA regulations or (3) the ZIP code data entered did not correspond to a valid ZIP code.

The ASI-MV is a dynamic system where new sites are added to the network on a regular basis and some attrition or reduction in the number of participating sites exists over time. Data from all ASI-MV sites contributing assessments at any given time throughout this timeframe provide the data for all study analyses. A sensitivity analysis was performed to evaluate any potential impact on abuse estimates for primary study objectives of geographical variation in the ASI-MV network via examination of shared sites. The shared sites sensitivity analysis was restricted to those sites within the total ASI-MV network of sites which had contributed data (i.e., at least one ASI-MV assessment) during the pre-REMS (baseline), REMS implementation (time 1) and continuing active REMS phase (time 2). The purpose of this sensitivity analysis was to determine the extent to which results for the primary objectives change across the time periods when evaluated among a shared set of sites. Per request of the RPC metrics team, two additional sensitivity analyses were performed on primary study objectives which stratify observations for past 30-day abuse of ER/LA opioids stratified by patient drug problem severity and treatment modality.

Statistical Analysis

All analyses were conducted using the GLIMMIX procedure in SAS 9.4. To estimate and compare changes in the probability of abuse between specific drug groups over time, a mixed effects negative binomial regression model was employed. In this model, the fixed effects includes a drug-indicator variable (ER/LA product group, IR prescription opioids, and benzodiazepines), a period indicator variable (pre-REMS period, REMS implementation period, and active REMS period), and the interaction between both effects. Both variables are treated as categorical. The binary dependent variable is endorsement/no endorsement of abuse in the past 30 days for any of drugs comprising each level of the drug groups. The random ZIP code effect was incorporated to account for nesting of patients in 3-digit home ZIP codes.

Generalizability

Treatment centers within the NAVIPPRO system are not randomly recruited to join the network. Therefore, results of the analyses conducted on the patient data collected from these treatment centers may not be generalizable to all patients in substance abuse treatment in the U.S. The ASI-

MV draws patients from 816 3-digit ZIP codes. The data set is not nationally representative and thus is not intended to be used for estimating national incidence and prevalence rates.

According to NAVIPPRO, the demographic characteristics of patients within the ASI-MV population are comparable to the demographic characteristics of demographics of the population captured by the Treatment Episode Dataset (TEDS), which is maintained by SAMHSA and includes data from a large majority of publically-funded substance abuse treatment centers. The two populations are similar with respect to gender, age, and educational characteristics with some noted differences in the racial and employment characteristics between the two populations.

3.3.3 Key Results

3.3.3.1 Past 30-day abuse of ER/LA opioids and comparators

Table 15 shows the total number of assessments and abuse events for the pre-implementation, implementation (transition) and active REMS periods. Note that the lengths of the three time periods vary.

Table 15. Total number of ASI-MV assessments and past 30-day abuse reports for ER/LA opioids and comparator drugs in the pre-implementation, implementation, and active REMS periods, NAVIPPRO study

	PRE IMPLEMENTATION (N = 130,629)	IMPLEMENTATION (N = 55,189)	ACTIVE PERIOD (N = 76,236)
ER/LA opioids	11,199	5,192	7,208
IR opioids	18,947	8,844	11,852
Benzodiazepines	13,859	5,677	7,808
Morphine ER	1,757	977	1,329
Oxycodone ER	1,749	978	1,575
Methadone	3,599	2,054	2,860
Oxycodone ER	7,702	3,036	3,869
Hydromorphone ER	21	13	28
Tapentadol ER	3	7	18
Fentanyl TDS	998	469	657
Buprenorphine TDS	93	128	225
Hydrocodone ER	N/A	N/A	21

* Baseline: Pre-REMS period: July 2010 – June 2012; Time 1: Implementation Period: July 2012 – June 2013; Time 2 Active Period: July 2013 – December 2014.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Means analyses

Modest but statistically significant reductions in mean past 30-day abuse rates were observed for ER/LA opioids in both the ASI-MV and CHAT systems, comparing the pre-implementation to

active periods (Table 16). Reductions were of greater magnitude for analyses using the U.S. census denominator (first column) than the percent of ASI-MV assessments (second column). Reductions in ER/LA opioid abuse rates were not significantly different from reductions in the prevalence of IR opioid or benzodiazepine abuse. Changes in abuse rates for individual ER/LA opioids varied widely. Among the ER/LA opioids with relatively large market share, the largest reductions were observed for ER oxycodone. The magnitude of reduction in ER/LA opioid abuse was greater in the CHAT program (last column), although the estimates were less precise.

Table 16. Change in Past 30-day Abuse Prevalence in the ASI-MV and CHAT surveillance systems for ER/LA opioids, IR opioids, benzodiazepines, and individual ER/LA opioid compounds, per 100,000 U.S. Census population (U.S. Census column) and as a proportion of ASI-MV assessments (ASI-MV column)

	U.S. CENSUS		ASI-MV		CHAT	
	% CHANGE PRE TO ACTIVE PERIOD (95% CI)	P-VALUE	% CHANGE PRE TO ACTIVE PERIOD (95% CI)	P-VALUE	% CHANGE PRE TO ACTIVE PERIOD* (95% CI)	P-VALUE
ER/LA Opioids	-20.45 (-25.38, -15.20)	<.0001	-6.68 (-10.44, -2.76)	0.0010	-25.64 (-41.58, -5.35)	0.0161
IR Prescription Opioids	-18.2 (-22.8, -13.3)	<.0001	-6.33 (-9.58, -2.95)	0.0003	-13.32 (-24.88, 0.03)	0.0504
Benzodiazepines	-16.6 (-21.6, -11.3)	<.0001	-9.466 (-13.16, -6.02)	<.0001	19.84 (-3.35, 48.59)	0.0990
Morphine ER	-10.3 (-19.7, 0.1)	0.0513	-2.33 (-11.37, 7.65)	0.6353	4.90 (-51.91, 128.81)	0.9043
Oxymorphone ER	-12.2 (-21.4, -2.0)	0.0203	-2.48 (-11.47, 7.42)	0.6108	-47.11 (-75.51, 14.21)	0.1049
Methadone	-2.4 (-10.7, 6.7)	0.5968	10.67 (2.47, 19.53)	0.0098	--	--
Buprenorphine TDS	242.8 (163.7, 345.6)	<.0001	240.28 (164.06, 338.55)	<.0001	--	--
Fentanyl TDS	-14.7 (-25.2, -2.7)	0.0180	-7.77 (-18.23, 4.02)	0.1875	--	--
Oxycodone ER	-40.7 (-45.3, -35.7)	<.0001	-30.95 (-35.52, -26.07)	<.0001	-25.11 (-42.10, -3.15)	0.0275
Hydromorphone ER	81.5 (2.0, 222.9)	0.0427	79.16 (1.13, 217.37)	0.0456	--	--
Tapentadol ER	733.6 (144.3, 2744.0)	0.0007	673.15 (133.96, 2,455.16)	0.0008	--	--
Hydrocodone ER	--	--	--	--	--	--

*Within CHAT, there were fewer than 10 cases of abuse in the pre-REMS period and/or the post period for methadone, hydromorphone ER, tapentadol ER, hydrocodone ER, buprenorphine, and fentanyl.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

A sensitivity analysis was conducted among a set of shared sites that contributed at least one assessment during each of the three periods. This analysis yielded smaller relative percent changes in the prevalence of ER/LA opioid abuse among those assessed using the ASI-MV (-4.7%, 95% CI -8.83 to -0.42)).

A second sensitivity analysis stratified the ASI-MV sample by the setting in which individual was assessed for treatment (Table 17). Here, significant reductions between the pre- and active periods were seen in all settings except residential/inpatient treatment, which had the second highest prevalence of ER/LA opioid abuse (methadone treatment having the highest).

Table 17. Change in past 30-day ER/LA opioid abuse prevalence among all ASI-MV assessments, comparing the pre-implementation to implementation and active REMS periods, stratified by treatment setting

	PRE IMPLEMENTATION	IMPLEMENTATION	ACTIVE PERIOD	PRE VS. IMPLEMENTATION: RELATIVE RISK (% CHANGE)	% CHANGE 95% CI	P-VALUE	PRE VS. ACTIVE PERIOD: RELATIVE RISK (% CHANGE)	% CHANGE 95% CI	P-VALUE
RESIDENTIAL/INPATIENT									
Prevalence (abuse cases per 100 ASI-MV assessments) within Residential/Inpatient setting	17.22	17.49	17.00	1.02 (1.6)	(-3.6, 7.0)	0.5526	0.99 (-1.2)	(-5.7, 3.4)	0.5964
OUTPATIENT/NON-METHADONE									
Prevalence (abuse cases per 100 ASI-MV assessments) within Outpatient/non-methadone setting	7.40	6.34	6.37	0.86 (-14.3)	(-20.6, -7.5)	<.0001	0.86 (-13.9)	(-19.8, -7.5)	<.0001
METHADONE									
Prevalence (abuse cases per 100 ASI-MV assessments) within a methadone maintenance setting	26.19	22.92	18.61	0.88 (-12.5)	(-22.9, -0.6)	0.0400	0.71 (-28.9)	(-38.1, -18.4)	<.0001
CORRECTIONS*									
Prevalence (abuse cases per 100 ASI-MV assessments) within a corrections setting	2.97	2.76	2.68	0.93 (-6.8)	(-16.4, 3.8)	0.1990	0.90 (-9.7)	(-18.3, -0.2)	0.0454
OTHER/ UNSPECIFIED									
Prevalence (abuse cases per 100 ASI-MV assessments) within an "Other" setting	6.38	5.55	3.86	0.87 (-13.1)	(-23.1, -1.8)	0.024	0.60 (-39.5)	(-46.9, -31.1)	<.0001

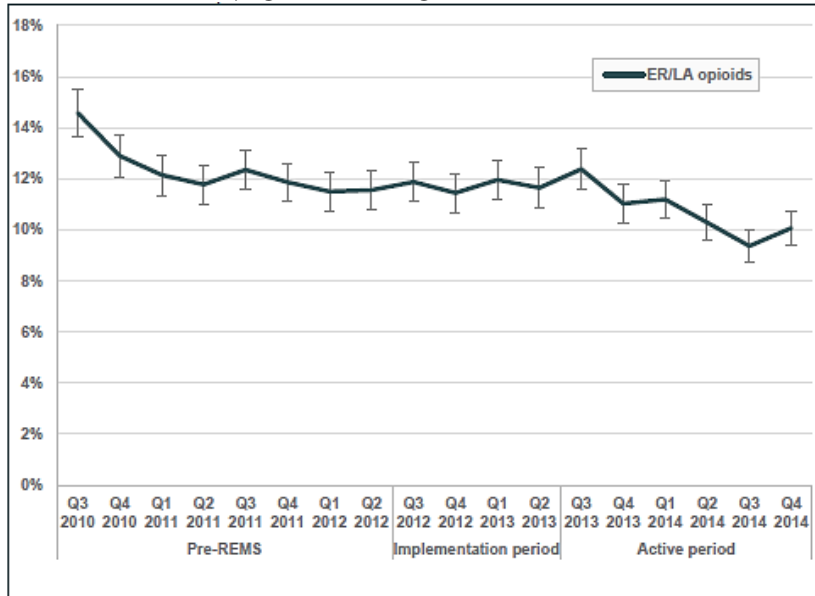
*Corrections strata represents individuals assessed by the ASI-MV who evaluated in one of the following settings: Drug Court, Probation/praole, DUI/DWI, or other corrections

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Trend analyses

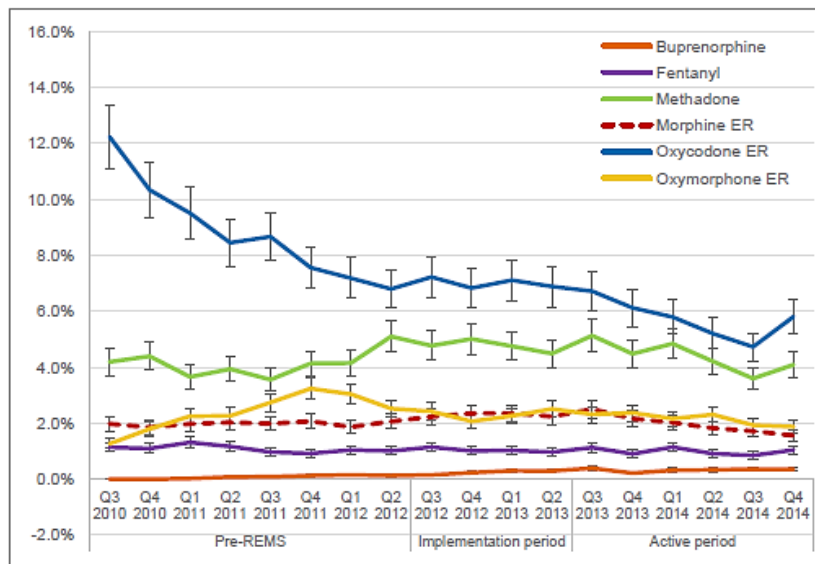
Visual inspection of trends across the three REMS study periods (Figure 13) shows decreasing trends in ER/LA opioid abuse prevalence in the ASI-MV sample during the pre-REMS and active periods. Inspection of abuse trends for individual opioid compounds (Figure 14) suggests that these trends were driven largely by abuse trends for ER oxycodone, a compound with a large market share and high abuse prevalence.

Figure 13. Trends in Past 30-day Abuse Prevalence for ER/LA Opioids, Among all ASI-MV Assessments, Q3 2010 to Q4 2014



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Figure 14. Trends in Past 30-day Abuse Prevalence for Individual ER/LA Opioid Compounds, Among all ASI-MV Assessments, Q3 2010 to Q4 2014



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Analysis of these trends, shown in Table 18 below, confirms significant negative slopes for ER/LA opioid abuse prevalence overall during the pre-implementation and active periods. Significant negative slopes were seen for ER oxycodone during the pre-period and for ER morphine during the active period. No analyses were presented comparing slopes across the three study periods to assess whether the REMS implementation was associated with a

significant change in abuse trends for ER/LA opioids as a class or for individual ER/LA opioid compounds.

Table 18. Trend Analysis Results for Past 30-day Abuse Rates for ER/LA Opioids Overall and for Individual ER/LA Opioid Compounds, Among All ASI-MV Assessments

	PRE IMPLEMENTATION*		P-VALUE [‡]	IMPLEMENTATION*		P-VALUE [‡]	ACTIVE PERIOD*		P-VALUE [‡]
	INTERCEPT [†]	SLOPE ^{††}		INTERCEPT [†]	SLOPE ^{††}		INTERCEPT [†]	SLOPE ^{††}	
ER/LA opioids as a group	0.0942	0.9751	<.0001	0.0824	1.0032	0.8357	0.0847	0.9762	0.0062
Morphine ER	0.01944	1.0056	0.7756	0.02289	1.0021	0.9691	0.02435	0.9137	0.0029
Oxycodone ER	0.01642	1.106	<.0001	0.02255	1.0187	0.7329	0.02414	0.9556	0.1243
Methadone	0.03888	1.0172	0.3137	0.04924	0.9773	0.6422	0.05016	0.9465	0.6422
oxycodone ER	0.115	0.9237	<.0001	0.07127	0.9897	0.822	0.06393	0.9555	0.0671
Fentanyl TDS	0.01193	0.9715	0.203	0.01119	0.9513	0.4486	0.0106	0.976	0.5029
Buprenorphine TDS	0.000139	1.4653	<.0001	0.001704	1.2496	0.0264	0.003108	1.0246	0.6291

*Baseline: Pre-REMS period: July 2010 – June 2012; Time 1: Implementation Period: July 2012 – June 2013; Time 2 Active Period: July 2013 – December 2014

[†] The intercepts reflect the estimated probability of abusing a given drug/compound at the beginning of the time period.

^{††} The slopes reflect the factor by which the probability changes from one quarter to the next during a time period. This slope estimate is a risk ratio, i.e., risk of abuse during quarter *k* divided by risk of abuse during quarter *k* + 1. Therefore, if the risk ratio during the consecutive quarters are the nearly the same in a given period, the risk ratio will be near 1.0. For example, the probability of abusing ER/LA opioids as a group during the pre-period are slightly decreasing from one quarter to the next as indicative of a risk ratio of .98.

[‡] The p-values are derived from the test of the significance of the slopes within a time period, where the null hypothesis states that the risk ratio = 1.0, suggesting no change in the probability of abuse from one quarter to the next. Note that statistical power is a function of several factors (e.g., number of abuses cases, sample size, effect size), and as a result, some tests presented in the table above may be overpowered (e.g., the test of a significant slope during the pre-period for the ER/LA opioid group having RR = .98 and significant at p<.0001). Consequently, it is recommended that both the effect size (risk ratio) and statistical significance (p-value) be taken into account when determining the practical significance of findings.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

3.3.3.2 Reported source of ER/LA opioids

Table 19 depicts changes in the reported sources of procurement of ER/LA opioids among those reporting abuse of ER/LA opioids. Across the three REMS study periods, the overall distribution of procurement source remained fairly stable. The most common source of procurement was “illicit,” and the proportion of abusers reporting this source did not change across periods. The percent of individuals who reported obtaining the drugs from their own prescription and the percent getting them from a family member or friend both decreased slightly but significantly. The largest relative decrease was seen in the small fraction of individuals obtaining their drugs from multiple doctors. Patterns were fairly similar across individual ER/LA opioid compounds with relatively large market share (morphine ER, methadone, oxycodone ER, fentanyl TDS).

Table 19. Change in Reported Source of ER/LA Opioid Procurement, Among Those Assessed by the ASI-MV and Reporting Abuse of ER/LA Opioids

	PRE IMPLEMENTATION	IMPLEMENTATION	ACTIVE PERIOD	PRE VS. IMPLEMENTATION: RELATIVE RISK (% CHANGE)	% CHANGE 95% CI	P-VALUE	PRE VS. ACTIVE PERIOD: RELATIVE RISK (% CHANGE)	% CHANGE 95% CI	P-VALUE
Own Prescription	20.95	20.51	18.99	0.9791 (-2.09)	(-8.48, 4.76)	0.5402	0.9067 (-9.33)	(-14.92, -3.37)	0.0026
My own prescription from several doctors	2.25	1.70	1.25	0.7557 (-24.43)	(-40.77, -3.60)	0.0242	0.5550 (-44.50)	(-56.64, -28.96)	< .0001
Family member or friend	46.22	45.21	43.80	0.9781 (-2.19)	(-5.71, 1.47)	0.2367	0.9476 (-5.24)	(-8.42, -1.95)	0.0021
Illicit**	58.10	57.25	57.96	0.9855 (-1.45)	(-4.40, 1.59)	0.3446	0.9977 (-0.23)	(-2.94, 2.56)	0.8690

*Abuse = any abuse in the past 30 days prior to assessment

**Illicit defined as: Bought it online without a doctor’s visit, bought it from a dealer (a known seller), wrote or bought a fake prescription, stole them, traded for it, other.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

3.3.4 Discussion of NAVIPPRO System Studies

Small but statistically significant reductions in past 30-day abuse rates were observed for ER/LA opioids in both the ASI-MV and CHAT systems, comparing the pre-implementation to the active REMS periods. In the ASI-MV study, reductions in ER/LA opioid abuse rates were not significantly different from reductions observed for IR opioids or benzodiazepines. The reductions in ER/LA opioid abuse prevalence even were smaller after restricting the sample to sites that contributed data during each study year. This restricted analysis is necessary to minimize potential bias created by shifts in the study sites over time. Because of potential shifts in the distribution of settings with very different abuse patterns, analyses stratified by setting are also important. These stratified analyses found wide variation in effect size in various settings, with significant reductions in outpatient and correctional settings but not in residential/inpatient treatment settings, where the prevalence of past 30-day ER/LA opioid abuse did not change. These differences across ASI-MV sub-populations are difficult to interpret with regard to assessing possible impacts of the REMS.

Changes in abuse prevalence rates for individual ER/LA opioids also varied considerably. Among the ER/LA opioids with interpretable rates, the largest reductions were observed for ER oxycodone, and these occurred primarily during the pre-REMS period. Because analyses did not adjust for changes in prescribed availability, divergent drug utilization trends may have contributed to the variation in results across individual ER/LA opioid compounds. It is not known to what degree changes in ER/LA opioid utilization might have been due to the REMS as opposed to other factors.

Among those abusing ER/LA opioids, the distribution of drug source was fairly stable across study periods, with most obtaining the drugs through illicit channels or from a friend or family member and a small minority reporting obtaining drugs from their own prescriptions or from multiple doctors. However, decreases were seen in the proportion of ER/LA opioid abusers who

obtained ER/LA opioids from their own prescription, from multiple doctors, and from friends or family. The pathways through which individuals obtain prescription opioids for abuse are complex and undoubtedly influenced by a variety of factors, including many efforts to reduce inappropriate prescribing and diversion.

The CHAT adolescent study found significant reductions in reported ER/LA opioid abuse prevalence. These results were consistent with reductions seen in adolescent intentional abuse calls in the Poison Center study but discordant with the increases in non-medical use of ER/LA and IR opioids seen in the RADARS College Survey study. The CHAT study did not include trend analyses, however, to determine whether reductions pre-dated the REMS, as was seen in the Poison Center study.

The NAVIPPRO ASI-MV and CHAT studies share many strengths and limitations with the RADARS Treatment Center study. Although these studies can provide product-specific abuse estimates in large high-risk populations, their convenience sampling and changing survey instruments limit inferences that can be drawn from observed trends. In addition, the combined effects of the many external factors potentially affecting the RADARS Treatment Center abuse trends could also influence abuse trends in the NAVIPPRO studies. As with the RADARS study, it is difficult to relate results from the high-risk ASI-MV and CHAT populations to the potential effects of REMS prescriber training and patient education materials, particularly considering that only a minority of abusers report obtaining their drugs directly from a provider. While the REMS could theoretically reduce diversion from friends or family and limit availability of these drugs for abuse in these populations, it is also theoretically possible that improved recognition of abuse and addiction among patients could lead to increased referrals for substance abuse treatment. The net effect of these REMS-related behavior changes on ER/LA opioid abuse prevalence, as measured by the NAVIPPRO system, is difficult to predict.

3.4 Washington State Medical Examiner Study

3.4.1 Objectives

To evaluate trends before and after the ER/LA REMS implementation in mortality rates associated with prescription opioids.

3.4.2 Methods

Mortality surveillance monitoring and analysis was performed using the Washington state medical examiner database. The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System team performed this analysis based on data collected on drug-related deaths by the Washington state medical examiner's office. Little detail was provided in the study report on the data collection process, outcome definitions, or format of the data used for these analyses. However, because these data were derived directly from medical examiner reports and death certificates, they include information on specific prescription opioids mentioned as contributing to the death. Notably, this is in contrast to the CDC's National Vital

Statistics System mortality databases,³⁹ in which many prescription opioids (e.g. oxycodone, hydrocodone, oxymorphone, morphine) are grouped together into a single ICD-10 code category. An ecological time-series design was used to compare death rates between the period prior to the ER/LA REMS launch (January 2005 through June 2012), the Implementation Period (July 2012 through June 2013), and the Active Period (July 2013 and later). Deaths attributed to prescription opioids (either singly or in combination) were analyzed. The unit of analysis was a drug mention, so a death involving multiple drugs could contribute to event counts for more than one drug or drug category.

Comparisons of death rates associated with prescription opioids across the study periods were made for the following categorizations:

- A group that includes all opioids that have ER/LA opioid formulations that are subject to the REMS (e.g., methadone, morphine, oxycodone, oxymorphone), excluding hydrocodone (prior to 2014 all hydrocodone products were IR only)
- Each type of opioid that has an ER/LA opioid formulation subject to the REMS (even though the medical examiner data cannot distinguish between ER and IR opioid formulations), excluding ER hydrocodone
- A group that includes all prescription opioids except hydrocodone
- A comparator group comprised of benzodiazepines
- IR hydrocodone (prior to 2014 all hydrocodone products were IR only)

Three denominators were used in the calculation of mortality rates: population, number of prescriptions dispensed, and number of dosing units dispensed from pharmacies. The population estimates were obtained by extrapolating data from the 2000 and 2010 US censuses at the state level for each time period. Data on projected number of prescriptions dispensed by drug for each participating state are purchased from IMS Health and are available starting in 2006. These prescription data are summed to determine the total number of prescriptions dispensed for each of the comparator groups. Data on projected number of dosing units dispensed by drug for each participating state code are also purchased from IMS Health, and data are summed to determine the total number of units dispensed for each of the comparator groups.

Poisson regression was used to compare changes in rates over time for mentions of opioids that have an ER/LA opioid formulation to changes in rates for benzodiazepines and IR hydrocodone. Time was divided into three periods: Pre-ER/LA REMS Implementation (2005 through June 2012), Implementation (July 2012- June 2013), and Active Period (July 2013 and forward). Two different methods of analysis were applied to the data: the means model (using bootstrapping methods) and the piecewise linear model. In the means model, mean mortality rates are compared across the three periods. The piecewise linear model was used to assess temporal mortality trends.

³⁹ <http://www.cdc.gov/nchs/deaths.htm>

Drug product was categorized as either the study group or a comparator group. The total number of deaths that mention one or more opioids with an ER/LA formulation or a comparator drug was computed and used as the dependent variable in the Poisson regression models. Three different denominators were entered as offsets in the Poisson model: general population, prescriptions dispensed, and tablets (units) dispensed.

3.4.3 Key Results

Table 20 shows the raw counts of drug mentions for deaths included in the Washington state medical examiner study across the three REMS study periods. Of the individual opioid compounds, methadone was mentioned in the greatest number of deaths, followed by oxycodone and morphine. It should be noted that, in this study, the pre-implementation period was many times longer than either the transition or active periods.

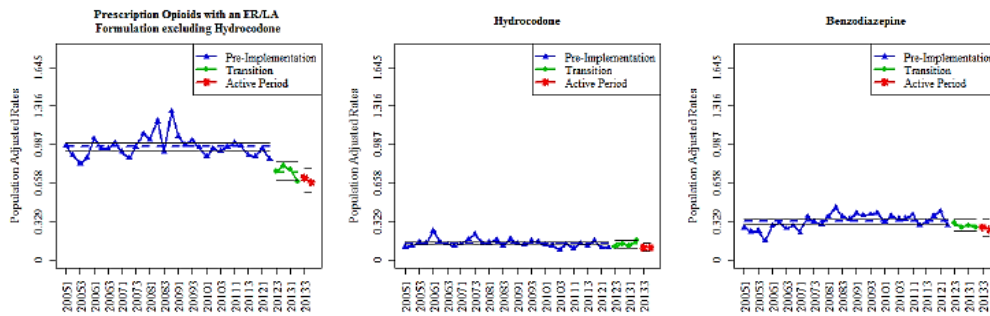
Table 20. Number of deaths in which drug or drug group was mentioned, by REMS study period, Q1 2005 – Q4 2013, Washington State Medical Examiner study

Drug Group	Pre-Implementation Mentions	Transition Mentions	Active Period Mentions
Prescription Opioids with an ER/LA Formulation excluding Hydrocodone	3,818	418	191
Hydrocodone	546	73	28
Benzodiazepine	1,297	161	75
All Prescription Opioids excluding Hydrocodone	4,630	490	213
Hydromorphone	287	30	13
Morphine	691	100	32
Oxymorphone	8	4	4
Oxycodone	1,102	156	66
Tapentadol	1	0	0
Fentanyl	231	24	21
Buprenorphine	4	1	0
Methadone	2,092	169	82

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Figure 17 and Table 21 show the mean population-adjusted death rates for prescription opioids with an ER/LA formulation (excluding hydrocodone), hydrocodone, and benzodiazepines. The results indicate significant decreases in the mean overdose death rate for prescription opioids with an available ER/LA formulation, comparing the pre- to transition but not the transition to active REMS periods. Although formal trend analyses were not conducted, population-adjusted death rates for opioids with an ER/LA formulation appear to peak around 2009 and then begin to decline. Non-significant decreases in deaths involving hydrocodone and benzodiazepines are seen across the study periods, and the differences between reductions in these deaths and those involving opioids with an ER/LA formulation were not significant.

Figure 17. Washington state medical examiner mean death rates per 100,000 population for prescription opioids with an ER/LA formulation (excluding hydrocodone) and comparators, Q1 2005-Q4 2013



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Table 21. Washington state medical examiner means analysis for death rates per 100,000 population for prescription opioids with an ER/LA formulation (excluding hydrocodone) and comparators, Q1 2005-Q4 2013

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
Prescription Opioids with an ER/LA Formulation excluding Hydrocodone	Pre	1.930	Pre versus Transition	-22.41%(-30.28%,-13.65%)	<.001	.
	Transition	1.498	Transition versus Active	-9.55%(-24.55%,8.43%)	0.278	.
	Active	1.355	Pre versus Active	-29.82%(-39.84%,-18.14%)	<.001	.
Hydrocodone	Pre	0.276	Pre versus Transition	-5.25%(-25.77%,20.95%)	0.665	0.142
	Transition	0.262	Transition versus Active	-24.08%(-50.88%,17.35%)	0.215	0.467
	Active	0.199	Pre versus Active	-28.06%(-50.78%,5.15%)	0.089	0.906
Benzodiazepine	Pre	0.656	Pre versus Transition	-12.03%(-27.55%,6.81%)	0.196	0.267
	Transition	0.577	Transition versus Active	-7.79%(-33.35%,27.58%)	0.624	0.919
	Active	0.532	Pre versus Active	-18.88%(-38.44%,6.88%)	0.137	0.369

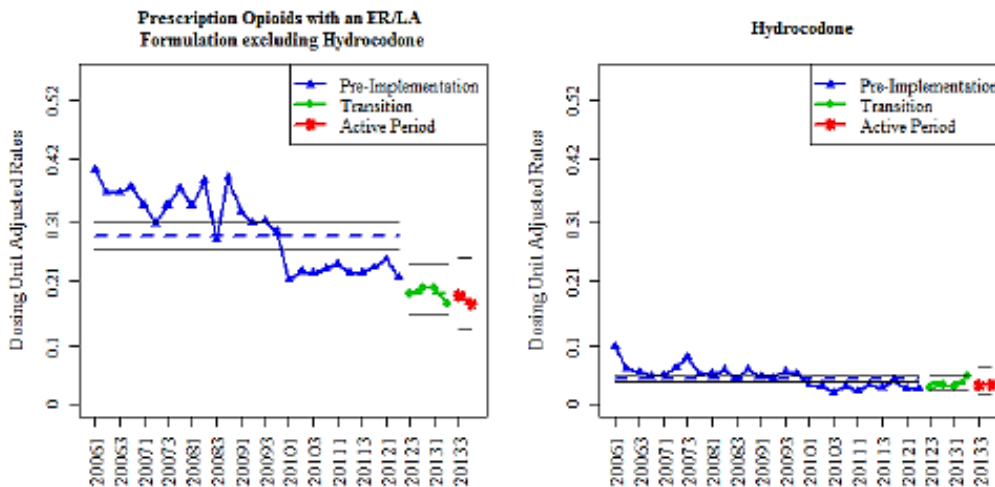
*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
 #The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the prescription opioids with an ER/LA formulation excluding hydrocodone group is not different than the corresponding difference in pairs of means for the comparator group.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Figure 18 and Table 22 show the mean dosage unit-adjusted death rates for prescription opioids with an ER/LA formulation (excluding hydrocodone), hydrocodone, and benzodiazepines. The results indicate significant decreases in the mean death rate for prescription opioids with an ER/LA formulation, comparing the pre- to transition but not the transition to active REMS periods. Although formal trend analyses were not conducted for these data, there appears to be a downward trend in utilization-adjusted deaths involving opioids with an ER/LA formulation

during the pre-period. Non-significant decreases are seen across study periods for deaths involving hydrocodone.

Figure 18. Washington state medical examiner mean death dosage unit rates for prescription opioids with an ER/LA formulation (excluding hydrocodone) and comparators, Q1 2006-Q4 2013



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Table 22. Washington state medical examiner means analysis for death dosage unit rates for prescription opioids with an ER/LA formulation (excluding hydrocodone) and comparators, Q1 2006 - Q4 2013

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values*	Between Drug Interaction p-values#
Prescription Opioids with an ER/LA Formulation excluding Hydrocodone	Pre	0.287	Pre versus Transition	-34.26%(-48.51%,-16.06%)	0.001	.
	Transition	0.189	Transition versus Active	-5.91%(-37.65%,42.00%)	0.768	.
	Active	0.178	Pre versus Active	-38.14%(-56.43%,-12.18%)	0.008	.
Hydrocodone	Pre	0.042	Pre versus Transition	-19.42%(-47.46%,23.58%)	0.316	0.412
	Transition	0.034	Transition versus Active	-5.96%(-55.89%,100.5%)	0.871	0.999
	Active	0.032	Pre versus Active	-24.23%(-60.92%,46.90%)	0.405	0.590

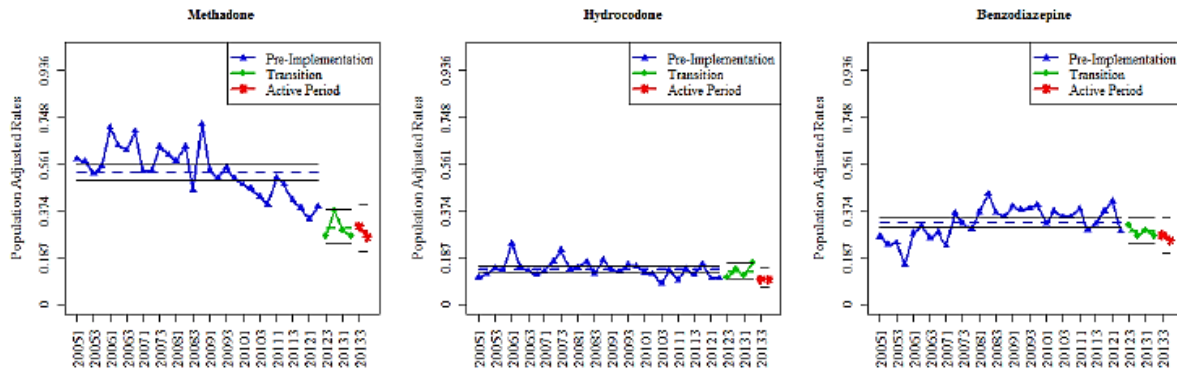
*The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
#The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the prescription opioids with an ER/LA formulation excluding hydrocodone group is not different than the corresponding difference in pairs of means for the comparator group.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Results differed considerably among individual opioids with an ER/LA formulation. Although methadone is arguably not representative of ER/LA opioid patterns overall, it is perhaps useful to examine individually in this study as it was the only opioid with a relatively large market share available only as a long-acting drug. Moreover, of all the opioid compounds analyzed, methadone contributed to the greatest number of deaths (Table 20). Figure 19 and Table 23 show population-adjusted rates for deaths involving methadone. Again, means analyses indicate

significant reductions comparing pre- versus transition but not transition versus active periods, but visual inspection again suggests downward trends already occurring during the pre-period.

Figure 19. Washington state medical examiner mean death rates per 100,000 population for methadone and comparators, Q1 2005-Q4 2013



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Table 23. Washington state medical examiner mean death rates per 100,000 population for methadone and comparators, Q1 2005-Q4 2013

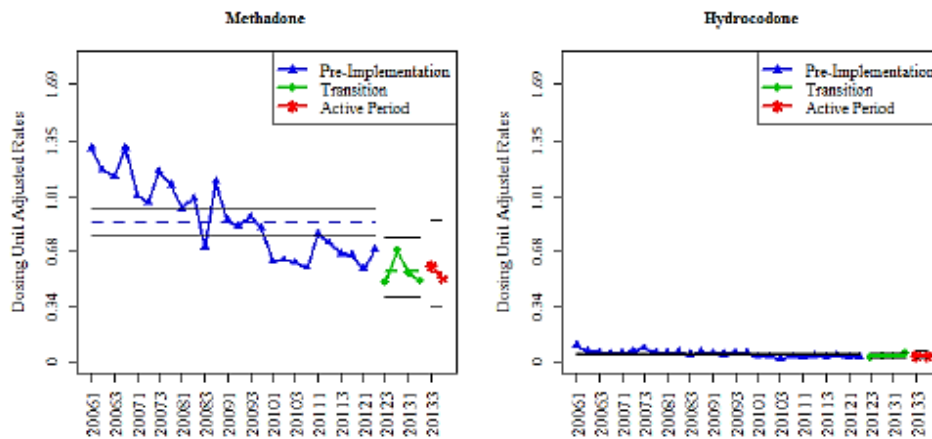
Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values [*]	Between Drug Interaction p-values [#]
Methadone	Pre	1.058	Pre versus Transition	-42.75%(-54.69%,-27.66%)	<.001	.
	Transition	0.605	Transition versus Active	-3.96%(-35.21%,42.38%)	0.841	.
	Active	0.582	Pre versus Active	-45.01%(-60.44%,-23.57%)	<.001	.
Hydrocodone	Pre	0.276	Pre versus Transition	-5.25%(-25.77%,20.95%)	0.665	0.003
	Transition	0.262	Transition versus Active	-24.08%(-50.88%,17.35%)	0.215	0.433
	Active	0.199	Pre versus Active	-28.06%(-50.78%,5.15%)	0.089	0.295
Benzodiazepine	Pre	0.656	Pre versus Transition	-12.03%(-27.55%,6.81%)	0.196	0.006
	Transition	0.577	Transition versus Active	-7.79%(-33.35%,27.58%)	0.624	0.876
	Active	0.532	Pre versus Active	-18.88%(-38.44%,6.88%)	0.137	0.076

^{*}The within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
[#]The between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the methadone group is not different than the corresponding difference in pairs of means for the comparator group.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Dosage unit-adjusted rates also suggest downward trends in methadone-related deaths during the pre-REMS period, as shown in Figure 20.

Figure 20. Washington state medical examiner mean death dosage unit rates for methadone and comparators, Q1 2006-Q4 2013



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

3.4.4 Discussion of Washington Medical Examiner Study

This study suggests a modest but statistically significant decrease in the mean number of deaths involving opioids with an available ER/LA formulation across REMS study periods. These reductions were not significantly larger than those observed for IR hydrocodone. Although formal trend analyses were not conducted, inspection of the data suggests that reductions may have begun prior to full implementation of the REMS. Pre-period decreases are also apparent in the utilization-adjusted analyses and in the trends for methadone, the only long-acting opioid analgesic in the group with relatively large market share for which no short-acting counterpart exists. Methadone was a contributory drug in a large proportion of deaths involving an opioid with an ER/LA formulation, and therefore, overall trends would be heavily influenced by trends in deaths involving methadone. However, trends in methadone-related overdose deaths may not be an ideal indicator of the impact of the ER/LA opioid REMS on overdose deaths, both because methadone deaths may involve drug obtained from opioid addiction treatment programs as well as prescriptions for pain, and because methadone has been the subject of specific large-scale overdose prevention efforts.⁴⁰

A strength of this study was its ability to generate population-based incidence rates for deaths involving specific opioid compounds over a relatively long time period. The ability to distinguish different opioids mentioned in a drug overdose death case is an advantage over currently available national-level drug-related mortality data. A major limitation is that the category intended to assess deaths involving ER/LA opioids likely includes a large number of deaths that

⁴⁰<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124346.htm>; http://emergency.cdc.gov/coca/ppt/2012/08_01_12_Methadone_FIN.pdf

actually involved only IR opioids, particularly IR oxycodone. Although this drug category excludes hydrocodone, based on the information provided, it is unclear whether those cases that *also* mentioned hydrocodone as a contributory drug were specifically excluded. It is also unclear whether mentions for hydrocodone would also include cases where prescription opioids with an ER/LA formulation were also involved.

Finally, trends in opioid utilization, abuse, and overdose death vary widely by state.⁴¹ Especially considering the aggressive initiatives that occurred in Washington state during the study period aiming to encourage safer prescribing practices and reduce opioid overdoses,⁴² results may not be generalizable to other regions of the country.

4 OVERALL INTERPRETATION OF EPIDEMIOLOGIC SURVEILLANCE STUDIES

In interpreting the results of the surveillance studies included in this assessment, several questions must be considered. First, do the data indicate significant changes in the rates of abuse-related outcomes following implementation of the REMS? Second, if so, can any observed changes reasonably be attributed, in whole or part, to the REMS? Finally, if significant changes are not seen, or changes cannot reasonably be attributed to the REMS, does this imply that the REMS has failed to achieve its goals in mitigating the adverse outcomes associated with ER/LA opioid analgesics?

Question #1: Do the studies provide evidence that there were significant changes in the rates of abuse-related outcomes following implementation of the REMS?

Overall, the studies suggest that significant decreases occurred for some, but not all, safety outcomes across REMS study periods. However, the studies also indicate that, in general, observed decreases (1) began prior to implementation of the REMS, and (2) were not limited to products covered by the REMS. In addition, each of the studies had considerable limitations that affected the interpretation of the results. Attachment B summarizes in tabular format the key findings and methodological limitations of each of the surveillance studies. Overall, the surveillance studies suggest that:

- Rates of poison center exposure calls involving both ER/LA and IR opioids have decreased significantly, but downward trends began during the pre-REMS period and the trajectory of these trends did not change meaningfully with the introduction of the REMS. This pattern was fairly consistent across call types, including abuse, misuse,

⁴¹ http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6409a1.htm?s_cid=ss6409a1_e; <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6326a2.htm>; <http://www.ncsl.org/research/health/drug-overdose-death-rate-postcard.aspx>

⁴² <http://www.doh.wa.gov/ForPublicHealthandHealthcareProviders/HealthcareProfessionsandFacilities/PainManagement>

pediatric unintentional exposure, and calls resulting in major medical outcome, hospitalization, or death. It is unknown how well trends in opioid-related poison center calls reflect trends in actual misuse, abuse, overdose, and death.

- The prevalence of self-reported recent abuse of both ER/LA and IR opioids has decreased significantly among those entering opioid addiction treatment, but downward trends began during the pre-REMS period and the trajectory of these trends did not change meaningfully with the introduction of the REMS. In a broader population of high-risk individuals being assessed for substance abuse treatment in various settings, the reduction in the proportion reporting recent ER/LA opioid abuse was very small—less than 5% when a consistent set of assessment sites are used—and not significantly different from reductions seen in IR opioid or benzodiazepine abuse. Reductions in ER/LA opioid abuse appear to be driven largely by decreases in ER oxycodone abuse during the pre-REMS period. The magnitude of reduction in ER/LA opioid abuse was larger among adolescents, but estimates were less precise than for adults. Both of these studies are limited by potential biases created by a shifting study sample and changes in the survey instrument over time.
- Among college students surveyed, non-medical use of both ER/LA and IR opioids increased across REMS study periods. It is unknown how well this internet-based sample represents college students nationally.
- Overall, the incidence of ED visits and hospitalizations for prescription opioid overdose did not change significantly after introduction of the REMS, either among ER/LA opioid users or all enrollees in either a commercial insurance or Medicaid plan. The incidence of heroin overdose increased significantly. These results must be considered exploratory because medical codes for opioid overdose have not been adequately validated and because fatal overdoses are poorly captured in claims data.
- Deaths involving opioids with an available ER/LA formulation decreased in Washington state from the pre- to active REMS periods, but decreases were not significantly greater than decreases seen in deaths involving IR hydrocodone. Downward trends appear to have begun prior to full implementation of the REMS, particularly for methadone, which accounted for the largest proportion of overdose deaths. In most cases, medical examiner case reports do not distinguish between involvement of ER/LA and IR opioid formulations, when both formulations are marketed.

Question #2: Can observed changes reasonably be attributed, in whole or part, to the REMS?

To answer this question, we can turn to some fundamental principles for making causal inferences based on observational data, often referred to as the Bradford Hill Criteria.⁴³ Of these

⁴³ Sir Austin Bradford Hill, "The Environment and Disease: Association or Causation?" *Proc R Soc Med*. 1965.

principles, the following are most relevant to this discussion: Temporality, plausibility, alternative explanations, and consistency.

- a. *Temporality: Did the proposed cause (implementation of the REMS) occur before the proposed effect (changes in abuse-related outcomes)?*

No, results from several studies suggest pre-existing downward trends in ER/LA opioid abuse-related outcomes that preceded implementation of the REMS. While these trends are encouraging from a broader public health perspective, they complicate the assessment of the REMS' impact on these outcomes. The piecewise linear model analyses do not suggest that the REMS significantly altered the trajectory of trends in ER/LA opioid-related outcomes.

- b. *Plausibility: Is there is a plausible mechanism through which the REMS, at current levels of implementation, could reasonably be expected to meaningfully change the abuse-related outcomes measured in these studies?*

This is perhaps the central question in interpreting these surveillance data. It is unknown how many providers would need to be trained, and to what extent the training would need to change clinical practice and prescribing behavior to detect a measurable effect on surveillance outcomes. Although the absolute number of providers participating in REMS-compliant training was impressive for a single coordinated prescriber education initiative, only about 10% of current ER/LA prescribers had completed a REMS-compliant training at the time of these analyses.⁴⁴ Moreover, no study has directly measured the effect of the REMS-compliant training on prescriber or patient knowledge, behavior, or outcomes, for example by comparing changes in these behaviors or outcomes among prescribers or patients who received REMS education to those who did not.

Even if the REMS were to have a widespread impact on prescriber and patient behaviors, the causal pathway from behavior change to changes in the measured surveillance outcomes is often not straightforward. For example, while safer storage of prescription opioids might lead to less diversion and lower availability of ER/LA opioids for abuse among those entering treatment, improved provider recognition of abuse and addiction could theoretically lead to *increased* referrals for substance abuse treatment. While safer opioid dosing and use might be expected result in fewer emergency department visits or poison center calls, increased risk awareness and earlier recognition of overdose could also lead to *increased* use of these services in overdose situations. These are just a few examples of how even positive effects of REMS messages might have varying effects on surveillance data trends. Given the complexity of the causal pathways, the limited reach of the REMS trainings relative to the number of prescribers, and the unknown impact of the REMS intervention on prescriber and

⁴⁴ Igor Cerny, DRISK review of “*Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report*,” January 2016.

patient behavior, it is very difficult to envision a clear mechanism through which the REMS would be expected to result in measurable changes in many of the outcomes in these surveillance studies.

- c. *Alternative explanations: Are there factors other than the REMS that can, in whole or part, explain observed changes in abuse-related outcomes?*

Downward trends in abuse outcomes during the pre-REMS period, as well as significant reductions in drug classes other than ER/LA opioid analgesics in some studies, suggest the influence of factors other than the REMS itself. This observation is not surprising, considering the many other interventions implemented during the study period to improve the safety of prescription opioids and reduce inappropriate opioid prescribing, abuse, and overdose (see Appendix 7). Given the many different overlapping efforts and secular trends, however, it is exceedingly difficult to tease out what contribution, if any, was made by the REMS to the safety outcomes of interest. Additionally, biases in study population selection, sampling fractions, and outcome measurement in individual studies may have contributed to changes in observed trends or lack thereof.

Most of the studies included one or more comparator drug classes to try to isolate the impact of the REMS from the effects of these other efforts. The differences between ER/LA opioids and comparators varied by study: several studies found reductions in ER/LA opioid-related outcomes to be significantly greater than for comparators (RADARS Poison Center and Treatment Center, CHAT), while others found no significant differences (ASI-MV, WA State Medical Examiner). A challenge in this regard is that many REMS messages also apply to other drugs with abuse potential and could potentially affect safety outcomes for these other drugs, particularly IR opioids and benzodiazepines. Moreover, it is likely that most ER/LA opioid prescribers also prescribe IR opioids, and that many also prescribe benzodiazepines. To try to isolate the effects of the REMS from those of other interventions and trends, a more informative study might compare changes over time in specified measures—for example specific clinical practices, prescribing patterns, or patient outcomes—among prescribers who take a REMS-compliant training to a group of prescribers who do not, controlling for individual-level baseline confounding factors.

- d. *Consistency: Were findings relatively consistent across studies using different designs and populations?*

In looking for meaningful causal relationships, we expect to find similar patterns across different populations and study designs. Among the eight different surveillance studies with abuse-related outcomes (not including drug utilization), some patterns were seen across multiple studies, for example, the downward trends in event rates during the pre-REMS period. Other studies examining similar outcomes diverged in their findings. For example, the significant decreases in prescription opioid overdose death seen in the Washington State Medical Examiner study were not consistent with the essentially unchanged prescription opioid overdose rates in the HIRD and Medicaid studies. Even within the HIRD study, the

direction of effect differed considerably across ER/LA opioid user subgroups and analyses. Finally, the increases in prescription opioid misuse seen in the RADARS college survey findings diverged sharply from patterns seen in the other studies, a discrepancy that is concerning but difficult to explain.

In summary, the surveillance studies do not suggest that observed changes can reasonably be attributed, in whole or part, to the REMS.

Question #3: Do the data suggest that the ER/LA opioid analgesic REMS is not making progress toward its goals?

While the submitted studies do not allow us to conclude that the REMS is impacting rates of adverse outcomes related to inappropriate prescribing, abuse, and misuse of ER/LA opioids, they also do not suggest that the REMS has been *ineffective* or has failed to contribute to overall efforts to reduce these outcomes. Even if the REMS educational messages were having meaningful desired effects on behavior in prescribers and patients exposed to them, it is doubtful that these studies would be capable of detecting the impact of these behavior changes on the measured surveillance outcomes due to:

- considerable individual study limitations
- the complexity of the causal pathways from prescriber and patient behavior changes to changes in measured surveillance outcomes
- the unknown proportion of prescribers that would need to be trained to see a measurable effect on these outcomes, and
- the influence of the many concurrent efforts in this area and the difficulty detecting REMS-specific effects amidst this “noise.”

5 CONCLUSION

Despite considerable methodological limitations, the data suggest encouraging downward trends in some, but not all, outcomes; however, they do not indicate whether the REMS itself is contributing to these changes. The submitted surveillance studies may provide some useful contextual information but are unable to show whether the ER/LA opioid analgesic REMS is making progress toward the goal of reducing serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of these drugs. Nor do the studies demonstrate that the REMS is failing to achieve its goals, however.

The lack of studies that directly examine the impact of completing REMS-compliant training on prescriber knowledge, practice, or patient outcomes limits the ability of these studies to evaluate the effectiveness of the REMS and guide specific changes to the program. To assess the impact of the REMS trainings directly, pre-post changes in prescriber behavior and/or patient outcomes for a group of providers who participate in REMS-compliant training would need to be compared to those in a group who do not participate in such training. Conducting such a study would be challenging and resource intensive, but the feasibility of this type of investigation should be

explored if more rigorous evaluation of the impact of the ER/LA opioid analgesic REMS is needed.

6 Epidemiologic Considerations for Future ER/LA Opioid Analgesic REMS Assessments

Further scientific discussion is needed to determine the best way to move forward with the evaluation of the ER/LA opioid analgesic REMS in a complex landscape of concurrent interventions and imperfect data sources. Without being able to link prescriber participation in REMS training to changes in practice or patient outcomes, it is exceedingly difficult to assess the impact of the REMS on any of the surveillance outcomes. Discussion is needed to explore whether it would be worthwhile and feasible to conduct a study that directly examines the association between provider participation in trainings and specific desired changes in prescribing or practice behaviors or patient outcomes. Although it would be challenging, this type of study could augment and complement an evaluation on the impact of REMS training on prescriber knowledge and self-reported behavior change. A discussion of such a study would need to address issues such as study design, sample size, data sources, cohort selection and defining exposure, defining and operationalizing outcome metrics, and controlling for confounding.

While it may not be possible to make a direct causal link between the REMS intervention and changes in rates of misuse, abuse, and overdose nationally, information on overall trends in the safety outcomes of interest may be valuable to inform decisions about modifying or expanding the REMS. Nationally representative surveys and national-level drug overdose death data may more be useful for this purpose than much of the surveillance data submitted in this assessment. One advantage of nationally-representative data is their ability to more reliably assess trends over time. This advantage is typically offset by long lag-times for data to become available and lack of granularity with respect to specific drug products and formulations.

The surveillance studies submitted in this assessment each have strengths and limitations, as described in our review. Below are some study-specific considerations that may be useful in discussing a path forward for the ER/LA opioid analgesic REMS assessment.

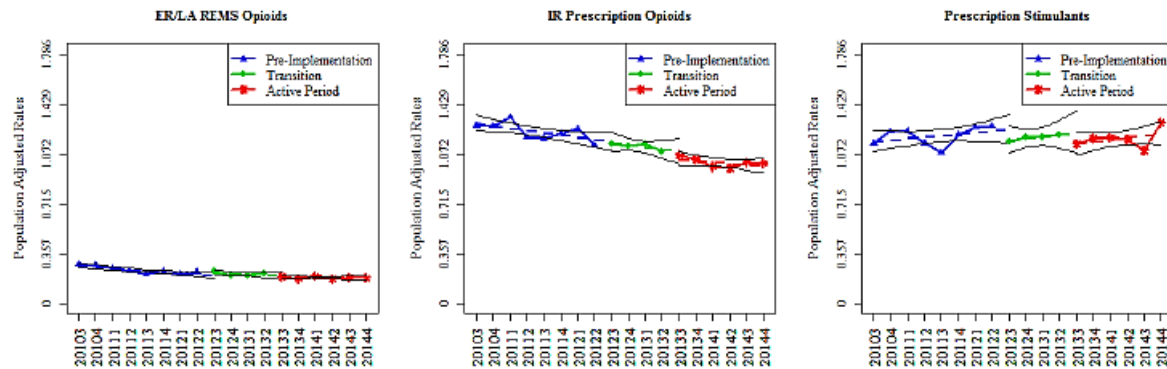
1. Treatment center abuse data are not particularly useful in assessing whether the REMS is meeting its goals. The causal pathways between the REMS activities and product-specific abuse prevalence in these populations are ambiguous, and the combined effects of unmeasured, or unmeasurable, confounding in these convenience samples may be an insurmountable challenge in attempting to evaluate overall trends in abuse rates for ER/LA opioids and comparators over time or to evaluate the impact of the REMS on these outcomes.
2. Despite their limitations, poison center exposure call data may provide some useful contextual information regarding trends in certain opioid-related adverse outcomes. However, it is likely not possible to link the REMS causally to changes in poison control

call trends. If poison control data are included in future REMS assessments, we recommend the following:

- a. Because of evidence suggesting secular trends pre-dating the REMS, trend analyses using appropriate models should be included, and results of means analyses should be interpreted within the context of the trend analysis results.
 - b. Other data sources should be used to examine the risk of death associated with ER/LA opioids. Poison center data are not appropriate for studying this outcome in this setting.
 - c. Further scientific inquiry would be valuable to better understand the degree to which patterns and trends seen in poison center data reflect population rates of misuse, abuse and overdose for different drug classes.
3. The HIRD commercially-insured and Medicaid studies may be useful sources for evaluating the change in clinical characteristics and overdose incidence among ER/LA opioid recipients and other insured individuals. Without being able to link participation in REMS training to changes in these metrics, however, causal inference will remain quite limited. If claims-based studies are included in future assessments, the following modifications are suggested to improve the quality and interpretability of the studies:
- a. Linkage to National Death Index data (RPC has indicated intent to include in upcoming assessments)
 - b. Validation of opioid overdose claims (RPC has indicated intent to address in upcoming assessments)
 - c. Trend analyses, including examination of overdose trends during the pre-REMS period
 - d. Expansion of the Medicaid cohort to increase sample size and allow analyses stratified by new-user and non-new user status
 - e. Consideration of one or more comparison groups, such as individuals receiving only IR opioids
 - f. Further exploration of the observed changes in the clinical risk profile in the ER/LA opioid user cohorts, suggesting trends toward more use in higher-risk patients (adverse selection).
4. Because of the lack of specificity regarding ER/LA formulations involved in deaths and the many other initiatives in Washington state to combat prescription opioid abuse and overdose, the Washington state medical examiner data are limited in their ability to assess the impact of the REMS on overdose death. Inclusion of multiple states and linkage of state medical examiner data to PDMPs or other sources of dispensing data could be explored as a means of assessing the dispensing history of decedents and evaluating the association between overdose death and receipt of particular drugs or drug classes. Again, causal inference would be limited due to the many other factors that may be influencing prescribing and overdose trends.

Attachment A: Additional RADARS Poison Center Trend Analysis Figures and Tables

Figure 1: Piecewise Linear Regression Visual Trend Analyses Misuse Exposure Calls Population-adjusted Rates, RADARS Poison Center, Q3 2010 to Q4 2014



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

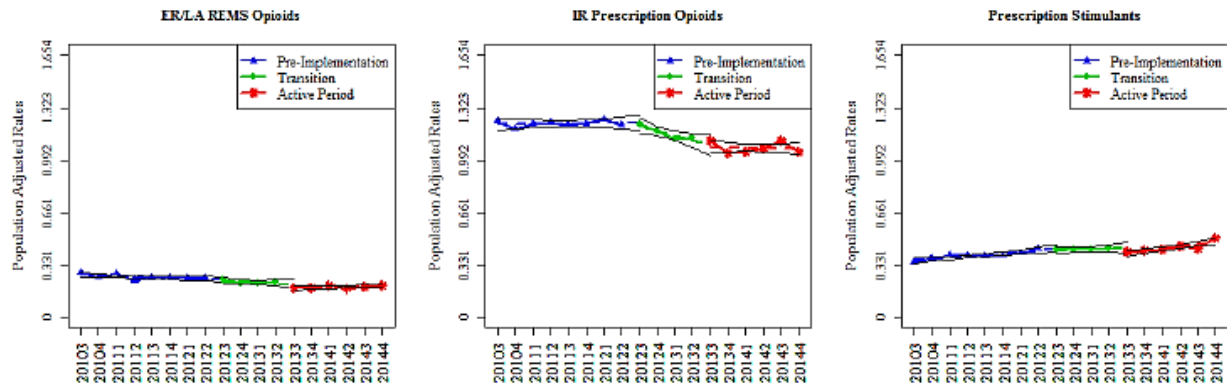
Table 1: Piecewise Linear Regression Analyses Misuse Exposure Calls, Population-adjusted Rates, RADARS Poison Center, Q3 2010 to Q4 2014

Drug Group	Time Period	Estimated Rate in 20123	P-value for Difference at 20123	Estimated Rate in 20133	P-value for Difference at 20133	Slope (95% CI)	Comparison	Within Drug Contrast p-values	Between Drug Interaction p-values
ER/LA REMS Opioids	Pre	0.199		.		-3.69%(-5.33%,-2.02%)	Pre versus Transition	0.605 ^c	
	Transition	0.217	0.190 ^a	0.197		-2.31%(-7.19%,2.84%)	Transition versus Active	0.573 ^d	
	Active	.		0.185	0.463 ^b	-0.64%(-3.47%,2.29%)	Pre versus Active	0.069 ^e	
IR Prescription Opioids	Pre	1.154		.		-1.35%(-2.39%,-0.31%)	Pre versus Transition	0.944 ^c	0.633 ^f
	Transition	1.150	0.929 ^a	1.084		-1.47%(-4.49%,1.65%)	Transition versus Active	0.787 ^d	0.732 ^g
	Active	.		1.032	0.335 ^b	-0.99%(-2.69%,0.75%)	Pre versus Active	0.719 ^e	0.171 ^h
Prescription Stimulants	Pre	1.243		.		0.90%(-0.67%,2.49%)	Pre versus Transition	0.937 ^c	0.735 ⁱ
	Transition	1.167	0.279 ^a	1.219		1.09%(-3.29%,5.67%)	Transition versus Active	0.952 ^d	0.696 ^j
	Active	.		1.141	0.358 ^b	1.25%(-1.10%,3.65%)	Pre versus Active	0.811 ^e	0.216 ^k

^ap-value comparing the rate estimated by the Pre-Implementation period regression line at 3Q2012 versus the rate estimated by the Transition period regression line at 3Q2012 within drug group.
^bp-value comparing the rate estimated by the Transition period regression line at 3Q2013 versus the rate estimated by the Active Period regression line at 3Q2013 within drug group.
^cp-value comparing the slope of the Pre-Implementation period regression line to the slope of the Transition period regression line within drug group.
^dp-value comparing the slope of the Transition period regression line to the slope of the Active Period regression line within drug group.
^ep-value comparing the slope of the Pre-Implementation period regression line to the slope of the Active Period regression line within drug group.
^fp-value comparing the difference in slopes for the Pre-Implementation and Transition period regression lines for the ER/LA REMS opioids to the difference in slopes for the Pre-Implementation and Transition period regression lines for IR prescription opioids.
^gp-value comparing the difference in slopes for the Transition and Active Period regression lines for the ER/LA REMS opioids to the difference in slopes for the Transition and Active Period regression lines for IR prescription opioids.
^hp-value comparing the difference in slopes for the Pre-Implementation and Active Period regression lines for the ER/LA REMS opioids to the difference in slopes for the Pre-Implementation and Active Period regression lines for IR prescription opioids.
ⁱp-value comparing the difference in slopes for the Pre-Implementation and Transition period regression lines for the ER/LA REMS opioids to the difference in slopes for the Pre-Implementation and Transition period regression lines for prescription stimulants.
^jp-value comparing the difference in slopes for the Transition and Active Period regression lines for the ER/LA REMS opioids to the difference in slopes for the Transition and Active Period regression lines for prescription stimulants.
^kp-value comparing the difference in slopes for the Pre-Implementation and Active Period regression lines for the ER/LA REMS opioids to the difference in slopes for the Pre-Implementation and Active Period regression lines for prescription stimulants.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Figure 2: Piecewise Linear Regression Visual Trend Analyses Exposure Calls Resulting in Major Medical Outcome, Hospitalization, or Death, Population-adjusted Rates, RADARS Poison Center, Q3 2010 to Q4 2014



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Table 2: Piecewise Linear Regression Analyses Exposure Calls Resulting in Major Medical Outcome, Hospitalization, or Death, Population-adjusted Rates, RADARS Poison Center, Q3 2010 to Q4 2014

Drug Group	Time Period	Estimated Rate in 2012:3	P-value for Difference at 2012:3	Estimated Rate in 2013:3	P-value for Difference at 2013:3	Slope (95% CI)	Comparison	Within Drug Contrast p-values	Between Drug Interaction p-values
ER/LA REMS Opioids	Pre	0.234		.		-1.48%(-2.92%,0.01%)	Pre versus Transition	0.730 ^c	
	Transition	0.228	0.630 ^a	0.207		-2.29%(-6.53%,2.15%)	Transition versus Active	0.148 ^d	
	Active	.		0.181	0.065 ^b	1.47%(-1.07%,4.07%)	Pre versus Active	0.049 ^e	
IR Prescription Opioids	Pre	1.225		.		0.11%(-0.64%,0.86%)	Pre versus Transition	0.014 ^c	0.443 ^f
	Transition	1.207	0.585 ^a	1.081		-2.72%(-4.80%,-0.59%)	Transition versus Active	0.046 ^d	0.665 ^g
	Active	.		1.074	0.859 ^b	-0.24%(-1.42%,0.95%)	Pre versus Active	0.628 ^e	0.047 ^h
Prescription Stimulants	Pre	0.428		.		2.37%(1.30%,3.45%)	Pre versus Transition	0.302 ^c	0.788 ⁱ
	Transition	0.419	0.574 ^a	0.432		0.76%(-2.05%,3.64%)	Transition versus Active	0.094 ^d	0.733 ^j
	Active	.		0.401	0.102 ^b	3.54%(2.03%,5.07%)	Pre versus Active	0.219 ^e	0.303 ^k

^ap-value comparing the rate estimated by the Pre-Implementation period regression line at 3Q2012 versus the rate estimated by the Transition period regression line at 3Q2012 within drug group.
^bp-value comparing the rate estimated by the Transition period regression line at 3Q2013 versus the rate estimated by the Active Period regression line at 3Q2013 within drug group.
^cp-value comparing the slope of the Pre-Implementation period regression line to the slope of the Transition period regression line within drug group.
^dp-value comparing the slope of the Transition period regression line to the slope of the Active Period regression line within drug group.
^ep-value comparing the slope of the Pre-Implementation period regression line to the slope of the Active Period regression line within drug group.
^fp-value comparing the difference in slopes for the Pre-Implementation and Transition period regression lines for the ER/LA REMS opioids to the difference in slopes for the Pre-Implementation and Transition period regression lines for IR prescription opioids.
^gp-value comparing the difference in slopes for the Transition and Active Period regression lines for the ER/LA REMS opioids to the difference in slopes for the Transition and Active Period regression lines for IR prescription opioids.
^hp-value comparing the difference in slopes for the Pre-Implementation and Active Period regression lines for the ER/LA REMS opioids to the difference in slopes for the Pre-Implementation and Active Period regression lines for IR prescription opioids.
ⁱp-value comparing the difference in slopes for the Pre-Implementation and Transition period regression lines for the ER/LA REMS opioids to the difference in slopes for the Pre-Implementation and Transition period regression lines for prescription stimulants.
^jp-value comparing the difference in slopes for the Transition and Active Period regression lines for the ER/LA REMS opioids to the difference in slopes for the Transition and Active Period regression lines for prescription stimulants.
^kp-value comparing the difference in slopes for the Pre-Implementation and Active Period regression lines for the ER/LA REMS opioids to the difference in slopes for the Pre-Implementation and Active Period regression lines for prescription stimulants.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

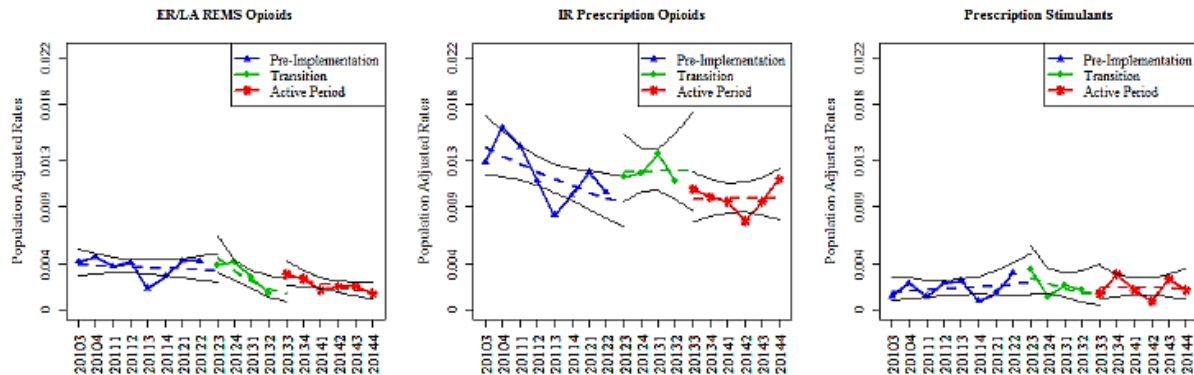
Table 3: Mean Exposure Calls with Outcome of Death, Population-adjusted Rates, RADARS Poison Center Program, Q3 2010 to Q4 2014

Drug Group	Time Period	Mean Rate	Comparison	% Change (95% CI)	Within Drug Contrast p-values ^a	Between Drug Interaction p-values ^b
ER/LA REMS Opioids	Pre	0.004	Pre versus Transition	-18.36%(-42.79%,16.50%)	0.264	.
	Transition	0.003	Transition versus Active	-29.43%(-53.25%,6.52%)	0.097	.
	Active	0.002	Pre versus Active	-42.39%(-59.22%,-18.61%)	0.002	.
IR Prescription Opioids	Pre	0.012	Pre versus Transition	2.53%(-15.27%,24.06%)	0.798	0.268
	Transition	0.012	Transition versus Active	-19.69%(-34.67%,-1.27%)	0.037	0.582
	Active	0.010	Pre versus Active	-17.66%(-31.11%,-1.57%)	0.033	0.072
Prescription Stimulants	Pre	0.002	Pre versus Transition	13.36%(-35.07%,97.94%)	0.659	0.330
	Transition	0.002	Transition versus Active	-10.63%(-49.92%,59.47%)	0.704	0.515
	Active	0.002	Pre versus Active	1.31%(-39.02%,68.31%)	0.960	0.072

^aThe within drug contrast p-values are for testing the hypothesis that there is no difference in mean rates for the comparison time periods within a drug group.
^bThe between drug interaction p-values are for testing the hypothesis that the difference in mean rates for the comparison time periods for the ER/LA REMS opioids group is not different than the corresponding difference in pairs of means for the comparator group.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Figure 3: Piecewise Linear Regression Visual Trend Analyses Exposure Calls Resulting in Death, Population-adjusted Rates, RADARS Poison Center, Q3 2010 to Q4 2014



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

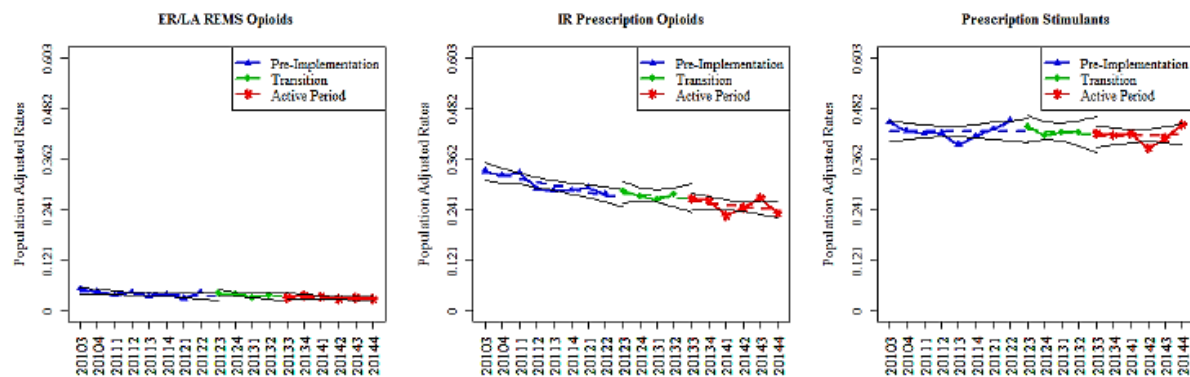
Table 4: Piecewise Linear Regression Analyses Exposure Calls Resulting in Death, Population-adjusted Rates, RADARS Poison Center, Q3 2010 to Q4 2014

Drug Group	Time Period	Estimated Rate in 2012 ³	P-value for Difference at 2012 ³	Estimated Rate in 2013 ³	P-value for Difference at 2013 ³	Slope (95% CI)	Comparison	Within Drug Contrast p-values	Between Drug Interaction p-values
ER/LA REMS Opioids	Pre	0.003		.		-1.80%(-8.37%,5.25%)	Pre versus Transition	0.016 ^c	
	Transition	0.005	0.264 ^a	0.001		-26.32%(-41.10%,-7.83%)	Transition versus Active	0.216 ^d	
	Active	.		0.003	0.047 ^b	-13.01%(-24.23%,-0.13%)	Pre versus Active	0.124 ^e	
IR Prescription Opioids	Pre	0.009		.		-5.22%(-9.45%,-0.80%)	Pre versus Transition	0.400 ^c	0.012 ^f
	Transition	0.012	0.126 ^a	0.012		0.42%(-11.52%,13.98%)	Transition versus Active	0.997 ^d	0.281 ^g
	Active	.		0.010	0.252 ^b	0.45%(-6.77%,8.22%)	Pre versus Active	0.193 ^e	0.048 ^h
Prescription Stimulants	Pre	0.002		.		6.13%(-8.95%,23.71%)	Pre versus Transition	0.218 ^c	0.960 ⁱ
	Transition	0.003	0.740 ^a	0.001		-19.36%(-46.43%,21.39%)	Transition versus Active	0.383 ^d	0.879 ^j
	Active	.		0.002	0.507 ^b	-0.76%(-20.72%,24.22%)	Pre versus Active	0.628 ^e	0.735 ^k

^ap-value comparing the rate estimated by the Pre-Implementation period regression line at 3Q2012 versus the rate estimated by the Transition period regression line at 3Q2012 within drug group.
^bp-value comparing the rate estimated by the Transition period regression line at 3Q2013 versus the rate estimated by the Active Period regression line at 3Q2013 within drug group.
^cp-value comparing the slope of the Pre-Implementation period regression line to the slope of the Transition period regression line within drug group.
^dp-value comparing the slope of the Transition period regression line to the slope of the Active Period regression line within drug group.
^ep-value comparing the slope of the Pre-Implementation period regression line to the slope of the Active Period regression line within drug group.
^fp-value comparing the difference in slopes for the Pre-Implementation and Transition period regression lines for the ER/LA REMS opioids to the difference in slopes for the Pre-Implementation and Transition period regression lines for IR prescription opioids.
^gp-value comparing the difference in slopes for the Transition and Active Period regression lines for the ER/LA REMS opioids to the difference in slopes for the Transition and Active Period regression lines for IR prescription opioids.
^hp-value comparing the difference in slopes for the Pre-Implementation and Active Period regression lines for the ER/LA REMS opioids to the difference in slopes for the Pre-Implementation and Active Period regression lines for IR prescription opioids.
ⁱp-value comparing the difference in slopes for the Pre-Implementation and Transition period regression lines for the ER/LA REMS opioids to the difference in slopes for the Pre-Implementation and Transition period regression lines for prescription stimulants.
^jp-value comparing the difference in slopes for the Transition and Active Period regression lines for the ER/LA REMS opioids to the difference in slopes for the Transition and Active Period regression lines for prescription stimulants.
^kp-value comparing the difference in slopes for the Pre-Implementation and Active Period regression lines for the ER/LA REMS opioids to the difference in slopes for the Pre-Implementation and Active Period regression lines for prescription stimulants.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Figure 4: Piecewise Linear Regression Visual Trend Analyses Pediatric Unintentional Exposure Calls, Population-adjusted Rates, RADARS Poison Center, Q3 2010 to Q4 2014



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Table 5: Piecewise Linear Regression Analyses Pediatric Unintentional Exposure Calls, Population-adjusted Rates, RADARS Poison Center, Q3 2010 to Q4 2014

Drug Group	Time Period	Estimated Rate in 2012 ³	P-value for Difference at 2012 ³	Estimated Rate in 2013 ³	P-value for Difference at 2013 ³	Slope (95% CI)	Comparison	Within Drug Contrast p-values	Between Drug Interaction p-values
ER/LA REMS Opioids	Pre	0.034		.		-4.05%(-7.82%,-0.13%)	Pre versus Transition	0.867 ^c	
	Transition	0.041	0.223 ^a	0.033		-5.06%(-15.58%,6.76%)	Transition versus Active	0.830 ^d	
	Active	.		0.035	0.780 ^b	-3.65%(-9.93%,3.07%)	Pre versus Active	0.916 ^e	
IR Prescription Opioids	Pre	0.270		.		-2.52%(-4.03%,-0.98%)	Pre versus Transition	0.614 ^c	0.734 ^f
	Transition	0.281	0.490 ^a	0.267		-1.29%(-5.75%,3.39%)	Transition versus Active	0.918 ^d	0.812 ^g
	Active	.		0.261	0.764 ^b	-1.56%(-4.05%,0.99%)	Pre versus Active	0.524 ^e	0.897 ^h
Prescription Stimulants	Pre	0.429		.		0.05%(-1.28%,1.40%)	Pre versus Transition	0.667 ^c	0.978 ⁱ
	Transition	0.432	0.869 ^a	0.418		-0.82%(-4.49%,2.99%)	Transition versus Active	0.591 ^d	0.966 ^j
	Active	.		0.414	0.863 ^b	0.35%(-1.65%,2.38%)	Pre versus Active	0.812 ^e	0.975 ^k

¹p-value comparing the rate estimated by the Pre-Implementation period regression line at 3Q2012 versus the rate estimated by the Transition period regression line at 3Q2012 within drug group.

²p-value comparing the rate estimated by the Transition period regression line at 3Q2013 versus the rate estimated by the Active Period regression line at 3Q2013 within drug group.

³p-value comparing the slope of the Pre-Implementation period regression line to the slope of the Transition period regression line within drug group.

⁴p-value comparing the slope of the Transition period regression line to the slope of the Active Period regression line within drug group.

⁵p-value comparing the slope of the Pre-Implementation period regression line to the slope of the Active Period regression line within drug group.

⁶p-value comparing the difference in slopes for the Pre-Implementation and Transition period regression lines for the ERLA REMS opioids to the difference in slopes for the Pre-Implementation and Transition period regression lines for IR prescription opioids.

⁷p-value comparing the difference in slopes for the Transition and Active Period regression lines for the ERLA REMS opioids to the difference in slopes for the Transition and Active Period regression lines for IR prescription opioids.

⁸p-value comparing the difference in slopes for the Pre-Implementation and Active Period regression lines for the ERLA REMS opioids to the difference in slopes for the Pre-Implementation and Active Period regression lines for IR prescription opioids.

⁹p-value comparing the difference in slopes for the Pre-Implementation and Transition period regression lines for the ERLA REMS opioids to the difference in slopes for the Pre-Implementation and Transition period regression lines for prescription stimulants.

¹⁰p-value comparing the difference in slopes for the Transition and Active Period regression lines for the ERLA REMS opioids to the difference in slopes for the Transition and Active Period regression lines for prescription stimulants.

¹¹p-value comparing the difference in slopes for the Pre-Implementation and Active Period regression lines for the ERLA REMS opioids to the difference in slopes for the Pre-Implementation and Active Period regression lines for prescription stimulants.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Attachment B: Summary Table of Surveillance Study Findings

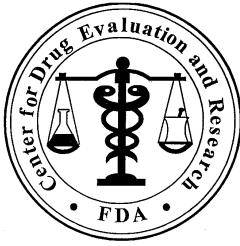
Study	Brief Study Description	Key Study Findings	Comments
HIRD			
Commercially-insured	Claims-based longitudinal analysis of opioid overdose incidence among a commercially-insured cohort	<p>Most analyses found no significant decrease in overdose among ER/LA users across REMS periods.</p> <p>Adjusted for multiple risk factors, significant 20% reduction in overdose among non-new ER/LA opioid users, comparing active to pre-REMS period.</p> <p>After excluding opioids with abuse-deterrent properties, there were no significant reductions in the incidence of opioid overdose among ER/LA opioid recipients.</p> <p>No significant change in opioid overdose incidence among all enrollees.</p> <p>Significant increase in heroin overdose among ER/LA recipients and all enrollees</p>	<p>Results must be considered exploratory because codes not validated and fatal overdoses mostly not captured</p> <p>Adjusting for patient risk factors may not be appropriate, as risk assessment and patient selection for ER/LA opioid use are part of REMS interention.</p> <p>Reason for changes in ER/LA user clinical profile unclear.</p> <p>Unclear how to interpret discrepant results between new and non-new users with respect to assessing REMS impact.</p> <p>Only comparator was heroin, for which overdose trends likely influenced by many external factors.</p> <p>Many analyses: raises concern for chance findings due to testing of multiple hypotheses.</p> <p>Large proportion of opioid overdose cases had no antecedent opioid prescription</p> <p>Unknown what proportion of prescribers in database participated in REMS training or whether participants' patients had fewer overdoses</p>
Medicaid	Claims-based longitudinal analysis of opioid overdose incidence among Medicaid sub-cohort	<p>Incidence of overdose among ER/LA users 3x rate in commercially-insured.</p> <p>No significant changes in incidence of opioid overdose across REMS periods, either among ER/LA opioid recipients (crude or adjusted for risk factors) or among all enrollees.</p> <p>Significant increase in heroin overdose among Medicaid enrollees</p>	<p>Results must be considered exploratory because codes not validated and fatal overdoses mostly not captured</p> <p>Small sample, underpowered to stratify by new/prevalent ER/LA users</p> <p>Appears to include only a single state or some other sub-cohort of Medicaid enrollees—unclear generalizability</p> <p>Only comparator was heroin, for which overdose trends likely influenced by many external factors.</p> <p>Unknown what proportion of prescribers in database participated in REMS training or whether participants' patients had fewer overdoses</p>

RADARS			
<p>Poison Center</p>	<p>Ecological time series analysis of exposure calls to 48 U.S. poison control centers</p>	<p><u>Intentional Abuse:</u></p> <ul style="list-style-type: none"> • Significant downward trends in ER/LA opioid abuse calls during pre-period, with no significant change in trend (slope) across study periods. • Mean call rates decreased significantly (-44%) for ER/LA and IR opioids and prescription stimulants. Reductions significantly larger for the ER/LA opioids than for IR opioids or stimulants. For ER/LA opioids, largest decreases in abuse were from pre-REMS to transition periods (-32%). • Patterns similar for adolescents when analyzed separately. • Patterns similar for individual ER/LA opioids with relatively large market share. • Adjusting for utilization slightly attenuated reductions for ER/LA and IR opioids. <p><u>Misuse (intentional and unintentional):</u></p> <ul style="list-style-type: none"> • Significant downward trends during pre-period for ER/LA and IR opioid misuse calls, with no changes in trend (slope) across study periods. • Mean reductions for ER/LA opioids were significant but of smaller magnitude (-22%) and not significantly different from IR opioids. <p><u>Calls resulting in major medical outcome, hospitalization, or death:</u></p> <ul style="list-style-type: none"> • Significant downward trend in pre-period for ER/LA opioids, with significant <i>increase</i> in slope comparing pre- to active periods. • Mean rates decreased significantly for both ER/LA and IR opioids. Reductions significantly larger for ER/LA opioids for all but the transition to active period comparisons. Small but significant increase in stimulants. <p><u>Pediatric unintentional exposure calls (age <6 years):</u></p> <ul style="list-style-type: none"> • Significant downward trends in ER/LA opioid abuse calls during pre-period, with no significant change in trend (slope) across study periods. • Mean rates decreased significantly for ER/LA opioids (21%) but reduction not significantly IR opioids. No change for prescription stimulants. 	<ul style="list-style-type: none"> • Means analysis results cannot be interpreted without consideration of trend analyses and pre-existing downward trends in pre-REMS period. • It is unknown how well trends and patterns in poison center calls reflect trends and patterns in actual misuse and abuse of prescription opioids nationally, given the many factors that may influence whether an exposed individual or caregiver uses this service. • It is unclear how accurately the poison centers are able to classify 1) specific products, especially when there are various formulations and generic products, and 2) exposure categories (e.g. intentional abuse, suicide attempt, adverse reaction) that reflect the actual nature of the event. • Does not capture overdoses resulting in death before help is sought.
<p>Treatment Center</p>	<p>Ecological time series analysis of cross-sectional surveys of individuals entering methadone clinics and other</p>	<ul style="list-style-type: none"> • Significant downward trends in both ER/LA and IR opioid abuse prevalence during the pre-period. For the ER/LA opioid group, differences in slope between the three periods not statistically significant. • Mean abuse prevalence for ER/LA opioids decreased significantly (-47%) from the pre- 	<ul style="list-style-type: none"> • Means analysis results cannot be interpreted without consideration of trend analyses and pre-existing downward trends in pre-REMS period. • Difficult to directly relate trends in this population to the REMS. Study population

	treatment centers	<p>to active periods, although most of this reduction occurred between the pre- and transition periods (-40%). Reduction was attenuated slightly after adjusting for utilization (-39%).</p> <ul style="list-style-type: none"> The decrease in ER/LA opioid abuse prevalence significantly greater than for IR opioids. 	<p>limited to those entering treatment for opioid addiction, and most obtain their opioids from sources other than their own doctor, for example from a friend or dealer.</p> <ul style="list-style-type: none"> REMS provider training could conceivably improve identification of patients with opioid use disorders and increase referrals to treatment.
College Survey	Ecological time series analysis of cross-sectional surveys of national sample of college students	<ul style="list-style-type: none"> Significant increases in past 90-day non-medical use drug mention rates for both ER/LA (+85%) and IR (+71%) opioids. Mentions of stimulants remained fairly stable. 	<ul style="list-style-type: none"> Results were discordant with the pattern seen in the other studies of abuse trends among adolescents, including the RADARS Poison Center and CHAT studies.
NAVIPPRO			
ASI-MV	Ecological time series analysis of cross-sectional surveys of adults being assessed for substance abuse problems	<ul style="list-style-type: none"> Modest but significant reductions in past 30-day abuse rates for both ER/LA (-7%, -20%) and IR (-6%, -18%) opioids, and benzodiazepines (-9, -16%), using ASI-MV assessments or census population as denominators, respectively. “Shared sites” analysis restricted to sites contributing data each study year, reductions were attenuated (-5%, -14% for ER/LA opioids) and no longer significant (using ASI-MV assessment denominator.) Magnitude of reduction varied widely across sub-populations, stratified by addiction severity and treatment modality Changes in abuse prevalence varied considerably across individual ER/LA opioids. Distribution of procurement source fairly stable across study periods, with most common source of procurement being “illicit.” Significant reductions in reported sources of “own provider,” “multiple providers,” and “friend/family” Significant negative slopes in ER/LA opioid abuse prevalence during both pre-REMS and active periods—no formal comparison of trends across study periods. 	<ul style="list-style-type: none"> Difficult to link results to REMS interventions due to many other individual and community-level influences on abuse prevalence rates Rates not adjusted for changes in drug utilization. Observed trends may partially reflect changes in prescribed availability, either as a result of the REMS or due to other factors affecting utilization patterns. No formal pre-post REMS trend analyses (e.g. segmented regression, piecewise linear models). Differences across sub-populations difficult to interpret and to relate to possible impacts of the REMS.
CHAT	Ecological time series analysis of cross-sectional surveys of adolescents being assessed for substance abuse	<ul style="list-style-type: none"> Significant reductions in past 30-day abuse rates for ER/LA (-26%) but not IR opioids or benzodiazepines. 	<ul style="list-style-type: none"> Smaller sample—less precise estimates with wide confidence intervals CHAT results very different from RADARS College Survey program but similar to poison center adolescent abuse call trends. Likely represent very different populations, but differences could be partly due to selection or measurement biases.

Washington State Medical Examiner

Overdose Mortality	Ecological time series of opioid overdose death rates in Washington state	<ul style="list-style-type: none"> Significant decreases in mean rate of deaths involving opioids with an ER/LA formulation, comparing pre- to transition and pre- to active periods but not comparing the transition to active periods. Reductions not significantly larger than those observed for hydrocodone. Non-significant decreases in deaths involving hydrocodone and benzodiazepines. Patterns similar for utilization-adjusted analyses, but apparent decreasing trends during pre-period. Patterns similar for methadone (only ER/LA with relatively large market share and without short-acting counterpart), with downward trend apparent during pre-period. 	<ul style="list-style-type: none"> Majority of the reduction in deaths involving opioids with an ER/LA formulation occurred prior to the full implementation of the REMS. Category intended to assess trends in deaths involving ER/LA opioids likely includes a large number of deaths due to IR opioids, particularly IR oxycodone. Results from Washington state may not be generalizable to other regions of the country, considering aggressive state-level interventions to reduce opioid overdose. Trends in methadone overdose may not be representative of ER/LA opioids as a class.
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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 Translational Sciences
Office of Biostatistics**

Date: April 6, 2016

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

From: **Joo-Yeon Lee, Ph.D., Statistical Reviewer
Ya-Hui Hsueh, Ph.D., Statistical Reviewer
Rima Izem, Ph.D., Team Leader
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Division of Biometrics VII (DB7)
Office of Biostatistics**

Subject: **DB7 Review of 36th Month Assessment of the Risk Evaluation and Mitigation Strategy for the Extended Release and Long-Acting Opioid Analgesics: Surveillance Studies (Assessment Element 5)**

EXECUTIVE SUMMARY

This is a statistical review of Assessment Element 5 in Extended Release/Long Acting (ER/LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) 36 months assessment. This review is in response to a consult request from the Division of Risk Management (DRISK). General comments are summarized here and additional comments are in Section 6 of this review. On April 2011, the agency requested that the applicant holders of ER/LA opioid analgesics implement and assess class-wide REMS. The applicant holders formed an industry working group called the REMS Program Companies (RPC) to prepare the REMS proposal. On July 9, 2012, the agency approved the RPC's proposed REMS. This thirty-six months assessment report includes 8 assessment elements. This is a review of the statistical aspects of assessment element 5.

The strength of this assessment is that it presents results on hard clinical outcomes on ER/LA opioid products over time and quantifies change in these clinical outcomes from pre to post REMS period. There are five different components under assessment element 5, each targeting

different endpoints: emergency department visit and hospitalization, intentional abuse misuse and death, unintentional abuse misuse and death, substance abuse in treatment center program and mortality rates resulting from drug poisoning. For each component various data sources were analyzed. These databases with objectives are summarized in Table 2. These clinical outcomes motivated the implementation of the REMS and are important to track over time when evaluating the potential benefits and burdens of REMS.

Two main statistical limitations with the design and models of change from pre-to-post analyses in this report are first that the change cannot be causally attributed solely to REMS interventions and second that results are not easily generalizable to the US population of interest.

Causality of REMS intervention to change cannot be inferred from any analyses in this report. All the analyses are confounded with time and it is known that many interventions occurred in the same time frame as REMS. We refer to the Division of Epidemiology II Review for more detailed discussion on other database and causality limitations.

The observed event rates in this report cannot be easily generalized to the US population of interest because the databases are all convenience samples of the targeted population at each time point and the sampling fraction likely varies over time. Sensitivity analyses using additional information on covariates and external sources could calibrate or standardize these results and test impact of different sampling fractions on measured change.

Statistical analyses used to assess each objective varied and are summarized in Table 3. Analyses of HIRD and Medicaid data in component 1 were on subject level data and adjusted for some subject level covariates. Poisson analyses with NAVIPPRO data on abuse, in component 4, aggregated data in time (at period level) in a ZIP code spatial scale. The analyses did not adjust for ZIP code level covariates but adjusted for spatial correlation. Finally, Poisson analyses with RADARS data and Washington Medical Examiner data, in components 2 to 5, aggregated in space across all geographic regions in a quarterly time scale. They did not adjust for any covariates in time. Thus, it is impossible to integrate the analyses across databases in one summary of change, even for the same outcome.

Additional specific statistical comments related to each database are in Section 6 of this review.

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1 BACKGROUND

Extended release (ER) and long-acting (LA) opioid analgesics (hereafter ER/LA opioids) are indicated for treatment of chronic moderate-to-severe pain. These drugs have known serious adverse reactions such as life-threatening respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, and death.

On April 2011, the agency requested a class-wide, single Risk Evaluation and Mitigation Strategy (REMS) to the applicant holders of ER/LA opioids. The applicant holders formed an industry working group called the REMS Program Companies (RPC) to prepare the REMS proposal. On July 2012, the agency approved the RPC's proposed REMS which include a Medication Guide, Elements to Assure Safe Use (ETASU) and a timetable for submission of assessments of the REMS. The RPC scheduled 4 consecutive REMS assessments.

The RPC submitted a thirty-six month assessment report to the agency for review which includes 8 assessment elements. The purpose of this review is to evaluate the statistical methods and results in assessment element 5: Surveillance monitoring for misuse, abuse, overdose, addiction, and death associated with ER/LA opioids, as well as resulting interventions.

Division of Biometrics 7 reviewed the statistical methods in RADARS and NAVIPPRO databases submitted in the previous report (twenty-four month FDA assessment report). As a result, Division of Biometrics 7 asked clarifying questions on the statistical methods, recommended alternate models in NAVIPPRO database and recommended use of non-parametric test for analyses with small number of time-points (pre or post REMS). The 24th month assessment report had very few measurements post-REMS, so statistical analyses in the report were not very informative and the statistical review focused on comments about methods to be used in future reports. The RPC submitted responses to FDA clarifying questions, NAVIPPRO analyses were conducted on zipcode level with sensitivity analyses restricted to stable sites and RADARS incorporated non-parametric tests in their analyses for the thirty-six month FDA assessment report.

2 SCOPE OF REVIEW

The materials reviewed are the following

- Statistical Review and Evaluation of twenty-four month report by Dr. Ya-Hui Hsueh archived in Food and Drug Administration Document Archiving, Reporting and Regulatory Tracking System (DARRTS) on Feb 9, 2015.
- Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report submitted to FDA by RPC on June 30, 2015
 - Section 8: Assessment Element 5, Surveillance Monitoring

- Appendix 12: Healthcore-Surveillance Monitoring of Emergency Departments Protocol
- Appendix 13: Healthcore-Surveillance Monitoring of Emergency Departments Data Analysis Plan
- Appendix 11: Healthcore-Surveillance Monitoring of Emergency Departments Report Section, Appendix 11
- Appendix 15: RMPDC-Surveillance Monitoring Using RADARS® System-Protocol
- Appendix 16: RMPDC-Surveillance Monitoring Using RADARS® System-Statistical Analysis Plan
- Appendix 17: Surveillance Monitoring Using RADARS® System-Full Report, Appendix 17
- Appendix 18: Inflexxion- Surveillance Monitoring of Substance Abuse Treatment Seekers Protocol
- Appendix 19: Inflexxion- Surveillance Monitoring of Substance Abuse Treatment Seekers Full Report

3 DATA SOURCES

There are five required components under Assessment Element 5, and multiple data sources were used to assess each component such as HealthCore Integrated Research DatabaseSM (hereafter HIRD), Researched Abuse, Diversion and Addiction-Related Surveillance[®] (hereafter RADARS), National Addictions Vigilance Intervention and Prevention Program[®] (hereafter NAVIPPRO), Medicaid and Washington State Medical examiner database.

Descriptions of each data source are summarized in **Table 1**. Please refer to Division of Epidemiology II review for more details on each data source.

Table 1: Description of Data Sources for Assessment 5

ASSESSMENT 5 COMPONENT	DATA SOURCE	DESCRIPTION
Component 1- Emergency Department Visits	HealthCore Integrated Research Database SM (HIRD)	The HIRD SM is a broad, clinically rich and geographically diverse spectrum of longitudinal claims data from health plan members in the Northeastern, Mid-Atlantic, Southeastern, Midwest, Central, and Western regions of the US.
	Medicaid Data	Medicaid program for one state for which de-identified data are currently available for research.
Component 2- Intentional Exposures Among Adolescents and Adults	RADARS [®] System	The RADARS [®] System provides post-marketing surveillance of prescription medication abuse, misuse, and diversion to pharmaceutical companies, regulatory agencies and policy-making organizations.
Component 3- Unintentional Exposures Among Infants and Children		
Component 4- Substance Abuse Treatment Programs		
	NAVIPPRO [®]	The NAVIPPRO [®] System provides real-time, product-specific surveillance information from a network of several hundred substance abuse treatment centers around the US in order to monitor emerging trends in substance abuse from adults and adolescents, respectively.
Component 5- Mortality Rates	State Medical Examiner Databases (Washington)	Data provided via State Department of Health Vital Statistics Office.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

4 SUMMARY OF ASSESSMENT ELEMENT 5 BY COMPONENT

There are five different components under assessment 5:

- Emergency department (ED) visits for opioid overdose and poisoning events
- Intentional exposures among adolescents and adults, including severity and deaths
- Unintentional exposures among infants and children, including severity and deaths
- Rates of individuals in substance abuse treatment programs abusing ER/LA opioid, as well as source of acquiring the ER/LA opioid, as compared to comparator immediate-release (hereafter IR) opioids and benzodiazepines
- Mortality rates resulting from drug poisoning associated with active pharmaceutical ingredients included in the ER/LA opioid REMS

Below are tables summarizing objectives (Table 1) and methods and findings (Table 2) of the 5 components in this assessment. Each component is discussed further in the next following sections.

Table 2: Summary of 5 Different Components of Assessment Element 5

Components and Objectives	Databases	ERLA and comparators	Outcomes	Time Periods
Component 1: Assess the incidence of Emergency Department (ED) visit and hospitalization due to opioid overdose and poisoning before and after REMS implementation	HIRD ¹ and U.S Medicaid	ERLA ³ (Indirect) Comparator: Heroin	ED visit and hospitalization due to opioid overdose/poisoning Death Overdose/poisoning due to heroin	Pre-REMS 07/2010 –06/2012 Transition 07/2012- 06/2013 Post-REMS 07/2013-08/2014
Component 2 and 3: Determine if there are changes in rates of <u>intentional</u> abuse, misuse, and death among adolescents and adults and <u>unintentional</u> abuse, misuse, and death among infants and children following implementation of the ER/LA REMS	RADARS ² poison center program	ERLA ³ Comparators: IR opioid; Prescription stimulants	Multiple outcomes including abuse, misuse and death (see Table 2 for details)	Pre-REMS 07/2010 –06/2012 Transition 07/2012- 06/2013 Post-REMS 07/2013-12/2014
Component 4: Examine the change in mean rates and trend of substance abuse before and after implementation of REMS	RADARS ² treatment center program and NAVIPPRO ⁴	ERLA ³ RADARS: Comparators: IR opioid; Prescription stimulants NAVIPPRO: Comparators ² : IR opioid; Benzodiazepine	Abuse defined as in the past 30 days	Pre-REMS 07/2010 –06/2012 Transition 07/2012- 06/2013 Post-REMS 07/2013-12/2014
Component 5: evaluate trends before and after the ER/LA REMS implementation for changes in mortality rates associated with prescription opioids	Washington State Medical Data Examiner	ERLA: ERLA ³ opioids without hydrocodone; Hydrocodone Comparator: benzodiazepine	Opioid associated mortality	Pre-REMS 2005 –06/2012 Transition 07/2012- 06/2013 Post-REMS 07/2013-12/2013

1 HIRD: Healthcare Integrated Research Database

2 RADARS: Researched Abuse, Diversion and Addiction-Related Surveillance

3 ERLA comprises hydrocodone ER, hydromorphone ER, morphine ER, oxycodone ER, oxycodone, Tapentadol ER, Methadone, Fentanyl Transdermal Delivery Systems and Buprenorphine Transdermal Delivery Systems

4 NAVIPPRO: National Addictions Vigilance Intervention and Prevention Program

Source: Reviewer's table summarizing information in the Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Table 3: Summary of Statistical Methods and Findings

Components	Statistical Methods	Findings by database
1	<p>Incidence rate was calculated as the number of patients divided by the total person-time within each REMS period.</p> <p>Poisson model was applied to patient –level data to estimate incidence rate ratio between each REMS period. These rates were also adjusted by multiple covariates.</p> <p>Patients were stratified by new users and non- new users in HIRD data but not in Medicaid data.</p>	<p>HIRD: crude rates of opioid overdose and poisoning events were higher in post-REMS period than pre-REMS period among all users and new-users. After adjustment for covariates, the increase pre-post decreased or reversed (see Figure 2). Incidence rates of heroin overdose in HIRD increased from pre to post- REMS period. This increase remains after adjusting for potential confounders.</p> <p>Medicaid: incidence rates of opioid overdose/ poisoning as well as incidence rates of heroin overdose were substantially higher than those in HIRD population. Within Medicaid population, there is little difference in opioid overdose between different periods with or without adjustment of confounders</p>
2 and 3	<p>Poisson models were used on total quarterly events. Poisson models had 3 possible offsets in each quarter based on population, number of prescriptions dispensed, and number of dosing units dispensed. These three offsets were from all 3 digit zipcodes covered by the database.</p> <p>Mean models assumed a constant rate pre and post, linear trend model assumed linear trend in each period None of the models adjusted for covariates or calibrated the results to external sources</p>	<p>RADARS (poison center program): Intentional and unintentional abuse rates in all drugs showed significant reduction in post-REMS period compared to pre-REMS periods.</p> <p>There is no obvious decreasing or increasing trend over time within post-REMS period.</p> <p>Trends over time varied greatly between drugs.</p>
4	<p>RADARS (same as component 2 and 3)</p> <p>NAVIPPRO Mixed effects negative binomial regression model on abuse events at the zipcode and three REMS periods level (NOT quarterly). Models had 2 possible offsets in each zipcode and time period. Those are based on total number of ASI assessments or US. Census population. None of the models adjusted for covariates or calibrated the results to external sources.</p>	<p>RADARS (treatment centers): Abuse rates showed similar overall pattern to those in component 2 and 3. The magnitude of mean abuse rates seemed to be much higher in treatment center program than poison center program throughout all study periods.</p> <p>NAVIPPRO (treatment centers): Significant reductions in abuse of ER/LA opioid, IR opioids, and Benzodiazepines from pre-REM period to post-REM period.</p>
5	Same as component 2 and 3	Significant reduction in mortality rates in ER/LA opioids group excluding hydrocodone after implementation of REMS compared to pre-REMS period. Reduction was not statistically significant for hydrocodone group only.

Source: Reviewer’s table summarizing information in the Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

4.1 (Component 1) Emergency department visits for opioid overdose and poisoning events using HIRDSM and Medicaid

Objective

The main objective of the study in this component is to assess the incidence of Emergency Department (ED) visit and hospitalization due to opioid overdose and poisoning before and after REMS implementation.

Data Source

To meet this objective, a retrospective cohort study using data from HIRD and US Medicaid was conducted. Three time periods were taken into consideration to assess the effectiveness of REMS over time; pre-REMS period (July 2010 –June 2012), transition period (July 2012- June 2013) and post-REMS period (July 2013-August 2014).

Inclusion criteria for the primary analysis are as follows;

- At least one dispensing of an ER/LA opioid after 01 July 2010; and
- At least six months of continuous health plan eligibility prior to the first recorded dispensing of an opioid that occurs during an included REMS period

Patients were followed from the time of first ER/LA opioid dispensing in a REMS period until the end of REMS period, the end of health plan eligibility or the first occurrence of a study outcome within the REMS period.

Exposure

ER/LA opioids including hydrocodone ER, hydromorphone ER, morphine ER, oxymorphone ER, oxycodone ER, oxycodone, Tapentadol ER, Methadone, Fentanyl Transdermal Delivery Systems and Buprenorphine Transdermal Delivery Systems were identified by National Drug Code.

Patients were defined as either new users or non-new users at the index date (starting date) during each study REMS period (Pre, Transition and Post). New users are defined as the patients with no previous record on dispensing of an ER/LA opioid analgesic at any time before the index date. Non-new users are the patients with a pharmacy dispensing during the REMS period-specific baseline period. Patients were defined as new users within each REMS period. For example, a patient who used ER/LA opioids for the first time during pre-REMS period and continued to use during the transition period was considered a new user during the pre-REMS period and a non-new user during the transition and post-REMS periods.

In the Medicaid database, stratification by new users or non-new users was not made due to the small sample size.

Outcomes

Outcomes of interest include

- ED visits and hospitalizations due to opioid overdose/poisoning,
- ED visits and hospitalization due to opioid overdoses/poisoning resulting in mortality,
- All-cause mortality (will be added in year two of the study).

In addition, overdose/poisoning due to heroin is a secondary outcome. Follow up started at index date and ended at the end of the REMS period.

Statistical Analysis

The (on study) incidence rate of each outcome was calculated as the number of patients with each outcome divided by the total person-time at risk within each REMS period by all users, new user and non-new user. In addition, the (on treatment) incidence rate was calculated as the number of patients with each outcome divided by the total duration of exposure to adjust for difference in duration of exposure between REMS periods. The primary analysis was using exposed person-time.

Incidence rate ratios (hereafter IRR) were computed by comparing pre-period vs transition, transition vs. post-period, and pre-period vs. post-period. Poisson regression was applied to patient-level data to estimate IRR using on study person-time as an offset variable. The model was fitted per subgroup (all user, new user and non-new user) per outcome.

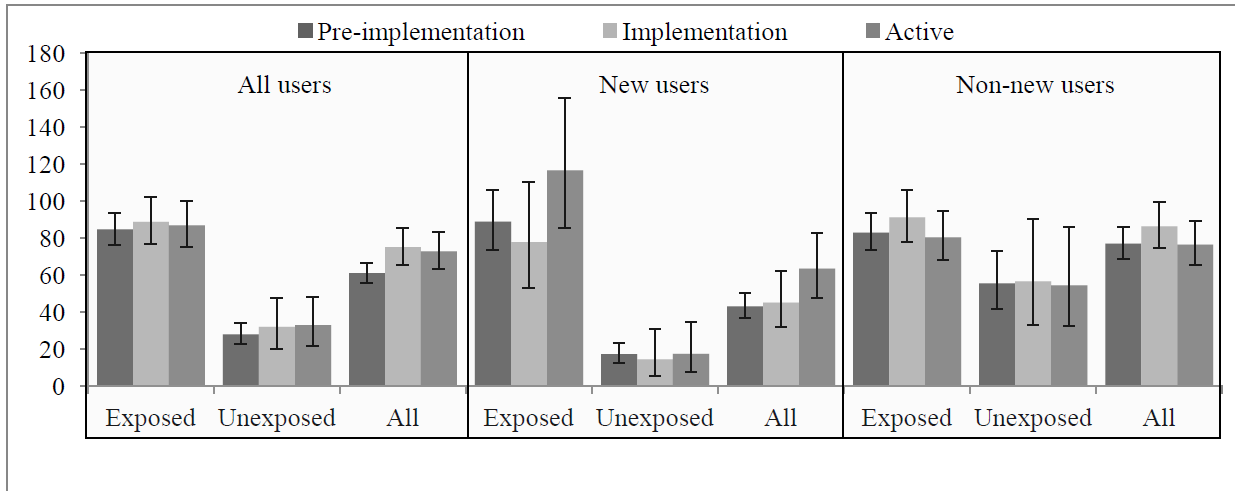
In addition to crude estimates of IRR, adjusted IRR was estimated by including patient and treatment characteristics such as age, gender, geographic, region of patient residence, clinical comorbidities (pain diagnosis, psychiatric comorbidities, history of overdose/poisoning), and concomitant prescription drug use (number of prescribers of opioid analgesics, type of ER/LA opioid analgesics, use of immediate release opioid analgesics, or non-opioid medications of abuse potential). Adjustment for covariates was done in the regression.

The final covariates were selected based on both stepwise procedure and manual review. So, adjusted covariates were different for each subgroup (all users, new users and non-new users groups). For example, during exposed person-time, the covariates of region, Deyo-Charlson comorbidity index, use of benzodiazepines, use of sleep medications, chronic pain, alcohol abuse, anxiety disorder, depressive disorder, bipolar disorder and history of overdose were adjusted for the IRR of opioid overdose events for all users, and the covariates of sleep medications, chronic pain, alcohol abuse, anxiety disorder, depressive disorder and history of overdose were adjusted for the IRR for new-users.

Results

Figure 1 and Figure 2 display incidence rate and IRR of ER/LA opioid overdose/poisoning in HIRD population. Among all users and new users crude incidence rate is higher in post-period compared to pre-period regardless of exposure person-time. However, adjustment for potential confounders lowered the IRR. There is little difference in incidence rates between pre and post periods among non-new users.

Figure 1: Unadjusted Incidence of ER/LA Opioids Overdose/Poisoning per 10K person-year using HIRD data



Exposed: Exposed person-time includes any time during a treatment episode, Unexposed: unexposed person-time includes time after a treatment episode, All: all person-time including both exposed and unexposed person-time.

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Figure 2: IRR of ER/LA Opioid Overdose Events in HIRD data: Post-period vs. Pre-period by all user/new users/non-new users for all person-time and exposed person-time only

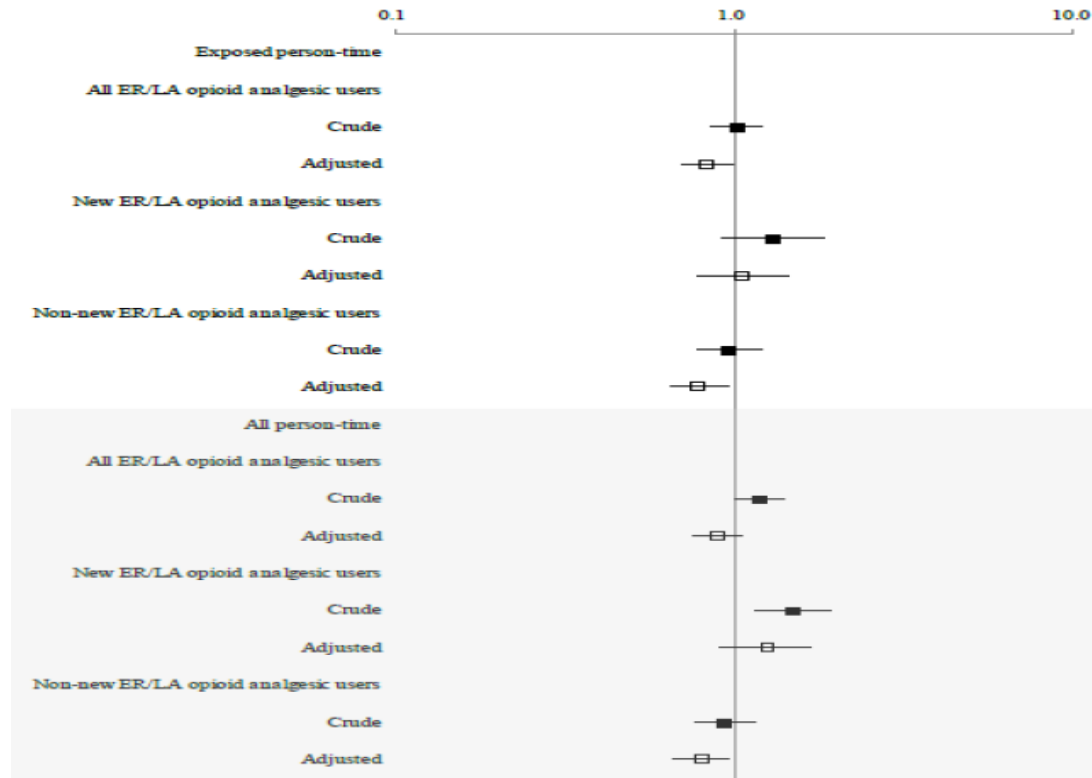


Figure 3 and Figure 4 show the incidence rate and IRR of heroin overdose/poisoning. Across all subgroups (all user/new-users/non-new users) the incidence rate is much higher in post-period compared to pre-period, which remains even after adjusting for potential confounders in the model.

Figure 3: Incidence of Heroin Overdose/Poisoning per 10K person-years in HIRD Data

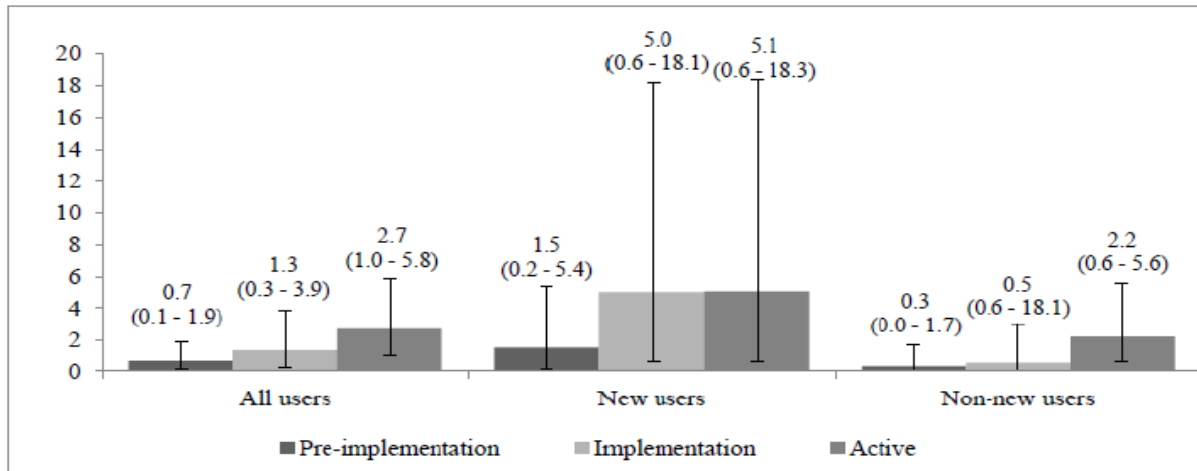
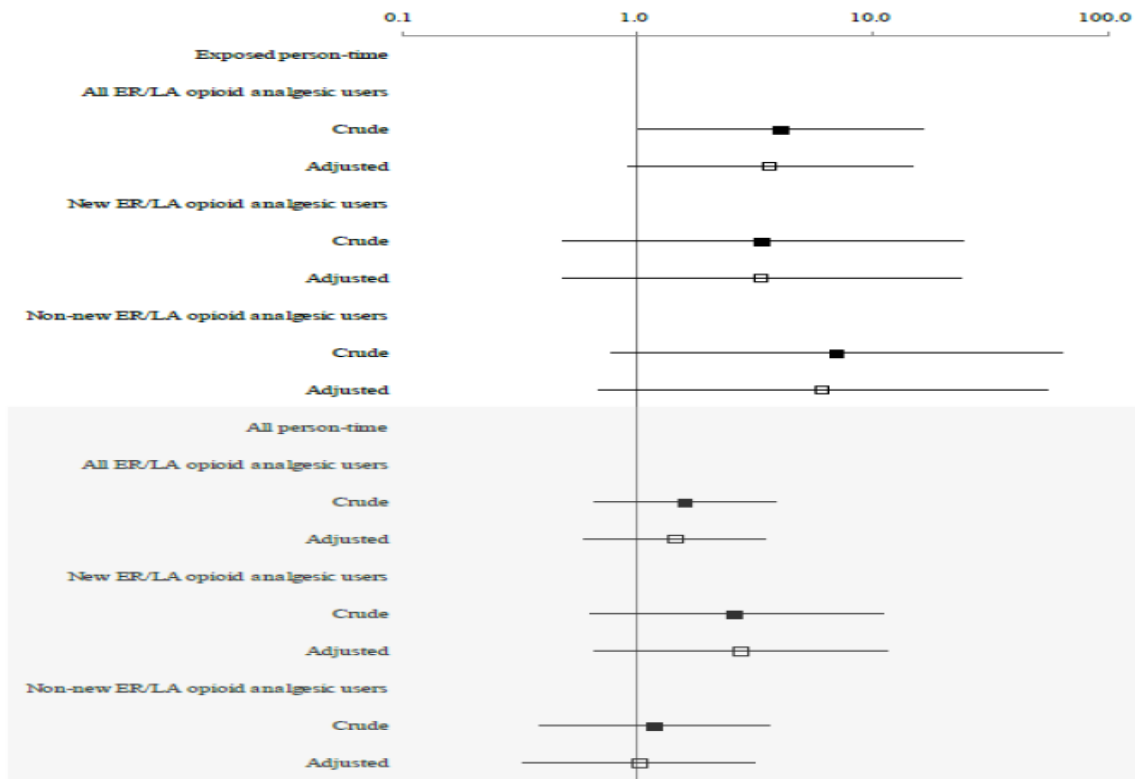


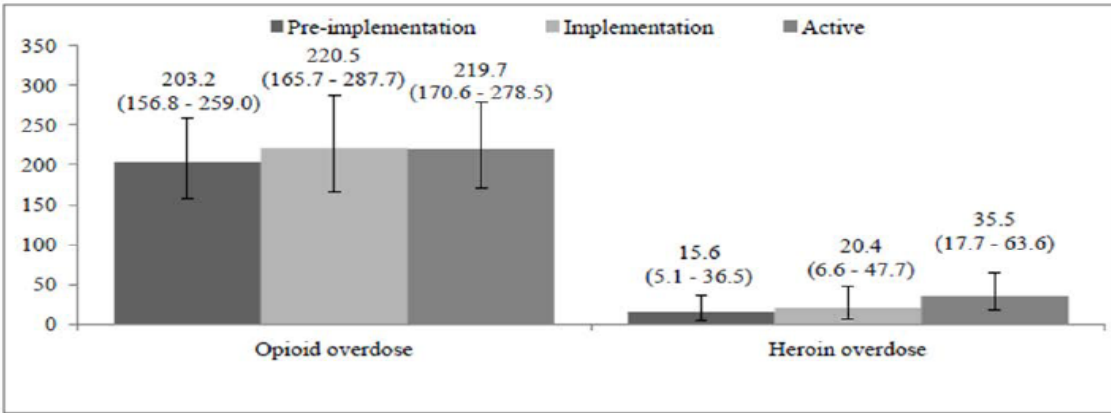
Figure 4: IRR of Heroin Overdose Events in HIRD Data: Pre-period vs. Post-period by All users/new users/non new-users For Exposed Person-time and All Person-time



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

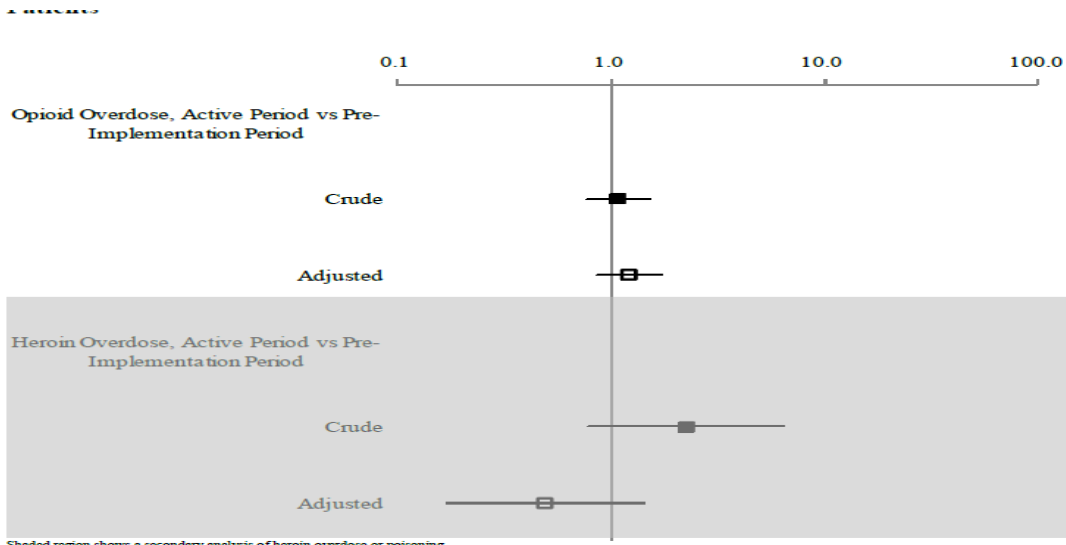
In Medicaid population, the incidence rates of opioid overdose/ poisoning as well as incidence rate of heroin overdose were substantially higher than those in HIRD population (Figure 5). Within Medicaid population, there is little difference in opioid overdose between different periods with or without adjustment of confounders. However, crude incidence rate of heroin overdose showed increasing trend over time, which seemed to be due to confounders as adjusted IRR becomes below 1 (**Figure 6**).

Figure 5: Incidence of ER/LA Opioids and Heroin Overdose/Poisoning During Opioid Exposure Per 10K Person-years in Medicaid Data



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Figure 6: Incidence Rate Ratio of ER/LA Opioid and Heroin Overdose in Medicaid Population.



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Reviewer's comments:

- *The applicant holder did not provide details on their Poisson model. Especially, it is not clear how the covariates were used (e.g. categorical/continuous, linear/non-linear etc.) in the adjusted model.*
- *As the applicant holder stated, one patient could remain in the subsequent periods as a non-new user if a patient was defined as a new-user in the prior period and was not censored. This review found some potential issues as follows ;*
 - *It is not clear how the applicant holder's Poisson model could account for any possible correlation within a patient in the analysis with all-users group. It is likely that those who remained in the study would have higher probability to get events later.*
 - *It is not clear how the baseline covariates were defined for those who continued to remain in the study in new users and non- new users analyses. Some of these covariates could vary over time.*

4.2 (Components 2 and 3) Intentional exposures among adolescents and adults and Unintentional exposures among infants and children using RADARS system poison center program

Data Sources

RADARS System includes data from three different programs: poison center program, treatment center program and college survey program. Assessment component 2 and 3 use data from poison center program in RADARS.

As in analyses from HIRD, three time periods were taken into consideration; pre-REMS period (July 2010 –June 2012), Transition period (July 2012- June 2013) and Post-REMS period (July 2013-December 2014). Please note that post-REMS period is slightly longer here than in HIRD data analysis.

Objective

The primary objective of this study is to determine if there are changes in rates of abuse, misuse, overdose, addiction, and death following implementation of the ER/LA opioid REMS.

Exposure

ER/LA opioids are evaluated as an individual drug as well as overall group in comparison with IR opioids and Prescription stimulants. Each individual ER/LA drug comprise of hydrocodone ER, hydromorphone ER, morphine ER, oxymorphone ER, oxycodone ER, oxycodone, Tapentadol ER, Methadone, Fentanyl Transdermal Delivery Systems and Buprenorphine Transdermal Delivery Systems.

Outcomes

There are multiple outcome variables evaluated to meet the objective. The outcomes with definition in poison center program are listed in Table 4.

Table 4: Outcomes Definitions

Outcome	Definition
Abuse	Exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high euphoric effect or some other psychotropic effect
Misuse	Exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of psychotropic effect
Major Medical Outcome, Hospitalization or Death	Any exposure resulting in a major medical outcome, hospitalization, or death
Death	Medical outcome including death
Under 20 Years Treated/Evaluated and Released	Any exposure resulting in a managed healthcare facility outcome of “treated/evaluated and released (< 20 years of age)
Adult Treated/Evaluated and Released	Any exposure resulting in a managed healthcare facility outcome of “treated/evaluated and released” (≥ 20 years of age)
Pediatric Unintentional Exposures	Unintentional exposures included unintentional therapeutic errors and unintentional general exposure : see below (< 6 years of age)
Child and Adolescent Unintentional Exposures	Unintentional Exposures (6-19 years of age)
Adult Unintentional Exposures	Unintentional exposures (≥ 20 years of age)
Unintentional Therapeutic Errors	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
Pediatric Unintentional General Exposures	Those cases with a reason code of unintentional general which consists primarily of accidental unsupervised ingestions such as a toddler getting into a grandparent’s prescription medicine (< 6 years of age)
Pediatric Unintentional General Exposures resulting in Major Medical Outcome, Hospitalization, or Death	Pediatric unintentional general exposures (as defined above) resulting in a major medical outcome, hospitalization, or death
Pediatric Unintentional General Exposures Treated/Evaluated and Released	Pediatric unintentional general exposures (as defined above) with a managed healthcare facility outcome of “treated/evaluated and released
Adolescent Intentional Abuse.	Cases that have a reason for exposure of intentional abuse (6-19 years of age), subset of abuse

Source: Reviewer’s table based on information in the Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Statistical Analysis

The total number of event outcome in the 3-digit ZIP codes covered by RADARS system for each quarter was analyzed. The data were used to calculate rates per quarter from third quarter of 2010 through the last quarter of 2014. Quarterly rates were averaged for the three time periods to obtain mean rate for each period. The quarterly rates used three different denominators or offsets in the Poisson models: population, prescription dispensed and dosing units dispensed. Estimates

from IMS Health were used for total prescriptions dispensed and total dosing units dispensed at the 3-digit ZIP code level, and total population was estimated by interpolation and extrapolation from United States Census data from 2000 and 2010.

Two different models, mean model and piecewise linear models are applied to the data. These models have different objectives in that the mean model intends to compare the mean rates between time periods and between drugs. The piecewise linear model assesses the difference in linear trends of event rates between time periods and between drugs.

Specifically, the applicant holder's mean model is

$$\ln(y) = \beta_{ij}(\text{drug}_i)(\text{period}_j) + \ln(\text{offset})$$

Where:

- y is the number of events in a quarter and is assumed to follow a Poisson distribution with drug group specific over/under-dispersion parameters,**
- period (j=1,2,3) denotes three indicator variables with values for Pre-Pre-, Transition, or Active,**
- drug (i=1,2,3) denotes indicator variables with values for either the ER/LA REMS opioid group or one of the comparator groups,**
- the offset variable is either population, prescriptions dispensed, or units dispensed in a particular quarter.**

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

The piecewise model is

$$\ln(y) = a_{ij}(\text{drug}_i)(\text{period}_j) + \beta_{ij}(\text{drug}_i)(\text{period}_j)(\text{time}) + \ln(\text{offset})$$

Where:

- y is the number of events in a quarter and is assumed to follow a Poisson distribution with drug group specific over/under-dispersion parameters,**
- period (j=1,2,3) denotes indicator variables with values for Pre-, Transition and Active periods,**
- drug (i=1,2,3) denotes three indicator variables with values for either the ER/LA REMS opioid group or the comparator groups,**
- time is a continuous variable representing the quarter number**
- the offset variable is either population, prescriptions dispensed, or units dispensed in a particular quarter.**

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Results

The applicant holder analyzed data by three different denominators or offsets (population, prescription and dosing units). There is no consensus on which denominator is more appropriate.⁴⁵ However, the REMS intervention is on prescribers with possible impact on number of prescriptions sold. Thus, the Division of Risk Management review team found rates with number of prescription sold as offset or denominator more interpretable for REMS evaluation. Therefore, this review will discuss the results only using that offset.

Intentional exposures among adolescents and adults (component 2)

Table 5 summarizes the result from the applicant holder’s mean model analyses to compare the mean rates in pre-REMS period to those in post-REMS period for intentional abuse and misuse outcomes. In this section the major outcomes related to intentional abuse and misuse are discussed and the results of other outcomes are all presented in Attachment A.

Across all outcomes including intentional abuse, misuse and death the results show a significant decrease after ER/LA opioid REMS’s implementation in ER/LA. The change from pre-REMS period to post-REMS period is larger in ER/LA opioid group than the change in the comparator groups (IR opioids and Stimulants).

Figure 7 displays the forest plot of % change with actual mean rates in pre and post periods including individual ER/LA opioid drugs. The figure shows the results for the top 5 drugs with highest market share. Overall, the mean rates of all three outcomes decreased in all five individual drugs, and the difference is statistically significant for intentional abuse and misuse outcomes but not for death outcome based on the applicant holder’s model. The greatest reduction is shown in Oxymorphone in all three outcomes.

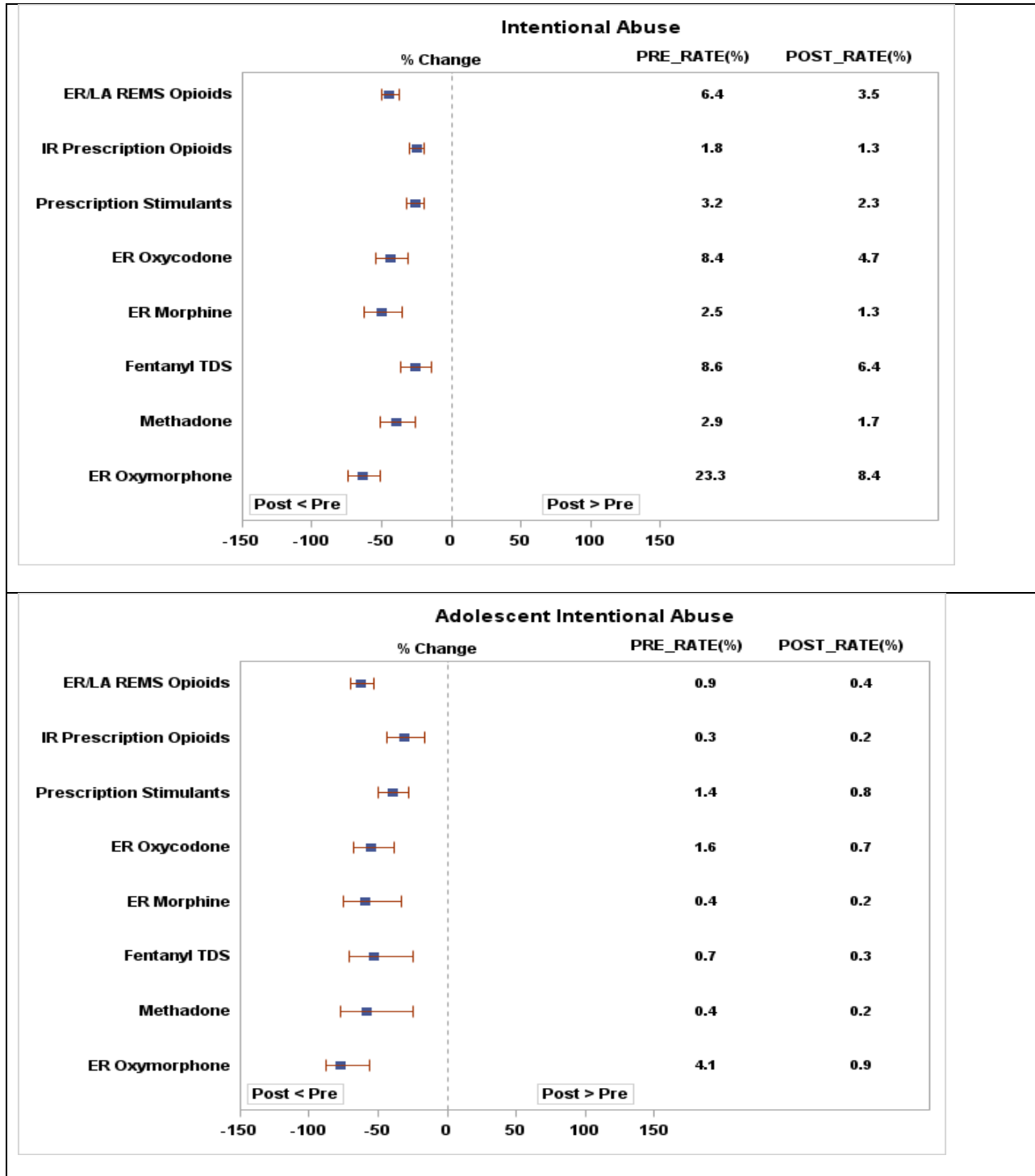
Table 5: Percent Change From Pre to Post REMS Periods for Rates of Intentional Abuse, Misuse and Death, Adjusted for Number of Prescriptions Dispensed

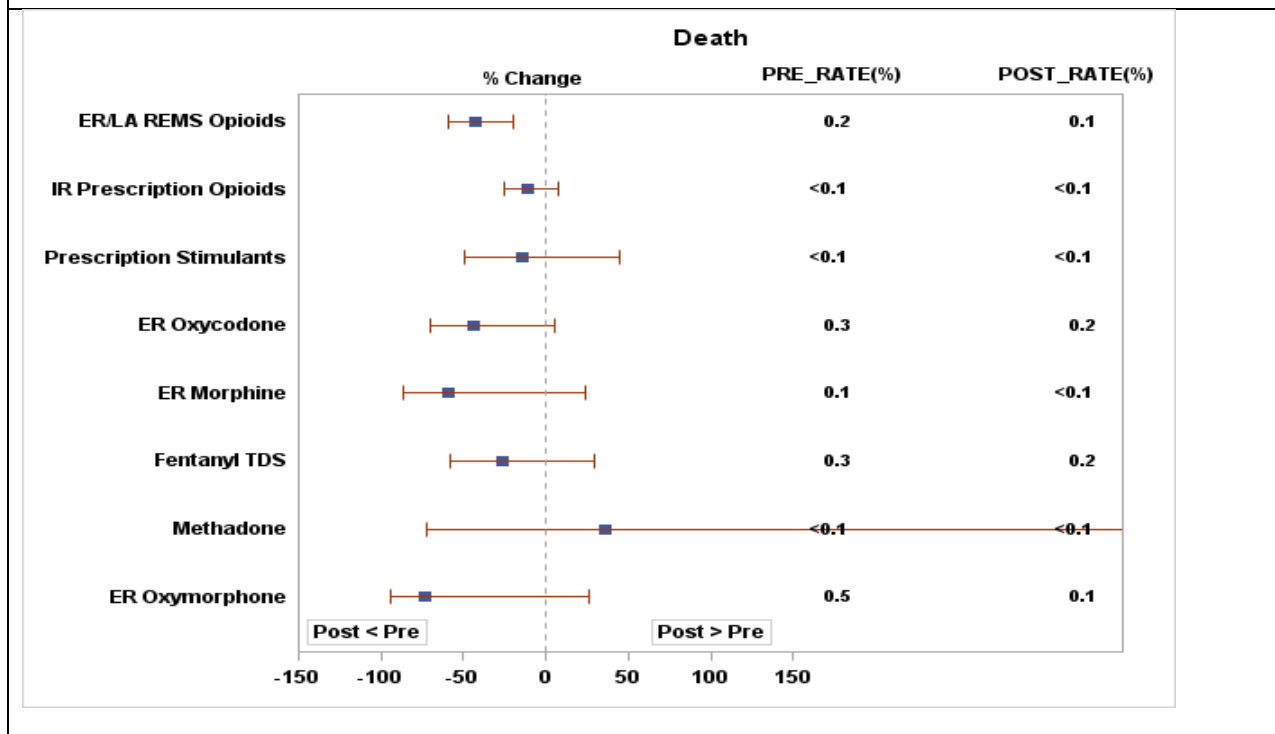
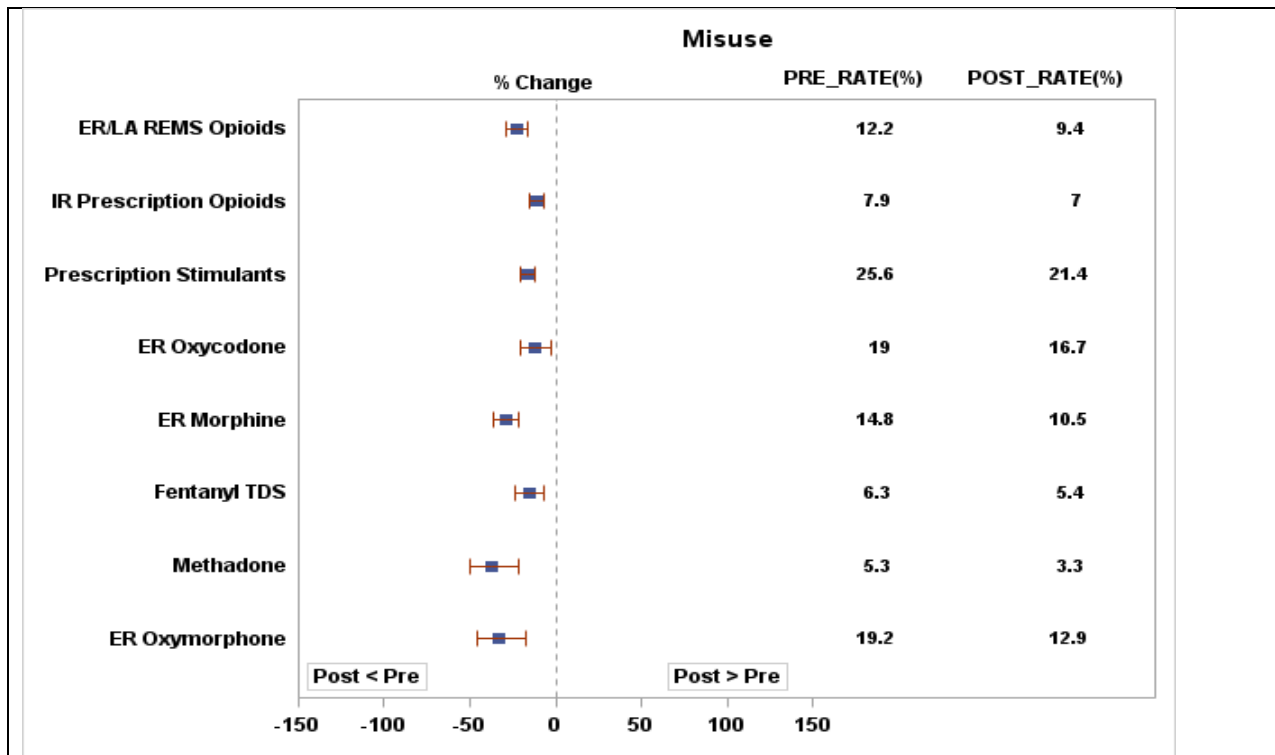
	Intentional Abuse		Misuse	Death
	All	Adolescents		
ER/LA Opioids	-44.4% (-50.3, -37.8)	-62.3% (-69.7, -53.1)	-23.0% (-29.0, -16.6)	-42.8% (-59.4, -19.3)
IR Opioids	-25.0% (-30.4,- 19.10)	-31.5% (-43.7, -16.8)	-10.9% (-15.0, -6.7)	-10.6% (-25.6, 7.4)
Prescription Stimulant	-26.3% (-32.5, -19.4)	-39.8% (-49.6, -28.2)	-16.1% (-20.1, -11.9)	-13.8% (-48.8, 45.1)

Source: Reviewer’s table summarizing information from multiple tables in Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report.

⁴⁵ Secora et al. Measures to quantify the abuse of prescription opioids: a review of data sources and metrics. *Pharmacoepidemiology drug safety*. 2014;23:1227-37

Figure 7: Forest Plot of Prescription Adjusted Rates of Intentional Abuse, Misuse and Death



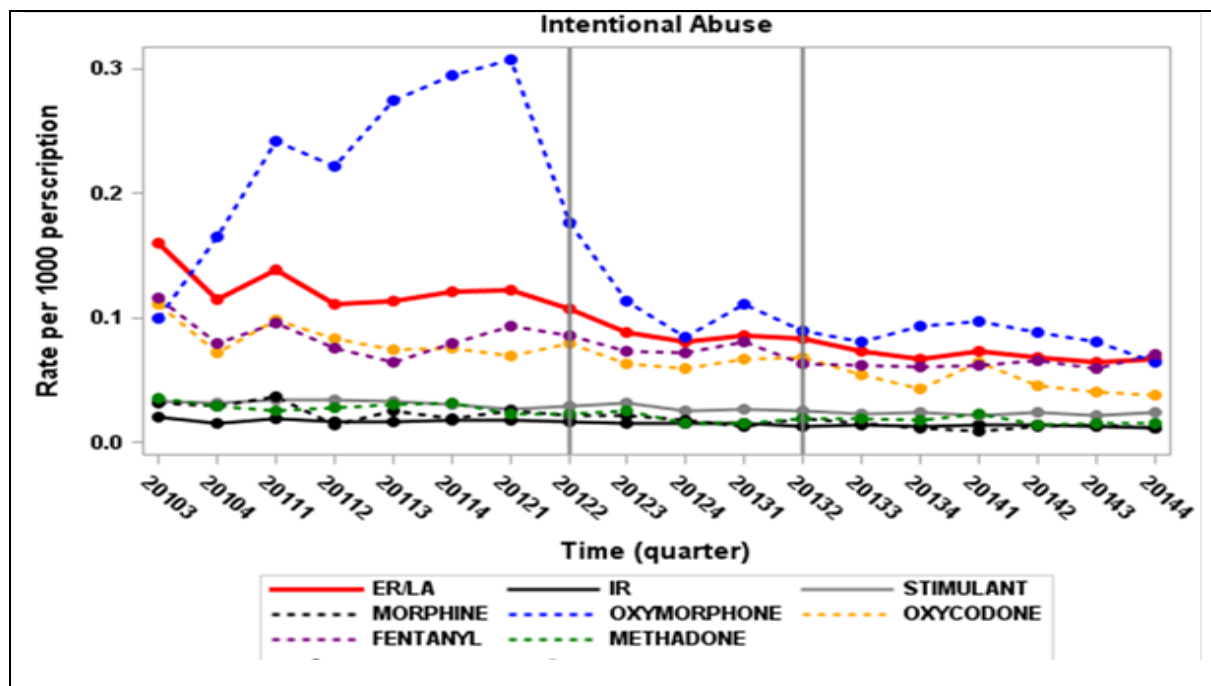


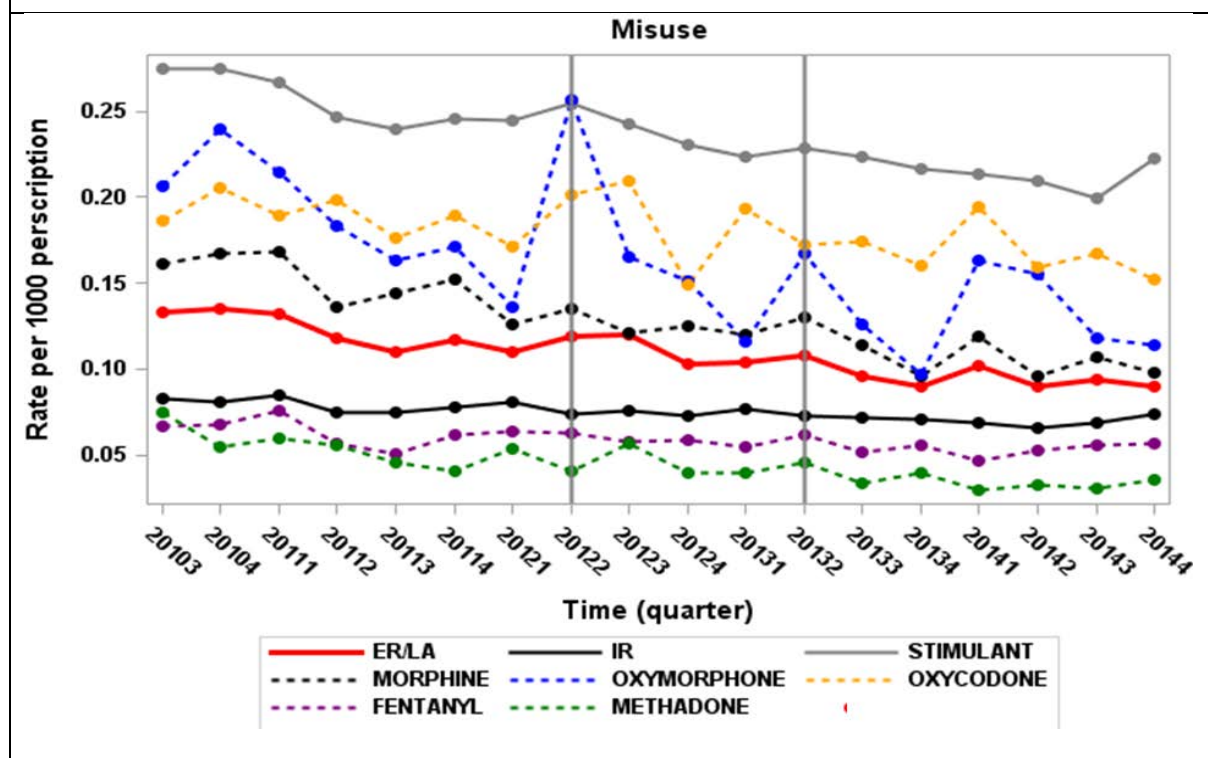
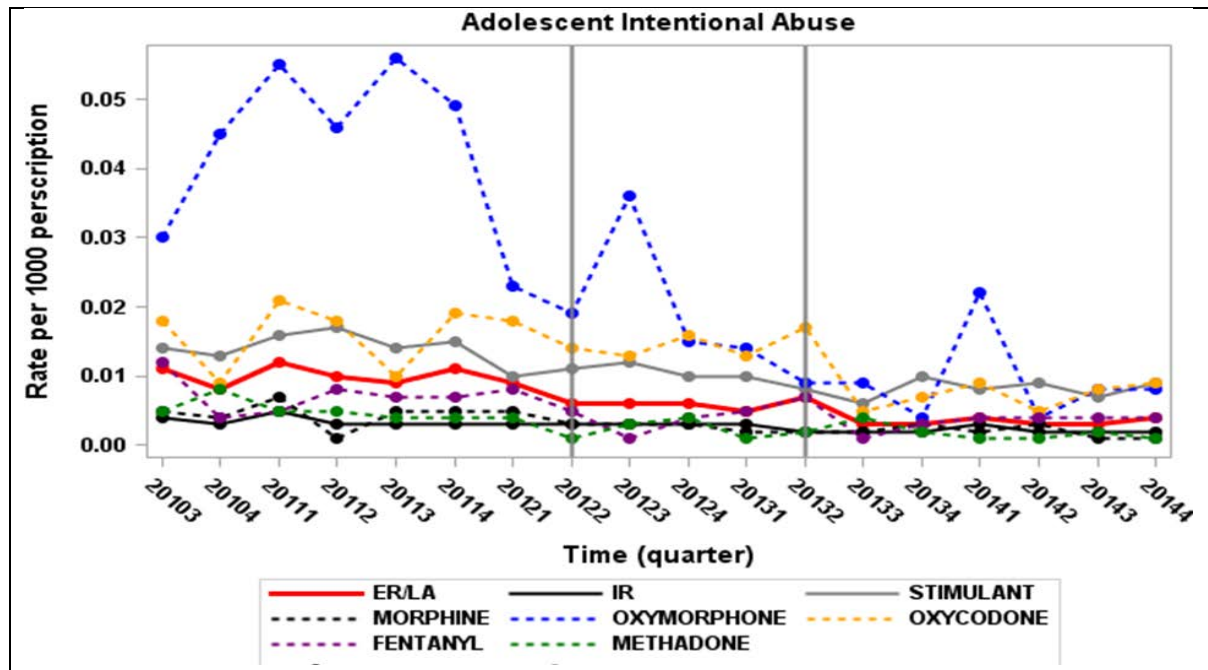
Source: Reviewer's figure summarizing information from multiple tables in Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

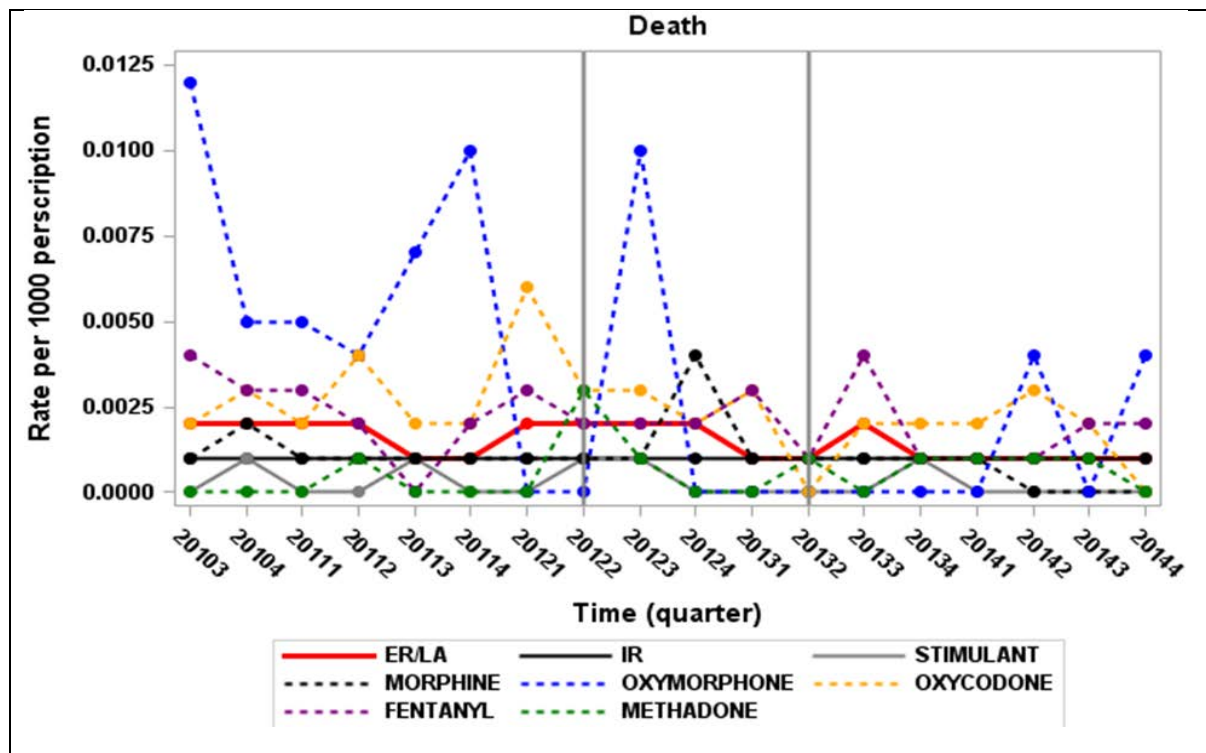
Figure 8 shows the observed mean rates at each quarter for three outcomes by drug. Although the applicant holder fitted piecewise linear models, the linearity assumption doesn't seem to hold for all drugs and all time periods based on visual inspection of the data. This is also supported by 95% CI of estimates of slope in the applicant holder's results (95% CI contains 0 for all ER/LA opioids drugs). Please note that three solid lines represent overall ER/LA opioids and two comparators (IR opioids and Stimulants), and the five dotted lines are for five individual ER/LA opioid drugs.

For intentional abuse, ER/LA opioids appears to be decreasing throughout the study period but within post period there is no apparent decreasing trend. There is no specific trend shown in IR opioids and stimulants. Among the individual ER/LA drugs only oxymorphone seems to decrease in rates but it also exhibits big variability in all three outcomes. A similar trend is observed in misuse outcome but decreasing trend in morphine and stimulant seems to be more obvious than in abuse outcome. Due to the low event rates, there is no obvious trend in death outcome.

Figure 8: Time Trend of Observed Prescription Adjusted Rates for Intentional Abuse, Misuse and Death Outcomes







In each panel, the three different time periods are separated by two grey lines.

Source: Reviewer's figure summarizing information from multiple tables in *Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report*

Unintentional exposure among infants and children (component 3)

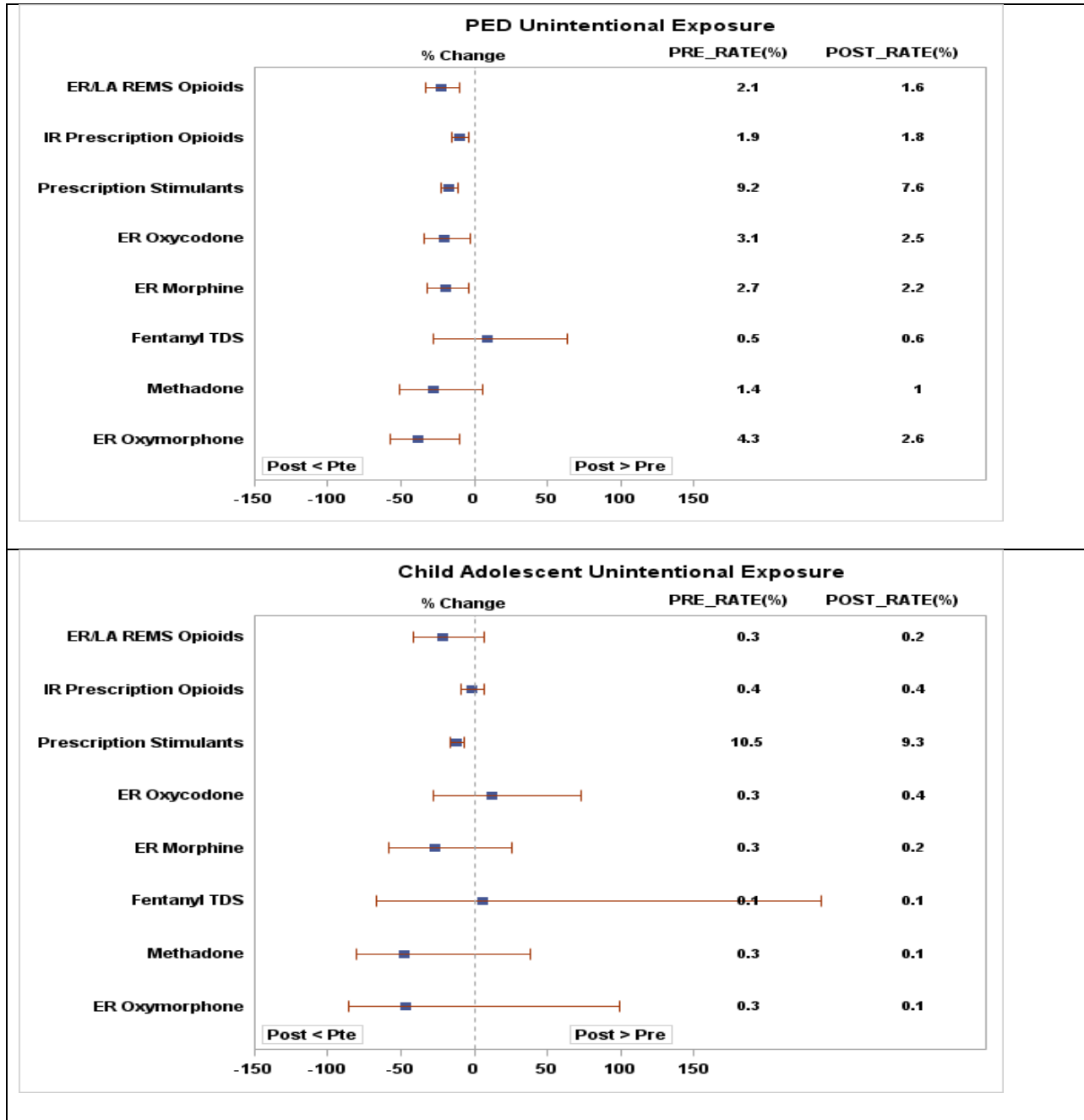
The prescription adjusted mean rates of unintentional exposure were found to be reduced for both pediatrics (under 6 years old) and children and adolescents age group (6-19 years old) in post REMS period compared to pre REMS period for ER/LA opioids and two comparators (Table 6). However, the applicant holder's analysis showed that the difference of mean rates in children and adolescent groups are not statistically significant (Figure 9). Similar patterns are seen in the individual drug. There is no apparent increasing or decreasing trend shown for unintentional exposure outcome throughout every time period. However, the unintentional exposure to prescription stimulants seems to constantly decrease over time in pediatric group (Figure 10).

Table 6: Percent Change from Pre to Post REMS Periods for Unintentional Abuse Exposure in Pediatric (under 6 years old) and Child/adolescent (6-19 years old) Population, Adjusted for Number of Prescription Dispensed

	Unintentional Abuse	
	Pediatrics	Children and Adolescent
ER/LA Opioids	-22.4% (-33.1, -10.0)	-21.4% (-42.0, 6.7)
IR Opioids	-10.0% (-15.8, -3.7)	-1.3% (-9.2, 7.3)
Prescription Stimulant	-17.0% (-22.8, -10.7)	-11.8% (-16.4, -6.9)

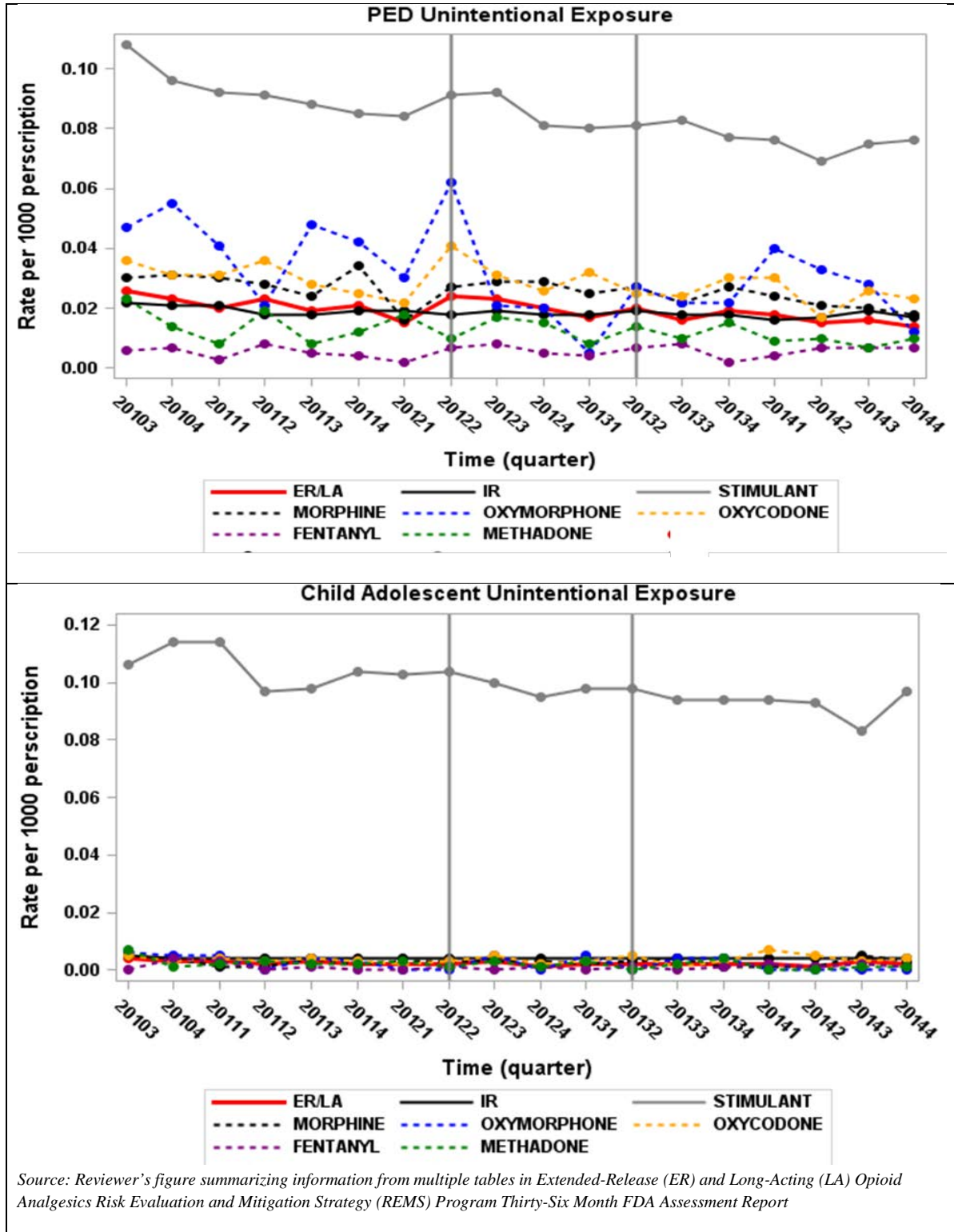
Source: Reviewer's table summarizing information from multiple tables in Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Figure 9: Forest Plot of Prescription Adjusted Unintentional Abuse Exposure For Pediatrics and Child / Adolescents



Source: Reviewer's figure summarizing information from multiple tables in Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Figure 10: Observed Prescription Adjusted Rates for Intentional Abuse Exposure, Misuse and Death Outcomes Over Time (ER/LA Opioid drugs and comparators)



Source: Reviewer's figure summarizing information from multiple tables in Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Reviewer's comments:

- *The observed event rates in this report cannot be easily generalized to the US population of interest because the databases are all convenience samples of the targeted population at each time point.*
- *The number of ZIP codes covered by this database is not consistent across different time period. Thus, the database varies geographically over time and may impact the sampling fraction. Sensitivity analyses using additional information on covariates and external sources could calibrate or standardize these results and test impact of different sampling fractions on measured change.*
- *The unit of analysis is a quarter, and none of the applicant holder's analyses adjusted for potential confounders.*
- *The piecewise linear model assumed that mean rates at each quarter linearly decrease or increase within time period. However, the observed data doesn't seem to support that linearity assumption. In addition, certain drugs such as hydrocodone, tapentadol have only a few time points so it is not reasonable to fit linear model to those cases.*
- *Statistical inference (p-value and 95% CI) used in RADARS were based on large samples asymptotic tests and these may not be valid for small number of quarters. However, the 95% CI from bootstrapping method (non-parametric method) showed similar results.*

4.3 (Component 4) Rates of individuals in substance abuse treatment program using NAVIPPRO System and RADARS treatment center program

The objective of component 4 is to examine the change in mean rates and trend of substance abuse before and after implementation of REMS. Data from NAVIPPRO and RADARS treatment center program were analyzed to meet this objective.

4.3.1 NAVIPPRO

Objective

The primary objective for this study is to estimate changes in population-based prevalence of past 30-day abuse of ER/LA products as a group across a pre-REMS period (baseline), REMS implementation (time 1) and continuing active REMS phase (time 2). The study included data on IR and Benzodiazepine as comparators.

Statistical Evaluation

In response to FDA statistical comments on the 24th month assessment report, the applicant holder changed the unit of their primary analysis to be patient home 3-digit zipcode and time period. Note that the study periods are pre, transition and post-REMS but not quarters. A mixed effect negative binomial regression was modeled to account for between zipcode variability. The applicant holder proposed to use the following two denominators in the model as offsets: (1) total number of assessments by patient home 3-digit zipcode per quarter and (2) U.S. Census population. Specifically, the applicant holder's models are as follows;

MODEL:

$$abuse_{ijk} \sim \text{NegBin}(\mu_{ijk}, k)$$

$$\eta_{ijk} = \log(\mu_{ijk}) = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij} + \text{offset} + z_k$$

where,

- $abuse_{ijk}$ is a yes/no response to abuse of the i^{th} drug in the j^{th} period for the k^{th} ZIP code
- μ_{ijk} is the probability of observing an abuse response for the i^{th} drug during the j^{th} period for the k^{th} ZIP code
- $\log(\mu_{ijk})$ is the logit link function of π_{ijk}
- μ is the overall mean
- α_i is the fixed effect of the i^{th} drug
- β_j is the fixed effect of the j^{th} period
- $(\alpha\beta)_{ij}$ is the interaction effect between the i^{th} drug and the j^{th} period
- z_k is the random effect of the k^{th} ZIP code assumed to be i.i.d. $\sim (0, \sigma_z^2)$
- offset is the log of the total number of ASI assessments or U.S. Census population (log_N)
- k is the estimated dispersion parameter which significantly improved model fit, $p < 00001$ compared to the Poisson regression.

In addition, in response to statistical comments on the 24th assessment report, the report included a sensitivity analysis which used common sites contributing data across the three study periods to the primary analyses. This analysis was only restricted to ER/LA opioid and not the comparators. The main analyses in this database found significant reductions in past 30-day abuse of ER/LA opioid, IR opioids, and Benzodiazepines from the pre-REMS period to the active REMS period. The sensitivity analyses on ER/LA opioid, conducted among the common sites across the three study periods, showed similar results as the primary analysis.

Reviewer's Comments

- *The observed event rates in this report cannot be easily generalized to the US population of interest because the databases are all convenience samples of the targeted population at each time point.*
- *In the main analyses, the number of ZIP codes covered by this database is not the same for different time periods. Thus, the database varies geographically over time and may impact the sampling fraction. Sensitivity analyses using additional information on covariates and external sources could calibrate or standardize these results and test impact of different sampling fractions on measured change. The sensitivity analyses restricted to common sites address some of this issue but not sufficiently enough as the zip codes still vary over time.*
- *In NAVIPPRO system, each person can contribute multiple abuse events in the ER/LA class in the same assessment if they abused more than one drug in the class. Thus, the rates from these analyses are rates of abuse events rather than rate of unique abusers. The proposed denominators used in the model as offsets are hard to interpret.*

4.3.2 RADARS Treatment Center Program

Exposure

ER/LA opioids are evaluated as an individual drug as well as overall group in comparison with IR opioids. ER/LA opioid drug class in these analyses comprise hydrocodone ER, hydromorphone ER, morphine ER, oxycodone ER, oxycodone, Tapentadol ER, Methadone, Fentanyl Transdermal Delivery Systems and Buprenorphine transdermal Delivery Systems.

Outcomes

The abuse outcome was analyzed, which was defined as a survey respondent endorsing the use of an ER/LA opioid “to get high” in the past 30 days.

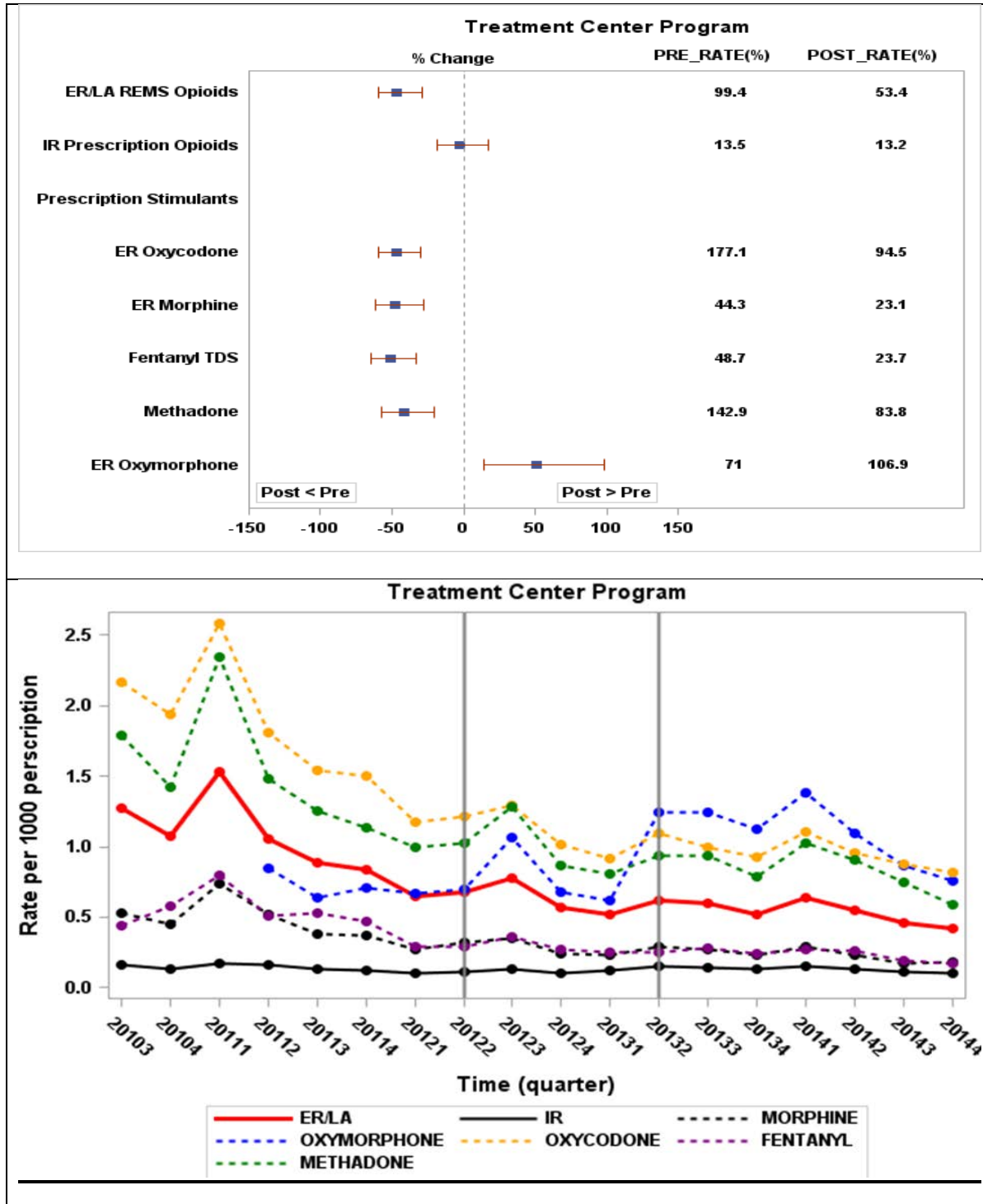
Statistical Analysis

The same models described in Section 4.2 were used in RADARS treatment center program data.

Results

Similar pattern to the abuse rates in poison center program appeared in the treatment center program (Figure 11); statistically significant reduction was shown in post-REMS period compared to pre-REMS period for ER/LA opioids. Also decreasing trend in abuse rates seems to be more pronounced in treatment center program compared to poison center program. However, the magnitude of abuse rates is much higher in treatment center program than poison center program in throughout all time periods.

Figure 11: Prescription-adjusted Mean abuse Rates of ER/LA Opioids and IR Prescription Opioids (upper panel) and Prescription-adjusted Mean Rates Over Time (lower panel) from RADARS Treatment Center Program Data



Source: Reviewer's figure summarizing information from multiple tables in Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Reviewer's comments: The same comments about RADARS poison center analyses hold for the RADARS treatment center analyses. Refer to comments in Section 4.2.

4.4 (Component 5) Mortality Rates resulting from drug poisoning associated with active pharmaceutical ingredients included in the ER/LA opioid analgesics: Washington State Medical Examiner Database

Data Source

Medical Examiner data from Washington state was analyzed to assess mortality rates from ER/LA opioid drug poisoning.

Objective

The specific objective for component 5 is to evaluate trends before and after the ER/LA REMS implementation for changes in mortality rates associated with prescription opioids during 2005-2015.

Exposure

ER/LA opioids without hydrocodone were the main drug of interest. Hydrocodone was analyzed as a separate category and benzodiazepine was used as a comparator.

Outcome

The main outcome was opioid associated mortality rates. Three denominators were used to estimate mortality rates: population, number of prescriptions dispensed, and number of dosing units dispensed from pharmacies.

Statistical Analyses

In these analyses, the pre-REMS time period is longer than in other elements. The time periods are Pre-REMS period (2005 – June 2012), transition period (July 2012- June2013), and post REMS period (July 2013 – December 2013).

As in RADARS analyses, Poisson regression was applied to aggregate level data (quarterly ZIP code) to compare mortality rates over time. The same mean model in element 2 was used for the analysis. The applicant holder also planned to do the same piecewise linear model as in element 2 but the report didn't provide the results. In addition, the statistical analysis plan states that drug-specific overdispersion parameter would be considered in the model but it is not clear whether the applicant holder implemented it or not.

Results

Table 7 shows the main result from the applicant holder's analysis. It is not clear why the applicant holder did not provide the result of benzodiazepine for prescription-adjusted rates. For ER/LA opioids, the table shows significant reduction in mortality rates after implementation of REMS compared to pre-REMS period but the reduction is not statistically significant for

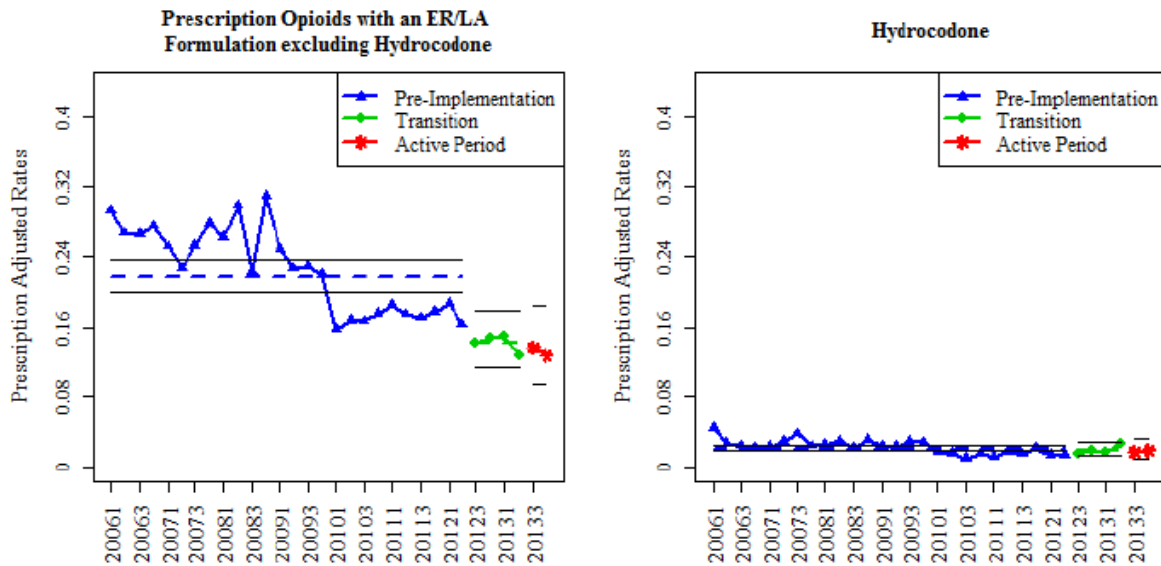
hydrocodone group. In addition, the decreasing trend is shown even before REMS was implemented (Figure 12).

Table 7: Prescription-adjusted mean rates by each drug group

DRUG GROUP	MEAN RATE	COMPARISON	% CHANGE (95% CI)
Prescription Opioids with an ER/LA Formulation excluding Hydrocodone	0.131	Pre versus Active	-39.44% (-57.36%,-14.00%)
Hydrocodone	0.018	Pre versus Active	-17.32% (-54.48%,50.17%)

Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Figure 12: Observed Prescription Adjusted Rates Over Time for Opioid-Related Mortality Rates from Washington State Medical Examiner Database



Source: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report

Reviewer's comments:

- The same comment for the piecewise model in the analysis of RADARS data in Section 4.2 hold for these analyses as well.
- The number of quarters included in the analyses is very unbalanced between pre and post REMS period (40 quarters in pre-REMS: 2005Q1-2012Q2 vs. 2 quarters in post-REMS

period: 2013Q3-2013Q4). Therefore, the applicant holder's analysis to compare mortality rates between pre and post REMS period is not reliable.

5 CONCLUSION

Here is the summary of results:

- The data from HIRD showed that the crude rates of ER/LA opioid overdose and poisoning events appeared to be higher in post-REMS period than pre-REMS period among all users and new-users but adjustment for potential confounders lowered the incidence rate ratio (IRR).
- Incidence rates of heroin overdose in HIRD data were much higher in post- REMS period, which remains after adjusting for potential confounders.
- Intentional and unintentional abuse rates from RADARS poison center program showed significant reduction in post-REMS period compared to pre-REMS periods but there is no obvious decreasing trend shown within post-REMS period. Also there seemed to be variability in the trend between drugs.
- Abuse rates from RADARS treatment center program showed similar pattern to those in the poison center program. The magnitude of mean abuse rates seemed to be much higher in treatment center program than poison center program throughout all study periods.
- Washington state medical examiner data showed significant reduction in mortality rates in ER/LA opioids group excluding hydrocodone after implementation of REMS compared to pre-REMS period but the reduction was not statistically significant for hydrocodone group only.

6 STATISTICAL COMMENTS

Two main statistical limitations with these data sources for measuring change from pre to post REMS are first that all data sources are convenience samples of the US population of interest in each time frame and second that statistical measures of changes in outcomes from pre to post cannot be causally attributed to REMS interventions only.

Convenience sampling is a limitation because at each time point one cannot easily generalize the observed event rates in the database to the US population of interest. Moreover, the sampling fraction, defined as the fraction of the US population of interest captured by the database, likely changed over time in each database in an unknown way. Thus, outcomes over time in a database could vary due to database sampling fraction changes rather than true change of outcomes due to any intervention. Sensitivity analyses could test impact of different sampling fractions on measured change.

Causality of REMS intervention to change cannot be inferred from any analyses in this report. All the analyses are confounded with time and it is known that many interventions occurred in the same time frame as REMS. It would be impossible for statistical analyses to correct for all the secular trends to attribute the change solely to REMS.

Analyses of HIRD and Medicaid data in component 1 were on subject level data and corrected for some subject level covariates. Poisson analyses with NAVIPPRO data on abuse, in component 4, aggregated data in time (at period level) in a ZIP code spatial scale. The analyses did not correct for ZIP code level covariates but did some correction to spatial correlation. Finally, Poisson analyses with RADARS data and Washington Medical Examiner data, in components 2 to 5, aggregated in space across all geographic regions in a quarterly time scale. They did not correct for any covariates in time. Thus, it is impossible to integrate the analyses in one summary of change, even for the same outcome.

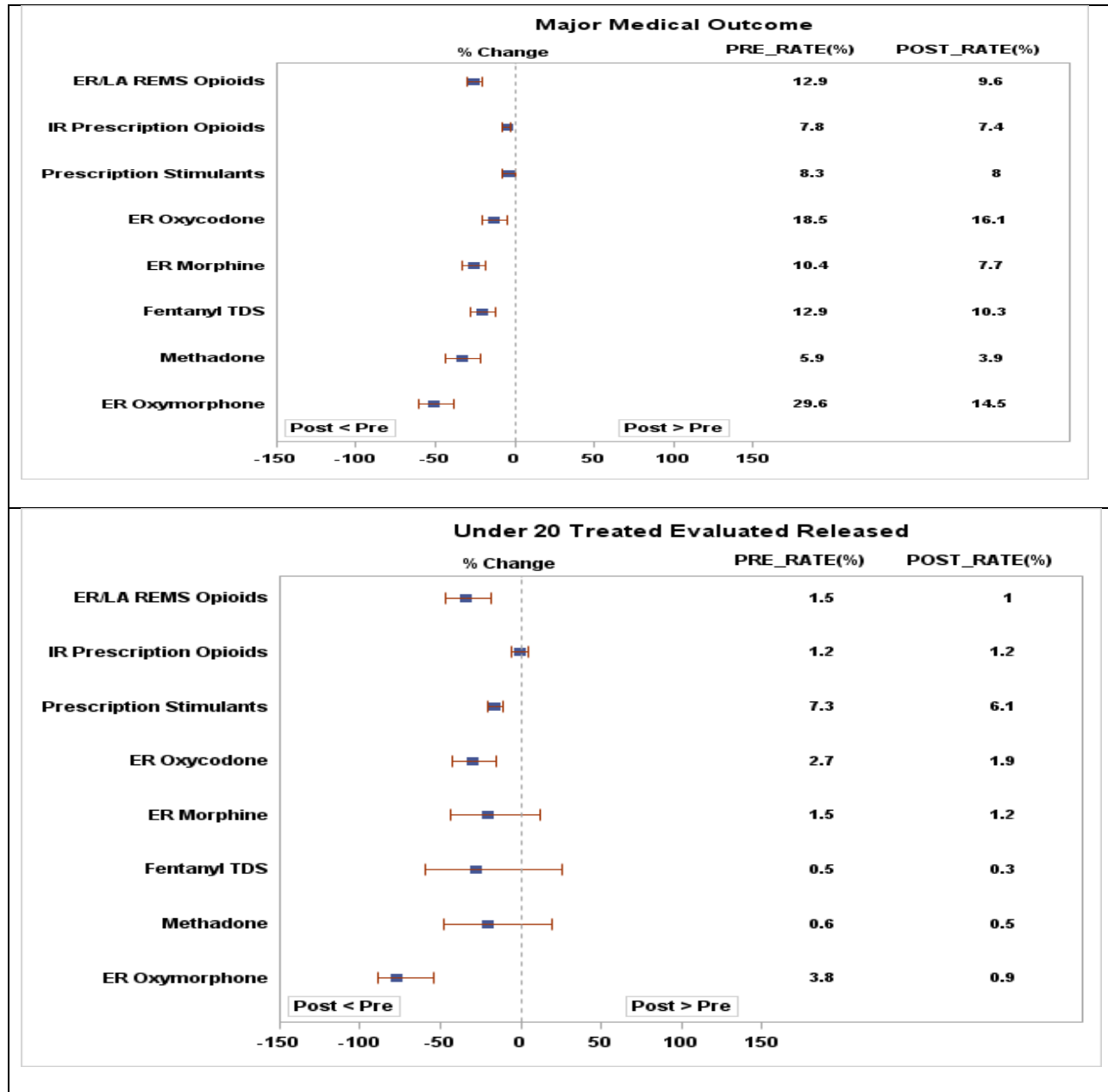
We summarize below some specific issues related to each statistical analysis,

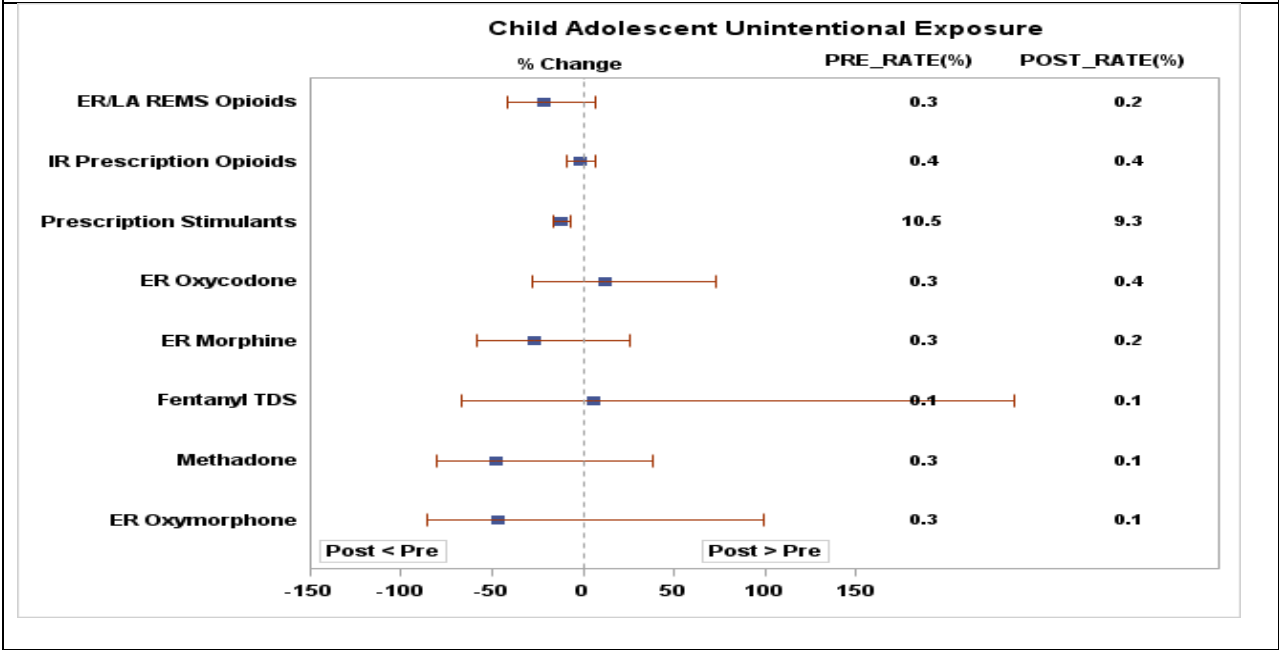
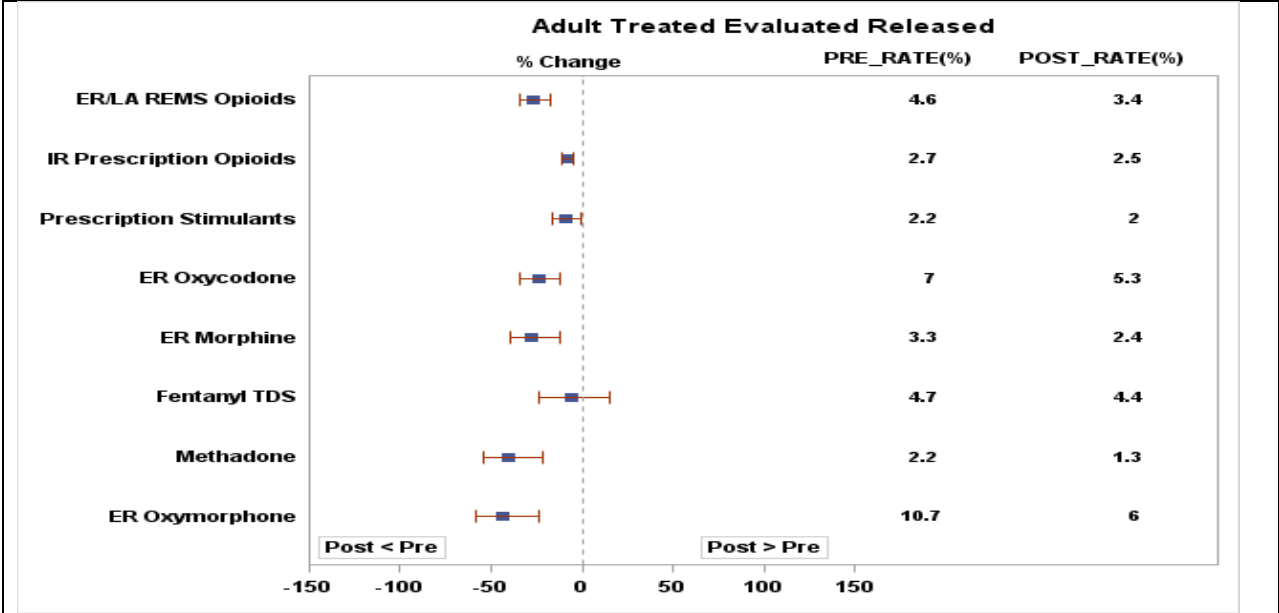
- The time period the applicant holders defined is not consistent across different data sources
- In the analyses of HIRD data,
 - The applicant holders did not provide details on their Poisson model. Especially, it is not clear how the covariate were used (e.g. categorical/continuous, linear/non-linear etc.) in the adjusted model.
 - As the applicant holders stated, one patient could remain in the subsequent periods as a non-new user if a patient was defined as a new-user in the prior period and was not censored. This review found some potential issues as follows
 - It is not clear how the applicant holder's Poisson model could account for any possible correlation within a patient in the analysis with all-users group. It is likely that those who remained in the study would have higher probability to get events later.
 - It is not clear how the baseline covariates were defined for those who continued to remain in the study in new users and non- new users analyses. Some of these covariates could vary over time.
- In the analyses of RADARS (both the poison control center and treatment center data) and Washington State medical examiner data
 - The piecewise linear model assumed that mean rates at each quarter linearly decrease or increase within time period. However, the observed data doesn't seem to support that linearity assumption. In addition, certain drugs such as hydrocodone, tapentadol in RADARS data and post-REMS period in Washington State medical examiner data have only a few time points so it is not reasonable to fit linear model to those cases.

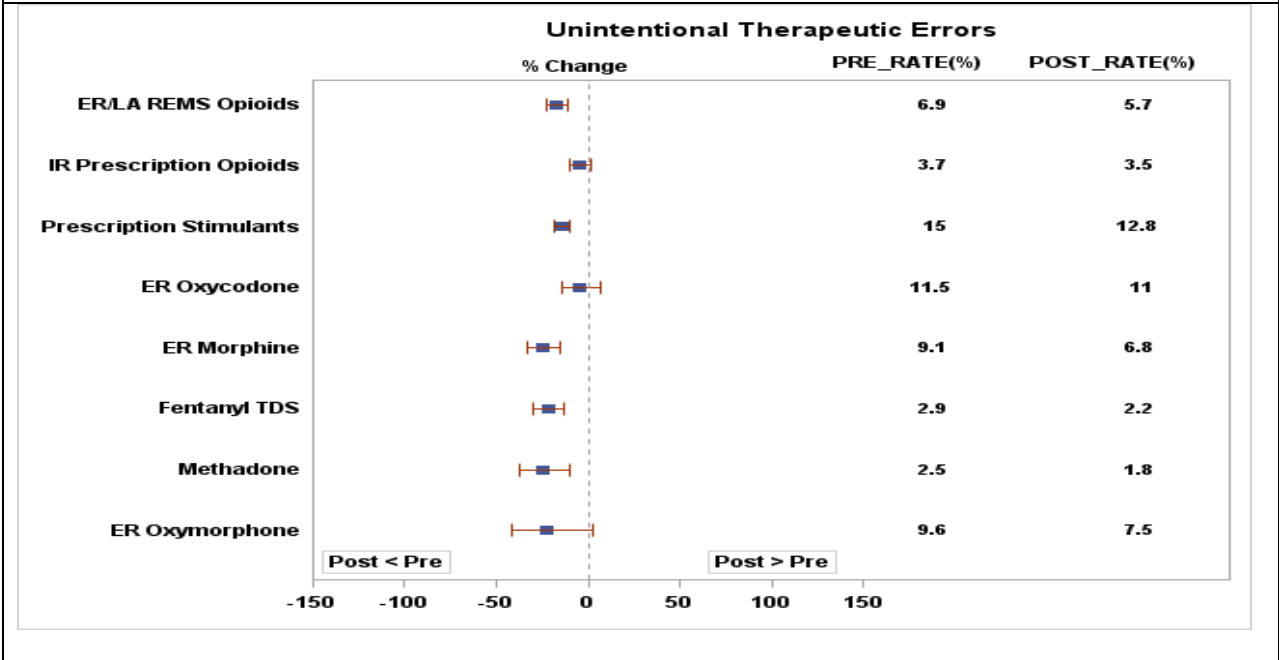
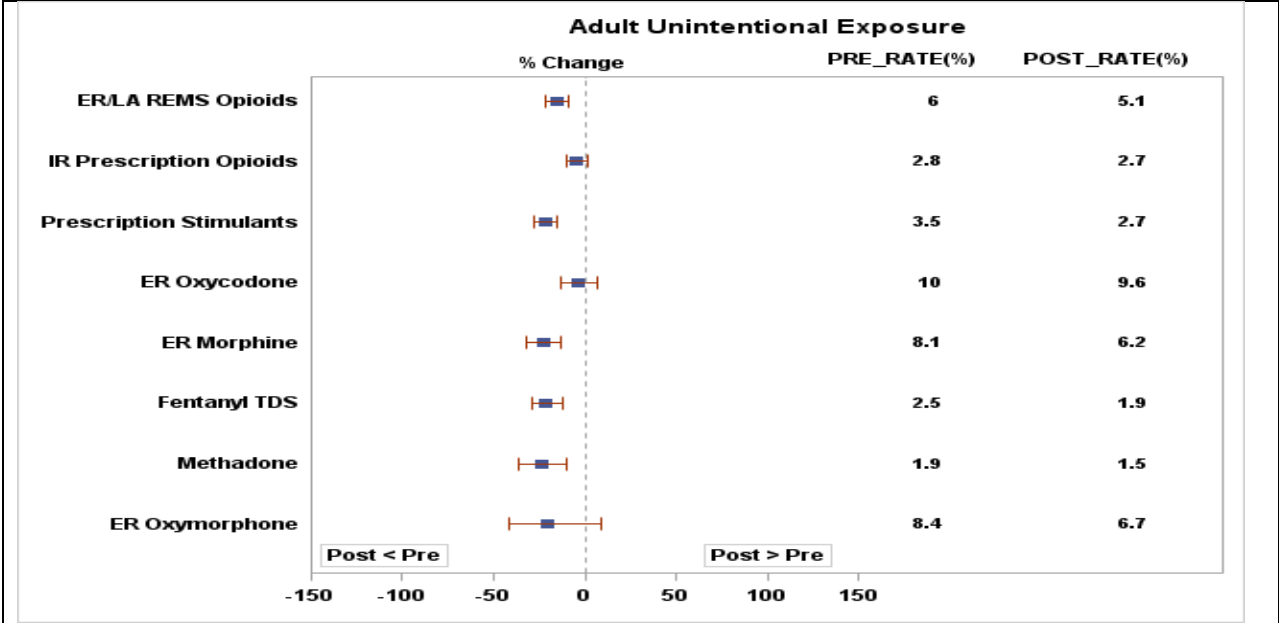
- The number of ZIP covered in RADARS data (both the poison control center and treatment center data) and NAVIPPRO is not the same across different time periods. This likely impacts sampling fraction over time.
- There is large variability in market share (i.e. number of prescription) among individual ER/LA opioid drugs, which was used as an offset variable in the applicant holder's Poisson model in the analysis of data from RADARS. Therefore, the mean rate of overall ER/LA opioid class is not numerically the same as the average of mean rates of individual drugs.
- The number of quarters included in the analyses of Washington State medical examiner data is very unbalanced between pre and post REMS period (40 quarters in pre-REMS: 2005Q1-2012Q2 vs. 2 quarters in post-REMS period:2013Q3-2013Q4). Therefore, the applicant holder's analysis to compare mortality rates between pre and post REMS period is not reliable.
- Comments for NAVIPPRO
 - The ZIP codes covered by this database is not consistent across different time period. Thus, the database varies geographically over time and may impact the sampling fraction.
 - In NAVIPPRO system, each person can contribute multiple abuse events in the ER/LA class in the same assessment if they abused more than one drug in the class. Thus, the rates from these analyses are rates of abuse events rather than rate of unique abusers.
 - The proposed denominators used in the model as offsets are hard to interpret. The preferred denominator by the DRISK reviewer is the number of prescriptions sold by ZIP code or the number of prescriptions sold in the U.S.

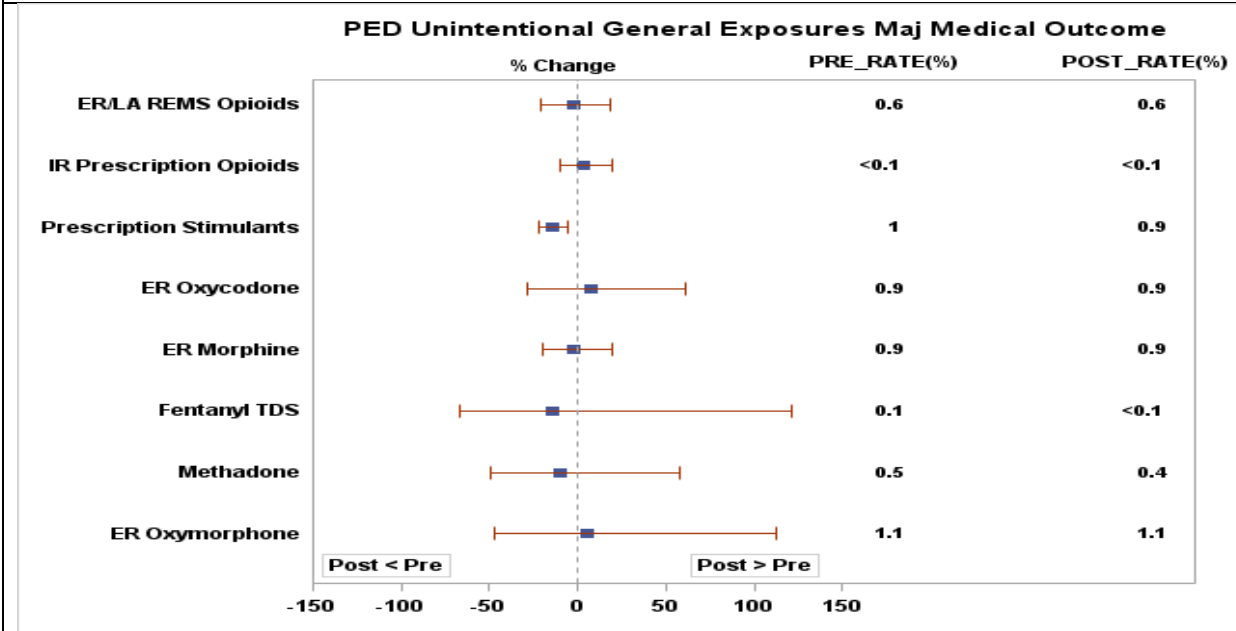
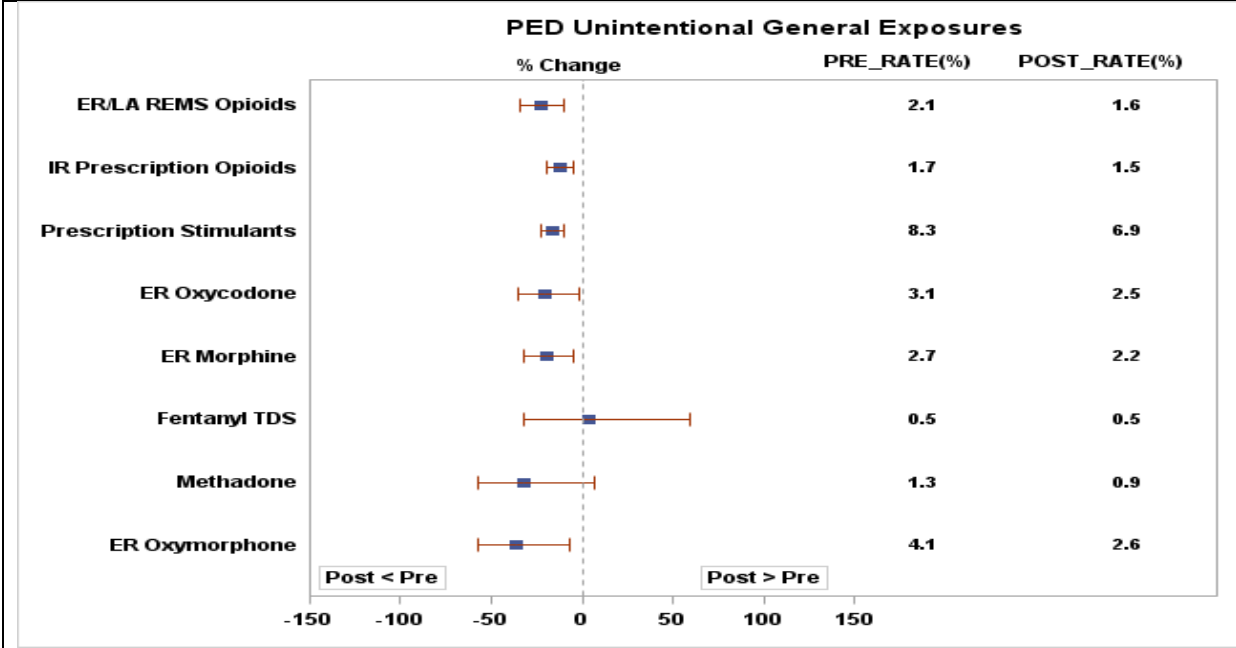
Attachment A: Supplemental Figures for RADARS analyses

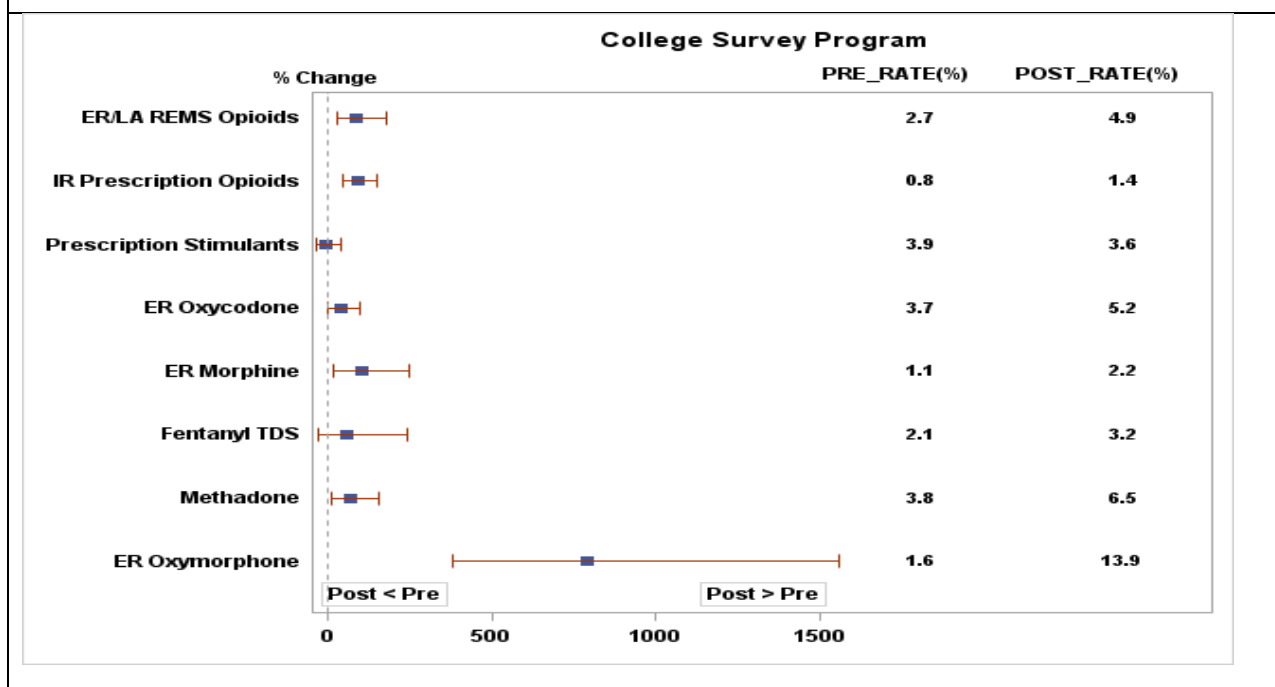
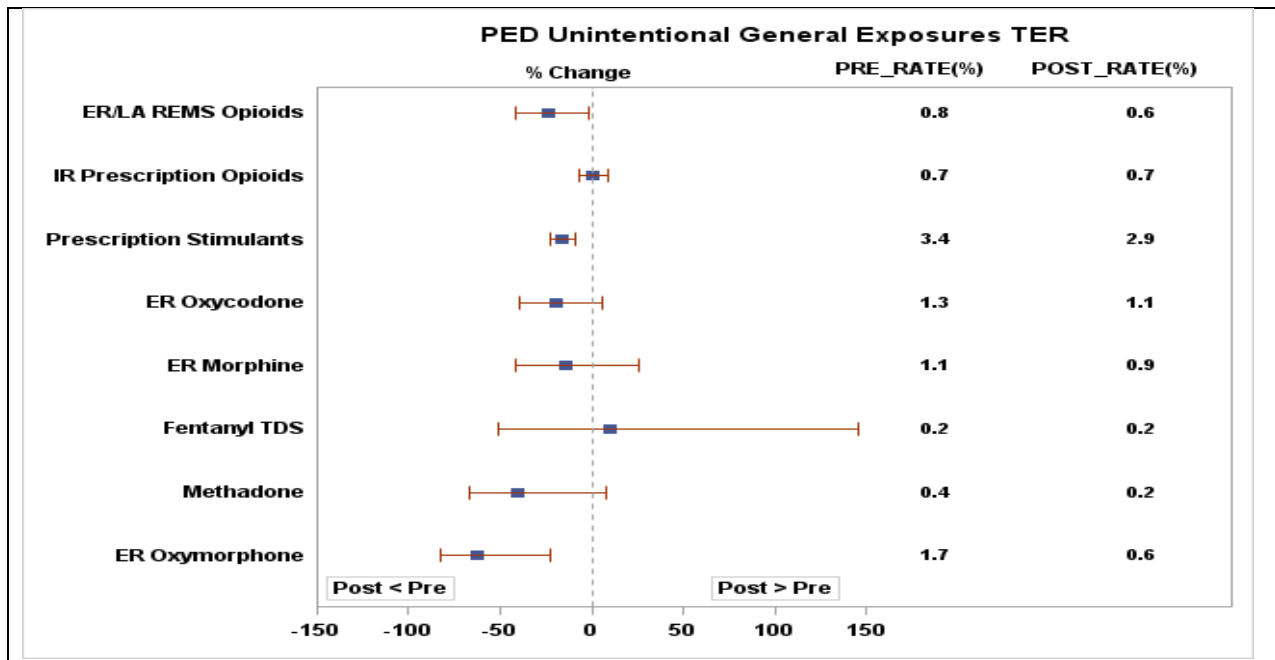
1. Forest Plots for additional outcomes analyzed in components 2 and 3.





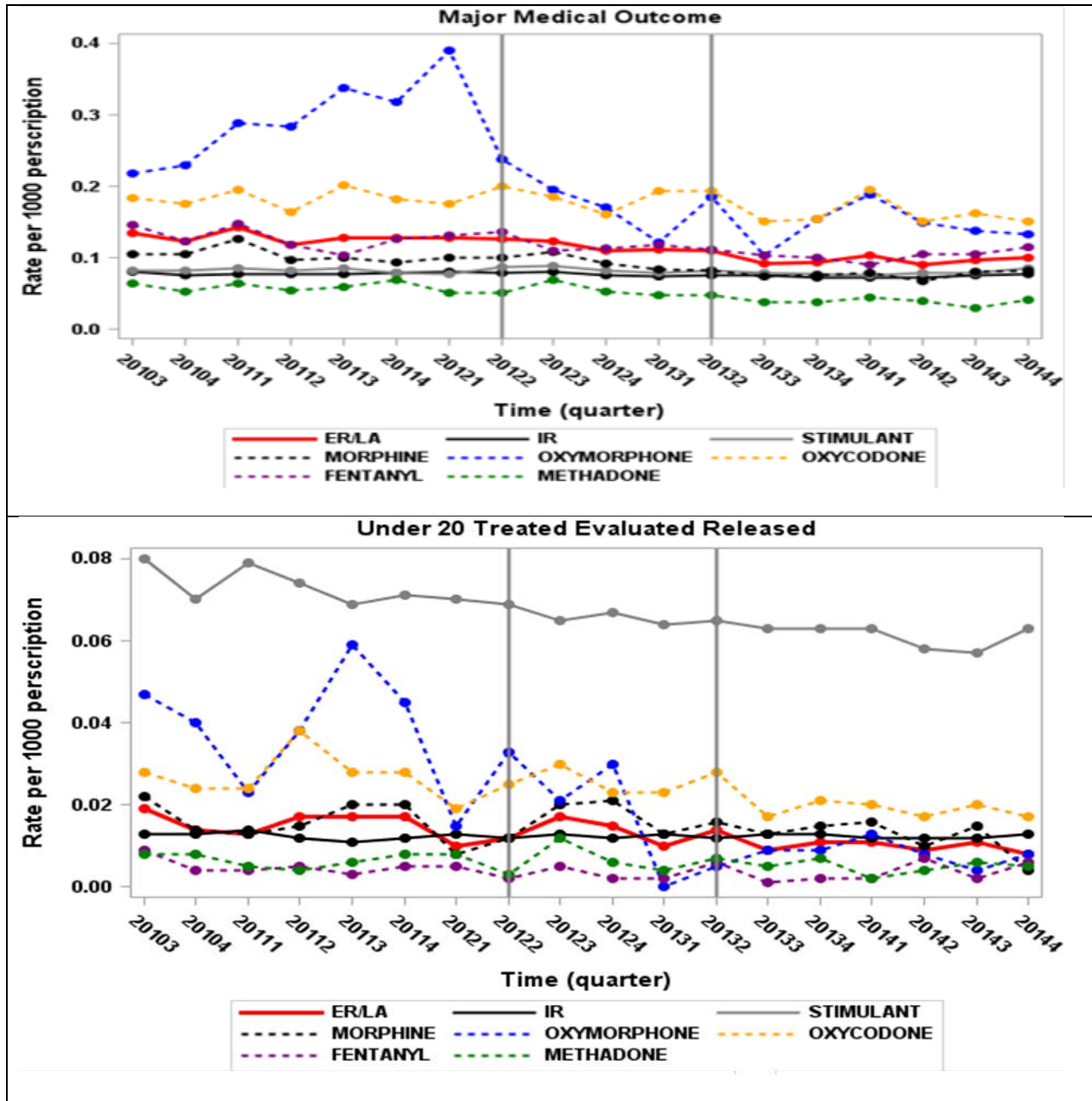


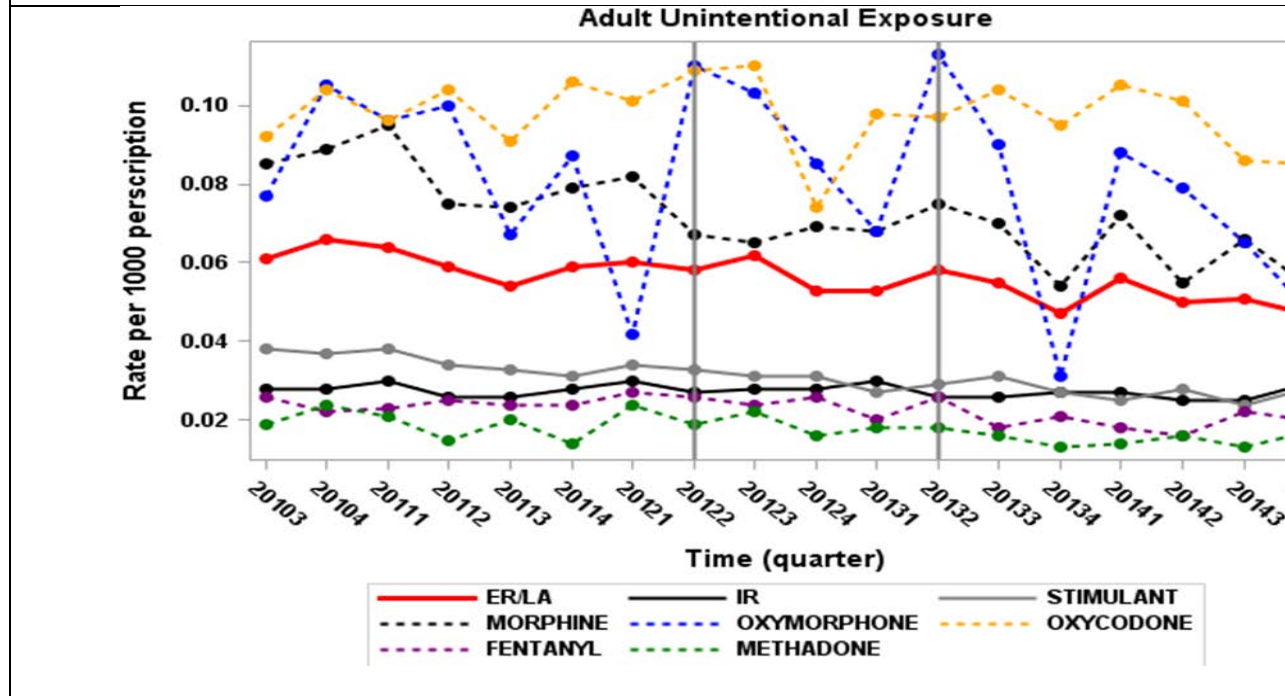
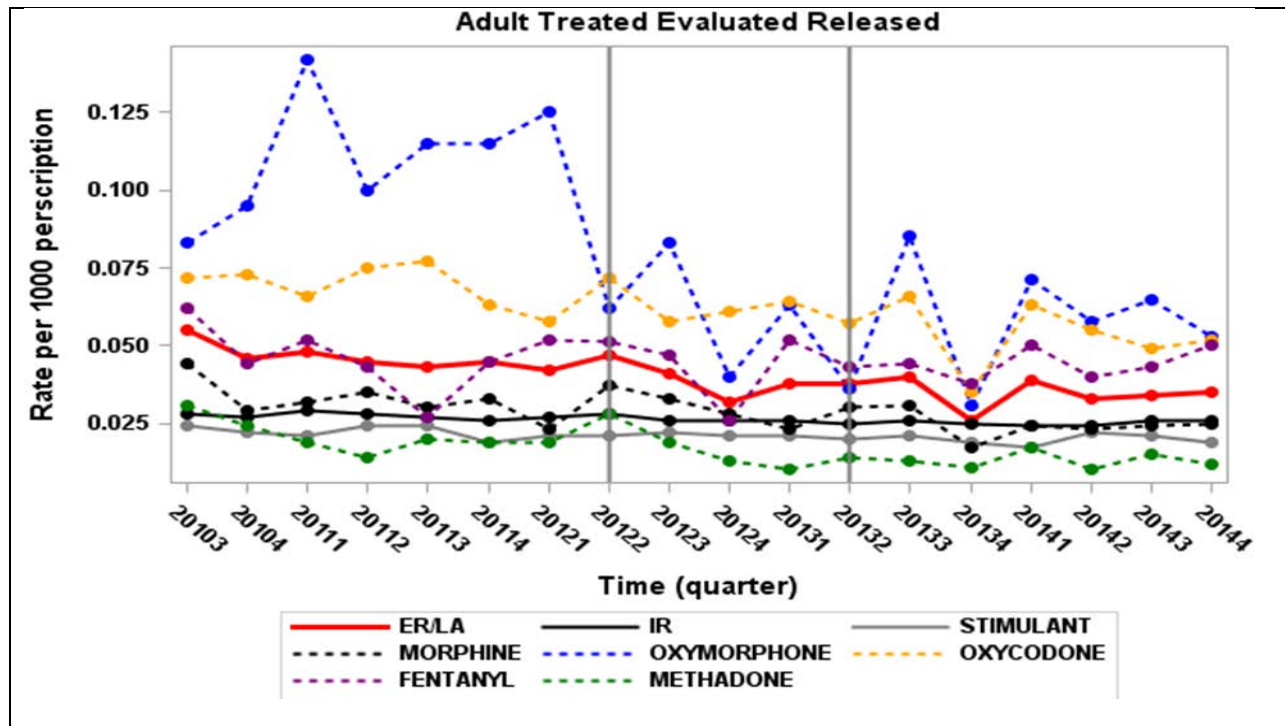


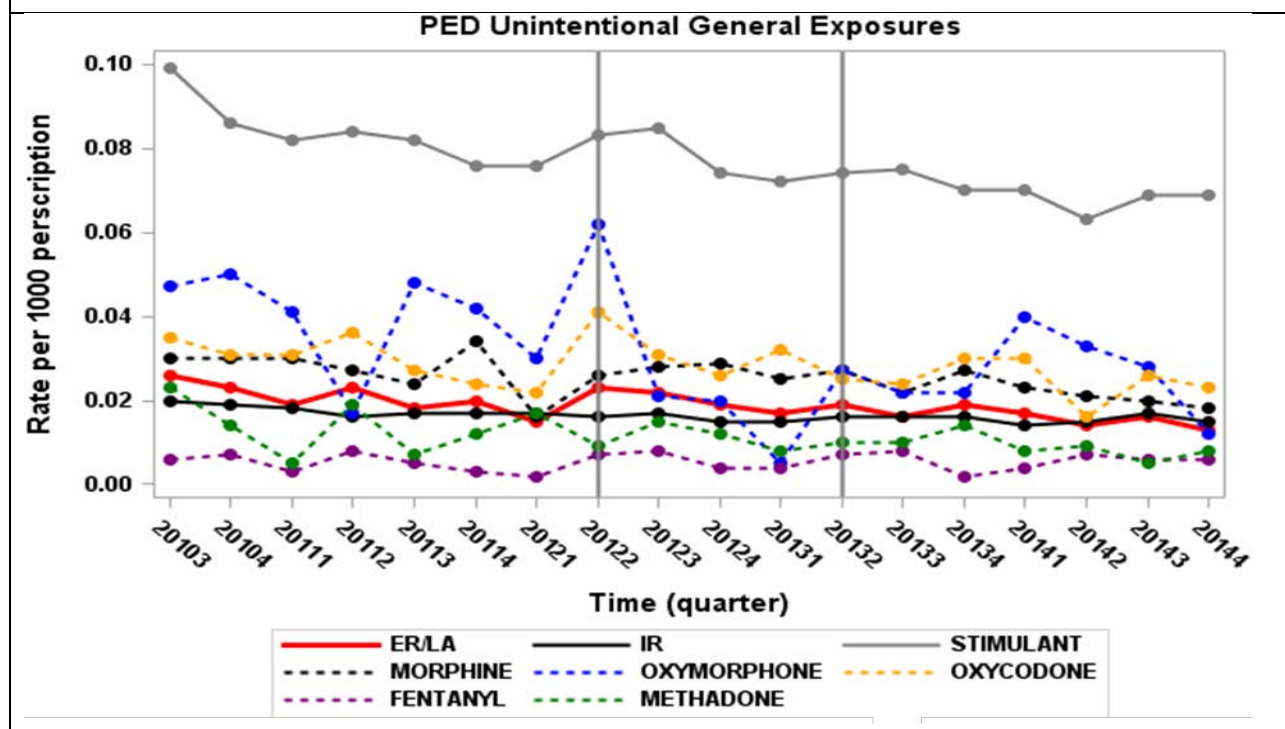
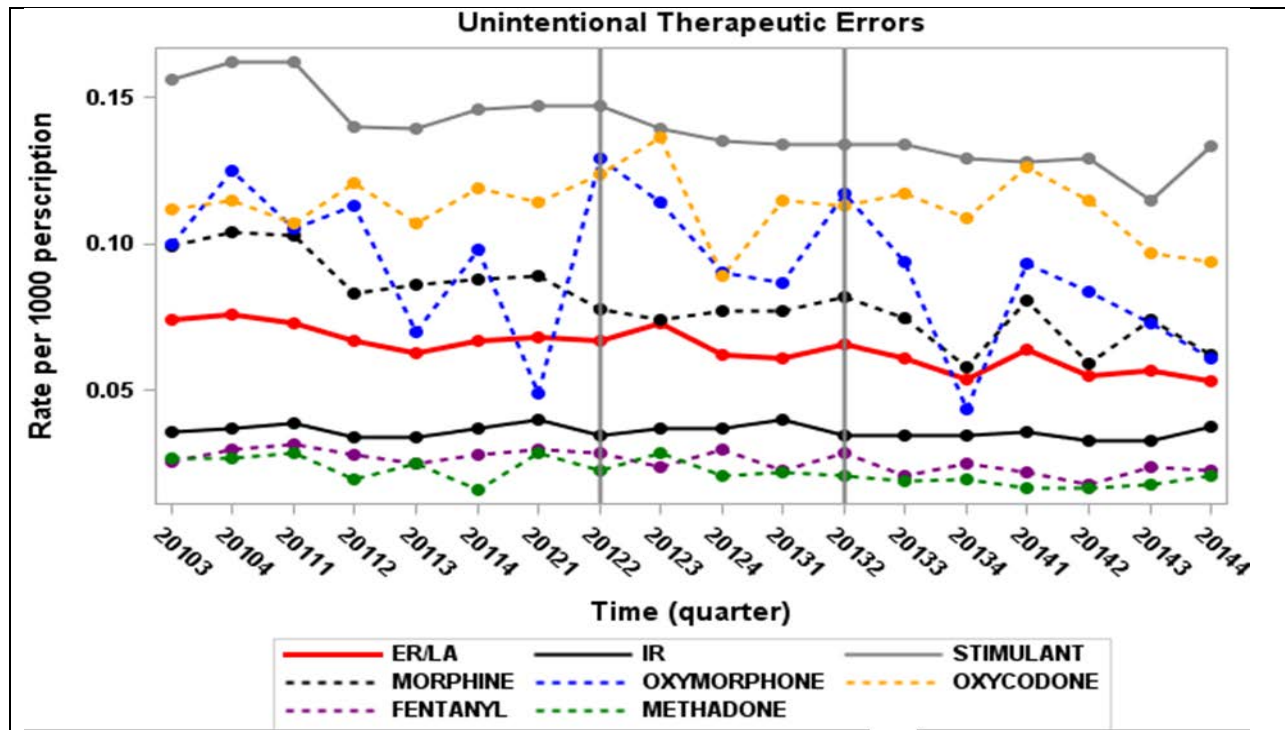


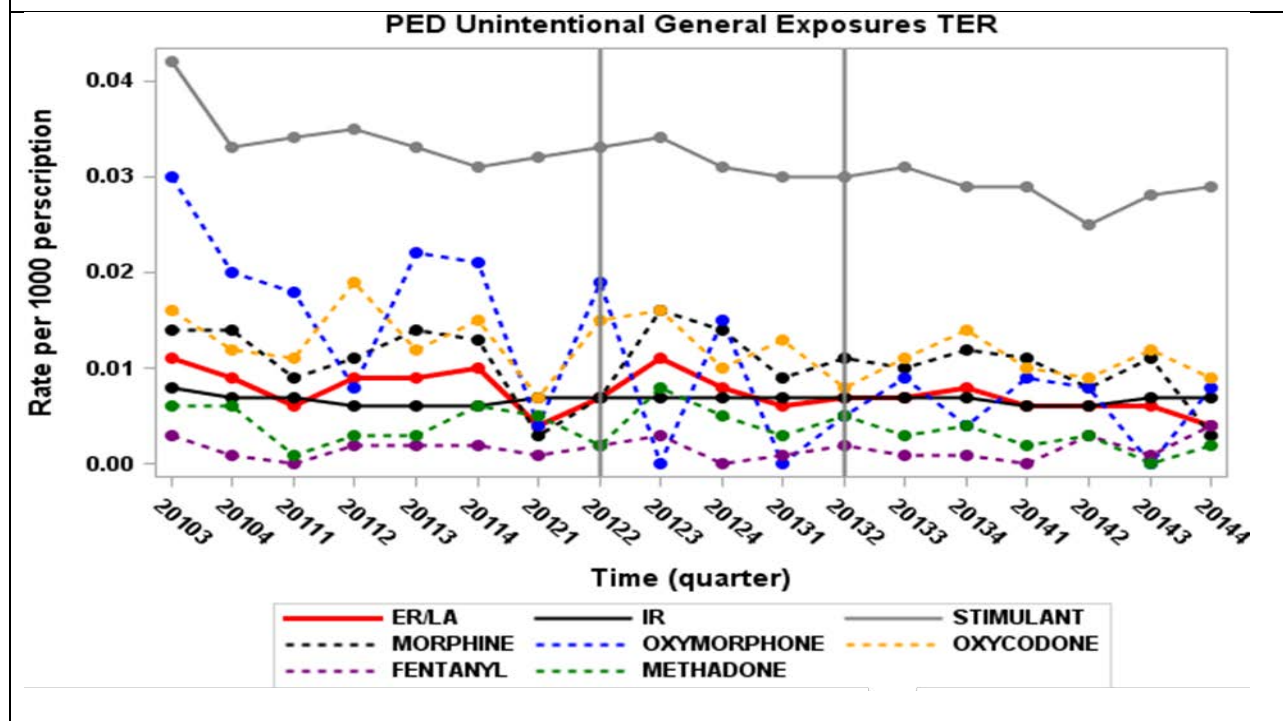
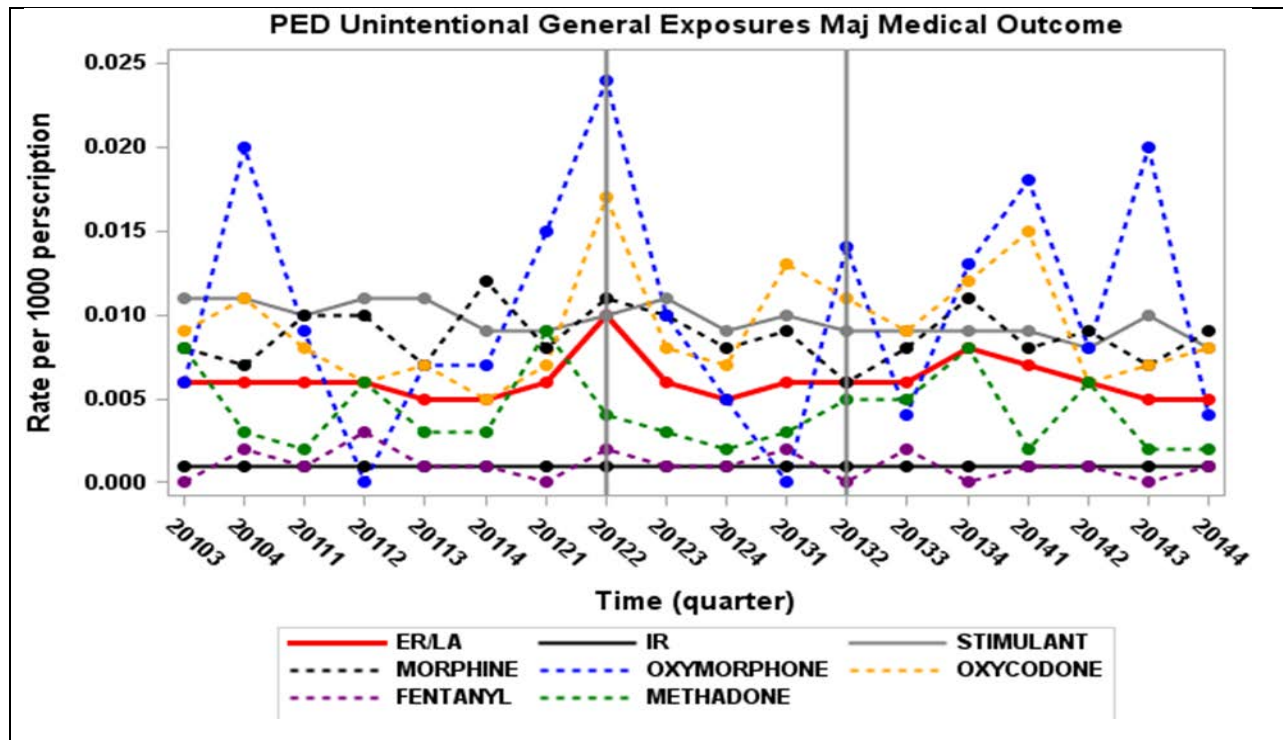
Source: the reviewer's plot based on the applicant holder's tables in the report

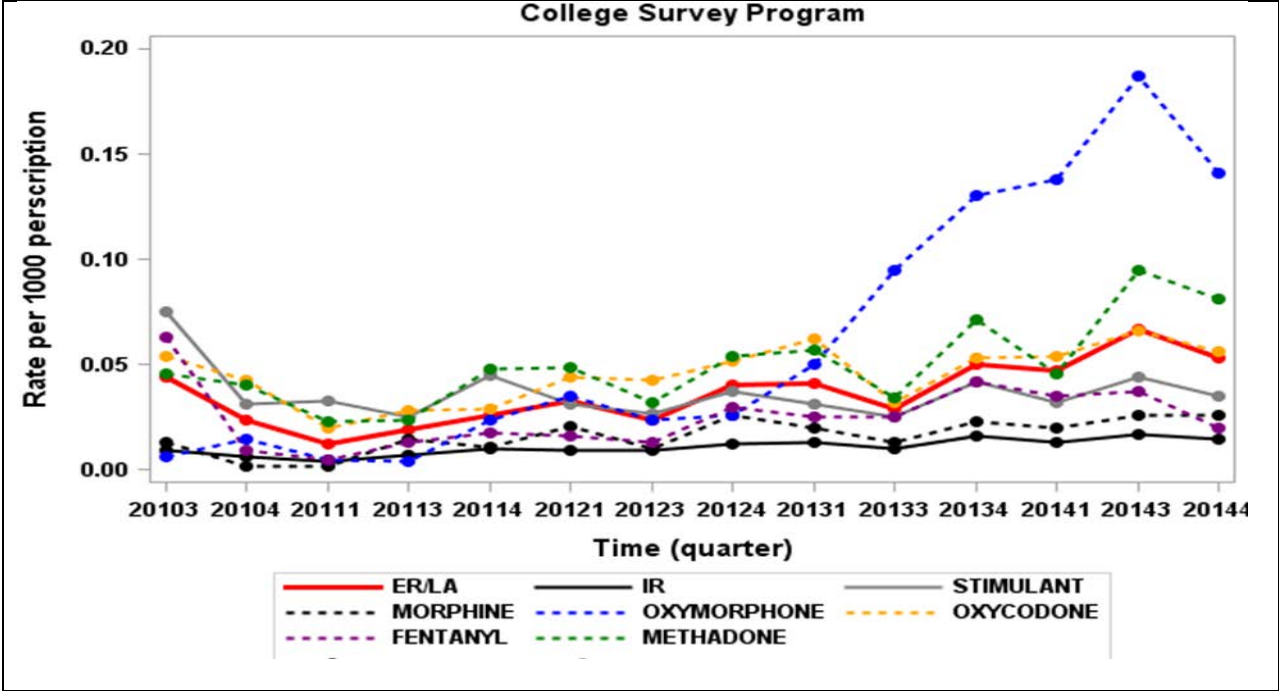
2. Trend Plots for additional outcomes analyzed in components 2 and 3.











Source: the reviewer's plot based on the applicant holder's tables in the report



**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: April 6, 2016

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

From: **Jennie Wong, PharmD, Drug Use Analyst
Rajdeep Gill, PharmD, Team Leader
Grace Chai, PharmD, Deputy Director
Division of Epidemiology II
Office of Pharmacovigilance and Epidemiology (OPE)
Office of Surveillance and Epidemiology (OSE)**

Subject: **DEPI II Review of 36th Month Assessment of the Risk Evaluation and Mitigation Strategy for the Extended Release and Long-Acting Opioid Analgesics: Evaluation of Drug Utilization Data (Assessment Elements 6, 7, and 8)**

EXECUTIVE SUMMARY

The Division of Risk Management (DRISK) consulted the Division of Epidemiology II (DEPI II), requesting a review of the Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program **Thirty-Six Month** FDA Assessment Report submitted by the REMS Program Companies, or “RPC”. DEPI II was requested to review Assessment 6 (Evaluation of Drug Utilization Patterns) but also comment on the methodology for Assessment 7 (Evaluation of Changes in Prescribing Behaviors) and 8 (Monitoring Patterns of Prescribing to Identify Changes in Access to ER/LA Opioid Analgesics). DEPI II was tasked to assess whether the drug utilization databases (IMS Health National Prescription Audit™ (NPA) and IMS Health, LifeLink patient-level longitudinal prescription (LRx) were appropriately utilized by the RPC and whether the conclusions drawn are appropriate, keeping in mind the REMS goal.

The goal of the REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. The RPC reported a significant decrease in ER/LA opioid analgesic

prescriptions dispensed and patients treated from pre-implementation to active period. However, in this large study population, small changes in study metrics can be statistically significant, but may not be clinically relevant. We (FDA) also note that the decreasing trend in the total number of ER/LA opioid analgesic prescriptions dispensed appears to have begun before the implementation of the REMS. The prescription data also show only certain ER/LA opioid analgesics decreased in utilization; the decrease in total ER/LA opioid analgesic prescriptions appears to be largely due to a decrease in prescriptions dispensed for oxycodone ER. Of note, prescriptions dispensed for morphine ER increased during the same time period. In addition, there was a decrease in the IR opioid market during the examined time, although utilization of oxycodone IR increased.

Overall, additional data sources are needed to ascertain the impact of the ER/LA REMS on patient access to ER/LA opioid therapy, as typical utilization data sources alone are insufficient. Longitudinal studies that track changes in prescribing behavior before and after REMS-compliant training by prescribers who have undergone ER/LA REMS training vs. prescribers who have not, as well as an assessment of the impact on utilization trends at the patient level should also be considered for future submissions. Secondly, information on appropriateness of use of drug products cannot be ascertained by typical drug utilization data. The RPC would need to address this by designing studies that utilize appropriate data resources.

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1 INTRODUCTION

The Division of Risk Management (DRISK) consulted the Division of Epidemiology II (DEPI II), requesting a review of the Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report submitted jointly by the applicant holders. DEPI II was requested to review Assessment 6 but also comment on the methodology for Assessments 7 and 8.

The Assessment Elements are as follows:

Assessment Element 6: Evaluation of drug utilization patterns (IMS data)

Assessment Element 7: Evaluation of changes in prescribing behavior-Evaluation of changes in prescribing behavior of prescribers, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills.

Assessment Element 8: Monitoring patterns of prescribing to identify changes in access to ER/LA opioid analgesics.

1.1 BACKGROUND

In April 2011, the U.S. Food and Drug Administration (FDA) determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) for all extended-release (ER) and long-acting (LA) opioids was necessary to support national efforts to address the prescription drug abuse epidemic and to ensure that the benefits continue to outweigh the risks associated with use of these products.

In the interest of public health and to minimize the burden on the healthcare delivery system from having multiple unique REMS programs, pharmaceutical companies subject to this REMS (the REMS Program Companies, or “RPC”) joined together to implement this REMS for all ER/LA opioid drug products. The RPC supports this REMS as part of a national effort to address the epidemic of prescription drug abuse in the United States. The RPC has been actively involved in providing input to FDA as it developed the class-wide ER/LA Opioid Analgesics REMS. The ER/LA Opioid Analgesics REMS provides a structure for all of the companies of the RPC to efficiently implement risk evaluation and mitigation activities across all ER/LA opioid analgesics in a uniform manner. The REMS was approved by FDA on July 9th, 2012 (<http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm>).

REMS assessments have been submitted to the FDA at six months, twelve months and twenty-four months since REMS approval. The RPC submitted this thirty-six month assessment report as the fourth report since approval of the ER/LA Opioid Analgesics REMS on July 9, 2012.

2 REVIEW METHODS AND MATERIALS

The focus of this review will be evaluation of the drug utilization patterns provided in Assessment 6 but DEPI will also comment on the methodology portion for changes in prescribing behaviors in Assessment 7 and changes in access in Assessment 8 of the results presented in the following **Thirty-Six Month** Assessment Report submitted by the RPC:

- REMS Program Companies. (2015). Assessment Report: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Thirty-Six Month FDA Assessment Report. Assessment Report Date: July 7, 2015, for NDA 019813:SDN 795 / eCTD 0131

Please note that FDA reviewer’s comments are provided in italicized font following summaries of the ER/LA opioids REMS assessment report provided by RPC.

In addition, independent FDA drug utilization analyses were also conducted analyzing prescription trends for ER/LA opioids and selected IR opioids using proprietary drug utilization databases available to the Agency. A study period of 2010 through 2015 was analyzed to explore utilization patterns of selected opioids dispensed from the outpatient retail setting. (See Attachment A for FDA drug utilization analyses)

The previous DEPI review of the proposed drug utilization study provided guidance for the current review:

- Gill, Rajdeep. (2014). Review for a drug utilization study: “REMS Opioid Utilization Analysis Custom Methodology”. FDA/CDER/OSE. Uploaded in AIMS under RCM# 2014-638 dated April 28, 2014

3 ANALYSIS OF ASSESSMENT ELEMENTS 6, 7, AND 8

3.1 REMS Assessment Objectives:

The RPC is responsible for the implementation of the FDA-approved plan to assess / evaluate effects of the ER/LA Opioid Analgesics REMS.

- Assessment Element 6: Evaluation of drug utilization patterns
- Assessment Element 7: Evaluation of changes in prescribing behavior
- Assessment Element 8: Evaluation of changes in access to ER/LA opioid analgesics

3.1.1 Assessment Element 6: Drug Utilization Patterns

The specific objectives of the drug utilization study for the pre-implementation through the active period of the REMS are defined in Assessment 6 by the RPC report as follows:

- 1) National trends in number of prescriptions dispensed for the selected products below by patient characteristics (age group, gender, pay type) and prescriber specialty. Products included:
 - ER/LA opioids included in the class REMS, by class and molecule
 - Comparator products/classes
 - Immediate release (IR) opioids analgesics not covered by the class REMS for ER/LA opioids
 - Fentanyl
 - Fentanyl citrate
 - Hydrocodone-acetaminophen
 - Hydrocodone-ibuprofen
 - Hydromorphone
 - Morphine sulfate
 - Oxycodone

- Oxymorphone
 - Tapentadol
- Celecoxib
- Benzodiazepines
 - Alprazolam
 - Chlordiazepoxide
 - Clorazepate dipotassium
 - Diazepam
 - Halazepam
 - Lorazepam
 - Oxazepam

- 2) To show switches (absolute and rates of switching) from ER/LA opioids to comparator analgesic (IR opioids and celecoxib) with introduction of the REMS

3.1.2 Assessment Element 7: Changes in Prescribing Behavior

The specific objectives of the study to evaluate changes in prescribing behavior of prescribers for the pre-implementation through the active period of the REMS in Assessment 7 are:

- 1) To assess changes over time in the proportion of opioid-non-tolerant patients prescribed products indicated for use in opioid-tolerant patients only (i.e. fentanyl transdermal patches, extended-release hydromorphone and extended release morphine >90mg) or higher dosage strengths of opioid products labeled to only be used in opioid-tolerant patients
- 2) Describe changes in the proportion of patients with ER/LA opioid early refill prescriptions and compare over time
- 3) Describe changes in the proportion of patients with concomitant use of benzodiazepines with ER/LA opioids and compare this proportion over time

3.1.3 Assessment Element 8: Changes in Access

The specific objectives of the study to evaluate changes in access for the pre-implementation through the active period of the REMS in Assessment 8 are:

Changes in prescribing will be compared among prescribers from specialties whose prescribing is hypothesized to be relatively unaffected by the REMS (such as oncologists and hospice providers) versus those for whom the REMS could have greater impact on prescribing (e.g., dentists, ER medicine). Changes in monthly prescription volume and average monthly prescription volume will be evaluated by prescriber specialty.

3.2 Review of ER/LA REMS Assessment Methods

3.2.1 Data Source

The Assessments conducted by the RPC were based on two IMS Health databases:

IMS Health, National Prescription Audit™ (NPA™)

IMS Health, LifeLink™ patient-level longitudinal (LRx)

The assessments were based on data from a national level prescription database to capture prescription activity as well as a patient level longitudinal database to capture patient activity in a sample of patients from IMS Health. Prescription activity is tracked from the volume of pharmaceutical prescriptions dispensed through outpatient retail pharmacies. The prescription data is a national level estimate of the drug activity from retail pharmacies. Patient activity is from a sample of retail and mail-order pharmacies. Prescriber information is also recorded for each transaction. Eligibility criteria are applied to control for complete patient history. Eligibility criteria include a requirement of the pharmacies being used by each patient to consistently supply data to the database for the entire study window as well as a requirement of each patient to have activity in the database prior to the study period.

Please note that FDA reviewer's comments are provided in italicized font following summary of the ER/LA opioids REMS assessment report provided by RPC.

Reviewer Comments:

The prescription and patient level databases appear to be sufficient to assess the U.S. outpatient retail drug utilization patterns. These data sources capture utilization in the primary setting where ER/LA opioid analgesic products are dispensed. Independent FDA sales analyses for the ER/LA opioid analgesic products by number of bottles/packages (i.e. eaches) sold from manufacturers to all U.S. channels of distribution showed that approximately 79% were distributed to outpatient retail pharmacies during July 2010 through December 2014.⁴⁶ The outpatient retail pharmacy settings are well represented in IMS Health, National Prescription Audit™ (NPA™) database, but utilization in the long-term care, clinic, or inpatient settings are not captured.

However, two major limitations must be noted. First, in the absence of specific prescriber training information, cross-sectional drug utilization data alone are insufficient to assess the impact of the ER/LA REMS program. Longitudinal studies that track changes in prescribing behavior before and after REMS-compliant training by prescribers who have undergone ER/LA REMS training vs. prescribers who have not, as well as an assessment of the impact on utilization trends by the respective patient populations should be considered for future submissions. Secondly, information on appropriateness of use of drug products cannot be ascertained by typical drug utilization data. The RPC would need to address this by designing studies that utilize appropriate data resources.

⁴⁶ IMS Health, IMS National Sales Perspectives™, July 2010-December 2014. Extracted February 2016. Source: NSP 2015-1545 ER/LA REMS molecules by Superchannels, 2-18-2016.

3.2.2 Assessment Element 6: Drug Utilization Patterns – Study Design

A retrospective cohort study that utilized a repeated cross-sectional design was used to estimate the number of prescriptions of (or number of unique individuals prescribed) a specific drug or group of drugs in each specified time period: a 24-month pre-implementation period, a 12-month implementation period, and an 18-month active period.

The analyses included and reported on patient activity before and after REMS implementation, spanning a 54-month period, July 2010 through December 2014.

Selection Periods:

- Pre-Implementation: July 2010 – June 2012
- Implementation: July 2012 – June 2013
- Active Period: July 2013 – December 2014

For this study, results were aggregated monthly. Another analysis measured the average number of prescriptions per quarter in the Pre-Implementation, Implementation, and Active Periods.

Changes in prescriptions for ER/LA opioids included in the class REMS were assessed relative to changes in comparator drug groups.

Prescription and patient counts were projected to the national level based on the LRx prescription sample with projection factors derived from the prescriptions in LRx relative to NPA.

Inclusion Criteria

Patients filling a prescription for a product of interest during the specified time period were included. Patients receiving study products (ER/LA opioids included in the class REMS) were all reported at the individual generic product level. Patients receiving comparator products were grouped into three product groups and reported at the product group level.

i. Definition of study and comparator products

- REMS ER/LA Opioid Analgesics
 - Extended-release, oral-dosage forms containing:
 - Hydrocodone bitartrate (approved in February 2014), Hydromorphone , Morphine sulfate, Morphine-naltrexone, Oxycodone (reformulated August 2010), Oxymorphone , Tapentadol
 - Fentanyl and buprenorphine-containing transdermal delivery systems
 - Methadone tablets and solutions that are indicated for use as analgesics
- Comparator Products
 - “IR Opioids” and other opioid analgesics, not covered by the class REMS for ER/LA opioids
 - Prescription Nonsteroidal Anti-Inflammatory Drug (NSAID), celecoxib, as an “analgesic control” group.
 - Benzodiazepines

ii. Patient Cohort

For each reporting month, patients who filled at least one Rx of the drug of interest were selected for the analysis. Patients were indexed on their first prescription by product in the reporting month.

All patients met the following eligibility requirements to be included in the cohort:

- Constant Store Panel: IMS requires that the pharmacies used by each patient consistently supply data to the LRx database for the entire study window
- Patient Start Date: IMS also requires that each patient had activity in the LRx database (for any drug of interest) prior to the study period.

These eligibility criteria are necessary to control for complete patient history in the LRx database. The use of the “constant store panel” and “patient start date” are standard practices for ensuring continuous eligibility in custom LRx projects.

Reviewer Comments:

In a previous communication, FDA requested RPC to provide rationale/clarification on the absence of including combination oxycodone/acetaminophen as one of the comparators. FDA drug utilization analyses show that including oxycodone/acetaminophen impacts the total volume of the selected IR group as a comparator, although the general trend over time appears similar.

In a communication from the RPC in May 2014 the RPC stated the following changes to the protocol: “The RPC will add combination oxycodone/acetaminophen, oxycodone/aspirin, and oxycodone/ibuprofen to this comparator group. As the analysis for the 24-month Assessment Report is currently underway, these products will first be included in the ‘other opioids’ group in the 36-month Assessment Report.” To date, oxycodone/acetaminophen has not been included in the comparator group at this 36-month submission. We believe that including oxycodone/acetaminophen to the IR opioid group will likely change the drug utilization results for all comparisons to IR opioids.

3.2.3 Assessment Element 7: Changes in Prescribing Behaviors – Study Design

A retrospective cohort study utilized a repeated cross-sectional design to estimate the number of prescriptions of (or number of unique individuals prescribed) a specific drug or group of drugs in each specified time period: a 24-month pre-implementation period, a 12-month implementation period, and an 18-month active period.

The investigators defined outcome measures that are both proxy measures of inattentive or problematic prescribing practices by prescribers of ER/LA opioids and are feasible to measure in the available data systems. Three such prescribing outcome measures are:

- Whether products that are indicated for use only in opioid-tolerant patients (i.e., fentanyl transdermal patches and extended-release hydromorphone

tablets and morphine extended release [90 mg unit strength or greater] tablets) are prescribed to non-opioid tolerant/opioid-naïve patients

- Whether products whose labels indicate that higher dosage strengths should only be used in opioid-tolerant patients are prescribed with a high starting dose in non-opioid tolerant/opioid-naïve patients
- Whether the proportion of patients prescribed ER/LA opioids who receive an early refill for an opioid prescription changes, and
- Whether the proportion of patients with concomitant use of benzodiazepine and ER/LA opioids changes

The analyses included and reported on patient activity before and after REMS implementation, spanning a 54-month period, July 2010 through December 2014.

Selection Periods:

- Pre-Implementation: July 2010 – June 2012
- Implementation: July 2012 – June 2013
- Active Period: July 2013 – December 2014

The Active Period from July 2013 to June 2014 (12-month Active Period) was utilized only for the analysis of early refill. Since a 6 month look-forward was required to determine an early refill, data are reported only up to June 2014.

For these analyses, results were aggregated and reported at the monthly level. For the tolerance analysis, patient counts were projected to the national level based on the LRx prescription sample with projection factors derived from the prescriptions in LRx relative to NPA.

Inclusion Criteria

All patients filling a prescription for a product of interest during the specified time period were included. Patients receiving ER/LA opioids included in the class REMS were reported either at the product level or individual generic strength level.

i. Definition of study and comparator products

- REMS ER/LA Opioid Analgesics, indicated for use in opioid-tolerant patients, reported at the product level:
 - Fentanyl TD
 - ER Hydromorphone
 - ER Morphine $\geq 90\text{mg}$
 - ER Morphine $< 90\text{mg}$ (as a comparator group)
- REMS ER/LA Opioid Analgesics, at the product strength level, for products and strengths with a high starting dosage strength for opioid-tolerant patients, reported at the product-strength level:
 - Buprenorphine: 10 mcg/hr, 15 mcg/hr, 20 mcg/hr

- Fentanyl: 12 mcg/hr, 25mcg/hr, 50 mcg/hr, 75mcg/hr, 100 mcg/hr
- Hydromorphone : 8 mg, 12 mg, 16 mg, 32 mg
- Morphine Sulfate: 100 mg, 100 mg/12hr, 100 mg/24hr, 130 mg/24hr,
- 150 mg/24hr, 200 mg, 200 mg/24hr
- Morphine sulfate capsules: 90 mg/24hr, 120 mg/24hr
- Oxycodone : 15 mg, 20 mg /12 hr, 30 mg, 40 mg, 40 mg /12 hr,
- 60 mg, 80 mg, 80 mg /12 hr, 160 mg /12 hr
- Oxymorphone : 7.5 mg, 7.5 mg /12 hr, 10 mg, 10 mg /12 hr, 15 mg,
- 15 mg /12 hr, 20 mg, 20 mg /12 hr, 30 mg, 30 mg /12 hr, 40 mg,
- 40 mg /12 hr
- Tapentadol : 100 mg /12 hr, 150 mg /12 hr, 200 mg /12 hr,
- 250 mg/12 hr
- REMS ER/LA Opioid Analgesics, reported at the product level:
 - Extended-release, oral-dosage forms containing: Hydromorphone, Morphine sulfate, Morphine-naltrexone, Oxycodone, Oxymorphone, Tapentadol
 - Fentanyl and buprenorphine-containing transdermal delivery systems
 - Methadone tablets and solutions that are indicated for use as analgesics

ii. Patient Cohort

For each reporting month, patients who filled at least one Rx in the market of interested were selected for the analysis. Patients were indexed on their first prescription by product in the reporting month.

All patients who met the following eligibility requirements were included in the cohort:

- Constant Store Panel: IMS requires that the pharmacies used by each patient consistently supply data to the LRx database for the entire study window
- Patient Start Date: IMS also requires that each patient had activity in the LRx database (for any market) prior to the study period.

These eligibility criteria maximize the available patient history in the LRx database.

iii. Opioid-Tolerant/Non-Opioid Tolerant Definition

To be defined as opioid tolerant, prior to an index prescription for one of the drugs listed below, a patient a patient must have at least one opioid episode that:

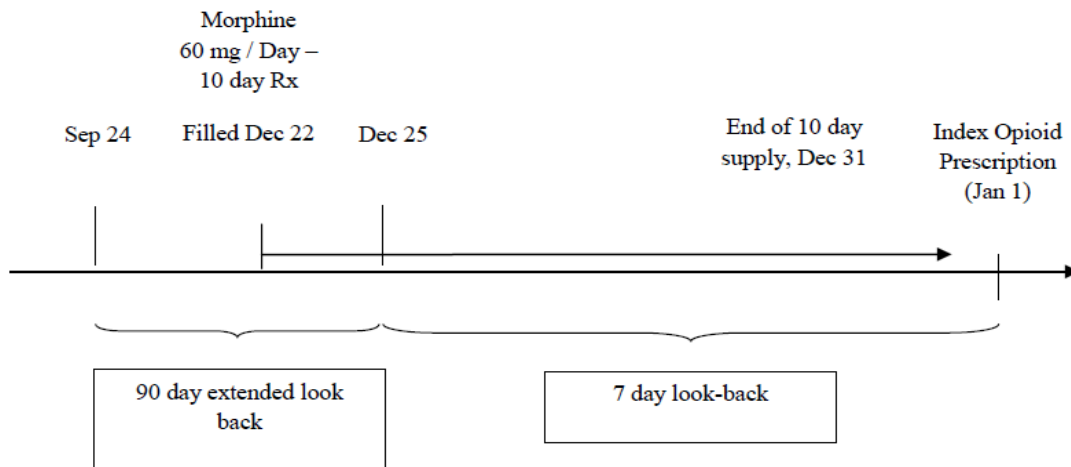
- is 7 consecutive days or longer
- has a daily dose equivalent to 60 mg oral morphine or greater, and
- includes the prior 7 consecutive days of an index opioid prescription.

Index prescriptions are defined as a fill for one of the following drugs of interest, identified as only being indicated for use with opioid tolerant patients:

- Fentanyl transdermal patches (Duragesic®)
- Hydromorphone extended release tablets (Exalgo®)

- Morphine extended release (90 mg unit strength or greater, tablets or capsules)
 - Avinza[®] 90 mg and 120 mg capsules
 - Kadian[®] 100 mg, 130 mg, 150 mg, and 200 mg capsules
 - MS Contin[®] 100 mg and 200 mg tablets

Individuals who received a prescription for oral morphine extended-release of less than 90 mg daily dose were used as the comparator. Note that morphine was selected because since it is a commonly prescribed ER/LA opioid in the U.S. The figure below shows the timeframe for calculation of opioid tolerance prior to the index opioid prescription:



Episode identification

- A 90-day extended look back period was added prior to the 7 days base look-back period. This was used to ensure capture of patients filling prescriptions that have days supply overlapping into the 7 day period.
- A patient's first prescription of interest in the prior 97 days was the start of an episode; subsequent prescriptions were categorized as part of the same episode if it was filled within the days supply of the prior prescription.
- The 90-day extended look back period was used to extend the length of an episode of continuous opioid use, if the prior prescriptions were also filled within the same episode of each other.

Morphine equivalent daily dose calculation:

Summation, for all drugs prescribed to a patient during the period of interest, of:

$$\frac{\text{Units dispensed} \times \text{Strength per unit} \times \text{Conversion factor}}{\text{Days supply}}$$

The Quantity Dispensed and Days Supply was obtained from the prescription claim. To calculate the daily dose of IR products prior to the index ER/LA opioid prescription, it was

assumed that the product was taken by the patient at the maximum prescribed dose on a daily basis, according to the days supply and quantity dispensed provided on the prescription claim.

Reviewer Comments:

FDA agrees with the study objectives; but the methodology and the data source selected are not designed to adequately address these objectives.

An over-estimation can occur for patients considered as “opioid-tolerant” due to the RPC’s selection of 97-day extended look-back period to determine opioid-tolerance. In the publication by Willy et al.⁴⁷, a 30-day or 60-day look back period was utilized versus an extended 97-day extended look-back period in the assessment of opioid tolerance because the longer time period may overestimate opioid tolerance. For example, a patient receiving an initial ER/LA prescription in April would be categorized as an “opioid-tolerant” patient if they received a 7-day supply of hydrocodone/acetaminophen prescribed as needed (PRN) within the previous 97-day period in January of the same year.

An under-estimation can occur for patients considered as “opioid-tolerant” for patients who receive prescriptions outside the IMS LRx database pharmacy sample, or if patients received prescriptions in settings of care not captured in the database (i.e. inpatient hospital settings, long-term care, or rehabilitation facilities etc.). Although the RPC states that eligibility criteria were applied to maximize the available patient history in the LRx database, the nature of the LRx database means it is unknown whether or not the patient’s complete medication history is captured. These restrictions will help maximize that, but without access to the patient’s complete medical history, one cannot assume that all medications are captured. A more appropriate database would be one which has the ability to look across multiple settings at the unique patient level so that opioid tolerance can be properly identified.

Furthermore, relying solely on electronic healthcare claims data or prescription data may over-estimate the number of patients classified as “opioid-tolerant”. For example, after a dental procedure a patient is often prescribed an opioid to be taken as needed for pain. Even though the patient has received the full quantity of the prescription, it does not mean the patient consumed/ingested the total amount of the opioid prescribed. However, according to the electronic prescription data, the patient may be incorrectly categorized as opioid-tolerant.

Analysis of Early Refill

Patients considered naïve or new to therapy if they did not fill any ERLA opioid prescriptions in the prior 3 months were indexed on their first fill in the reporting month. Each patient was followed at 6 month intervals to calculate the days between fills for the

⁴⁷Willy, M. E., Graham, D. J., Racoosin, J. A., Gill, R., Kropp, G. F., Young, J., Yang, J., Choi, J., MaCurdy, T. E., Worrall, C. and Kelman, J. A. (2014), Candidate Metrics for Evaluating the Impact of Prescriber Education on the Safe Use of Extended-Release/Long-Acting (ER/LA) Opioid Analgesics. *Pain Medicine*, 15: 1558–1568. doi: 10.1111/pme.12459

index product refill for up to 6 refills. Early refill was defined as two consecutive prescriptions for the same individual and the same drug with the number of days between prescriptions $\geq 15\%$ lower than the number of days of supply in the first prescription. A 6 month look-forward is required for this objective, data was reported only up to June 2014. Note that these data were not projected.

Reviewer Comment:

FDA agrees that early refill or early refill attempts by patients for consecutive ER/LA opioid prescriptions prescribed by the same prescriber may be a surrogate metric for abuse behavior, however, this measure has not been validated to our knowledge. But the proposed study methodology is inadequate to address the question posed by the ER/LA opioid REMS. Longitudinal studies that track changes in prescribing behavior at the unique prescriber level before and after REMS-compliant training should be considered for future submissions.

In addition, further exploration to quantify by reasons for early refill (i.e. number of refills due to lost/stolen medications, vacation override, changes in dosage, etc.) may be beneficial. Data on rejected or reversed prescriptions of prescription attempts that are not ultimately dispensed may also be informative for future submissions.

3.2.4 Assessment Element 8: Changes in Access - Study Design

The RPC conducted a retrospective cohort study that utilized a repeated cross-sectional design to estimate the number of prescriptions of a specific drug or group of drugs in each specified time period: a 24-month pre-implementation period, a 12-month implementation period, and an 18-month active period.

The RPC assessed changes in prescribing compared with healthcare providers from specialties hypothesized to be relatively unaffected by the REMS (e.g. oncologists, hospice providers) versus those for whom the REMS could have greater impact on prescribing (e.g. dentists, emergency medicine physicians). The analyses reported on patient activity spanning a 54-month period from July 2010 through December 2014. The results were aggregated and reported at monthly levels. Changes in prescriptions for ER/LA opioids included in the class REMS were assessed relative to changes in comparator drug groups. Prescription counts were projected to the national level based on the LRx prescription sample with projection factors derived from the prescriptions in LRx relative to NPA.

Inclusion Criteria

Patients filling a prescription for a product of interest during the specified time period were included. Patients receiving ER/LA opioids included in the class REMS were reported at the individual generic product level. Patients receiving comparator products were reported in three product group levels.

i. Definition of study and comparator products

- REMS ER/LA Opioid Analgesics, reported at the strength level:
 - Extended-release, oral-dosage forms containing: Hydrocodone bitartrate (approved in February 2014), Hydromorphone, Morphine sulfate, Morphine-naltrexone, Oxycodone, Oxymorphone, Tapentadol
 - Fentanyl and buprenorphine-containing transdermal delivery systems
 - Methadone tablets and solutions that are indicated for use as analgesics
- Comparator Products
 - “IR Opioids” and other opioid analgesics, not covered by the class REMS for ER/LA opioids;
 - Prescription Nonsteroidal Anti-Inflammatory Drug (NSAID), celecoxib, as an “analgesic control” group.
 - Benzodiazepines

ii. Patient Cohort

For each reporting month, patients who filled at least one Rx in the market of interest were selected for the analysis. Patients were indexed on their first prescription by product in the reporting month. All patients who met the following eligibility requirements were included in the cohort:

- Constant Store Panel: IMS required that the pharmacies used by each patient consistently supply data to the LRx database for the entire study window
- Patient Start Date: IMS also required that each patient had activity in the LRx database (for any market) prior to the study period.

Reviewer Comment:

In terms of the impact of the REMS on patient access, it is challenging to characterize the impact on patient access using the dispensed prescription data alone. The databases capture the prescription activity for patients who were ultimately able to access opioid medications. It is not known how these data are informative about patients who were unable to access opioid medication. In addition, these data do not show if patients encountered challenges or barriers to access.

Similar to the reviewer comment in Assessment 6, it is unclear how the products included in the comparator groups were defined. In previous communications with the RPC, FDA requested RPC to provide rationale/ clarification on the absence of the comparator combination oxycodone/acetaminophen.

3.3 Results

3.3.1 Assessment 6: Drug Utilization Patterns

The following results and graphs below were reported by the RPC in the 36-month assessment report:

The evaluation of drug utilization patterns via IMS data revealed that the total ER/LA opioid class had a significant decrease in prescriptions dispensed from pre-implementation (5.58 million prescriptions dispensed) to active period (5.34 million prescriptions dispensed) [Refer to RPC Table 71 below]. While overall prescription volumes decreased, morphine sulfate, oxycodone, fentanyl, and methadone retained the largest prescription share of all the ER/LA opioids evaluated during the study period.

As shown in RPC Table 71 below, the RPC also reported that when the ER/LA opioids were individually assessed, morphine sulfate, buprenorphine and hydromorphone showed a significant increase in prescription volume across study periods. In contrast, significant decreases were observed for oxymorphone, oxycodone, and methadone across study periods. Hydromorphone had the largest percent increase in volume across periods (pre-implementation to active period: 105.2% increase, $p < 0.001$), while the largest decrease was for oxycodone (20.4% decrease, $p = 0.004$). However, it is important to note that hydromorphone was launched in April 2010, before the implementation of the REMS and therefore, the time of launch may have impacted the results.

For the comparator products, the RPC reported an increase in prescription volume was observed for benzodiazepines only during the study period (pre-implementation to active period: 1.5% increase, $p = 0.020$). Celecoxib had a significant decrease in prescription volume from pre-implementation to active period (7.9% decrease, $p < 0.001$). The IR opioid group showed a significant decrease between pre-implementation and active period (7.6% decrease, $p = 0.033$).

Table 71: COMPARISON OF THE AVERAGE 3-MONTH PRESCRIPTION ACROSS PRE-IMPLEMENTATION, IMPLEMENTATION, AND ACTIVE PERIOD, SUMMARY TABLE

PRODUCTS	PRESCRIPTION VOLUME				PRE-IMPLEMENTATION VS ACTIVE PERIOD		
	PRE-IMPLEMENTATION		ACTIVE PERIOD		STATISTICAL COMPARISON	PERCENT CHANGE WITHIN PRODUCT TYPE	
	MEAN	95% CI	MEAN	95% CI		P-VALUE (T-TEST)	% CHANGE
ER/LA Opioids							
Buprenorphine	78,367	(47,843-108,892)	145,678	(127,527-163,828)	0.001	85.9%	(43.2%, 170%)
Fentanyl	1,244,228	(1,234,981-1,253,476)	1,226,565	(1,206,745-1,246,385)	0.048	-1.4%	(-3.2%, 0.4%)
Hydromorphone HCL	24,635	(15,718-33,552)	50,562	(43,058-58,066)	0.000	105.2%	(32.7%, 262%)
Methadone HCL	975,347	(957,239-993,454)	828,257	(792,964-863,550)	0.000	-15.1%	(-18.1%, -12.1%)
Morphine Sulfate	1,468,948	(1,412,895-1,525,001)	1,559,691	(1,533,508-1,585,874)	0.001	8.5%	(4.1%, 13.2%)
Morphine-Naltrexone	15,569	(-2,487-33,625)	0	(-01-01)	0.081	-100.0%	NA
Oxycodone HCL	1,506,501	(1,333,765-1,679,237)	1,199,722	(1,176,733-1,222,711)	0.004	-20.4%	(-28.4%, -10.2%)
Oxymorphone HCL	264,340	(229,249-299,432)	226,577	(222,088-231,065)	0.039	-14.3%	(-24.1%, -1.3%)
Tapentadol	34,981	(-1,830-71,792)	65,527	(63,594-67,460)	0.077	87.3%	(-43.9%, 2149.8%)
Total ER/LA Opioids	5,575,834	(5,492,547-5,659,120)	5,336,053	(5,261,224-5,410,881)	0.000	-4.3%	(-6.1%, -2.4%)
Comparators							
IR Opioids	37,339,058	(36,775,169-37,902,947)	34,519,228	(32,011,268-37,027,188)	0.033	-7.6%	(-14.5%, -0.5%)
Celecoxib	2,004,906	(1,940,976-2,068,836)	1,846,409	(1,784,750-1,908,068)	0.001	-7.9%	(-11.6%, -4.1%)
Benzodiazepines	20,922,561	(20,746,496-21,098,626)	21,226,458	(21,006,901-21,446,014)	0.020	1.5%	(-0.1%, 3%)

RPC reported that differences were observed in the absolute prescription volume and trends among patient groups during the period before and after implementation of the

REMS. When stratified by age, the 41 to 64 year age group had the highest prescription volume for the total ER/LA opioids. A significant decrease in the average quarterly prescription volume was observed for the 19 to 40 year age group and the 41 to 64 year age group across study periods. The largest percent decrease was observed for the 19 to 40 year olds, with a decrease of 20.7% from pre-implementation to active period ($p < 0.001$). A significant increase was observed for patients over the age of 64 years with an 8.8% increase from pre-implementation to active period ($p < 0.001$). Average quarterly prescription volume did not significantly change for the 0 to 18 year age group. There was a significant decrease in the average quarterly prescription volume for both men and women across study periods (pre-implementation to active period: 5.7% decrease, $p < 0.001$, and 3.2% decrease, $p = 0.001$, respectively). A decrease in average quarterly prescription volume was observed across nearly all payer types, with Medicaid having the highest percent decrease from pre-implementation to active period (38.8% decrease, $p < 0.001$). Medicare Part D was the only payer type to have an increase in prescription volume for the total REMS product from pre-implementation to active period (19.9% increase, $p < 0.001$).

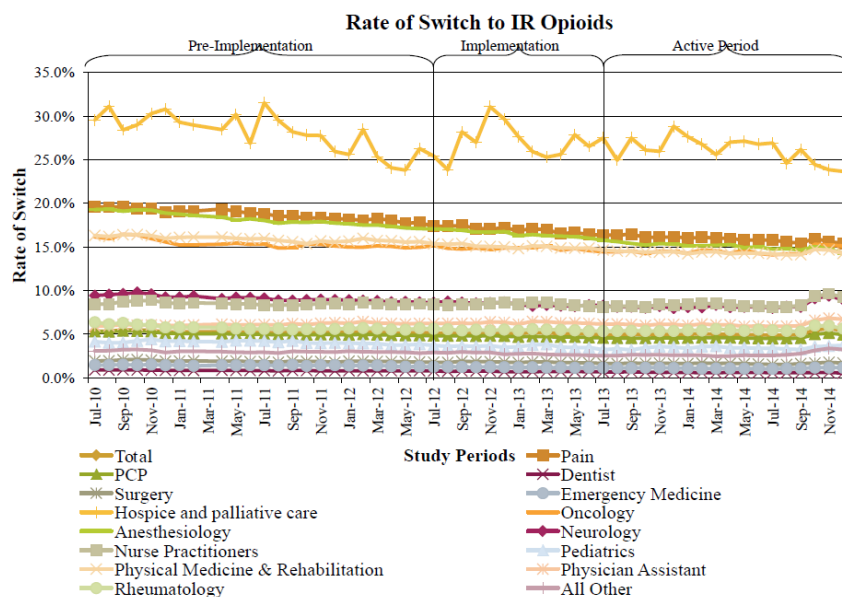
Change in the average quarterly prescription volume before and after implementation of the REMS was assessed by prescriber specialty. For ER/LA opioids, primary care providers (PCPs), pain specialists, anesthesiologists, physical medicine & rehabilitation specialists, nurse practitioners and physician assistants had the largest prescription volume. Total ER/LA opioids exhibited a decrease in average quarterly prescription volume for most of the specialties from pre-implementation to active period. The exceptions were the pain specialty (no change), hospice and palliative medicine and physical medicine & rehabilitation and all other specialties (significant decreases from pre-implementation to active period), anesthesiologists (significant increase from pre-implementation to active period), and nurse practitioners and physician assistants who saw significant increases across study periods. The largest significant decreases in average prescription volume per quarter were observed for dentists (pre-implementation to active period: 48.5% decrease, $p < 0.001$) and emergency medicine (25.5% decrease, $p < 0.001$). The largest increases were observed for nurse practitioners (pre-implementation to active period: 33.7% increase, $p < 0.001$) and physician assistants (31.2% increase, $p < 0.001$). Across the largest part of the prescribing specialties, hydromorphone or buprenorphine had the largest increase in prescription volume, while oxycodone had the largest decrease in volume.

Finally, the RPC reported that switching from REMS products to the non-REMS opioid group or celecoxib was assessed overall and by prescriber specialty. For the overall change in average monthly switching from REMS products across study periods, the monthly percentage of patients switching from REMS products to IR opioids significantly decreased from pre-implementation to active period (4.1% decrease, $p = 0.001$). A 5.0% increase was observed in the percentage of patients switching to celecoxib from pre-implementation to active period ($p < 0.001$). The proportion of patients who switched from REMS products to the IR opioids was highest for the anesthesiology, pain, and hospice and palliative medicine specialties, where approximately 19.3%, 19.6%, and 31.5% of patients switched to IR opioids, respectively. The switch rate from REMS products to celecoxib was also highest for these same three specialties, with switch rates of approximately 21.7%, 23.2% and 55.6%. The monthly switch rate from REMS products to celecoxib notably fluctuated for

hospice and palliative care ranging from 5.0% to 55.6%. From pre-implementation to active period, the largest decreases in the proportion of patients who switched from REMS products to IR opioids were observed for two specialties with less compelling reasons to prescribe ER/LA opioids: dentists (from 0.84% to 0.62%; 26.3% decrease, $p < 0.001$) and emergency medicine specialists (from 1.43% to 1.11%; 22.3% decrease, $p < 0.001$), as well as anesthesiologists (from 18.2% to 15.1%; 17.1% decrease, $p < 0.001$). From pre-implementation to active period, proportion of patients who switched from REMS products to celecoxib generally increased or remained stable. The largest increases were observed for: pediatricians (from 3.66% to 4.07%; 11.3% increase, $p < 0.001$) and rheumatologists (from 3.69% to 3.91%; 5.9% increase, $p < 0.001$).

Figure 6.2a provided by RPC:

Figure 6.2a. Monthly rate of switch from ER/LA to IR opioids overall and by prescriber specialty (all specialties)



Reviewer Comment:

Cross-Sectional Prescription Data

The RPC reported that the total ER/LA opioid class had a significant decrease in both prescriptions dispensed and patients from the pre-implementation to active period.

FDA analyses were also conducted using proprietary drug utilization databases similar to those used by the RPC. (See Attachment A) The analyses show that although the total number of prescriptions dispensed for ER/LA opioids decreased; only approximately 8% fewer prescriptions were dispensed for ER/LA opioid prescriptions in 2015 compared to 2010. In addition, the decreasing trend in the number of ER/LA prescriptions dispensed appears to have begun before the implementation of the REMS.

The meaning of the “statistically significant” decrease noted by the RPC is unclear. In large study populations, precise measurements can lead to small changes that are statistically significant but may not be clinically relevant. Moreover, FDA drug

utilization analyses through 2015 revealed that although the overall utilization of ER/LA opioid analgesics as a class has decreased, not all the individual molecules comprising the ER/LA group continue to show a decreasing trend in prescriptions. The decrease in total ER/LA opioid prescriptions appears to be largely due to decreases in prescriptions dispensed for oxycodone ER and methadone; whereas morphine ER utilization increased from years 2010 to 2015 (See Figure 1 in Attachment A). Of note, the reformulation of oxycodone ER took effect in August 2010, along with many other changes in the opioid market.

The RPC also reported an increase in the utilization of benzodiazepines and a decrease in celecoxib prescriptions. FDA's drug utilization analyses also found a decrease in celecoxib utilization; however, benzodiazepine (alprazolam, chlordiazepoxide, clorazepate, diazepam, halazepam, lorazepam, oxazepam) utilization remained steady from 2011 to 2015⁴⁸.

As reported by the RPC, the comparator IR opioid group showed a significant decrease in prescription volume between pre-implementation and active period. FDA drug utilization analyses revealed that the overall decrease in IR opioid analgesics was driven by the large market share of hydrocodone/acetaminophen products. Of note, the decreasing trend in the number of IR prescriptions during the active period occurred around the time that hydrocodone combination analgesic products were re-scheduled from schedule III of the Controlled Substances Act to the more restrictive schedule II⁴⁹. However, upon stratification of IR molecules, we did observe an increase in oxycodone IR prescriptions over time. Prescriptions for morphine IR, oxymorphone IR and hydromorphone IR increased over time as well (See Figure 2 in Attachment A).

Reviewer Comments:

Switch analyses

There was also an initial concern that the implementation of the ER/LA opioid REMS program would cause prescribers to switch from prescribing ER/LA opioids to prescribing IR opioid products in the market instead. Although this may have occurred, it cannot be clearly identified based on high level trends in dispensed prescription data. Longitudinal patient-level analysis would be necessary to demonstrate switching.

The RPC conducted additional analyses of data at the prescriber level (Figure 6.2a from the REMS assessment below). Although the RPC concludes that the changes in switch rates for majority of the prescriber specialties appear to stay the same or decrease very slightly, FDA found the data inconclusive because data on the reasons for switching from ER/LA opioids to any of the comparators (i.e. REMS too burdensome, prescriber

⁴⁸ IMS Health, National Prescription Audit. Data Extracted March 2016.

⁴⁹ Jones, C, Lurie, P, Throckmorton, D. Effect of US Drug Enforcement Administration's Rescheduling of Hydrocodone Combination Analgesic Products on Opioid Analgesic Prescribing. Journal of American Medical Association (JAMA) Internal Medicine. March 2016; 176(3):399-402. Accessed on 2/22/2016 at <http://archinte.jamanetwork.com/>

not REMS trained, clinical reason (i.e. ER/LA opioid analgesic not needed), other programs at the state, healthcare system, or payer level changing prescribing practice) were not provided.

Limitations of the drug utilization data:

As stated above, two overall limitations must be noted for these analyses. First, in the absence of specific prescriber training information, national trends in drug utilization data alone are insufficient to assess the impact of the ER/LA REMS program.

Longitudinal studies that track changes in prescribing behavior before and after REMS-compliant training should be considered for future submissions. Secondly, information on appropriateness of use of drug products cannot be ascertained by drug utilization data. The RPC would need to address this by designing studies that utilize appropriate data resources.

3.3.2 Assessment Element 7: Changes in Prescribing Behaviors

The following result and graphs below were reported by the RPC in the 36-month assessment report:

The RPC reports that the results of the evaluation of changes in prescribing behaviors showed that the proportion of non-tolerant patients being prescribed ER/LA opioids intended for opioid-tolerant patients changed significantly only for ER hydromorphone. Specifically, the proportion of non-tolerant patients dispensed ER hydromorphone decreased 8.8% from pre-implementation to the active period ($p < 0.001$).

Changes described in terms of proportion of non-tolerant patients prescribed *high starting dose* ER/LA opioid products differed, depending on products and strengths. For several strengths, the average proportion of non-tolerant patients prescribed high starting dose fentanyl, oxycodone, oxymorphone, and tapentadol decreased significantly from the pre-implementation to active period. Conversely, for several strengths, there was an increase in the average proportion of non-tolerant patients prescribed high starting dose buprenorphine during the study periods whereas the proportion of non-tolerant patients prescribed hydromorphone and morphine sulfate remained the same throughout the study periods.

Table 76 provided by RPC:

Table 76: COMPARISON OF THE AVERAGE MONTHLY PROPORTION OF OPIOID NON-TOLERANT PATIENTS PRESCRIBED PRODUCTS INDICATED FOR OPIOID-TOLERANT PATIENTS ONLY ACROSS PRE-IMPLEMENTATION, IMPLEMENTATION, AND ACTIVE PERIOD

ER/LA OPIOID	PATIENT VOLUME				PERCENT CHANGE WITHIN PRODUCT TYPE	
	PRE-IMPLEMENTATION		ACTIVE PERIOD		PRE-IMPLEMENTATION VS IMPLEMENTATION	PRE-IMPLEMENTATION VS ACTIVE
	MEAN	95% CI	MEAN	95% CI	% CHANGE	% CHANGE
Fentanyl TD						
Total patient volume	312,579	(309,896-315,262)	322,013	(318,086-325,940)	0.136	312,579
% Non-tolerant	50.3%	(49.40%-51.27%)	49.5%	(48.29%-50.62%)	-1.2%	-1.7%
ER Hydromorphone						
Total patient volume	6,522	(5,332-7,713)	13,500	(12,585-14,415)	0.943	6,522
% Non-tolerant	48.9%	(48.18%-49.65%)	44.6%	(43.23%-45.97%)	-3.9%	-8.8%
ER Morphine ≥90mg						
Total patient volume	53,368	(52,870-53,866)	45,696	(44,510-46,883)	0.000	53,368
% Non-tolerant	30.3%	(28.97%-31.55%)	29.4%	(27.87%-30.91%)	-2.2%	-2.9%
ER Morphine <90mg						
Total patient volume	355,537	(346,954-364,120)	412,384	(405,676-419,091)	0.000	355,537
% Non-tolerant	52.1%	(51.04%-53.13%)	51.3%	(50.07%-52.55%)	-1.4%	-1.5%

Reviewer Comment:

As shown in RPC Table 76 above, the RPC reported that there were significant decreases in hydromorphone ER use in non-tolerant patients as well as the use of high starting doses of fentanyl, oxycodone ER, oxymorphone ER, and tapentadol in non-

tolerant patients. However, there is no discernable pattern to these results, making them difficult to interpret.

The RPC also utilized the prescription data to evaluate changes in prescriber behavior. While inappropriate prescribing of formulations reserved for opioid-tolerant patients to non-tolerant patients increased during this period, early refills showed a downward trend for most products included in the REMS. Different patterns in change were seen in terms of early refill rates and proportion of patients with early refills. The rate of early refill decreased during the study periods for all ER/LA opioids except morphine-naltrexone which decreased slightly during the first 6 months of pre-implementation, and increased thereafter. The proportion of patients with early refills increased over time for most ER/LA opioids. There was a slight increase in the proportion of patients with early refills for fentanyl, buprenorphine, methadone, oxycodone, and tapentadol, while a slight decrease was observed for hydromorphone, oxycodone and morphine sulfate. For oxycodone, tapentadol and hydromorphone, a trend towards a decrease in the proportion of patients with early refills was observed early during pre-implementation, followed by an increase in the proportion until the end of the active period. In terms of early refill prescription volume, a significant decrease from pre-implementation was observed for almost all products (with the exception of buprenorphine and hydromorphone, for which a significant increase was observed, and for morphine-naltrexone [statistical comparisons could not be conducted]). It is crucial to note that since refill data was not projected to national estimates, changes observed during the study period may have been impacted, at least in part, by sample fluctuations

Reviewer Comments:

It appears that the majority of ER/LA opioid analgesics demonstrated either a decrease or no significant change in the early refill rate over the REMS time periods with the exception of buprenorphine which was reported as a significant increase. However, it is unclear whether these results show that the ER/LA opioid REMS was effective and made an impact because the changes in early refill rate for many drugs appear to begin during the pre-REMS period.

In addition, changes in early refill rates during pre-implementation versus the active period appear reflective of changes in the overall utilization trends.

Longitudinal studies that track changes in prescribing behavior at the unique prescriber level before and after REMS-compliant training should be considered for future submissions. In addition, further exploration to quantify the reason for early refill (i.e. lost/stolen medications, vacation override, changes in dosage, etc.) may be beneficial. Data on rejected or reversed prescriptions of prescription attempts that are not ultimately dispensed may also be informative for future submissions.

Finally, changes across periods among the patients who concomitantly used benzodiazepine in combination with ER/LA opioids were assessed. Results revealed a decrease in the proportion of patients with concomitant use of benzodiazepine and all

ER/LA opioids, except morphine- naltrexone, from the pre-implementation to the active period.

Reviewer Comments:

Of note, a recent publication shows that, overall, concomitant prescribing of opioids with benzodiazepines increased from 2002-2014, although among chronic opioid users, concomitant prescribing of benzodiazepines appear to decrease slightly starting around 2011⁵⁰.

Although benzodiazepines were agreed-upon comparators, the changes in utilization levels make it difficult to interpret and understand the results of concomitancy analyses with respect to the REMS. It is also not clear how this specific metric relates to the REMS goals. For future submissions, the RPC should consider

- *providing more detail on how these changes measure progress in achieving the goals of the REMS*
- *including additional comparators to provide a relatively constant baseline for estimating changes*

3.3.3 Assessment Element 8: Changes in Access

The following result and graphs below were reported by the RPC in the 36-month assessment report:

Irrespective of the prescriber specialty, the RPC reported the prescription volume for the majority of the REMS products either had no significant change or had significant decreases from pre-implementation to the end of the active period. Few REMS products had an increase in their prescription volume. Oxymorphone, morphine sulfate capsules, oxycodone, and methadone generally had a decrease in prescription volume from pre-implementation to active period. Conversely, the prescription volumes for hydromorphone and morphine sulfate showed increases over the study period. When evaluated by prescriber specialty, the average monthly prescription volume for the majority of the individual ER/LA opioids prescribed by hospice and palliative care specialists, and many of the ER/LA opioids prescribed by pediatricians remained stable over the duration of the study period. Across study periods, average monthly prescription volume of total ER/LA opioids remained stable for pain specialists and physical medicine & rehabilitation specialists. The prescription volume for some specialty categories decreased significantly over the study period. Dentists had the largest percent decrease in the average monthly prescription volume for total ER/LA opioids, with a 35.6% ($p < 0.001$) decrease between pre-implementation and implementation, and a 48.5% ($p < 0.001$) decrease between pre-implementation and active period. A significant increase across periods was observed for nurse practitioners and physician assistants, with an increase of 33.7% and 31.2% from pre-implementation to active period, respectively (both $p < 0.001$). A significant increase (2.8%,

⁵⁰ Hwang CS, et al. *Trends in the Concomitant Prescribing of Opioids and Benzodiazepines, 2002-2014*. AJPM. In press 2016

p = 0.013) was observed for anesthesiologists from pre-implementation to active period only.

Reviewer Comments:

As noted above, trends in prescriptions dispensed alone are inadequate to address the question of the impact of the REMS on patient access. The RPC analyzed dispensed prescription trends by prescriber specialty to see if there were differences in the volume of prescribing of ER/LA opioids by prescriber specialty. However, increases or decreases in prescriptions dispensed are inadequate to inform on the impact to patient access.

In addition, the databases only capture the prescription activity for patients who were ultimately able to access opioid medications. It is not known how these data are informative about the patients who were unable to access opioid medication. Moreover, these data do not show if patients who ultimately received prescriptions encountered challenges to obtain access.

The RPC highlights that Dentists had the largest percent decrease in the average monthly prescriptions volume for total ER/LA opioids although the number of prescriptions prescribed by Dentists in the context of all ER/LA prescriptions dispensed only represented a very small proportion (<1%) compared to all the other specialties. ER/LA opioids prescriptions written by nurse practitioners and physician assistants increased during the examined time, this may be due to various changes in regulations regarding prescribing rights that occurred during the examined time. Of note in recent years, various state regulations have authorized mid-level practitioners (i.e., nurse practitioners, nurse midwives, nurse anesthetists, and physician assistants) to dispense controlled substances in the course of professional practice in the state in which they practice.⁵¹

For comparator products, the RPC reported that there was a general decrease or no change in average monthly prescription volume from pre-implementation to active period for the majority of the prescriber specialties. However, the average quarterly prescription volume for the comparator products significantly increased across study periods for both nurse practitioners and physician assistants. A significant increase in prescribing of IR opioids was also observed for pain, anesthesiology and physical medicine & rehabilitation specialties, while a significant increase in prescribing of celecoxib was also observed for pain and anesthesiology specialties, and a significant increase in prescribing of benzodiazepines was observed for pediatricians.

Overall, of the more than 600 prescribers surveyed, the majority felt that the ease of access was “about right” and that the REMS does not have any impact on patient access

⁵¹ U.S. Department of Justice. Drug Enforcement Administration. Office of Diversion Control. Mid-Level Practitioners Authorization by State. (n.d.). Retrieved February 18, 2016, from <http://www.deadiversion.usdoj.gov/drugreg/practioners/>

to opioids. Similarly, the patient population surveyed reported satisfaction with their access to ER/LA opioid analgesic prescriptions, their ability to obtain medication from a pharmacy, and their general access to ER/LA opioid analgesic medication. Prescriber and patient survey results related to questions of access were similar to those seen in previous reports.

Reviewer Comments:

The metrics reported by the RPC do not relate directly to patient access. Dispensed prescription data alone are inadequate to inform on patient access. Longitudinal patient level data linked to other data sources such as patient and prescriber survey data may be needed. For example, providers may not follow up with patients to determine if patient actually went to the pharmacy to fill the prescription. As for the patient population surveyed, surveys should include patients who could NOT access ER/LA opioids. It is more important to survey patients who have trouble having access to ER/LA opioids so we can determine if the access issue is due to the REMS or other factors.

4 FDA DRUG UTILIZATION ANALYSES

FDA also conducted drug utilization analyses of ER/LA opioids and selected IR opioids using proprietary drug utilization databases available to the Agency from 2010 through 2015. (See Attachment 1 for FDA drug utilization review). FDA analyses focused on outpatient retail pharmacy settings.

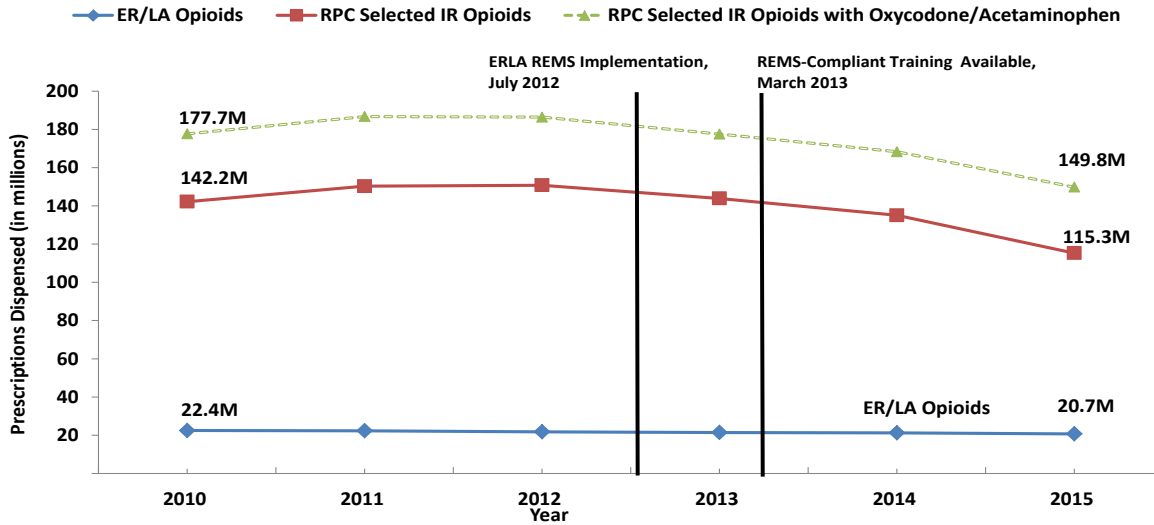
**Please note the number in the figures provided in the FDA drug utilization analyses may appear different from Figure 1 under section 2.1 titled Opioid Treatment for Pain in this document because the time period examined and the IR opioid molecules selected are not the same.*

The figure below shows the nationally estimated number of prescriptions dispensed for selected ER/LA opioids, RPC selected IR opioids in the REMS Assessment, and the selected IR opioids including oxycodone/acetaminophen in the U.S. outpatient retail pharmacy setting from 2010-2015. Prescriptions dispensed for ER/LA opioid products decreased by approximately 8%, from 22.4 million prescriptions in 2010 to 20.7 million prescriptions in 2015. However, the decreasing trend began prior to the implementation of the ER/LA REMS.

The following graph shows the RPC's selected IR opioid group (red line) compared to the IR opioid group with the addition of oxycodone/acetaminophen (green dotted line). Although the overall trend in IR opioid prescriptions dispensed over time appears similar between the two IR opioid groups (red line and green dotted line); however, including oxycodone/acetaminophen increased the IR opioid prescription volume by approximately 20%.

Figure 5.1

Nationally estimated number of prescriptions for ER/LA opioids and selected IR opioid products dispensed from U.S. outpatient retail pharmacies



Source: IMS Health, National Prescription Audit™. Extracted January 2016

*RPC Selected IR Opioids assessed as comparators in the ERLA REMS assessment: fentanyl, fentanyl citrate, hydrocodone/acetaminophen, hydrocodone-ibuprofen, hydromorphone, morphine sulfate, oxycodone, oxymorphone, tapentadol

5 DISCUSSION

The 36-month REMS assessment report includes information on all eight Assessment Elements. For the purpose of this review, comments are provided for Assessment 6 (Evaluation of Drug Utilization Patterns) to assess whether the drug utilization databases IMS Health, National Prescription Audit™ (NPA) and IMS Health, LifeLink patient-level longitudinal prescription (LRx) were appropriately utilized and whether the conclusions drawn are appropriate keeping in mind the ER/LA opioid REMS goals. In addition, brief comments were also provided on methodology for Assessment 7 (Evaluation of Changes in Prescribing Behaviors) and 8 (Monitoring Patterns of Prescribing to Identify Changes in Access to ER/LA Opioid Analgesics).

In general, we agree that the prescription and patient level databases utilized appear sufficient to assess the utilization of the ER/LA opioid products within the retail setting because approximately 79% of these drug products were distributed to the outpatient retail channels.

The RPC reported a significant decrease in ER/LA opioid prescriptions dispensed and patients treated from pre-implementation to active period. However, in large study populations such as the one analyzed, small changes in study metrics can be statistically significant but may not be clinically relevant. Moreover, FDA drug utilization analyses show that the decrease began before the implementation of the REMS. Furthermore, the decreasing trend, which appears to be primarily driven by oxycodone ER, appears to have started before the implementation of the REMS and is not reflective of the appropriateness of the use.

We also observed a decrease in the total selected IR opioids market during the examined time, which appeared to be primarily driven by a decrease in prescriptions dispensed for combination hydrocodone/acetaminophen. There was a notable *increase* in prescriptions dispensed for oxycodone IR. Longitudinal patient-level analysis would be necessary to demonstrate switching behavior in terms of shifting of utilization from ER/LA opioids to IR opioids. However, the utilization data alone are insufficient to ascertain the impact of the ER/LA REMS on patient access to ER/LA opioid therapy. Longitudinal studies that track changes in prescribing behavior before and after REMS-compliant training by prescribers who have undergone ER/LA REMS training vs. prescribers who have not trained, as well as, an assessment of the impact on utilization trends by the respective patient populations should be considered for future submissions. Without the ability to differentiate prescribing patterns by physicians who have or have not undergone ER/LA opioid REMS training, it is not possible to measure the contribution of the REMS to any observed changes in utilization of ER/LA opioids.

It is challenging to conclude whether REMS is the only or main factor affecting the utilization of various opioid analgesics. The newly developed opioids with abuse deterrent properties, such as oxycodone ER, may also have an impact on the utilization although the extent of the impact is unknown. Federal and state level regulations may also have impacted the prescribing and eventually the utilization of opioid analgesics. We do not agree with RPC's conclusion "Assessment of drug utilization data showed a significant decrease in the total ER/LA opioid prescription volume since the introduction of the REMS", as it is not clear that this decrease had clinical relevance and the decrease was not seen across all the ER/LA molecules, such as morphine ER, which increased.

6 CONCLUSION

The ER/LA REMS Assessment reported a significant decrease in ER/LA prescriptions dispensed and patients treated from pre-implementation to active period. However, this decrease appears small and may not be clinically relevant as the decrease was not seen across all ER/LA opioids. The decreasing trend was primarily seen in the utilization of oxycodone ER which appeared to have begun before the implementation of the REMS. In addition, other factors and changes have occurred in the opioid markets such as the reformulation of oxycodone ER in 2010 and the rescheduling of combination hydrocodone/acetaminophen products in 2014.

The recommendations provided below may help the RPC provide clearer and more meaningful results for the utilization study in future submissions to the Agency, however, the FDA recognizes that the opioid market is dynamic, creating a challenging atmosphere to produce conclusive data on the true impact of the ER/LA opioid REMS on prescribing and goals to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications.

7 RECOMMENDATIONS

The Reviewer recommends that RPC should provide clarification/details for future submissions:

- Longitudinal studies that track changes in prescribing behavior before and after REMS-compliant training by prescribers who have undergone ER/LA REMS training vs. prescribers who have not trained, as well as, an assessment of the impact on utilization trends by the respective patient populations should be considered for future submissions
- Include the IR comparator products (i.e., combination oxycodone/acetaminophen, oxycodone/aspirin, and oxycodone/ibuprofen) as stated in a communication to the Agency in May 2014 during the review of the 24-month assessment report. As of the 36-month submission, this change to the analyses to the comparator groups was still not completed.
- Recommend obtaining additional data sources to provide insight into the reason for switching linked to prescribing for more meaningful results (i.e., REMS too burdensome, prescribers not REMS trained, clinical reason (i.e., ER/LA not needed), etc.)
- Recommend assessment of reason for early refill (i.e., increased pain, stolen/lost Rx, vacation overrides, etc.)
- Early refills may be under estimated, additional data on rejected/reversed prescription may provide additional insight into attempts at early refills

ATTACHMENT A: FDA DRUG UTILIZATION ANALYSES

Analysis of drug utilization data for ER/LA opioids and selected IR opioids were conducted by FDA using proprietary drug utilization databases available to the Agency for years 2010-2015.

TABLE 1. Approval Dates of various opioid analgesics.⁵²

Drug Name	Approval Date
Methadone	March 14, 1973
Morphine ER	May 29, 1987 (MS Contin); July 3, 1996 (Kadian); Feb 20, 2002 (Avinza); Aug 13, 2009 (Embeda)
Fentanyl Transdermal	August 7, 1990
Oxycodone ER*	December 12, 1995
Hydromorphone ER**	September 24, 2004 (Palladone) and March 1, 2010 (Exalgo)
Oxymorphone ER***	June 22, 2006
Buprenorphine	Oral formulation approved October 2002, Transdermal formulation approved June 30, 2010,
Tapentadol ER	August 25, 2011
Hydrocodone ER (Zohydro ER)****	October 25, 2013
Hydrocodone ER (Hysingla ER with abuse deterrent properties)	November 20, 2014 (not included in this review)
<p><i>*Reformulated Oxycodone ER was approved in April 2010, marketing began in August 2010.</i> <i>**Palladone (hydromorphone ER) was discontinued in July 2005.</i> <i>***Reformulated Oxymorphone ER was approved in December 2011.</i> <i>****Zohydro ER was approved in October 2013, marketing began in February 2014</i></p>	

Methods and Material

Proprietary drug utilization databases available to the Agency were used to conduct this analysis (see Attachment B for full database descriptions).

Determining Settings Of Care

The IMS Health, IMS National Sales Perspectives™ was used to determine the retail and non-retail channels of distribution for ER/LA opioid analgesic products by number of bottles/packages (i.e. eaches) sold from manufacturers to all U.S. channels of distribution. These data showed that approximately 79% ER/LA opioid analgesic products were distributed to outpatient retail pharmacies during July 2010 through December 2014.⁵³ As a result, outpatient retail pharmacy utilization patterns were examined in this review.

⁵² <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>; accessed May, 2015

⁵³ IMS Health, IMS National Sales Perspectives™, July 2010-December 2014. Extracted February 2016. Source: NSP 2015-1545 ER/LA REMS molecules by Superchannels, 2-18-2016.

Data Sources Used

IMS Health, National Prescription Audit (NPA) was used to obtain the nationally estimated number of prescriptions dispensed for ER/LA opioids and selected IR opioids from U.S. outpatient retail pharmacies from years 2010 through 2015.

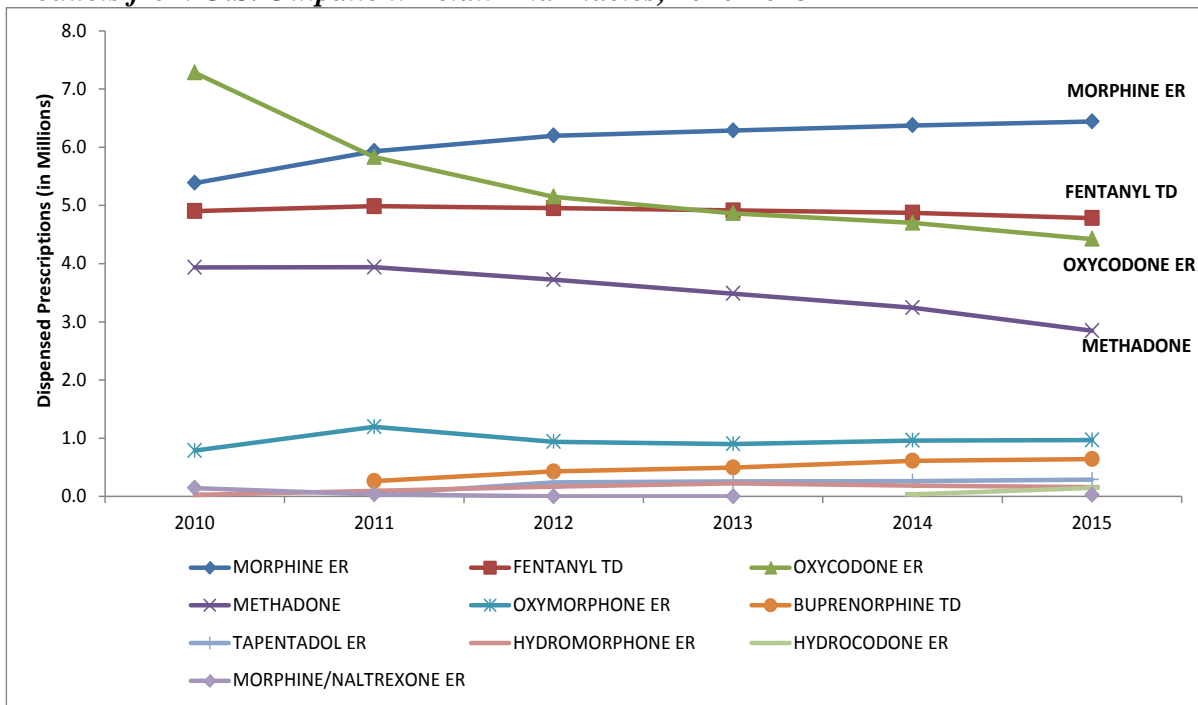
Results

ER/LA and Selected IR Opioids Prescription Data

Table 2 and Figures 1 and 2 below shows the nationally estimated number of prescriptions for ER/LA opioids and selected IR opioids dispensed from U.S. outpatient retail pharmacies from 2010 through 2015.

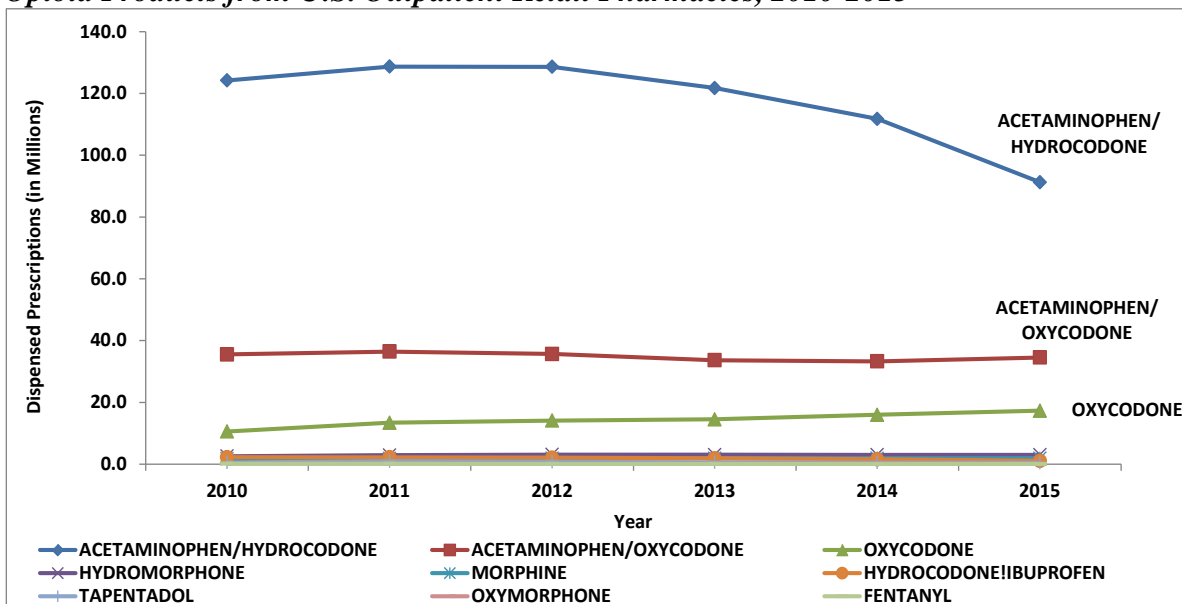
The nationally estimated number of prescriptions for ER/LA opioids dispensed from outpatient retail pharmacies decreased by approximately 8% from 22.4 million prescriptions in 2010 to 20.7 million prescriptions in 2015. Among the ER/LA opioids, prescriptions dispensed for morphine ER increased by approximately 20% from 5.4 million prescriptions in 2010 to 6.4 million prescriptions in 2015. Fentanyl transdermal prescriptions slightly decreased from approximately 4.9 million prescriptions in 2010 to 4.8 million prescriptions in 2015. Oxycodone ER prescriptions decreased by 39% from 7.3 million prescriptions in 2010 to 4.4 million prescriptions in 2015. Methadone prescriptions decreased by 28% from 3.9 million in 2010 to 2.8 million in 2015. Hydrocodone ER prescriptions accounted for less than 1% (150,000 prescriptions) of ER/LA opioid prescriptions dispensed in 2015. Of the selected IR opioid comparators (combination and single-entity), combination hydrocodone-acetaminophen products were the market leader accounting for approximately 61% of the selected IR opioids prescriptions dispensed in 2015. The number of prescriptions dispensed for hydrocodone-acetaminophen increased from 124 million in 2010 to a peak of 129 million in 2012 before decreasing to 91.3 million in 2015. Similarly, the number of prescriptions dispensed for oxycodone-acetaminophen products increased from 35.5 million in 2010 to a peak of 36.4 million in 2011 before decreasing to 34.5 million in 2015. Of note, prescriptions dispensed for oxycodone IR increased by approximately 64% from 10.6 million prescriptions in 2010 to 17.3 million prescriptions in 2015. Hydromorphone IR prescriptions increased from 2.6 million in 2010 to 3 million in 2015. Morphine IR prescriptions increased from 1.7 million in 2010 to 1.9 million in 2015.

Figure 1: Nationally Estimated Number of Dispensed Prescriptions for ER/LA Opioid Products from U.S. Outpatient Retail Pharmacies, 2010-2015



Source: IMS Health, National Prescription Audit. Data Extracted February 2016.

Figure 2: Nationally Estimated Number of Dispensed Prescriptions for Selected IR Opioid Products from U.S. Outpatient Retail Pharmacies, 2010-2015



Source: IMS Health, National Prescription Audit. Data Extracted February 2016.

Table 2: Nationally Estimated Number of Dispensed Prescriptions for ER/LA and Selected IR Opioid Products from U.S. Outpatient Retail Pharmacies, 2010-2015

	Year 2010		Year 2011		Year 2012		Year 2013		Year 2014		Year 2015	
	TRx (N)	Share%	TRx (N)	Share%	TRx (N)	Share%	TRx (N)	Share%	TRx (N)	Share%	TRx (N)	Share%
TOTAL MARKET	200,168,321	100%	209,072,874	100%	208,248,480	100%	198,997,382	100%	189,588,080	100%	170,553,987	100%
TOTAL ERLA OPIOIDS	22,462,980	11.2%	22,319,643	10.7%	21,805,919	10.5%	21,434,697	10.8%	21,246,074	11.2%	20,731,995	12.2%
MORPHINE ER	5,385,056	24.0%	5,930,492	26.6%	6,196,859	28.4%	6,286,818	29.3%	6,374,626	30.0%	6,440,147	31.1%
FENTANYL TD	4,902,993	21.8%	4,988,438	22.3%	4,952,358	22.7%	4,914,213	22.9%	4,872,801	22.9%	4,783,258	23.1%
OXYCODONE ER	7,280,394	32.4%	5,830,959	26.1%	5,147,999	23.6%	4,864,965	22.7%	4,698,658	22.1%	4,423,041	21.3%
METHADONE	3,935,176	17.5%	3,938,155	17.6%	3,724,469	17.1%	3,484,194	16.3%	3,242,006	15.3%	2,846,300	13.7%
OXYMORPHONE ER	786,768	3.5%	1,196,858	5.4%	939,799	4.3%	901,157	4.2%	960,838	4.5%	967,940	4.7%
BUPRENORPHINE TD		0.0%	266,321	1.2%	431,767	2.0%	497,655	2.3%	613,027	2.9%	643,565	3.1%
TAPENTADOL ER		0.0%	37,531	0.2%	242,044	1.1%	259,276	1.2%	264,027	1.2%	289,448	1.4%
HYDROMORPHONE ER	27,011	0.1%	95,808	0.4%	170,619	0.8%	226,418	1.1%	185,005	0.9%	160,589	0.8%
HYDROCODONE ER		0.0%		0.0%		0.0%		0.0%	35,086	0.2%	149,940	0.7%
MORPHINE/NALTREXONE ER	145,582	0.6%	35,081	0.2%	5	0.0%	1	0.0%		0.0%	27,767	0.1%
TOTAL SELECTED IR OPIOIDS	177,705,341	88.8%	186,753,231	89.3%	186,442,561	89.5%	177,562,685	89.2%	168,342,006	88.8%	149,821,992	87.8%
ACETAMINOPHEN/HYDROCODONE	124,204,496	69.9%	128,691,470	68.9%	128,635,398	69.0%	121,760,596	68.6%	111,774,295	66.4%	91,256,631	60.9%
ACETAMINOPHEN/OXYCODONE	35,528,422	20.0%	36,435,239	19.5%	35,653,999	19.1%	33,659,964	19.0%	33,295,592	19.8%	34,542,402	23.1%
OXYCODONE	10,574,085	6.0%	13,424,322	7.2%	14,104,482	7.6%	14,509,658	8.2%	15,969,435	9.5%	17,312,635	11.6%
HYDROMORPHONE	2,587,658	1.5%	2,905,247	1.6%	3,078,602	1.7%	3,038,446	1.7%	3,025,525	1.8%	3,005,279	2.0%
MORPHINE	1,683,760	1.0%	1,789,906	1.0%	1,841,579	1.0%	1,866,191	1.1%	1,889,736	1.1%	1,885,670	1.3%
HYDROCODONE/IBUPROFEN	2,245,444	1.3%	2,199,610	1.2%	2,083,288	1.1%	1,867,983	1.1%	1,597,237	1.0%	1,068,976	0.7%
TAPENTADOL	534,049	0.3%	920,642	0.5%	785,315	0.4%	598,498	0.3%	517,979	0.3%	489,012	0.3%
OXYMORPHONE	180,884	0.1%	239,521	0.1%	163,361	0.1%	186,530	0.1%	212,097	0.1%	212,744	0.1%
FENTANYL	166,543	0.1%	147,274	0.1%	96,537	0.1%	74,819	0.0%	60,110	0.0%	48,643	0.0%

Source: IMS Health, National Prescription Audit. Data Extracted February 2016.

ATTACHMENT B: Database Description and Limitations

Findings from this review should be interpreted in the context of the known limitations of the databases used. We focused our analysis on only the outpatient retail pharmacy settings where the majority of sales of opioids were distributed to; therefore, these estimates may not apply to other settings of care in which these products are used (e.g. mail-order setting, clinics, non-federal hospitals, etc.). The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS 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 non-retail 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.

IMS Health, National Prescription Audit

The 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 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 86% 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 40 - 70% (varies by class and geography) of mail service pharmacies and approximately 45-55% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

Appendix 1. Approved Risk Evaluation and Mitigation Strategy for the Extended-Release and Long-Acting (ER/LA) Opioid Analgesics

Initial REMS Approval: 07/2012
Most Recent Modification: 10/2015

**EXTENDED-RELEASE (ER) AND LONG-ACTING (LA) OPIOID
ANALGESICS RISK EVALUATION AND MITIGATION
STRATEGY (REMS)**

GOAL

The goal of this REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of extended-release or long-acting (ER/LA) opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

I. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each ER/LA opioid analgesic prescription in accordance with 21 CFR § 208.24.

The Medication Guides for ER/LA opioids are part of the ER/LA Opioid Analgesic REMS program and will be available through the ER/LA Opioid Analgesic REMS website www.ER-LA-opioidREMS.com.

B. Elements to Assure Safe Use

1. Training will be made available to healthcare providers who prescribe ER/LA opioid analgesics.
 - a. Training will be considered “REMS-compliant training” under this REMS if: 1) it, for training provided by CE providers, is offered by an accredited provider to licensed prescribers, 2) it includes all elements of the [FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics \(“FDA Blueprint”\)](#), 3) it includes a knowledge assessment of all of the sections of the FDA Blueprint, and 4) it is subject to independent audit to confirm that conditions of the REMS training have been met.
 - b. The NDA/ANDA holders of ER/LA opioid analgesic products (“NDA/ANDA holders”) will ensure that REMS-compliant training is made available to prescribers of ER/LA opioid analgesics and will achieve the following performance goals:
 - i. Not later than March 1, 2013, the first REMS-compliant training will be made available.
 - ii. Within two years from the time the first REMS-compliant training becomes available, 80,000 prescribers (based on 25% of the 320,000 active prescribers in 2011) will have been trained;
 - iii. Within three years from the time the first REMS-compliant training becomes available, 160,000 prescribers (based on 50% of the 320,000 active prescribers in 2011) will have been trained;
 - iv. Within four years from the time the first REMS-compliant training becomes available, 192,000 prescribers (based on 60%

of the 320,000 active prescribers in 2011) will have been trained.

- c. The content of the REMS-compliant training will be based on the learning objectives established by the [FDA Blueprint](#). The FDA Blueprint contains core messages to be conveyed to prescribers in the training about the risks and appropriate prescribing practices for the safe use of ER/LA opioid analgesics. The NDA/ANDA holders will direct providers of REMS-compliant training to the FDA Blueprint, via the REMS website (www.ER-LA-opioidREMS.com), and via its Request for Grant Applications. No less than annually, NDA/ANDA holders will direct providers of REMS-compliant training to consult the FDA Blueprint for possible revisions (e.g., changes to the drug specific information).
- d. NDA/ANDA holders will ensure that independent audits of the educational materials used by the providers of REMS-compliant training are conducted. The audits must:
 - i. Be conducted by an auditor independent of the NDA/ANDA holders. (Accreditation bodies of CE providers would be considered independent of the NDA/ANDA holders and would be eligible to conduct the audits.)
 - ii. Evaluate:
 - 1. whether the content of the training covers all components of the [FDA Blueprint](#) approved as part of the REMS;
 - 2. whether the knowledge assessment measures knowledge of all sections of the FDA Blueprint; and
 - 3. for training conducted by CE providers, whether the training was conducted in accordance with the standards for CE of the Accreditation Council for Continuing Medication Education[®] (ACCME[®]), or of another CE accrediting body appropriate to the prescribers' medical specialty or healthcare profession.
 - iii. Be conducted on a random sample of 1) at least 10% of the training funded by the NDA/ANDA holders, and 2) REMS-compliant training not funded by the NDA/ANDA holders but that will be counted towards meeting the performance goals in section [B.1.b](#).
- e. To facilitate prescriber awareness of the availability of the REMS and REMS-compliant training, within 30 calendar days of the approval of the REMS, the NDA/ANDA holders will make available, and then

maintain a web site that will contain information about the REMS specified below (www.ER-LA-opioidREMS.com):

- i. A current list of the REMS-compliant training that is supported by educational grants from the NDA/ANDA holders, when this information becomes available.
 - ii. A copy of the Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioid Analgesics.
 - iii. A copy of the Prescriber Letters 1, 2, and 3 (when mailed and for at least one year thereafter) (see section B.1.f).
- f. To make prescribers aware of the existence of the REMS and the prescriber training that will be made available under the REMS, the NDA/ANDA holders will electronically deliver (email or fax), or directly mail letters to all DEA-registered prescribers who are registered to prescribe Schedule II and III drugs:
 - i. [Prescriber Letter 1](#) will be sent not later than 60 days after the initial approval of this REMS, notifying prescribers of the existence of the REMS and the fact that prescriber training will be offered, and providing a copy of the [Patient Counseling Document \(PCD\)](#).
 - ii. [Prescriber Letter 2](#) will be sent not later than 30 days before the first prescriber REMS-compliant training required by the REMS is offered by providers and will notify prescribers of the imminent upcoming availability of accredited REMS CE courses.
 - iii. The prescribers will be identified via the DEA Registration Database.
 - iv. At least annually from the date of initial approval of the REMS, the DEA Registration Database will be reviewed and [Prescriber Letter 3](#) will be sent to all newly DEA-registered prescribers who are registered to prescribe Schedule II and III drugs to inform them of the existence of the REMS, provide them the [Patient Counseling Document \(PCD\)](#), and notify them of the availability of the REMS-compliant training and how to find REMS-compliant courses.
- g. To further ensure that prescribers are aware of the existence of the ER/LA Opioid Analgesic REMS and the prescriber training that will be made available under the REMS, the NDA/ANDA holders will electronically deliver (email or fax), or directly mail the following two letters to the professional organizations and state licensing entities listed in section [B.1.g.iii](#) with a request that the information be disseminated to their members:

- i. [Professional Organization/Licensing Board Letter 1](#) will be sent not later than 60 days after the approval of this REMS, notifying prescribers of the existence of the REMS and the fact that prescriber training will be offered, and providing a copy of the [Patient Counseling Document \(PCD\) on Extended-Release/Long-Acting Opioids](#).
- ii. [Professional Organization/Licensing Board Letter 2](#) will be sent not later than 30 days before the first prescriber REMS-compliant training required by the REMS is offered by providers and will notify prescribers of the imminent upcoming availability of accredited REMS CE courses.
- iii. The letter and enclosures referenced above, will be sent to the following entities:
 - a) State Licensing Boards of:
 - 1) Medicine (allopathic and osteopathic)
 - 2) Nursing
 - 3) Dentistry
 - b) Associations of State Licensing Boards:
 - 1) Federation of State Medical Boards
 - 2) National Council of State Boards of Nursing
 - 3) American Association of Dental Boards
 - c) Learned Societies and Professional Associations, including, but not limited to:
 - 1) American Academy of Addiction Psychiatry
 - 2) American Academy of Family Physicians
 - 3) American Academy of Hospice and Palliative Medicine
 - 4) American Academy of Neurology
 - 5) American Academy of Nurse Practitioners
 - 6) American Academy of Nursing
 - 7) American Academy of Orofacial Pain
 - 8) American Academy of Pain Management
 - 9) American Academy of Pain Medicine
 - 10) American Academy of Physical Medicine and Rehabilitation
 - 11) American Academy of Physician Assistants

- 12) American Association of Colleges of Osteopathic Medicine
- 13) American Association of Colleges of Nursing
- 14) American Association of Poison Control Centers
- 15) American Board of Medical Specialties
- 16) American Board of Orofacial Pain
- 17) American College of Nurse Practitioners
- 18) American College of Osteopathic Family Physicians
- 19) American College of Physicians
- 20) American College of Rheumatology
- 21) American Dental Association
- 22) American Dental Education Association
- 23) American Medical Association
- 24) American Medical Directors Association
- 25) American Nurses Association
- 26) American Nurses Credentialing Center
- 27) American Osteopathic Association
- 28) American Osteopathic Association of Addiction Medicine
- 29) American Pain Society
- 30) American Society of Addiction Medicine
- 31) American Society for Pain Management Nursing
- 32) American Society of Anesthesiologists
- 33) American Society of Pain Educators
- 34) Association of American Medical Colleges
- 35) Council of Medical Specialty Societies
- 36) Hospice and Palliative Nurses Association
- 37) National Association of Managed Care Physicians
- 38) National Association of State Controlled Substances Authorities
- 39) National Commission on Certification of Physician Assistants
- 40) National Hospice and Palliative Care Organization
- 41) American College of Emergency Physicians

42) Society of Emergency Medicine Physician Assistants

- h. NDA/ANDA holders will ensure that an interim single toll-free number call center is implemented no later than July 23, 2012, and a fully operational centralized call center is implemented no later than 90 calendar days after the approval of the REMS.

The following materials are part of the ER/LA Opioid Analgesic REMS and are appended:

- [Patient Counseling Document \(PCD\) on Extended-Release/Long-Acting Opioid Analgesics](#)
- [FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics](#)
- [Prescriber Letter 1](#)
- [Prescriber Letter 2](#)
- [Prescriber Letter 3](#)
- [Professional Organization/Licensing Board Letter 1](#)
- [Professional Organization/Licensing Board Letter 2](#)
- [ER/LA Opioid Analgesic REMS website \(www.ER-LA-opioidREMS.com\)](#)

II. Implementation System

The ER/LA Opioid Analgesic REMS can be approved without the Elements to Assure Safe Use specifically described under FDCA 505-1(f)(3) (B), (C), and (D) of the Act; therefore an implementation system is not required.

III. Timetable for Submission of Assessments

REMS assessments will be submitted to the FDA at 6 months and 12 months after the initial approval date of the REMS (July 9, 2012), and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. The NDA holders will submit each assessment so that it will be received by the FDA on or before the due date based on the initial approval date of the REMS.

Appendix 2. FDA Blueprint

Introduction for the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics

In April 2011, FDA announced the elements of a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of extended-release and long-acting (ER/LA) opioid analgesics outweigh the risks. The REMS supports national efforts to address the prescription drug abuse epidemic.

As part of the REMS, all ER/LA opioid analgesic companies must provide:

- Education for prescribers of these medications, which will be provided through accredited continuing education (CE) activities supported by independent educational grants from ER/LA opioid analgesic companies.
- Information that prescribers can use when counseling patients about the risks and benefits of ER/LA opioid analgesic use.

FDA developed core messages to be communicated to prescribers in the Blueprint for Prescriber Education (FDA Blueprint), published the draft FDA Blueprint for public comment, and considered the public comments when finalizing the FDA Blueprint. This final FDA Blueprint contains the core educational messages. It is approved as part of the ER/LA Opioid Analgesic REMS and will remain posted on the FDA website for use by CE providers to develop the actual CE activity. A list of all REMS-compliant CE activities that are supported by independent educational grants from the ER/LA opioid analgesic companies to accredited CE providers will be posted at www.ER-LA-opioidREMS.com as that information becomes available.

The CE activities provided under the FDA Blueprint will focus on the safe prescribing of ER/LA opioid analgesics and consist of a core content of about three hours. The content is directed to prescribers of ER/LA opioid analgesics, but also may be relevant for other healthcare professionals (e.g., pharmacists). The course work is not intended to be exhaustive nor a substitute for a more comprehensive pain management course.

Accrediting bodies and CE providers will ensure that the CE activities developed under this REMS will be in compliance with the standards for CE of the Accreditation Council for Continuing Medical Education (ACCME)^{1,2} or another CE accrediting body as appropriate to the prescribers' medical specialty or healthcare profession.

For additional information from FDA, including more detailed Questions and Answers about the REMS for ER/LA Opioid Analgesics, see <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm>.

¹Accreditation Council for Continuing Medical Education. 2015. [Accreditation Requirements. Criteria for CME Providers-Accreditation Criteria](#). Accessed on May 29, 2015.

²Accreditation Council for Continuing Medical Education. 2015. [Accreditation Requirements. Criteria for CME Providers-Standards for Commercial Support](#). Accessed on May 29, 2015.

FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics

Why Prescriber Education is Important

Health care professionals who prescribe extended-release (ER) and long-acting (LA) opioid analgesics (hereafter referred to as ER/LA opioid analgesics) are in a key position to balance the benefits of prescribing ER/LA opioid analgesics to treat pain against the risks of serious adverse outcomes including addiction, unintentional overdose, and death. Opioid misuse and abuse, resulting in injury and death, has emerged as a major public health problem.

- Based on the 2010 National Survey on Drug Use and Health, public health experts estimate more than 35 million Americans age 12 and older used an opioid analgesic for non-medical use some time in their life—an increase from about 30 million in 2002.³
- In 2009, there were nearly 343,000 emergency department visits involving nonmedical use of opioid analgesics.⁴
- In 2008, nearly 36,500 Americans died from drug poisonings, and of these, nearly 14,800 deaths involved opioid analgesics.⁵
- Improper use of any opioid can result in serious side effects including overdose and death, and this risk can be greater with ER/LA opioid analgesics.

Appropriate prescribing practices and patient education are important steps to help address this public health problem. Health care professionals who prescribe ER/LA opioid analgesics have a responsibility to help ensure the safe and effective use of these drug products. ER/LA opioid analgesics should be prescribed only by health care professionals who are knowledgeable in the use of potent opioids for the management of pain.

The expected results of the prescriber education in this REMS are that the prescribers will:

- a. Understand how to assess patients for treatment with ER/LA opioid analgesics.
- b. Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
- c. Be knowledgeable about how to manage ongoing therapy with ER/LA opioid analgesics.
- d. Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
- e. Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

I. Assessing Patients for Treatment with ER/LA Opioid Analgesic Therapy

- a. Prescribers should consider risks involved with ER/LA opioid analgesics and balance these against potential benefits. Risks include:
 - i. Overdose with ER/LA formulations, as most dosage units contain more opioid than immediate-release formulations.

³Substance Abuse and Mental Health Services Administration. 2011. *Results from the 2010 National Survey on Drug Use and Health: Detailed Table*, Table 7.1.a. Rockville, MD. <http://www.samhsa.gov/data/NSDUH/2k10NSDUH/tabs/Sect7peTabs1to45.htm#Tab7.1A>. Accessed on May 29, 2015.

⁴Substance Abuse and Mental Health Services Administration. 2011. *Drug Abuse Warning Network, 2009: National Estimates of Drug-Related Emergency Department Visits*, Table 19. Rockville, MD. <http://www.samhsa.gov/data/2k11/DAWN/2k9DAWNED/HTML/DAWN2k9ED.htm#Tab19>. Accessed on May 29, 2015.

⁵Warner M, Chen LH, Makuc DM, Anderson RN, and Miniño AM. 2011. Drug Poisoning Deaths in the United States, 1980–2008, in U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, *NCHS Data Brief, No 81*. December 2011. Hyattsville, MD. <http://www.cdc.gov/nchs/data/databriefs/db81.pdf>. Accessed on May 29, 2015.

- ii. Life-threatening respiratory depression
- iii. Abuse by patient or household contacts.
- iv. Misuse and addiction.
- v. Physical dependence and tolerance.
- vi. Interactions with other medications and substances (See [table in Section VI](#) for product-specific information).
- vii. Risk of neonatal opioid withdrawal syndrome with prolonged use during pregnancy.
- viii. Inadvertent exposure/ingestion by household contacts, especially children.
- b. Prescribers should assess each patient's risk of abuse, including substance use and psychiatric history. Prescribers should:
 - i. Obtain a complete history and conduct a complete physical examination. The history should include assessment for a family history of substance abuse and psychiatric disorders, as well as special considerations regarding dose and adverse effects in geriatric patients, pregnant women, and children.
 - A history of substance abuse does not prohibit treatment with ER/LA opioid analgesics but may require additional monitoring and expert consultation.
 - ii. Be knowledgeable about risk factors for opioid abuse.
 - iii. Understand and appropriately use screening tools for addiction or abuse to help assess potential risks associated with chronic opioid therapy and to help manage patients using ER/LA opioid analgesics (e.g., structured interview tools).
 - iv. Adequately document all patient interactions and treatment plans.
- c. Prescribers should understand when to appropriately refer high risk patients to pain management specialists.
- d. Prescribers should understand opioid tolerance criteria as defined in the product labeling.
 - Prescribers should know which products and which doses are indicated for use only in opioid-tolerant patients. (See [table in Section VI](#) for product-specific information).

II. Initiating Therapy, Modifying Dosing, and Discontinuing Use of ER/LA Opioid Analgesics

- a. Prescribers should have awareness of federal and state regulations on opioid prescribing.
- b. Prescribers should be aware that:
 - i. Dose selection is critical, particularly when initiating therapy in opioid non-tolerant patients.
 - ii. Some ER/LA opioid analgesics are only appropriate for opioid-tolerant patients. (See [table in Section VI](#) for product-specific information)
 - iii. Dosage should be individualized in every case.
 - iv. Titration should be based on efficacy and tolerability. (See individual product labeling)
- c. Prescribers should be knowledgeable about when and how to supplement pain management with immediate-release analgesics, opioids and non-opioids.
- d. Prescribers should be knowledgeable about converting patients from immediate-release to ER/LA opioid products and from one ER/LA opioid product to another ER/LA opioid product.
- e. Prescribers should understand the concept of incomplete cross-tolerance when converting patients from one opioid to another.
- f. Prescribers should understand the concepts and limitations of equianalgesic dosing and follow patients closely during all periods of dose adjustments.
- g. Prescribers should understand the warning signs and symptoms of significant respiratory depression from opioids and monitor patients closely, especially at the time of treatment initiation and dose increases.
- h. Prescribers should understand that tapering the opioid dose is necessary to safely discontinue treatment with ER/LA opioid analgesics when therapy is no longer needed.

III. Managing Therapy with ER/LA Opioid Analgesics

- a. Prescribers should establish analgesic and functional goals for therapy and periodically evaluate pain control, functional outcomes, side-effect frequency and intensity, and health-related quality of life.
- b. Prescribers should be aware of the existence of Patient Prescriber Agreements (PPAs).
 - i. PPAs are documents signed by both prescriber and patient at the time an opioid is prescribed.
 - ii. PPAs can help ensure patients and caregivers understand the goals of treatment, the risks, and how to use the medications safely.
 - iii. PPAs can include commitments to return for follow-up visits, to comply with appropriate monitoring (such as random drug testing), and to safeguard the medication.
- c. Prescribers should monitor patient adherence to the treatment plan, especially with regard to misuse and abuse by:
 - i. Recognizing, documenting, and addressing aberrant drug-related behavior.
 - ii. Utilizing state Prescription Drug Monitoring Programs, where practical, to identify behaviors that may represent abuse.
 - iii. Understanding the utility and interpretation of drug testing (e.g., screening and confirmatory tests), and using it as indicated.
 - iv. Screening and referring for substance abuse treatment as indicated.
 - v. Performing medication reconciliation as indicated.
- d. Prescribers should understand how to anticipate and manage adverse events associated with ER/LA opioid analgesics.
- e. Prescribers should be aware that there are no adequate and well-controlled studies of ER/LA opioid analgesics in pregnant women. ER/LA opioid analgesics should be used during pregnancy only if the potential benefit justifies the risk to the fetus.
- f. Prescribers should be aware of the pregnancy status of their patients. If opioid use is required for a prolonged period in a pregnant woman, prescribers should advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
- g. Prescribers treating patients with ER/LA opioid analgesics should periodically assess benefits and side effects of these drugs, and the continued need for opioid analgesics.
- h. Prescribers should understand the need for reevaluation of patient's underlying medical condition if the clinical presentation changes over time.
- i. Prescribers should be familiar with referral sources for the treatment of abuse or addiction that may arise from the use of ER/LA opioid analgesics.

IV. Counseling Patients and Caregivers about the Safe Use of ER/LA Opioid Analgesics

- a. Prescribers should use the Patient Counseling Document as part of the discussion when prescribing opioid analgesics.
- b. Prescribers should explain product-specific information about the prescribed ER/LA opioid analgesic.
- c. Prescribers should explain how to take the ER/LA opioid analgesic as prescribed.
- d. Prescribers should explain the importance of adherence to dosing regimen, how to handle missed doses, and to contact their prescriber should pain not be controlled.
- e. Prescribers should inform patients and caregivers to read the specific ER/LA opioid analgesic Medication Guide they receive from the pharmacy.
- f. Prescribers should warn patients and caregivers that under no circumstances should an oral

ER/LA opioid analgesic be broken, chewed or crushed. In addition, and patches and buccal films should not be cut, torn, or damaged prior to use. Manipulating the ER/LA opioid analgesic described above may lead to rapid release of the ER/LA opioid analgesic causing

overdose and death. When a patient cannot swallow a capsule whole, prescribers should refer to the product labeling to determine if it is appropriate to sprinkle the contents of a capsule on applesauce or administer via a feeding tube.

- g. Prescribers should caution patients and caregivers that the use of other CNS depressants such as sedative-hypnotics and anxiolytics, alcohol, or illegal drugs with ER/LA opioid analgesics can cause overdose and death. Patients and caregivers should be instructed to only use other CNS depressants, including other opioids, under the instruction of their prescriber.
- h. Prescribers should instruct patients and caregivers to tell all of their doctors about all medications the patient is taking.
- i. Prescribers should warn patients and caregivers not to abruptly discontinue or reduce the ER/LA opioid analgesic and discuss how to safely taper the dose when discontinuing.
- j. Prescribers should caution patients and caregivers that ER/LA opioid analgesics can cause serious side effects that can lead to death, even when used as recommended. Prescribers should counsel patients and caregivers on the risk factors, signs, and symptoms of overdose and opioid-induced respiratory depression, gastrointestinal obstruction, and allergic reactions.
- k. Prescribers should counsel patients and caregivers on the most common side effects of ER/LA opioid analgesics, and about the risk of falls, working with heavy machinery, and driving.
- l. Patients or caregivers should call their prescriber for information about managing side effects.
- m. Prescribers should explain to patients and caregivers that sharing ER/LA opioid analgesics with others may cause them to have serious side effects including death, and that selling or giving away ER/LA opioid analgesics is against the law.
- n. Prescribers should counsel patients and caregivers to store ER/LA opioid analgesics in a safe and secure place away from children, family members, household visitors, and pets.
- o. Prescribers should warn patients and caregivers that ER/LA opioid analgesics must be protected from theft.
- p. Prescribers should counsel patients and caregivers to dispose of any ER/LA opioid analgesics when no longer needed by flushing them down the toilet.
- q. Prescribers should counsel patients and caregivers to inform them about side effects.
- r. Adverse events should be reported to the FDA at 1-800-FDA-1088 or via <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf>.

V. General Drug Information for ER/LA Opioid Analgesic Products

Prescribers should be knowledgeable about general characteristics, toxicities, and drug interactions for ER/LA opioid analgesic products. For example,

- a. ER/LA opioid analgesic products are scheduled under the Controlled Substances Act and can be misused and abused.
- b. Respiratory depression is the most important serious adverse effect of opioids as it can be immediately life-threatening.
- c. Constipation is the most common long-term side effect and should be anticipated.
- d. Drug-drug interaction profiles vary among the products. Knowledge of particular opioid-drug interactions, and the underlying pharmacokinetic and pharmacodynamic mechanisms,

allows for the safer administration of opioid analgesics.

- i. Central nervous system depressants (alcohol, sedatives, hypnotics, tranquilizers, tricyclic antidepressants) can have a potentiating effect on the sedation and respiratory depression caused by opioids.

- ii. Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol. Some drug levels may increase without dose dumping when exposed to alcohol. See individual product labeling.
 - iii. Using opioids with monoamine oxidase inhibitors (MAOIs) may result in possible increase in respiratory depression. Using certain opioids with MAOIs may cause serotonin syndrome.
 - iv. Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone (ADH).
 - v. Some opioids (methadone, buprenorphine) can prolong the QTc interval.
 - vi. Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids.
 - vii. See [table in Section VI](#) for product-specific information.
- e. Tolerance to sedating and respiratory-depressant effects of opioids is critical to the safe use of ER/LA opioid analgesics.
- i. For ER products, patients must meet the criteria for opioid tolerance, described in the [table in Section VI](#), before using:
 - a. certain products,
 - b. certain strengths,
 - c. certain daily doses, and
 - d. in specific indicated patient populations (e.g., pediatric patients).
 - iii. See the [table in Section VI](#) for product-specific information.
- f. ER/LA opioid analgesic tablets must be swallowed whole. ER/LA opioid analgesic capsules should be swallowed intact or when necessary, the pellets from some capsules can be sprinkled on applesauce and swallowed without chewing.
- g. For transdermal products, external heat, fever, and exertion can increase absorption of the opioid, leading to fatal overdose. Transdermal products with metal foil backings are not safe for use in MRIs.
- h. For buccal film products, the film should not be applied if it is cut, damaged, or changed in any way. Use the entire film.
- i. Follow the instructions for conversion in the Dosage and Administration section (2.1) in the *Prescribing Information* of each product when converting patients from one opioid to another.

VI. Specific Drug Information for ER/LA Opioid Analgesic Products

Prescribers should be knowledgeable about specific characteristics of the ER/LA opioid analgesic products they prescribe, including the drug substance, formulation, strength, dosing interval, key instructions, specific information about conversion between products where available, specific drug interactions, use in opioid-tolerant patients, product-specific safety concerns, and relative potency to morphine. The attached table is a reference. For detailed information, prescribers can refer to prescribing information available online via DailyMed at www.dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Avinza (morphine sulfate ER capsules) Belbuca (buprenorphine buccal film) Butrans (buprenorphine transdermal system) Dolophine (methadone HCl tablets) Duragesic (fentanyl transdermal system) Embeda (morphine sulfate ER-naltrexone capsules) Exalgo (hydromorphone HCl ER tablets) Hysingla ER (hydrocodone bitartrate ER tablets) Kadian (morphine sulfate ER capsules)	MorphaBond (morphine sulfate ER tablets) MS Contin (morphine sulfate ER tablets) Nucynta ER (tapentadol HCl ER tablets) Opana ER (oxymorphone HCl ER tablets) OxyContin (oxycodone HCl ER tablets) Targiniq ER (oxycodone HCl/naloxone HCl ER tablets) Zohydro ER (hydrocodone bitartrate ER capsules)
Dosing Interval	<ul style="list-style-type: none"> ▪ Refer to individual product information.

Key Instructions	<ul style="list-style-type: none"> ▪ Limitations of usage: <ul style="list-style-type: none"> • Reserve 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. • Not for use as an as-needed analgesic. • Not for mild pain or pain not expected to persist for an extended duration. • Not for use in treating acute pain. ▪ Individually titrate to a dose that provides adequate analgesia and minimizes adverse reactions. ▪ The times required to reach steady-state plasma concentrations are product specific; refer to product information for titration interval. ▪ Continually reevaluate to assess the maintenance of pain control and the emergence of adverse reactions. ▪ During chronic therapy, especially for non-cancer-related pain, periodically reassess the continued need for opioids. ▪ If pain increases, attempt to identify the source, while adjusting the dose. ▪ When an ER/LA opioid analgesic is no longer required, gradually titrate downward to prevent signs and symptoms of withdrawal in the physically-dependent patient. Do not abruptly discontinue these products. ▪ Solid oral dosage forms: <ul style="list-style-type: none"> • Swallow tablets and capsules whole: crushing, chewing, breaking, cutting or dissolving may result in rapid release and absorption of a potentially fatal dose of opioid. • Some capsules can be opened and pellets sprinkled on applesauce for patients who can reliably swallow without chewing and used immediately. See individual product information. • Exposure of some products to alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of opioid. • Dispose of unused product by flushing down the toilet. ▪ Transdermal dosage forms: <ul style="list-style-type: none"> • Avoid exposure to external heat. Patients with fever must be monitored for signs or symptoms of increased opioid exposure. • Location of application must be rotated. • Prepare skin by clipping, not shaving hair, and washing area only with water. ▪ Buccal film dosage form: <ul style="list-style-type: none"> • Do not use if the package seal is broken or the film is cut, damaged, or changed in any way. ▪ See individual product information for the following: <ul style="list-style-type: none"> • Dosage reduction for hepatic or renal impairment.
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Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Drug Interactions Common to the Class	<ul style="list-style-type: none"> ▪ Concurrent use with other central nervous system depressants (sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers, and alcohol) can increase the risk of respiratory depression, hypotension, profound sedation, or coma. Reduce the initial dose of one or both agents. ▪ Avoid concurrent use of mixed opioid agonist/antagonists (i.e., pentazocine, nalbuphine, and butorphanol) or partial opioid agonists (buprenorphine) in patients who have received or are receiving a course of therapy with a full opioid agonist. In these patients, mixed opioid agonist/antagonists and partial opioid agonists may reduce the analgesic effect and/or may precipitate withdrawal symptoms. ▪ Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. ▪ Concurrent use with anticholinergic medication increases the risk of urinary retention and severe constipation, which may lead to paralytic ileus.
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> ▪ Adult patients considered opioid-tolerant are those receiving, for one week or longer: <ul style="list-style-type: none"> ○ at least 60 mg oral morphine/day ○ 25 mcg transdermal fentanyl/hour ○ 30 mg oral oxycodone/day ○ 8 mg oral hydromorphone/day ○ 25 mg oral oxymorphone/day ▪ Pediatric patients (11 years and older) considered opioid-tolerant are those who are already receiving and tolerating a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent (applicable to OxyContin's pediatric indication only) ▪ See individual product information for which products: <ul style="list-style-type: none"> • Have strengths or total daily doses only for use in opioid-tolerant patients. • Are only for use in opioid-tolerant patients at all strengths.

Contraindications	<ul style="list-style-type: none"> ▪ Significant respiratory depression ▪ Acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment ▪ Known or suspected paralytic ileus ▪ Hypersensitivity (e.g., anaphylaxis) <p>See individual product information for additional contraindications.</p>
Relative Potency To Oral Morphine	<ul style="list-style-type: none"> ▪ These are intended as general guides. ▪ Follow conversion instructions in individual product information. ▪ Incomplete cross-tolerance and inter-patient variability require the use of conservative dosing when converting from one opioid to another - halve the calculated comparable dose and titrate the new opioid as needed.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Avinza	Morphine Sulfate ER Capsules, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg
Dosing Interval	Once a day
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patients is 30 mg. ▪ Titrate in increments of not greater than 30 mg using a minimum of 3 to 4 day intervals. ▪ Swallow capsule whole (do not chew, crush, or dissolve). ▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately. ▪ Maximum daily dose: 1600 mg due to risk of serious renal toxicity by excipient, fumaric acid.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ P-gp inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	90 mg and 120 mg capsules are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Belbuca	Buprenorphine Buccal Film, 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg
Dosing Interval	Every 12 hours (or once every 24 hours for initiation in opioid naïve patients and patients taking less than 30 mg oral morphine sulfate equivalents)

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Key Instructions	<ul style="list-style-type: none"> ▪ Opioid-naïve patients or patients taking less than 30 mg oral morphine sulfate equivalents: Initiate treatment with a 75 mcg buccal film, once daily, or if tolerated, every 12 hours. <ul style="list-style-type: none"> • Titrate to 150 mcg every 12 hours no earlier than 4 days after initiation. • Individual titration to a dose that provides adequate analgesia and minimizes adverse reactions should proceed in increments of 150 mcg every 12 hours, no more frequently than every 4 days. ▪ When converting from another opioid, first taper the current opioid to no more than 30 mg oral morphine sulfate equivalents per day prior to initiating Belbuca. <ul style="list-style-type: none"> • If prior daily dose before taper was 30 mg to 89 mg oral morphine sulfate equivalents, initiate with 150 mcg dose every 12 hours. • If prior daily dose before taper was 90 mg to 160 mg oral morphine sulfate equivalents, initiate with 300 mcg dose every 12 hours. • Titration of the dose should proceed in increments of 150 mcg every 12 hours, no more frequently than every 4 days. ▪ Maximum dose: 900 mcg every 12 hours due to the potential for QTc prolongation ▪ Severe Hepatic Impairment: Reduce the starting and incremental dose by half that of patients with normal liver function. ▪ Oral Mucositis: Reduce the starting and incremental dose by half that of patients without mucositis ▪ Do not use if the package seal is broken or the film is cut, damaged, or changed in any way
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 inhibitors may increase buprenorphine levels. ▪ CYP3A4 inducers may decrease buprenorphine levels. ▪ Benzodiazepines may increase respiratory depression. ▪ Class IA and III antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointes.
Use in Opioid-Tolerant Patients	Belbuca 600 mcg, 750 mcg, and 900 mcg are for use following titration from lower doses of Belbuca.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ QTc prolongation and torsade de pointes ▪ Hepatotoxicity
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.
Butrans	Buprenorphine Transdermal System, 5 mcg/hr, 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, 20 mcg/hr
Dosing Interval	One transdermal system every 7 days

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patients when converting from less than 30 mg morphine equivalents, and in mild to moderate hepatic impairment - 5 mcg/hr dose. ▪ When converting from 30 mg to 80 mg morphine equivalents - first taper to 30 mg morphine equivalent, then initiate with 10 mcg/hr dose. ▪ Titrate in 5 mcg/hour or 10 mcg/hour increments by using no more than two patches of the 5 mcg/hour or 10-mcg/hour system(s) with a minimum of 72 hours between dose adjustments. The total dose from all patches should not exceed 20 mcg/hour ▪ Maximum dose: 20 mcg/hr due to risk of QTc prolongation. ▪ Application <ul style="list-style-type: none"> • Apply only to sites indicated in the Full Prescribing Information. • Apply to intact/non-irritated skin. • Skin may be prepped by clipping hair, washing site with water only • Rotate site of application a minimum of 3 weeks before reapplying to the same site. • Do not cut. ▪ Avoid exposure to heat. ▪ Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 Inhibitors may increase buprenorphine levels. ▪ CYP3A4 Inducers may decrease buprenorphine levels. ▪ Benzodiazepines may increase respiratory depression. ▪ Class IA and III antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointe.
Use in Opioid-Tolerant Patients	Butrans 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, and 20 mcg/hr transdermal systems are for use in opioid- tolerant patients only.
Drug-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ QTc prolongation and torsade de pointe. ▪ Hepatotoxicity ▪ Application site skin reactions
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.
Dolophine	Methadone Hydrochloride Tablets, 5 mg and 10 mg
Dosing Interval	Every 8 to 12 hours

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose in opioid non-tolerant patients: 2.5 to 10 mg ▪ Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose and death. Use low doses according to the table in the full prescribing information. ▪ Titrate slowly, with dose increases no more frequent than every 3 to 5 days. Because of high variability in methadone metabolism, some patients may require substantially longer periods between dose increases (up to 12 days). ▪ High inter-patient variability in absorption, metabolism, and relative analgesic potency. ▪ Opioid detoxification or maintenance treatment shall only be provided in a federally certified opioid (addiction) treatment program (Code of
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Pharmacokinetic drug-drug interactions with methadone are complex. <ul style="list-style-type: none"> ▪ CYP 450 inducers may decrease methadone levels. ▪ CYP 450 inhibitors may increase methadone levels. ▪ Anti-retroviral agents have mixed effects on methadone levels. ▪ Potentially arrhythmogenic agents may increase risk for QTc prolongation and torsade de pointe. ▪ Benzodiazepines may increase respiratory depression
Use in Opioid-Tolerant Patients	Refer to full prescribing information.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ QTc prolongation and torsade de pointe. ▪ Peak respiratory depression occurs later and persists longer than analgesic effect. ▪ Clearance may increase during pregnancy. ▪ False positive urine drug screens possible.
Relative Potency To Oral Morphine	Varies depending on patient's prior opioid experience.
Duragesic	Fentanyl Transdermal System, 12, 25, 37.5*, 50, 62.5*, 75, 87.5*, and 100 mcg/hr (*These strengths are available only in generic form)
Dosing Interval	Every 72 hours (3 days)

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Key Instructions	<ul style="list-style-type: none"> ▪ Use product specific information for dose conversion from prior opioid ▪ Use 50% of the dose in mild or moderate hepatic or renal impairment, avoid use in severe hepatic or renal impairment ▪ Application <ul style="list-style-type: none"> • Apply to intact/non-irritated/non-irradiated skin on a flat surface. • Skin may be prepped by clipping hair, washing site with water only • Rotate site of application. • Titrate using a minimum of 72 hour intervals between dose adjustments. • Do not cut. ▪ Avoid exposure to heat. ▪ Avoid accidental contact when holding or caring for children. ▪ Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet. <p>Specific contraindications:</p> <ul style="list-style-type: none"> ▪ Patients who are not opioid-tolerant. ▪ Management of acute or intermittent pain, or in patients who require opioid analgesia for a short period of time. ▪ Management of post-operative pain, including use after out-patient or day surgery. ▪ Management of mild pain.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 inhibitors may increase fentanyl exposure. ▪ CYP3A4 inducers may decrease fentanyl exposure. ▪ Discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration.
Use in Opioid-Tolerant Patients	All doses of Duragesic are indicated for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ Accidental exposure due to secondary exposure to unwashed/unclothed application site. ▪ Increased drug exposure with increased core body temperature or fever. ▪ Bradycardia ▪ Application site skin reactions
Relative Potency To Oral Morphine	See individual product information for conversion recommendations from prior opioid
Embeda	Morphine Sulfate ER-Naltrexone Capsules, 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4 mg
Dosing Interval	Once a day or every 12 hours

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Key Instructions	<ul style="list-style-type: none"> ▪ Initial dose as first opioid: 20 mg/0.8 mg. ▪ Titrate using a minimum of 1 to 2 day intervals. ▪ Swallow capsules whole (do not chew, crush, or dissolve) ▪ Crushing or chewing will release morphine, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms. ▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ P-gp inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	Embeda 100 mg/4 mg capsule is for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Exalgo	Hydromorphone Hydrochloride Extended-Release Tablets, 8 mg, 12 mg, 16 mg or 32 mg
Dosing Interval	Once a day
Key Instructions	<ul style="list-style-type: none"> ▪ Use the conversion ratios in the individual product information. ▪ Start patients with moderate hepatic impairment on 25% dose that would be prescribed for a patient with normal hepatic function. ▪ Start patients with moderate renal impairment on 50%, and patients with severe renal impairment on 25% of the dose that would be prescribed for a patient with normal renal function. ▪ Titrate in increments of 4 to 8 mg using a minimum of 3 to 4 day intervals ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Do not use in patients with sulfite allergy—contains sodium metabisulfite.
Specific Drug Interactions	None
Use in Opioid-Tolerant Patients	All doses of Exalgo are indicated for opioid-tolerant patients only.
Drug-Specific Adverse Reactions	Allergic manifestations to sulfite component.
Relative Potency To Oral Morphine	Approximately 5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in the individual product information.
Hysingla ER	Hydrocodone bitartrate Extended-Release Tablets, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, and 120 mg
Dosing Interval	Every 24 hours (once-daily)

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Key Instructions	<ul style="list-style-type: none"> ▪ Opioid-naïve patients: initiate treatment with 20 mg orally once daily. During titration, adjust the dose in increments of 10 mg to 20 mg every 3 to 5 days until adequate analgesia is achieved. ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Consider use of an alternative analgesic in patients who have difficulty swallowing or have underlying gastrointestinal disorders that may predispose them to obstruction. ▪ Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. ▪ Use 1/2 of the initial dose and monitor closely for adverse events, such as respiratory depression and sedation, when administering Hysingla ER to patients with severe hepatic impairment or patients with moderate to severe renal impairment.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 inhibitors may increase hydrocodone exposure. ▪ CYP3A4 inducers may decrease hydrocodone exposure ▪ Concomitant use of Hysingla ER with strong laxatives (e.g., Lactulose) that rapidly increase GI motility may decrease hydrocodone absorption and result in decreased hydrocodone plasma levels. ▪ The use of MAO inhibitors or tricyclic antidepressants with Hysingla ER may increase the effect of either the antidepressant or Hysingla ER.
Use in Opioid-Tolerant Patients	A single dose of Hysingla ER greater than or equal to 80 mg is only for use in opioid tolerant patients.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ Use with caution in patients with difficulty swallowing the tablet or underlying gastrointestinal disorders that may predispose patients to obstruction. ▪ Esophageal obstruction, dysphagia, and choking have been reported with Hysingla ER. ▪ In nursing mothers, discontinue nursing or discontinue drug. ▪ QTc prolongation has been observed with Hysingla ER following daily doses of 160 mg. Avoid use in patients with congenital long QTc syndrome. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing Hysingla ER in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QTc interval. In patients who develop QTc prolongation, consider reducing the dose.
Relative Potency To Oral Morphine	See individual product information for conversion recommendations from prior opioid

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Kadian	Morphine Sulfate Extended-Release Capsules, 10 mg, 20mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 130 mg, 150 mg, and 200 mg
Dosing Interval	Once a day or every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Product information recommends not using as first opioid. ▪ Titrate using a minimum of 2-day intervals. ▪ Swallow capsules whole (do not chew, crush, or dissolve). ▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ P-gp inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	Kadian 100 mg, 130 mg, 150 mg, and 200 mg capsules are for use in opioid-tolerant-patients only
Product-Specific Safety Concerns	None
MorphaBond	Morphine Sulfate Extended-release Tablets, 15 mg, 30 mg, 60 mg, 100 mg
Dosing Interval	Every 8 hours or every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Product information recommends not using as first opioid. ▪ Titrate using a minimum of 1 to 2-day intervals. ▪ Swallow tablets whole (do not chew, crush, or dissolve).
Specific Drug Interactions	P-gp inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	MorphaBond 100 mg tablets are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
MS Contin	Morphine Sulfate Extended-release Tablets, 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg
Dosing Interval	Every 8 hours or every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Product information recommends not using as first opioid. ▪ Titrate using a minimum of 1 to 2-day intervals. ▪ Swallow tablets whole (do not chew, crush, or dissolve).
Specific Drug Interactions	P-gp inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	MS Contin 100 mg and 200 mg tablet strengths are for use in opioid-tolerant patients only.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Product-Specific Safety Concerns	None
Nucynta ER	Tapentadol Extended-Release Tablets, 50 mg, 100mg, 150 mg, 200 mg, and 250 mg
Dosing Interval	Every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Use 50 mg every 12 hours as initial dose in opioid nontolerant patients ▪ Titrate by 50 mg increments using a minimum of 3-day intervals. ▪ Maximum total daily dose is 500 mg ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Take one tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth. ▪ Dose once daily in moderate hepatic impairment with 100 mg per day <u>maximum</u>
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of tapentadol. ▪ Contraindicated in patients taking MAOIs.
Use in Opioid-Tolerant Patients	No product-specific considerations.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ Risk of serotonin syndrome ▪ Angioedema
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.
Opana ER	Oxymorphone Hydrochloride ER Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg
Dosing Interval	Every 12h dosing, some may benefit from asymmetric (different dose given in AM than in PM) dosing.
Key Instructions	<ul style="list-style-type: none"> ▪ Use 5 mg every 12 hours as initial dose in opioid non-tolerant patients and patients with mild hepatic impairment and renal impairment (creatinine clearance < 50 mL/min) and patients over 65 years of age ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. ▪ Titrate in increments of 5 to 10 mg using a minimum of 3 to 7-day intervals. ▪ Contraindicated in moderate and severe hepatic impairment.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ Alcoholic beverages or medications containing alcohol may result in the absorption of a potentially fatal dose of oxymorphone.
Use in Opioid-Tolerant Patients	No product specific considerations.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ Use with caution in patients who have difficulty in swallowing or have underlying GI disorders that may predispose them to obstruction, such as a small gastrointestinal lumen.
Relative Potency To Oral Morphine	Approximately 3:1 oral morphine to oxymorphone oral dose ratio
OxyContin	Oxycodone Hydrochloride Extended-release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
Dosing Interval	<ul style="list-style-type: none"> ▪ Every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ For Adults: <ul style="list-style-type: none"> • Initial dose in opioid-naïve and opioid non-tolerant patients is 10 mg every 12 hours. • If needed, adult dosage may be adjusted in 1 to 2 day intervals. • When a dose increase is clinically indicated, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose. ▪ For Pediatric patients (11 years and older): Use only in <u>opioid-tolerant</u> patients (see below, <i>Use in Opioid-Tolerant Patients</i> for dosing information). ▪ For all patients: <ul style="list-style-type: none"> • Hepatic impairment: start with one third to one half the usual dosage • Renal impairment (creatinine clearance <60 mL/min): start with one half the usual dosage. • Consider use of other analgesics in patients who have difficulty
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 inhibitors may increase oxycodone exposure. ▪ CYP3A4 inducers may decrease oxycodone exposure.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> ▪ For Adults: <ul style="list-style-type: none"> • Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in adult patients in whom tolerance to an opioid of comparable potency has been established. ▪ For Pediatric patients (11 years and older): <ul style="list-style-type: none"> • For use only in <u>opioid-tolerant</u> pediatric patients 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. • If needed, pediatric dosage may be adjusted in 1 to 2 day intervals.
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ Choking, gagging, regurgitation, tablets stuck in the throat, difficulty swallowing the tablet. ▪ Contraindicated in patients with gastrointestinal obstruction.
Relative Potency To Oral Morphine	Approximately 2:1 oral morphine to oxycodone oral dose ratio.
Targiniq ER	Oxycodone Hydrochloride / Naloxone Hydrochloride Extended-release tablets, 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg
Dosing Interval	<ul style="list-style-type: none"> ▪ Every 12 hours
Key Instructions	<ul style="list-style-type: none"> ▪ Opioid-naïve patients: initiate treatment with 10 mg/5 mg every 12 hours. ▪ Titrate using a minimum of 1 to 2 day intervals. ▪ Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12) of Targiniq ER ▪ May be taken with or without food. ▪ Swallow tablets whole. Do not chew, crush, split, or dissolve, as this will release oxycodone, possibly resulting in fatal overdose, and naloxone, possibly resulting in withdrawal symptoms. ▪ Hepatic impairment: contraindicated in moderate and severe hepatic impairment. In patients with mild hepatic impairment, start with one third to one half the usual dosage.
Specific Drug Interactions	<ul style="list-style-type: none"> ▪ CYP3A4 inhibitors may increase oxycodone exposure.
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> ▪ Single dose greater than 40 mg/20 mg or total daily dose of 80 mg/40 mg are for use in opioid-tolerant patients only
Product-Specific Safety Concerns	<ul style="list-style-type: none"> ▪ Contraindicated in patients with moderate to severe hepatic impairment.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Relative Potency To Oral Morphine	<ul style="list-style-type: none"> See individual product information for conversion recommendations from prior opioid.
Zohydro ER	Hydrocodone Bitartrate Extended-Release Capsules, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg
Dosing Interval	<ul style="list-style-type: none"> Every 12 hours
Key Instructions	<ul style="list-style-type: none"> Initial dose in opioid non-tolerant patient is 10 mg. Titrate in increments of 10 mg using a minimum of 3 to 7day intervals.
Specific Drug Interactions	<ul style="list-style-type: none"> Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of hydrocodone. CYP3A4 inhibitors may increase hydrocodone exposure. CYP3A4 inducers may decrease hydrocodone exposure.
Use in Opioid-Tolerant Patients	<ul style="list-style-type: none"> Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Relative Potency To Oral Morphine	Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio.
For detailed information, refer to prescribing information available online via DailyMed at www.dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda .	

Appendix 3. Patient Counseling Document (PCD)

to your healthcare provider

- **Do not** cut, break, chew, crush, dissolve, snort, or inject your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider.
- **Do not** drink alcohol while taking this medicine

For additional information on your medicine go to:
dailymed.nlm.nih.gov

- All the medicines you take, including over-the-counter (non-prescription) medicines, vitamins, and dietary supplements
- Any side effects you may be having

Take your opioid pain medicine exactly as prescribed by your healthcare provider.

Appendix 4. Extended-release and Long-acting Opioid Analgesic REMS Assessment Plan⁵⁴

⁵⁴ Information obtained from ER/LA Opioid Analgesics REMS approval letter, July 9, 2012.

1. The first REMS assessment, due not later than six months from the date of REMS approval letter, should provide a report on the actions you have taken to implement the REMS since it was approved. The report should include the following information:
 - a. Grant Proposals: The status of the requests for proposals for grants for CE training including: 1) how many have issued and when will the next requests for proposals issue; 2) the number of proposals submitted in response to each request; 3) the number of grants awarded; 4) a list of the grantees; 5) the date when each of the grantees will make their CE training available; 6) a high-level description of each program (e.g., web based, live); and 7) an estimate of how many prescribers are expected to be trained under each program.
 - b. Evaluation Grants: The status of the requests for proposals for special grants to CE providers or other CE organizations with expertise in assessing CE outcomes who agree to conduct long-term evaluation of prescribers of ER/LA opioids who have taken training funded under this REMS to determine these prescribers' knowledge retention and practice changes 6 months to 1 year after they completed the REMS-compliant training including: 1) the number of proposals submitted in response to each request, 2) the number of grants awarded, 3) a list of the grantees, 4) the date when each of the grantees will conduct their REMS-compliant training, and 5) the dates of their follow-up evaluation.
 - c. Functional Components:
 - i. Date when the ER/LA Opioid REMS website was live and functional.
 - ii. Prescriber Letter 1: 1) Date when letter was posted on the ER/LA Opioid REMS website, 2) number of prescriber letters electronically sent, received, undeliverable, and opened, and 3) number of prescriber letters mailed and undeliverable.
 - iii. Professional Organization/Licensing Board Letter 1: 1) Date when the letter was posted on the ER/LA Opioid REMS website, 2) number of letters electronically sent, received, undeliverable, and opened, and 3) number of letters mailed and undeliverable.
 - iv. Date when the single number toll free call center was operational.
 - v. Call Center: 1) Summary of frequently asked questions, 2) Problems reported, and 3) ER/LA Opioid Analgesics REMS questions versus product-specific questions.

2. The second REMS assessment, due one year from the date of this letter, should include the following information:
 - a. Functional Components:
 - i. Training: 1) Date the first REMS-compliant training was available; 2) a high-level description of the training (e.g., web based, live); 3) the number of prescribers that have undergone the training, and 4) an estimate of how many prescribers will be trained under the program(s).
 - ii. Prescriber Letter 2: 1) Date when letter was posted on the ER/LA Opioid REMS website, 2) number of prescriber letters electronically sent, received, undeliverable, and opened, and 3) number of prescriber letters mailed and undeliverable.
 - iii. Professional Organization/Licensing Board Letter 2: 1) Date when the letter was posted on the ER/LA Opioid REMS website, 2) number of letters electronically sent, received, undeliverable, and opened, and 3) number of letters mailed and undeliverable.
 - iv. Call Center: 1) Summary of frequently asked questions, 2) Problems reported, and 3) ER/LA Opioid Analgesics REMS questions versus product-specific questions.
 - b. Grant Proposals: An update on the status of the requests for proposals for grants for REMS-compliant training, including: 1) new grant requests for proposals published; 2) the number of proposals submitted in response to each request; 3) the number of grants awarded; 4) a list of the grantees; 5) the date when each grantee will make or has made their REMS-compliant training available; 6) a high-level description of each program (e.g., web based, live), and 7) an estimate of how many prescribers will be trained under each program.
 - c. Evaluation Grants: The status of the requests for proposals for special grants to CE providers who also agree to conduct long-term evaluation of prescribers of ER/LA opioids who have taken their ER/LA Opioid REMS-funded training to determine these prescribers' knowledge retention and practice changes 6 months to 1 year after they completed the REMS-compliant training including: 1) the number of proposals submitted in response to each request, 2) the number of grants awarded, 3) a list of the grantees, 4) the date when each of the grantees will conduct their REMS-compliant training, and 5) the dates of their follow-up evaluation.

3. The third REMS assessment, due two years from the date of this letter, should include the following information:
- a. Prescriber Letter 3: 1) Date when letter was posted on the ER/LA Opioid REMS website, 2) number of prescriber letters electronically sent, received, undeliverable, and opened, and 3) number of prescriber letters mailed and undeliverable.
 - b. Prescriber Training: The number of prescribers of ER/LA opioids who have completed REMS-compliant training. Performance goals, based on the 2011 estimate that 320,000 prescribers are active prescribers of ER/LA opioids (prescribers who have prescribed an ER/LA opioid within the last 12 months), are as follows:
 - i. Within two years from the time the first REMS-compliant training becomes available, 80,000 prescribers (based on 25% of active prescribers) are to have been trained;
 - ii. Within three years from the time the first REMS-compliant training becomes available, 160,000 prescribers (based on 50% of active prescribers) are to have been trained;
 - iii. Within four years from the time the first REMS-compliant training becomes available, 192,000 prescribers (based on 60% of active prescribers) are to have been trained.
 - c. Independent Audit: The results of an independent audit of the quality of the content of the educational materials used by providers to provide the REMS-compliant training. Audits must be conducted on a random sample of 1) at least 10% of the training funded under the ER/LA Opioid REMS, and 2) REMS-compliant training not funded under the ER/LA Opioid REMS that will be counted as REMS-compliant training for purposes of meeting the milestones in 3b., and must evaluate:
 - i. whether the content of the training covers all elements of the FDA “blueprint” approved as part of the REMS;
 - ii. whether the post-course knowledge assessment measures knowledge of all sections of the FDA “blueprint”; and

- iii. whether the training was conducted in accordance with the Accreditation Council for Continuing Medication Education (ACCME) standards for CE or appropriate standards for accreditation bodies.
 - d. Evaluation of Patient Understanding: The results of an evaluation of patients' understanding of the serious risks of these products and their understanding of how to use these products safely. This evaluation may include, for example, surveys of patients.
 - e. Surveillance Results: Results of surveillance for misuse, abuse, overdose, addiction, and death. Surveillance needs to include information on changes in abuse, misuse, overdose, addiction, and death for different risk groups (e.g., teens, chronic abusers) and different settings (e.g., emergency departments, addiction treatment centers, poison control call centers). The information should be drug-specific whenever possible.
 - f. Drug Utilization Patterns: An evaluation of drug utilization patterns, including: an evaluation of prescribing behaviors of the prescribers of ER/LA opioids, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills;
 - g. Patient Access: An evaluation of changes in patients' access to ER/LA Opioids.
 - h. Methodologies: A description of the data sources and the methodologies used to conduct all of the above described analyses.
 - i. Goals: An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.
4. The fourth and subsequent REMS assessments should include the following information:
- a. Prescriber Letter 3: 1) number of prescriber letters electronically sent, received, undeliverable, and opened, and 2) number of prescriber letters mailed and undeliverable.
 - b. Prescriber Training: The number of prescribers of ER/LA opioids who have completed REMS-compliant training ([see 3b above](#)).

- c. Independent Audit: The results of an independent audit of the quality of the content of the educational materials used by the CE providers to provide the REMS-compliant training (see 3c above).
- d. Evaluation of Prescriber Understanding:
 - i. The results of an evaluation of ER/LA opioid prescribers' awareness and understanding of the serious risks associated with these products and their awareness of appropriate prescribing practices for ER/LA opioids, comparing the awareness and understanding of prescribers who have taken the REMS-compliant training with those who have not taken such training. This evaluation may include, for example, surveys of healthcare providers.
 - ii. The results of any long-term evaluation of prescribers of ER/LA opioids who have taken ER/LA Opioid REMS-funded training to determine these prescribers' knowledge retention and practice changes 6 months to 1 year after they completed the REMS-compliant training.
- e. Evaluation of Patient Understanding: The results of an evaluation of patients' understanding of the serious risks of these products and their understanding of how to use these products safely. (See 3d above).
- f. Surveillance Results: Results of surveillance and monitoring for misuse, abuse, overdose, addiction, and death (see 3e above).
- g. Drug Utilization Patterns: An evaluation of drug utilization patterns (see 3f above).
- h. Patient Access: An evaluation of changes in patient access to ER/LA opioids.
 - 1)
 - i. Methodologies: A description of the data sources and the methodologies used to conduct all of the above described analyses.
 - 2)
 - j. Goals: An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Appendix 5. List of Approved ER/LA Opioid Analgesic Products

Product	Application Number	Applicant holder
Avinza (morphine sulfate)	NDA 021260	King Pharmaceuticals LLC
Belbuca (buprenorphine)	NDA 207932	Endo Pharms INC
Butrans (buprenorphine)	NDA 021306	Purdue Pharma LP
Dolophine (methadone hydrochloride)	NDA 006134	Roxane Laboratories, Inc
Duragesic (fentanyl transdermal system)	NDA 019813	Janssen Pharmaceuticals, Inc
Embeda (morphine sulfate and naltrexone hydrochloride)	NDA 022321	Alpharma Pharmaceuticals LLS
Exalgo (hydromorphone hydrochloride)	NDA 021217	Mallinckrodt INC The Pharmaceuticals Business of Covidien
Hysingla ER (hydrocodone bitartrate)	NDA 206627	Purdue Pharma LP
Kadian (morphine sulfate)	NDA 020616	Watson Laboratories, Inc.
Methadose (methadone hydrochloride)	ANDA 040050	Mallinckrodt Pharmaceuticals
Morphabond (morphine sulfate)	NDA 206544	Inspirion Delivery Technologies LLC
MS Contin (morphine sulfate)	NDA 019516	Purdue Pharma LP
Nucynta ER (tapentadol)	NDA 200533	Janssen Pharmaceuticals, Inc
Opana ER (oxymorphone hydrochloride)	NDA 201655	Endo Pharmaceuticals Inc
Opana ER (oxymorphone hydrochloride)	NDA 021610	Endo Pharmaceuticals Inc
OxyContin (oxycodone hydrochloride)	NDA 022272	Purdue Pharma LP
Targiniq ER (oxycodone and naloxone hydrochloride)	NDA 205777	Purdue Pharma LP
Zohydro ER (hydrocodone)	NDA 202880	Zogenix, Inc
fentanyl transdermal system	ANDA 076709	Actavis Laboratories, UT Inc
fentanyl transdermal system	ANDA 077154	Mallinckrodt Pharmaceuticals
fentanyl transdermal system	ANDA 077449	Aveva Drug Delivery Systems, Inc.

Product	Application Number	Applicant holder
		(An Apotex Company)
fentanyl transdermal system	ANDA 077775	Noven Pharmaceuticals, Inc.
fentanyl transdermal system	ANDA 076258	Mylan Technologies Inc.
fentanyl transdermal system	ANDA 077062	Par Pharmaceuticals Inc.
hydromorphone hydrochloride	ANDA 202144	Actavis Elizabeth LLC
hydromorphone hydrochloride extended-release	ANDA 204278	Paddock Laboratories, LLC
methadone hydrochloride	ANDA 040517	Mallinckrodt Pharmaceuticals
methadone hydrochloride	ANDA 090635	The Pharma Network, LLC
methadone hydrochloride	ANDA 087997	Roxane Laboratories, Inc
methadone hydrochloride	ANDA 087393	Roxane Laboratories, Inc
methadone hydrochloride	ANDA 089897	Roxane Laboratories, Inc
methadone hydrochloride	ANDA 090065	CorePharma, LLC
methadone hydrochloride	ANDA 203502	Aurolife Pharma LLC
methadone hydrochloride	ANDA 040241	Sandoz Inc.
methadone hydrochloride	ANDA 090707	VistaPharm Inc
morphine sulfate	ANDA 200824	Mylan Pharmaceuticals, Inc
morphine sulfate extended release	ANDA 202104	Upsher-Smith
morphine sulfate extended-release	ANDA 076412	Mallinckrodt Pharmaceuticals
morphine sulfate extended-release	ANDA 076438	Mallinckrodt Pharmaceuticals
morphine sulfate extended-release	ANDA 202718	Teva Pharmaceuticals USA
morphine sulfate extended-release	ANDA 200812	Par Pharmaceuticals, Inc.

Product	Application Number	Applicant holder
morphine sulfate extended-release	ANDA 075295	Vintage Pharmaceuticals LLC, d/b/a Qualitest Pharmaceuticals and a subsidiary of Endo Pharmaceuticals Inc.
morphine sulfate extended-release	ANDA 203602	Novel Laboratories, Inc.
morphine sulfate extended-release	ANDA 203849	Actavis Elizabeth LLC
morphine sulfate extended-release	ANDA 77855	Nesher Pharms
morphine sulfate extended-release	ANDA 76720	Nesher Pharms
morphine sulfate extended-release	ANDA 76733	Nesher Pharms
morphine sulfate extended-release	ANDA 078761	Sun Pharmaceuticals Industries, LTD
morphine sulfate extended-release	ANDA 074769	Rhodes Pharmaceuticals L.P.
morphine sulfate extended-release	ANDA 074862	Rhodes Pharmaceuticals L.P.
morphine sulfate extended-release	ANDA 079040	Actavis Elizabeth, LLC
oxymorphone hydrochloride	ANDA 079087	Impax Laboratories, Inc.
oxymorphone hydrochloride	ANDA 079046	Actavis Elizabeth, LLC
oxymorphone hydrochloride	ANDA 202946	Mallinckrodt Pharmaceuticals
oxymorphone hydrochloride	ANDA 200792	Par Pharmaceuticals
oxymorphone hydrochloride extended release	ANDA 200822	Roxane Laboratories, Inc
oxymorphone hydrochloride extended-release	ANDA 203506	Sun Pharmaceutical Industries Limited

Appendix 6. LIST OF ABBREVIATIONS

AAFP	American Academy of Family Physicians
AANP	American Association of Nurse Practitioners
ACCME	Accreditation Council for Continuing Medical Education
ADF	Abuse Deterrent Formulation
ANDA	Abbreviated New Drug Application
AOA	American Osteopathic Association
ASI-MV	Addiction Severity Index-Multimedia Version
CCCE	Conjoint Committee on Continuing Education
CDER	Center for Drug Evaluation and Research
CE	Continuing Educations
CHAT	Comprehensive Health Assessment for Teens
CME	Continuing Medical Education
CO*RE	Collaborative for REMS Education
CSP	College Survey Program
DEA	Drug Enforcement Administration
DAAAP	FDA's Division of Anesthesia, Analgesia, and Addiction Products
DEPI	FDA's Division of Epidemiology
DPV	FDA's Division of Pharmacovigilance
DRISK	FDA's Division of Risk Management
ED	Emergency Department
ETASU	Elements to Assure Safe Use
ER/LA	Extended-release/Long-acting
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDCA	Food, Drug & Cosmetic Act
HCP	Healthcare Provider
HIRD	HealthCore Integrated Research Database
ICD	International Classification of Diseases
IR	Immediate Release
IRR	Incidence Rate Ratio
LRx	IMS Health, LifeLink™ Patient-level Longitudinal Prescription
MTF	Monitoring the Future
NAVIPPRO	National Addictions Vigilance Intervention and Prevention Program
NDA	New Drug Application
NDI	National Death Index

NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NP	Nurse Practitioner
NPA	National Prescription Audit
NSAID	Non-steroidal Anti-inflammatory Drug
NSDUH	National Survey on Drug Use and Health
OTP	Opioid Treatment Program
PCC	Poison Control Center
PCD	Patient Counseling Document
PCP	Poison Center Program
PDMP	Prescription Drug Monitoring Program
PMR	Postmarketing Requirement
PPA	Patient Prescriber Agreement
RADARS	Researched Abuse, Diversion and Addiction-Related Surveillance
REMS	Risk Evaluation and Mitigation Strategy
RFA	Request for Application
RPC	REMS Program Companies
SAMSHA	Substance Abuse and Mental Health Services Administration
SE	Single Entity
SD	Standard Deviation
SKIP	Survey of Key Informants' Patients Program
TCP	Treatment Center Program
TDS	Transdermal System
US	United States

Appendix 7: Examples of Other Efforts to Reduce Inappropriate Prescribing and Abuse of Prescription Opioids

To address prescription opioid abuse and overdose, numerous interventions aimed at curbing inappropriate prescribing, diversion, misuse, abuse, and overdose have been initiated or expanded in recent years. These interventions occurred at the institution, community, state, and federal level. Many of these initiatives overlapped in time with the REMS program implementation and their impact must be considered when interpreting the results of the RPCs postmarketing study program. Outlined below are some of these efforts.

FDA Actions

Prior to and during the REMS study period, FDA took multiple actions related to opioids, particularly in relation to abuse and misuse of these drugs.⁵⁵ Two major actions are described below.

- **ER/LA Opioid Analgesic Safety Labeling Change**

On September 10, 2013, FDA announced class-wide safety labeling changes for all ER/LA opioid analgesics. The updated indication states that ER/LA opioids are 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. The updated label clarifies that 1) because of the risks of addiction, abuse, and misuse, these drugs should be reserved for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or IR opioids) are ineffective, not tolerated, or would otherwise be inadequate to provide sufficient management of pain, and 2) ER/LA opioid analgesics are not indicated for as-needed pain relief.

- **Approval of Abuse-deterrent Opioid Formulations**

Just prior to and during the study period, several reformulated ER/LA opioid analgesic products were introduced to the market. These products were designed with properties intended to deter abuse, particularly via routes of administration other than those by which they are intended to be taken. Although the effectiveness of abuse-deterrent opioid formulations is still being evaluated in postmarketing settings, the potential role of these drugs in reducing abuse and related adverse outcomes during the REMS study periods should be considered.

⁵⁵ <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm338566.htm>

Prescribing Guidelines, Prescriber Education, and Opioid Prescribing Legislation

Professional societies such as the American Pain Society, state task forces, healthcare delivery systems, and government agencies, for example the Veterans Administration and Department of Defense, have generated opioid prescribing guidelines with the goal of reducing adverse outcomes associated with prescription opioids. Although the guidelines vary, the general trend in recent years has been to recommend more cautious and judicious use of these drugs in the management of non-malignant pain.⁵⁶ In addition to the REMS-compliant continuing education offerings, more than 100 other opioid prescribing and pain management continuing education courses have been offered. Some states have mandated continuing education in opioid prescribing or pain management as a condition for licensure,⁵⁷ and at least one state (Washington) has passed legislation restricting prescribing of high-dose opioid regimens by non-specialists.⁵⁸

Law Enforcement Efforts

The Drug Enforcement Agency (DEA) and local law enforcement agencies have been heavily involved in efforts to reduce inappropriate prescribing and diversion of prescription opioids. These efforts are ongoing. One of the largest interventions occurring during the REMS study period involved addressing the large number of rogue pain clinics, or “pill mills” in south Florida. Between 2007 and 2010, South Florida saw an explosion in the number of pain management clinics—the number in a single county increasing from 4 to 142 during this period—with most prescribing large quantities of opioids with little medical documentation.⁵⁹ Many of these opioids were being abused or diverted, along with other drugs such as benzodiazepines and muscle relaxants, for abuse across multiple states in the eastern U.S. In response, the DEA and the state of Florida enacted several measures to better regulate these pain clinics. In January, 2010, the Florida legislature required pain clinics to register with the state, and shortly thereafter, the DEA and state law-enforcement agencies conducted statewide raids of clinics. Florida has reported that approximately 250 pain clinics were closed by 2013,

⁵⁶ <http://www.cdc.gov/drugoverdose/prescribing/common-elements.html>

⁵⁷ <http://www.amednews.com/article/20120213/profession/302139947/2/#minb>

⁵⁸ <http://www.doh.wa.gov/ForPublicHealthandHealthcareProviders/HealthcareProfessionsandFacilities/PainManagement>

⁵⁹ Russell Holske, Chief of Pharmaceutical Investigations Operations Division, Office of Diversion Control, U.S. Drug Enforcement Administration. Presentation to EU-US Dialogue on Drugs, Brussels, Belgium, May 15, 2013.

and the number of high-volume oxycodone dispensing prescribers declined from 98 in 2010 to 13 in 2012 and zero in 2013.⁶⁰

After these raids in Florida, dispensing rates between 2010 and 2012 dropped for certain drugs—oxycodone prescribing dropped 24%, hydrocodone prescribing dropped 10%, methadone prescribing dropped 10%, and alprazolam prescribing dropped 11%.⁶¹ In addition, DEA actions against wholesale distributors resulted in a >90% reduction in sales of oxycodone to Florida practitioners for office-based dispensing between June, 2010 and October, 2010.⁶² In Florida, deaths due to opioid pain relievers declined from 13.6 per 100,000 population in 2010 to 9.9 per 100,000 population in 2012. For oxycodone, it declined from 8.1 per 100,000 population in 2010 to 3.9 per 100,000 population in 2012.⁶³ Law enforcement efforts have not been limited to the state of Florida, and many other similar large-scale efforts have taken place in other states.

Payer-based Initiatives: Prior Authorization and Utilization Review and Restriction Programs

Both public and private payers have developed strategies to mitigate costs and patient harm due to over-prescribing, fraud, diversion, and abuse. These may have substantial effects on utilization of certain opioid products. One study found that state Medicaid programs with stricter prior authorization policies for controlled-release oxycodone saw a 34% decrease in use of this drug, while those with more lenient prior authorization policies had a non-significant increase in use.⁶⁴ In 2012, a health plan in Massachusetts instituted prior authorization for treatment lasting longer than 30-days, resulting in a 20% decrease in claims for short-acting opioids, and a 50% decrease in claims for long-acting opioids.⁶⁵ Multiple states have also implemented Medicaid “lock-in” programs, where high-utilizers of certain controlled substances are restricted to one prescriber and pharmacy for those drugs.

⁶⁰Johnson H; Paulozzi L; Porucznik C. Mack K. Herter B. Decline in Drug Overdose Deaths After State Policy Changes —Florida, 2010–2012. *MMWR*. 63 (26). 569-74. July 2014.

⁶¹Johnson, 2014.

⁶²Holske, 2013.

⁶³Johnson, 2014.

⁶⁴Morden, N. E., Zerzan, J.T., Rue, T.C., Heagerty, P.J., Roughead, E. E., Soumerai, S.B., Ross-Degnan, D., Sullivan, S.D. (2008) Medicaid prior authorization and controlled-release oxycodone. *Med Care*; 46: 573-80.

⁶⁵Blue Cross/ Blue Shield press release; April 8th, 2014:
<http://www.bluecrossma.com/visitor/newsroom/press-releases/2014/2014-04-08.html>

Prescription Drug Monitoring Programs (PDMPs)

A Prescription Drug Monitoring Program (PDMP) is a state-specific electronic database that collects dispensing data on controlled substances and other drugs of concern. To date, 49 states have passed statutes establishing a PDMP and most are actively collecting prescription data. These data are provided to authorized prescribers and pharmacists. State PDMP programs are at different stages of development and prescriber engagement. Some states are reporting tangible positive results that they attribute to these programs. After the implementation of the PDMP program in Oregon, the rate of unintentional and undetermined overdose deaths due to prescription opioids decreased from 6.5 per 100,000 residents in 2006 to 4.2 per 100,000 residents in 2012.⁶⁶ After New York instituted a PDMP, the number of opioid prescriptions decreased 9.53%, and “doctor-shopping” (5 prescribers/5 pharmacies in 3 months) episodes decreased 74.8%.⁶⁷

Increased access to treatment for addiction and overdose

- **Increased access to medically-assisted treatment for opioid addiction**

The use of buprenorphine-based opioid substitution therapy in office settings has increased dramatically in the past decade, particularly in primary care-based settings.⁶⁸ The impact of this expanding treatment sector on overdose rates and on the patient mix and reported drugs of abuse in surveillance settings, such as methadone maintenance clinics, is unknown.

- **Increasing access to naloxone for reversal of opioid overdose**

Programs providing naloxone to opioid addicts, patients, caregivers, first responders, and other laypersons have expanded dramatically over the past decade, and thousands of opioid overdose reversals have been reported.⁶⁹

⁶⁶ Drug Overdose Deaths, Hospitalizations, Abuse, and Dependency among Oregonians, 2014. Oregon Health Authority, Center for Prevention and Health Promotion, Injury and Violence Prevention Section. Published: 5/30/2014.

<http://public.health.oregon.gov/DiseasesConditions/InjuryFatalityData/Documents/oregon-drug-overdose-report.pdf>

⁶⁷ Brandeis University, PDMP Center of Excellence. COE Briefing: Mandating PDMP Participation by Medical Providers: Current Status and Experience in Selected States. Feb. 2014.

⁶⁸ Turner L, Kruszewski SP, Alexander GC. Trends in the use of buprenorphine by office-based physicians in the United States, 2003–2013. *Am J Addict.* 2015; 24(1): 24-29.

⁶⁹ Wheeler E, Jones TS, Gilbert MK, Davidson PJ (2015). Opioid Overdose Prevention Programs Providing Naloxone to Laypersons—United States, 2014. *MMWR Rep* 64 (23):631-5.

Appendix 8: Example One-Page Medication Guide

Medication Guide

HYSINGLA ER (hye-SING-luh)

(hydrocodone bitartrate) extended-release tablets, CII

HYSINGLA ER is:

- A strong prescription pain medicine that contains an opioid (narcotic). It 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.

Important information about HYSINGLA ER:

- Get emergency help right away if you take too much HYSINGLA ER (overdose). When you first start taking HYSINGLA ER, 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.
- Never give anyone else your HYSINGLA ER. They could die from taking it. Store HYSINGLA ER away from children and in a safe place to prevent stealing or abuse. Selling or giving away HYSINGLA ER is against the law.

Do not take HYSINGLA ER if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking HYSINGLA ER, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- heart rhythm problems (long QT syndrome)
- 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 HYSINGLA ER during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** HYSINGLA ER passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking HYSINGLA ER with certain other medicines can cause serious side effects and could lead to death.

When taking HYSINGLA ER:

- Do not change your dose. Take HYSINGLA ER exactly as prescribed by your healthcare provider.
- Take your prescribed dose every 24 hours, at the same time every day. Do not take more than your prescribed dose in 24 hours. If you miss a dose, take your next dose at your usual time the next day.
- Swallow HYSINGLA ER whole. Do not cut, break, chew, crush, dissolve, snort, or inject HYSINGLA ER because this may cause you to overdose and die.
- HYSINGLA ER should be taken 1 tablet at a time. Do not pre-soak, lick, or wet the tablet before placing it 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 HYSINGLA ER without talking to your healthcare provider.**
- After you stop taking HYSINGLA ER, flush any unused tablets down the toilet.

While taking HYSINGLA ER, DO NOT:

- Drive or operate heavy machinery until you know how HYSINGLA ER affects you. HYSINGLA ER 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 HYSINGLA ER may cause you to overdose and die.

The possible side effects of HYSINGLA ER 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, or you are feeling faint.

These are not all the possible side effects of HYSINGLA ER. 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.

Issue: MM/YYYY

Appendix 9: Example of Approved PI for ER/LA Product

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HYSINGLA ER safely and effectively. See full prescribing information for HYSINGLA ER.

HYSINGLA ER (hydrocodone bitartrate) extended-release tablets, for oral use, CII
Initial U.S. Approval: 1943

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; AND CYTOCHROME P450 3A4 INTERACTION

See full prescribing information for complete boxed warning.

- HYSINGLA ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow HYSINGLA ER whole to avoid exposure to a potentially fatal dose of hydrocodone. (5.2)
- Accidental ingestion of HYSINGLA ER, especially by children, can result in fatal overdose of hydrocodone. (5.2)
- Prolonged use of HYSINGLA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)
- Initiation of CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of hydrocodone from HYSINGLA ER.

INDICATIONS AND USAGE

HYSINGLA ER 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. (1)

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 HYSINGLA ER 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)
- HYSINGLA ER is not indicated as an as-needed (prn) analgesic. (1)

DOSAGE AND ADMINISTRATION

- For opioid-naïve patients, initiate with 20 mg tablets orally every 24 hours. (2.1)
- To convert to HYSINGLA ER from another opioid, follow the conversion instructions to obtain an estimated dose. (2.1)
- Dose titration of HYSINGLA ER may occur every 3 to 5 days (2.2)
- Tablets must be swallowed intact and are not to be crushed, dissolved, or chewed, due to the risk of overdose or death. (2.3, 5.1)
- Do not abruptly discontinue HYSINGLA ER in a physically dependent patient. (2.6)
- HYSINGLA ER tablets should be taken one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth (5.9)

DOSAGE FORMS AND STRENGTHS

Extended-release Tablets: 20, 30, 40, 60, 80, 100, and 120 mg (3)

CONTRAINDICATIONS

- Significant respiratory depression (4)
- Acute or severe bronchial asthma (4)
- Known or suspected paralytic ileus and GI obstruction (4)

- Hypersensitivity to any components of HYSINGLA ER or the active ingredient, hydrocodone bitartrate (4)

WARNINGS AND PRECAUTIONS

- Misuse, abuse, and diversion: HYSINGLA ER is an opioid agonist and a Schedule II controlled substance with a high potential for abuse similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone. (5.1)
- Interactions with CNS depressants: Concomitant use may cause profound sedation, respiratory depression, and death. If co-administration is required, consider dose reduction of one or both drugs. (5.4)
- Elderly, cachectic, debilitated patients, and those with chronic pulmonary disease: Monitor closely because of increased risk for life-threatening respiratory depression. (5.5, 5.6)
- Patients with head injury or increased intracranial pressure: Monitor for sedation and respiratory depression. Avoid use of HYSINGLA ER in patients with impaired consciousness or coma susceptible to intracranial effects of CO₂ retention. (5.7)
- Risk of Choking/GI Obstruction: Use with caution in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. (5.9, 5.10)
- Concomitant use of CYP3A4 inhibitors may increase opioid effects. (5.11)
- Impaired mental/physical abilities: Caution must be used with potentially hazardous activities. (5.12)
- QTc prolongation has been observed with HYSINGLA ER following daily doses of 160 mg. Avoid use in patients with congenital long QTc syndrome. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing HYSINGLA ER in patients with congestive heart failure, bradyarrhythmias electrolyte abnormalities, or who are taking medications that are known to prolong the QTc interval. In patients who develop QTc prolongation, consider reducing the dose. (5.14, 12.2)

ADVERSE REACTIONS

Most common treatment-emergent adverse events (≥ 5%) are constipation, nausea, vomiting, fatigue, upper respiratory tract infection, dizziness, headache, and somnolence. (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

- The CYP3A4 isoenzyme plays a major role in the metabolism of HYSINGLA ER. Drugs that inhibit CYP3A4 activity may cause decreased clearance of hydrocodone which could lead to an increase in hydrocodone plasma concentrations. (7.1)
- CNS depressants: Increased risk of respiratory depression, hypotension, profound sedation, coma or death. When combined therapy with CNS depressant is contemplated, the dose of one or both agents should be reduced. (7.2)
- Mixed Agonists/Antagonists: May precipitate withdrawal or decrease analgesic effect if given concurrently with HYSINGLA ER. (7.3)
- The use of MAO inhibitors or tricyclic antidepressants with HYSINGLA ER may increase the effect of either the antidepressant or HYSINGLA ER. (7.4)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers: Discontinue nursing or discontinue drug. (8.3)
- Hepatic impairment: Use half the initial dose of HYSINGLA ER in patients with severe hepatic impairment and monitor closely for adverse events such as respiratory depression. (8.6)
- Renal impairment: Use half the initial dose of HYSINGLA ER in patients with moderate and severe renal impairment and end-stage renal disease and monitor closely for adverse events such as respiratory depression. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; AND CYTOCHROME P450 3A4 INTERACTION

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FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; AND CYTOCHROME P450 3A4 INTERACTION

Addiction, Abuse, and Misuse

HYSINGLA ER 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 HYSINGLA ER, and monitor all patients regularly for the development of these behaviors or conditions [see *Warnings and Precautions (5.1)*].

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of HYSINGLA ER. Monitor for respiratory depression, especially during initiation of HYSINGLA ER or following a dose increase. Instruct patients to swallow HYSINGLA ER tablets whole; crushing, chewing, or dissolving HYSINGLA ER tablets can cause rapid release and absorption of a potentially fatal dose of hydrocodone [see *Warnings and Precautions (5.2)*].

Accidental Ingestion

Accidental ingestion of even one dose of HYSINGLA ER, especially by children, can result in a fatal overdose of hydrocodone [see *Warnings and Precautions (5.2)*].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of HYSINGLA ER 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 neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Warnings and Precautions (5.3)*].

Cytochrome P450 3A4 Interaction

The concomitant use of HYSINGLA ER with all cytochrome P450 CYP3A4 inhibitors may result in an increase in hydrocodone 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 hydrocodone plasma concentration. Monitor patients receiving HYSINGLA ER and any CYP3A4 inhibitor or inducer [see *Warnings and Precautions (5.14)* and *Clinical Pharmacology (12.3)*].

1 INDICATIONS AND USAGE

HYSINGLA ER 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.

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 HYSINGLA ER 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.
- HYSINGLA ER is not indicated as an as-needed analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

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

Initiate the dosing regimen for each patient individually, taking into account the patient's 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 with HYSINGLA ER. [see *Warnings and Precautions (5.2)*]

HYSINGLA ER is administered orally once daily (every 24 hours).

HYSINGLA ER tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth [see *Patient Counseling Information (17)*]. Crushing, chewing, or dissolving HYSINGLA ER tablets will result in uncontrolled delivery of hydrocodone and can lead to overdose or death [see *Warnings and Precautions (5.1)*].

Use of HYSINGLA ER as the First Opioid Analgesic

Initiate therapy with HYSINGLA ER 20 mg orally every 24 hours.

Use of HYSINGLA ER in Patients who are not Opioid Tolerant

The starting dose for patients who are not opioid tolerant is HYSINGLA ER 20 mg orally every 24 hours. Opioid tolerant patients 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, or an equianalgesic dose of another opioid.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression. [see *Warnings and Precautions (5.2)*]

Daily doses of HYSINGLA ER greater than or equal to 80 mg are only for use in opioid tolerant patients.

Conversion from Oral Hydrocodone Formulations to HYSINGLA ER

Patients receiving other oral hydrocodone-containing formulations may be converted to HYSINGLA ER by administering the patient's total daily oral hydrocodone dose as HYSINGLA ER once daily.

Conversion from Other Oral Opioids to HYSINGLA ER

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

Although tables of oral and parenteral equivalents are readily available, there is substantial inter-patient variability in the relative potency of different opioid drugs and formulations. As such, it is preferable to underestimate a patient's 24-hour oral hydrocodone requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral hydrocodone requirements and manage an adverse reaction.

To obtain the initial HYSINGLA ER dose, first use Table 1 to convert the prior oral opioids to a total hydrocodone daily dose and then reduce the calculated daily hydrocodone dose by 25% to account for interpatient variability in relative potency of different opioids.

Consider the following when using the information found 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 HYSINGLA ER.
- The table **cannot** be used to convert **from** HYSINGLA ER to another opioid. Doing so will result in an over-estimation of the dose of the new opioid and may result in fatal overdose

Table 1. Conversion factors to HYSINGLA ER (Not Equianalgesic Doses)

Opioid	Oral dose (mg)	Approximate oral conversion factor
Codeine	133	0.15
Hydromorphone	5	4
Methadone	30	1.5
Morphine	40	0.5
Oxycodone	20	1
Oxymorphone	10	2
Tramadol	200	0.1

To calculate the estimated total hydrocodone daily dose using Table 1:

- For patients on a single opioid, sum the current total daily dose of the opioid and then multiply the total daily dose by the approximate oral conversion factor to calculate the approximate oral hydrocodone daily dose.
- For patients on a regimen of more than one opioid, calculate the approximate oral hydrocodone dose for each opioid and sum the totals to obtain the approximate oral hydrocodone daily dose.
- For patients on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component of these products in the conversion.
- Reduce the calculated daily oral hydrocodone dose by 25%

Always round the dose down, if necessary, to the nearest HYSINGLA ER tablet strength available and initiate therapy with that dose. If the converted HYSINGLA ER dose using Table 1 is less than 20 mg, initiate therapy with HYSINGLA ER 20 mg.

Example conversion from a single opioid to HYSINGLA ER:

For example, a total daily dose of oxycodone 50 mg would be converted to hydrocodone 50 mg based on the table above, and then multiplied by 0.75 (ie, take a 25 % reduction) resulting in a dose of 37.5 mg

hydrocodone. Round this down to the nearest dose strength available, HYSINGLA ER 30 mg, to initiate therapy.

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 or for signs of over-sedation/toxicity after converting patients to HYSINGLA ER.

The dose of HYSINGLA ER can be gradually adjusted every three days, using increments of 10 to 20 mg, until adequate pain relief and acceptable tolerability have been achieved.

Conversion from Methadone to HYSINGLA ER

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 HYSINGLA ER

Eighteen hours following the removal of the transdermal fentanyl patch, HYSINGLA ER treatment can be initiated. For each 25 mcg/hr fentanyl transdermal patch, a dose of HYSINGLA ER 20 mg every 24 hours represents a conservative initial dose. Follow the patient closely during conversion from transdermal fentanyl to HYSINGLA ER, as there is limited experience with this conversion.

Conversion from Transdermal Buprenorphine to HYSINGLA ER

All patients receiving transdermal buprenorphine (≤ 20 mcg/hr) should initiate therapy with HYSINGLA ER 20 mg every 24 hours. Follow the patient closely during conversion from transdermal buprenorphine to HYSINGLA ER, as there is limited experience with this conversion.

2.2 Titration and Maintenance of Therapy

Individually titrate HYSINGLA ER to a dose that provides adequate analgesia and minimizes adverse reactions. Continually re-evaluate patients receiving HYSINGLA ER to assess the maintenance of pain control and the relative incidence of adverse reactions as well as monitoring for the development of addiction, abuse, or misuse. 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.

Adjust the dose of HYSINGLA ER in increments of 10 mg to 20 mg every 3 to 5 days as needed to achieve adequate analgesia.

Patients who experience breakthrough pain may require a dose increase of HYSINGLA ER, 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 HYSINGLA ER dose.

If unacceptable opioid-related adverse reactions are observed, the next daily dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.3 Administration of HYSINGLA ER

HYSINGLA ER is administered once daily (every 24 hours).

HYSINGLA ER must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth [see *Patient Counseling Information (17)*].

Crushing, chewing, or dissolving HYSINGLA ER tablets will result in uncontrolled delivery of hydrocodone and can lead to overdose or death [see *Warnings and Precautions (5.1)*].

Multiple tablets of lower dose strengths that provide the desired total daily dose can be taken as a once daily dose.

2.4 Patients with Hepatic Impairment

Patients with severe hepatic impairment may have higher plasma concentrations than those with normal function. Initiate therapy with ½ the initial dose of HYSINGLA ER in these patients and monitor closely for respiratory depression and sedation [see *Clinical Pharmacology (12.3)*].

2.5 Patients with Renal Impairment

Patients with moderate to severe renal impairment, and end-stage renal disease may have higher plasma concentrations than those with normal function. Initiate therapy with ½ the initial dose of HYSINGLA ER in these patients and monitor closely for respiratory depression and sedation [see *Clinical Pharmacology (12.3)*].

2.6 Discontinuation of HYSINGLA ER

Do not abruptly discontinue HYSINGLA ER. When the patient no longer requires opioid therapy, use a gradual downward titration of the dose to prevent signs and symptoms of withdrawal in the physically dependent patient. The dose may be reduced every 2-4 days. The next dose should be at least 50% of the prior dose. After reaching HYSINGLA ER 20 mg dose for 2-4 days, HYSINGLA ER can be discontinued.

3 DOSAGE FORMS AND STRENGTHS

- 20 mg film-coated extended-release tablets (round, green-colored, bi-convex tablets printed with “HYD 20”)
- 30 mg film-coated extended-release tablets (round, yellow-colored, bi-convex tablets printed with “HYD 30”)
- 40 mg film-coated extended-release tablets (round, grey-colored, bi-convex tablets printed with “HYD 40”)
- 60 mg film-coated extended-release tablets (round, beige-colored, bi-convex tablets printed with “HYD 60”)
- 80 mg film-coated extended-release tablets* (round, pink-colored, bi-convex tablets printed with “HYD 80”)
- 100 mg film-coated extended-release tablets (round, blue-colored, bi-convex tablets printed with “HYD 100”)
- 120 mg film-coated extended-release tablets (round, white-colored, bi-convex tablets printed with “HYD 120”)

4 CONTRAINDICATIONS

HYSINGLA ER is contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected paralytic ileus and gastrointestinal obstruction
- Hypersensitivity to any component of HYSINGLA ER or the active ingredient, hydrocodone bitartrate

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

HYSINGLA ER contains hydrocodone, a Schedule II controlled substance. As an opioid, HYSINGLA ER exposes users to the risks of addiction, abuse, and misuse [*see Drug Abuse and Dependence (9.1)*]. As extended-release products such as HYSINGLA ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of hydrocodone present.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed HYSINGLA ER and in those who obtain the drug illicitly. 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 HYSINGLA ER, and monitor all patients receiving HYSINGLA ER for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of HYSINGLA ER for the proper management of pain in any given patient.

Abuse or misuse of HYSINGLA ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the hydrocodone and can result in overdose and death [*see Drug Abuse and Dependence (9.1), and Overdosage (10)*].

Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing HYSINGLA ER. 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 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression from opioid use, 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 (10.2)*]. Carbon dioxide (CO₂) 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 HYSINGLA ER, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with HYSINGLA ER and following dose increases.

To reduce the risk of respiratory depression, proper dosing and titration of HYSINGLA ER are essential [see *Dosage and Administration* (2.1, 2.2)]. Overestimating the HYSINGLA ER dose when converting patients from another opioid product can result in fatal overdose with the first dose.

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

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of HYSINGLA ER during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized 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 neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

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.

5.4 Interactions with Central Nervous System Depressants

Hypotension, profound sedation, coma, respiratory depression, and death may result if HYSINGLA ER is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids).

When considering the use of HYSINGLA ER in a patient taking a CNS depressant, assess the duration use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression. If the decision to begin HYSINGLA ER is made, start with a lower HYSINGLA ER dose than usual (i.e., 20-30% less), monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant [see *Drug Interactions* (7.2)].

5.5 Use in Elderly, Cachectic, and Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating HYSINGLA ER and when HYSINGLA ER is given concomitantly with other drugs that depress respiration [see *Warnings and Precautions* (5.2)].

5.6 Use in Patients with Chronic Pulmonary Disease

Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with HYSINGLA ER, as in these patients, even usual therapeutic doses of HYSINGLA ER may decrease respiratory drive to the point of apnea [see *Warnings and Precautions* (5.2)]. Consider the use of alternative non-opioid analgesics in these patients if possible.

5.7 Use in Patients with Head Injury and Increased Intracranial Pressure

In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of opioid analgesics and their potential to elevate cerebrospinal

fluid pressure (resulting from vasodilation following CO₂ retention) may be markedly exaggerated. Furthermore, opioid analgesics can produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Monitor patients closely who may be susceptible to the intracranial effects of CO₂ retention, such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury.

Avoid the use of HYSINGLA ER in patients with impaired consciousness or coma.

5.8 Hypotensive Effect

HYSINGLA ER may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Monitor these patients for signs of hypotension after initiating or titrating the dose of HYSINGLA ER. In patients with circulatory shock, HYSINGLA ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of HYSINGLA ER in patients with circulatory shock.

5.9 Gastrointestinal Obstruction, Dysphagia, and Choking

In the clinical studies with specific instructions to take HYSINGLA ER with adequate water to swallow the tablet, 11 out of 2476 subjects reported difficulty swallowing HYSINGLA ER. These reports included esophageal obstruction, dysphagia, and choking, one of which had required medical intervention to remove the tablet [*see Adverse Reactions (6)*].

Instruct patients not to pre-soak, lick, or otherwise wet HYSINGLA ER 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 [*see Patient Counseling Information (17)*].

Patients with underlying gastrointestinal 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 gastrointestinal disorders resulting in a small gastrointestinal lumen.

5.10 Decreased Bowel Motility

HYSINGLA ER is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. Opioids diminish propulsive peristaltic waves in the gastrointestinal tract and decrease bowel motility. Monitor for decreased bowel motility in post-operative patients receiving opioids. The administration of HYSINGLA ER may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Hydrocodone may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis.

5.11 Cytochrome P450 CYP3A4 Inhibitors and Inducers

Since the CYP3A4 isoenzyme plays a major role in the metabolism of HYSINGLA ER, drugs that alter CYP3A4 activity may cause changes in clearance of hydrocodone which could lead to changes in hydrocodone plasma concentrations.

The clinical results with CYP3A4 inhibitors show an increase in hydrocodone plasma concentrations and possibly increased or prolonged opioid effects, which could be more pronounced with concomitant use of

CYP3A4 inhibitors. The expected clinical result with CYP3A4 inducers is a decrease in hydrocodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to hydrocodone.

If co-administration is necessary, caution is advised when initiating HYSINGLA ER treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved [*see Dosage and Administration 2.6, Drug Interactions (7.1)*].

5.12 Driving and Operating Machinery

HYSINGLA ER may impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Peak blood levels of hydrocodone may occur 14 – 16 hours (range 6 – 30 hours) after initial dosing of HYSINGLA ER tablet administration. Blood levels of hydrocodone, in some patients, may be high at the end of 24 hours after repeated-dose administration. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of HYSINGLA ER and know how they will react to the medication [*see Clinical Pharmacology (12.3)*].

5.13 Interaction with Mixed Agonist/Antagonist Opioid Analgesics

Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) in patients who have received, or are receiving, a course of therapy with a full opioid agonist analgesic, including HYSINGLA ER. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

5.14 QTc Interval Prolongation

QTc prolongation has been observed with HYSINGLA ER following daily doses of 160 mg [*see Clinical Pharmacology (12.2)*]. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing HYSINGLA ER in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QTc interval.

HYSINGLA ER should be avoided in patients with congenital long QT syndrome. In patients who develop QTc prolongation, consider reducing the dose by 33 – 50%, or changing to an alternate analgesic.

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 (5.2)*]
- Neonatal Opioid Withdrawal Syndrome [*see Warnings and Precautions (5.3)*]
- Interactions with Other CNS Depressants [*see Warnings and Precautions (5.4)*]
- Hypotensive effects [*see Warnings and Precautions (5.8)*]
- Gastrointestinal Effects [*see Warnings and Precautions (5.9, 5.10)*]

6.1 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.

A total of 1,827 patients were treated with HYSINGLA ER in controlled and open-label chronic pain clinical trials. Five hundred patients were treated for 6 months and 364 patients were treated for 12 months. The clinical trial population consisted of opioid-naïve and opioid-experienced patients with persistent moderate to severe chronic pain.

The common adverse reactions ($\geq 2\%$) reported by patients in clinical trials comparing HYSINGLA ER (20-120 mg/day) with placebo are shown in Table 2 below:

Table 2: Adverse Reactions Reported in $\geq 2\%$ of Patients during the Open-Label Titration Period and Double-Blind Treatment Period: Opioid-Naïve and Opioid-Experienced Patients

MedDRA Preferred Term	Open-label Titration Period (N=905) (%)	Double-blind Treatment Period	
		Placebo (N=292) (%)	HYSINGLA ER (N=296) (%)
Nausea	16	5	8
Constipation	9	2	3
Vomiting	7	3	6
Dizziness	7	2	3
Headache	7	2	2
Somnolence	5	1	1
Fatigue	4	1	1
Pruritus	3	<1	0
Tinnitus	2	1	2
Insomnia	2	2	3
Decreased appetite	1	1	2
Influenza	1	1	3

The adverse reactions seen in controlled and open-label chronic pain studies are presented below in the following manner: most common ($\geq 5\%$), common ($\geq 1\%$ to $< 5\%$), and less common ($< 1\%$).

The most common adverse reactions ($\geq 5\%$) reported by patients treated with HYSINGLA ER in the chronic pain clinical trials were constipation, nausea, vomiting, fatigue, upper respiratory tract infection, dizziness, headache, somnolence.

The common ($\geq 1\%$ to $< 5\%$) adverse events reported by patients treated with HYSINGLA ER in the chronic pain clinical trials organized by MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class were:

Ear and labyrinth disorders tinnitus

<i>Gastrointestinal disorders</i>	abdominal pain, abdominal pain upper, diarrhea, dry mouth, dyspepsia, gastroesophageal reflux disease
<i>General disorders and administration site conditions</i>	chest pain, chills, edema peripheral, pain, pyrexia
<i>Infections and infestations</i>	bronchitis, gastroenteritis, gastroenteritis viral, influenza, nasopharyngitis, sinusitis, urinary tract infection
<i>Injury, poisoning and procedural complications</i>	fall, muscle strain
<i>Metabolism and nutrition disorders</i>	decreased appetite
<i>Musculoskeletal and connective tissue disorders</i>	arthralgia, back pain, muscle spasms, musculoskeletal pain, myalgia, pain in extremity
<i>Nervous system disorders</i>	lethargy, migraine, sedation
<i>Psychiatric disorders</i>	anxiety, depression, insomnia
<i>Respiratory, thoracic and mediastinal disorders</i>	cough, nasal congestion, oropharyngeal pain
<i>Skin and subcutaneous tissue disorders</i>	hyperhidrosis, pruritus, rash
<i>Vascular disorders</i>	hot flush, hypertension

Other less common adverse reactions that were seen in <1% of the patients in the HYSINGLA ER chronic pain clinical trials include the following in alphabetical order: abdominal discomfort, abdominal distention, agitation, asthenia, choking, confusional state, depressed mood, drug hypersensitivity, drug withdrawal syndrome, dysphagia, dyspnea, esophageal obstruction, flushing, hypogonadism, hypotension, hypoxia, irritability, libido decreased, malaise, mental impairment, mood altered, muscle twitching, edema, orthostatic hypotension, palpitations, presyncope, retching, syncope, thinking abnormal, thirst, tremor, and urinary retention.

7 DRUG INTERACTIONS

7.1 Drugs Affecting Cytochrome P450 Isoenzymes

Inhibitors of CYP3A4

Co-administration of HYSINGLA ER with ketoconazole, a strong CYP3A4 inhibitor, significantly increased the plasma concentrations of hydrocodone. Inhibition of CYP3A4 activity by inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may prolong opioid effects. Caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved [*see Clinical Pharmacology (12.3)*].

Inducers of CYP3A4

CYP3A4 inducers may induce the metabolism of hydrocodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in hydrocodone plasma concentrations, lack of efficacy or, possibly, development of a withdrawal syndrome in a patient who had developed physical dependence to hydrocodone. If co-administration with HYSINGLA ER is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved [*see Clinical Pharmacology (12.3)*].

7.2 Central Nervous System Depressants

The concomitant use of HYSINGLA ER with other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol can increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving CNS depressants and HYSINGLA ER for signs of respiratory depression, sedation and hypotension.

When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced [*see Warnings and Precautions (5.4)*].

7.3 Interactions with Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) and partial agonist analgesics (buprenorphine) may reduce the analgesic effect of HYSINGLA ER or precipitate withdrawal symptoms in these patients. Avoid the use of mixed agonist/antagonist and partial agonist analgesics in patients receiving HYSINGLA ER.

7.4 MAO Inhibitors

HYSINGLA ER is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. No specific interaction between hydrocodone and MAO inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

7.5 Anticholinergics

Anticholinergics or other drugs with anticholinergic activity when used concurrently with opioid analgesics may increase the risk of urinary retention or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention and constipation in addition to respiratory and central nervous system depression when HYSINGLA ER is used concurrently with anticholinergic drugs.

7.6 Strong Laxatives

Concomitant use of HYSINGLA ER with strong laxatives (e.g., lactulose), that rapidly increase gastrointestinal motility, may decrease hydrocodone absorption and result in decreased hydrocodone plasma levels. If HYSINGLA ER is used in these patients, closely monitor for the development of adverse events as well as changing analgesic requirements.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of HYSINGLA ER use during pregnancy. Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. In animal reproduction studies with hydrocodone in rats and rabbits no embryotoxicity or teratogenicity was observed. However, reduced pup survival rates, reduced fetal/pup body weights, and delayed ossification were observed at doses causing maternal toxicity. In all of the studies conducted, the exposures in animals were less than the human exposure (see Animal Data). HYSINGLA ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly [*see Warnings and Precautions (5.3)*].

Data

Animal Data

No evidence of embryotoxicity or teratogenicity was observed after oral administration of hydrocodone throughout the period of organogenesis in rats and rabbits at doses up to 30 mg/kg/day (approximately 0.1 and 0.3-fold, respectively, the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons). However, in these studies, reduced fetal body weights and delayed ossification were observed in rat at 30 mg/kg/day and reduced fetal body weights were observed in rabbit at 30 mg/kg/day (approximately 0.1 and 0.3-fold, respectively, the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons). In a pre- and post-natal development study pregnant rats were administered oral hydrocodone throughout the period of gestation and lactation. At a dose of 30 mg/kg/day decreased pup viability, pup survival indices, litter size and pup body weight were observed. This dose is approximately 0.1-fold the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons.

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression in neonates. HYSINGLA ER is not recommended for use in women immediately prior to and during labor, when use of shorter acting analgesics or other analgesic techniques are more appropriate. HYSINGLA ER may 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.

8.3 Nursing Mothers

Hydrocodone is present in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue HYSINGLA ER, taking into account the importance of the drug to the mother. Infants exposed to HYSINGLA ER 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.

8.4 Pediatric Use

The safety and effectiveness of HYSINGLA ER in pediatric patients have not been established.

Accidental ingestion of a single dose of HYSINGLA ER in children can result in a fatal overdose of hydrocodone [*see Warnings and Precautions (5.2)*].

HYSINGLA ER gradually forms a viscous hydrogel (i.e., a gelatinous mass) when exposed to water or other fluids. Pediatric patients may be at increased risk of esophageal obstruction, dysphagia, and choking because of a smaller gastrointestinal lumen if they ingest HYSINGLA ER [*see Warnings and Precautions (5.9)*].

8.5 Geriatric Use

In a controlled pharmacokinetic study, elderly subjects (greater than 65 years) compared to young adults had similar plasma concentrations of hydrocodone [see *Clinical Pharmacology (12.3)*]. Of the 1827 subjects exposed to HYSINGLA ER in the pooled chronic pain studies, 241 (13%) were age 65 and older (including those age 75 and older), while 42 (2%) 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 HYSINGLA ER.

Hydrocodone may cause confusion and over-sedation in the elderly. In addition, because of the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease and concomitant use of CNS active medications, start elderly patients on low doses of HYSINGLA ER and monitor closely for adverse events such as respiratory depression, sedation, and confusion.

8.6 Hepatic Impairment

No adjustment in starting dose with HYSINGLA ER is required in patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment may have higher plasma concentrations than those with normal hepatic function. Initiate therapy with 1/2 the initial dose of HYSINGLA ER in patients with severe hepatic impairment and monitor closely for adverse events such as respiratory depression [see *Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

No dose adjustment is need in patients with mild renal impairment. Patients with moderate or severe renal impairment or end stage renal disease have higher plasma concentrations than those with normal renal function. Initiate therapy with 1/2 the initial dose of HYSINGLA ER in these patients and monitor closely for adverse events such as respiratory depression [see *Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

HYSINGLA ER contains hydrocodone bitartrate, a Schedule II controlled substance with a high potential for abuse similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone. HYSINGLA ER can be abused and is subject to misuse, abuse, addiction and criminal diversion. The high drug content in the extended-release formulation adds to the risk of adverse outcomes from abuse and misuse.

9.2 Abuse

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.

Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get “high,” or the use of steroids for performance enhancement and muscle build up.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: 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 to addicts and drug abusers. Drug seeking tactics include, but are not limited to, emergency calls or visits near the end of office hours, refusal to undergo appropriate

examination, testing or referral, repeated claims of “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers, people with untreated addiction, and criminals seeking drugs to sell. 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. Physicians 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.

HYSINGLA ER 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 law, is strongly advised.

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

Abuse may occur by taking intact tablets in quantities greater than prescribed or without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation. The risk is increased with concurrent use of HYSINGLA ER with alcohol or other central nervous system depressants

Risks Specific to Abuse of HYSINGLA ER

HYSINGLA ER is for oral use only. Abuse of HYSINGLA ER poses a risk of overdose and death.. Taking cut, broken, chewed, crushed, or dissolved HYSINGLA ER increases the risk of overdose and death.

With parenteral abuse, the inactive ingredients in HYSINGLA ER can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

Abuse Deterrence Studies

HYSINGLA ER is formulated with physicochemical properties intended to make the tablet more difficult to manipulate for misuse and abuse, and maintains some extended release characteristics even if the tablet is physically compromised. To evaluate the ability of these physicochemical properties to reduce the potential for abuse of HYSINGLA ER, a series of *in vitro* laboratory studies, pharmacokinetic studies and clinical abuse potential studies was conducted. A summary is provided at the end of this section.

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 HYSINGLA ER resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some extended-release properties despite manipulation. When subjected to an aqueous environment, HYSINGLA ER gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a hypodermic needle.

Clinical Abuse Potential Studies

Studies in Non-dependent Opioid Abusers

Two randomized, double-blind, placebo and active-comparator studies in non-dependent opioid abusers were conducted to characterize the abuse potential of HYSINGLA ER following physical manipulation and administration via the intranasal and oral routes. For both studies, 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 measured on a unipolar scale of 0 to 100 where 0 represents the strongest negative response (“definitely would not take drug again”) and 100 represents the strongest positive response (“definitely would take drug again”).

Intranasal Abuse Potential Study

In the intranasal abuse potential study, 31 subjects were dosed and 25 subjects completed the study. Treatments studied included intranasally administered tampered HYSINGLA ER 60 mg tablets, powdered hydrocodone bitartrate 60 mg, and placebo. Incomplete dosing due to granules falling from the subjects’ nostrils occurred in 82% (n = 23) of subjects receiving tampered HYSINGLA ER compared to no subjects with powdered hydrocodone or placebo.

The intranasal administration of tampered HYSINGLA ER was associated with statistically significantly lower mean and median scores for drug liking and take drug again ($P < 0.001$ for both), compared with powdered hydrocodone as summarized in Table 3.

Table 3. Summary of Maximum Scores (E_{max}) on Drug Liking and Take Drug Again VAS Following intranasal Administration of HYSINGLA ER and Hydrocodone Powder in Non-dependent Opioid Abusers

VAS Scale (100 point)	HYSINGLA ER	Hydrocodone
<i>Intranasal (n=25)</i>	Manipulated	Powder
Drug Liking*		
Mean (SE)	65.4 (3.7)	90.4 (2.6)
Median (Range)	56 (50–100)	100 (51–100)
Take Drug Again**		
Mean (SE)	36.4 (8.2)	85.2 (5.0)
Median (Range)	14 (0-100)	100 (1-100)

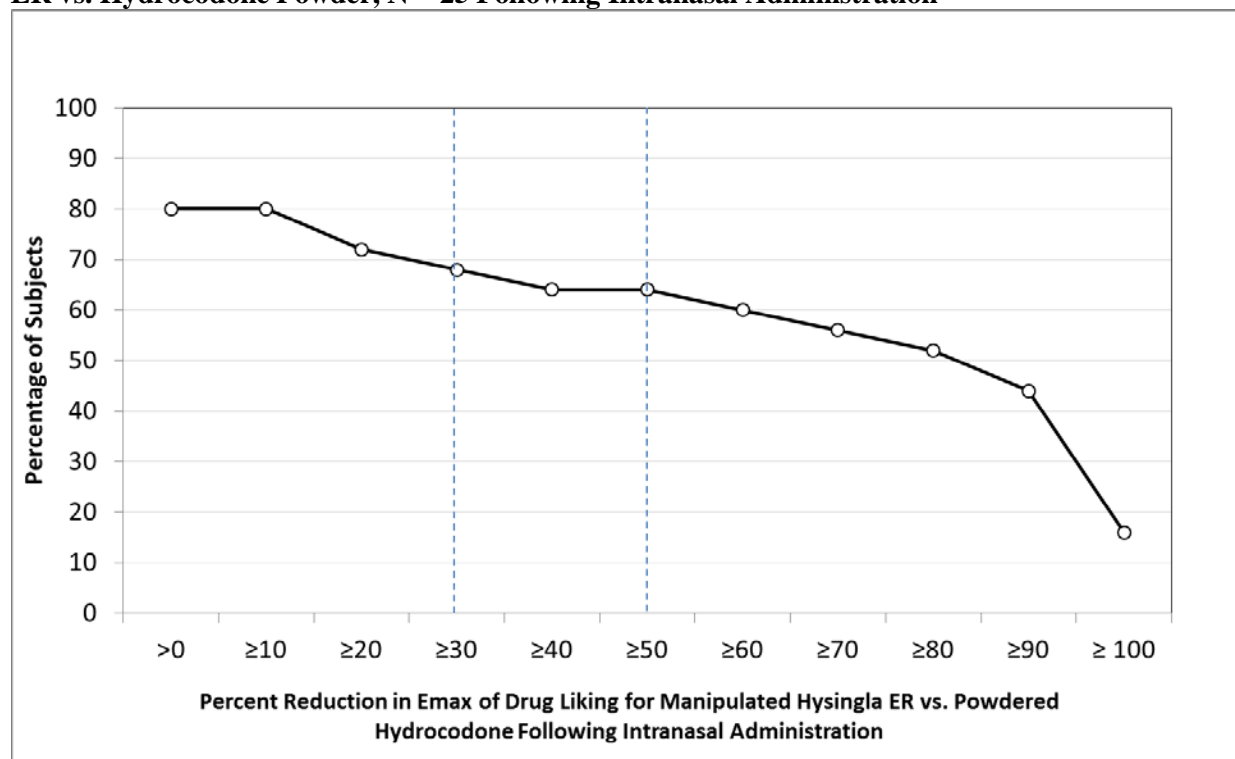
*Bipolar scale (0=maximum negative response, 50=neutral response, 100=maximum positive response)

** Unipolar scale (0=maximum negative response, 100=maximum positive response)

Figure 1 demonstrates a comparison of peak drug liking scores for tampered HYSINGLA ER compared with powdered hydrocodone in subjects (n = 25) who received both treatments intranasally. The Y-axis represents the percent of subjects attaining a percent reduction in peak drug liking scores for tampered HYSINGLA ER vs. hydrocodone powder greater than or equal to the value on the X-axis.

Approximately 80% (n = 20) of subjects had some reduction in drug liking with tampered HYSINGLA ER relative to hydrocodone powder. Sixty-eight percent (n = 17) of subjects had a reduction of at least 30% in drug liking with tampered HYSINGLA ER compared with hydrocodone powder, and approximately 64% (n = 16) of subjects had a reduction of at least 50% in drug liking with tampered HYSINGLA ER compared with hydrocodone powder. Approximately 20% (n = 5) of subjects had no reduction in liking with tampered HYSINGLA ER relative to hydrocodone powder.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for Manipulated HYSINGLA ER vs. Hydrocodone Powder, N = 25 Following Intranasal Administration



Oral Abuse Potential Study

In the oral abuse potential study, 40 subjects were dosed and 35 subjects completed the study. Treatments studied included oral administrations of chewed HYSINGLA ER 60 mg tablets, intact HYSINGLA ER 60 mg tablets, 60 mg aqueous hydrocodone bitartrate solution, and placebo.

The oral administration of chewed and intact HYSINGLA ER was associated with statistically lower mean and median scores on scales that measure drug liking and desire to take drug again ($P < 0.001$), compared to hydrocodone solution as summarized in Table 4.

Table 4. Summary of Maximum Scores (E_{max}) on Drug Liking and Take Drug Again VAS Following Oral Administration of HYSINGLA ER and Hydrocodone Solution in Non-dependent Recreational Opioid Users

VAS Scale (100 point)	HYSINGLA ER		Hydrocodone Solution
	Intact	Chewed	
<i>Oral</i> (n=35)			
Drug Liking*			
Mean (SE)	63.3 (2.7)	69.0 (3.0)	94.0 (1.7)
Median (Range)	58 (50–100)	66 (50–100)	100 (51–100)
Take Drug Again**			
Mean (SE)	34.3 (6.1)	44.3 (6.9)	89.7 (3.6)
Median (Range)	24 (0-100)	55 (0-100)	100 (1-100)

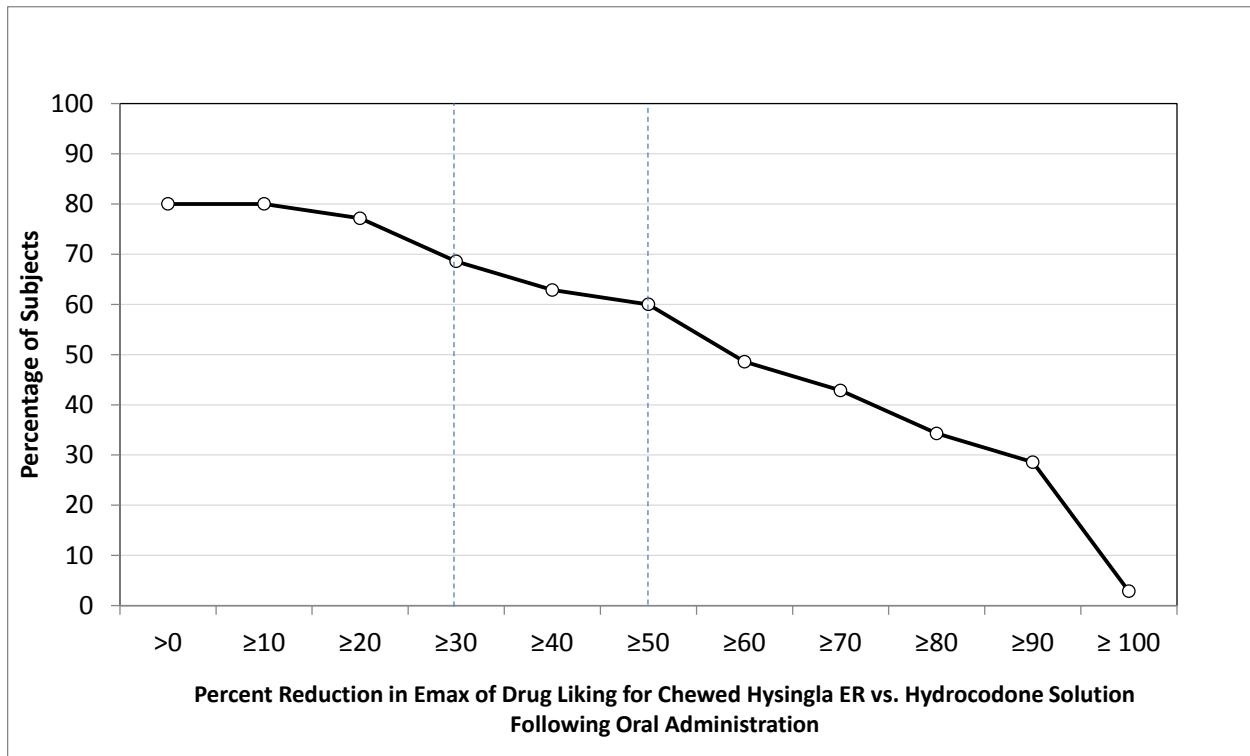
*Bipolar scale (0=maximum negative response, 50=neutral response, 100=maximum positive response)

** Unipolar scale (0=maximum negative response, 100=maximum positive response)

Figure 2 demonstrates a comparison of peak drug liking scores for chewed HYSINGLA ER compared with hydrocodone solution in subjects who received both treatments orally. The Y-axis represents the percent of subjects attaining a percent reduction in peak drug liking scores for chewed HYSINGLA ER vs. hydrocodone solution greater than or equal to the value on the X-axis.

Approximately 80% (n = 28) of subjects had some reduction in drug liking with chewed HYSINGLA ER relative to hydrocodone solution. Approximately 69% (n = 24) of subjects had a reduction of at least 30% in drug liking with chewed HYSINGLA ER compared with hydrocodone solution, and approximately 60% (n = 21) of subjects had a reduction of at least 50% in drug liking with chewed HYSINGLA ER compared with hydrocodone solution. Approximately 20% (n = 7) of subjects had no reduction in drug liking with chewed HYSINGLA ER relative to hydrocodone solution.

Figure 2. Percent Reduction Profiles for E_{max} of Drug Liking VAS for Chewed HYSINGLA ER vs. Hydrocodone Solution, N = 35 Following Oral Administration



The results of a similar analysis of drug liking for intact HYSINGLA ER relative to hydrocodone solution were comparable to the results of chewed HYSINGLA ER relative to hydrocodone solution.

Approximately 83% (n = 29) of subjects had some reduction in drug liking with intact HYSINGLA ER relative to hydrocodone solution. Eighty-three percent (n = 29) of subjects had a reduction of at least 30% in peak drug liking scores with intact HYSINGLA ER compared to hydrocodone solution, and approximately 74% (n = 26) of subjects had a reduction of at least 50% in peak drug liking scores with intact HYSINGLA ER compared with hydrocodone solution. Approximately 17% (n = 6) had no reduction in drug liking with intact HYSINGLA ER relative to hydrocodone solution.

Summary

The *in vitro* data demonstrate that HYSINGLA ER has physical and chemical properties that are expected to deter intranasal and intravenous abuse. The data from the clinical abuse potential studies, along with support from the *in vitro* data, also indicate that HYSINGLA ER has physicochemical properties that are expected to reduce intranasal abuse and oral abuse when chewed. However, abuse of HYSINGLA ER by the intravenous, intranasal, and oral routes is still possible.

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

HYSINGLA ER contains hydrocodone, 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, oxycodone, and oxymorphone. HYSINGLA ER can be abused and is subject to misuse, addiction, and criminal diversion [*See Warnings and Precautions (5.1) and Drug Abuse and Dependence (9)*].

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 results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

HYSINGLA ER should be discontinued by a gradual downward titration [*see Dosage and Administration (2.7)*]. If HYSINGLA ER is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms [*see Warnings and Precautions (5.3) and Use in Specific Populations (8.3)*].

10 OVERDOSAGE

10.1 Symptoms

Acute overdosage with opioids is often characterized by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, sometimes, pulmonary edema, bradycardia, hypotension, and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations [*see Clinical Pharmacology (12.2)*].

10.2 Treatment

In the treatment of HYSINGLA ER overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation.

Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

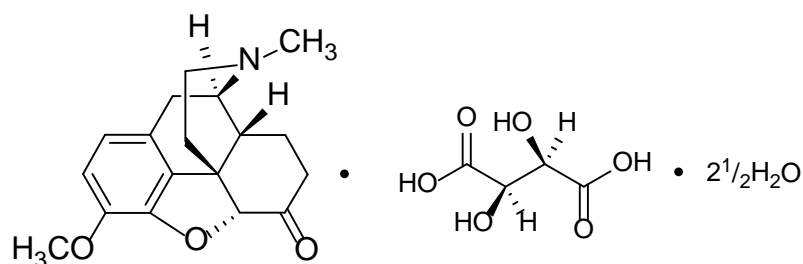
The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression that may result from opioid overdose. Nalmefene is an alternative opioid antagonist, which may be administered as a specific antidote to respiratory depression resulting from opioid overdose. Since the duration of action of HYSINGLA ER may exceed that of the antagonist, keep the patient under continued surveillance and administer repeated doses of the antagonist according to the antagonist labeling, as needed, to maintain adequate respiration.

Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression. Administer opioid antagonists cautiously to persons who are known, or suspected to be, physically dependent on HYSINGLA ER. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced 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

HYSINGLA™ ER (hydrocodone bitartrate) extended-release tablets are supplied in 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg and 120 mg film-coated tablets for oral administration. The tablet strengths describe the amount of hydrocodone per tablet as the bitartrate salt.

Hydrocodone bitartrate is an opioid agonist. Its chemical name is 4,5 α -epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). Its structural formula is:



Empirical formula: $C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2\frac{1}{2}H_2O$; Molecular weight: 494.49.

Hydrocodone bitartrate exists as fine white crystals or a crystalline powder. It is affected by light. It is soluble in water, slightly soluble in alcohol, and insoluble in ether and chloroform.

The 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg and 120 mg tablets contain the following inactive ingredients: Butylated Hydroxytoluene (BHT, an additive in Polyethylene Oxide), Hydroxypropyl Cellulose, Macrogol/PEG 3350, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Oxide, Polysorbate 80, Polyvinyl Alcohol, Talc, Titanium Dioxide, and Black Ink.

The 20 mg tablets also contain Iron Oxide Yellow and FD&C Blue #2 Aluminum Lake/Indigo Carmine Aluminum Lake.

The 30 mg tablets also contain Iron Oxide Yellow.

The 40 mg tablets also contain Iron Oxide Yellow, Iron Oxide Red, and Iron Oxide Black.

The 60 mg tablets also contain Iron Oxide Yellow and Iron Oxide Red.

The 80 mg tablets also contain Iron Oxide Red.

The 100 mg tablets also contain FD&C Blue #2 Aluminum Lake.

Black Ink Contains: Shellac Glaze (in Ethanol), Isopropyl Alcohol, Iron Oxide Black, N-Butyl Alcohol, Propylene Glycol and Ammonium Hydroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hydrocodone is a semi-synthetic opioid agonist with relative selectivity for the mu-opioid receptor, although it can interact with other opioid receptors at higher doses. Hydrocodone acts as an agonist binding to and activating opioid receptors in the brain and spinal cord, which are coupled to G-protein complexes and modulate synaptic transmission through adenylate cyclase. The pharmacological effects of hydrocodone including analgesia, euphoria, respiratory depression and physiological dependence are believed to be primarily mediated via μ opioid receptors.

12.2 Pharmacodynamics

Cardiac Electrophysiology

QTc interval prolongation was studied in a double-blind, placebo- and positive-controlled 3-treatment parallel-group, dose-escalating study of HYSINGLA ER in 196 healthy subjects. QTc interval prolongation was observed following HYSINGLA ER 160 mg per day. The maximum mean (90% upper confidence bound) difference in the QTc interval between HYSINGLA ER and placebo (after baseline-correction) at steady state was 6 (9) milliseconds, 7 (10) milliseconds, and 10 (13) milliseconds at HYSINGLA ER doses of 80 mg, 120 mg and 160mg respectively. For clinical implications of the prolonged QTc interval, see Warnings and Precautions (5.14).

Central Nervous System

The principal therapeutic action of hydrocodone is analgesia. In common with other opioids, hydrocodone causes respiratory depression, in part by a direct effect on the brainstem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation. Opioids depress the cough reflex by direct effect on the cough center in the medulla.

Hydrocodone 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 (10.1)*]. In addition to analgesia, the widely diverse effects of hydrocodone include drowsiness, changes in mood, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous system [*see Clinical Pharmacology (12.2)*].

Gastrointestinal Tract and Other Smooth Muscle

Hydrocodone 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 gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Hydrocodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System

Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

Immune System

In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

Concentration/Exposure—Efficacy Relationships

The minimum effective plasma concentration of hydrocodone for analgesia varies widely among patients, especially among patients who have been previously treated with agonist opioids. As a result, titrate the doses of individual patients to achieve a balance between therapeutic and adverse effects. The minimum effective analgesic concentration of hydrocodone for any individual patient may increase over time due to an increase in pain, progression of disease, development of a new pain syndrome and/or potential development of analgesic tolerance.

Concentration/Exposure—Adverse Experience Relationships

There is a general relationship between increasing opioid plasma concentration and increasing frequency of adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression. As with all opioids, the dose of HYSINGLA ER must be individualized [*see Dosage and Administration (2.1, 2.2)*]. The effective analgesic dose for some patients will be too high to be tolerated by other patients.

12.3 Pharmacokinetics

Absorption

HYSINGLA ER is a single-entity extended-release formulation of hydrocodone that yields a gradual increase in plasma hydrocodone concentrations with a median T_{max} of 14 – 16 hours noted for different dose strengths. Peak plasma levels may occur in the range of 6 -30 hours after single dose HYSINGLA ER administration.

Systemic exposure (AUC and C_{max}) increased linearly with doses from 20 to 120 mg. Both C_{max} and AUC increased slightly more than dose proportionally (Table 5). The mean terminal half-life ($t_{1/2}$) was similar for all HYSINGLA ER dose strengths ranging from 7 to 9 hours.

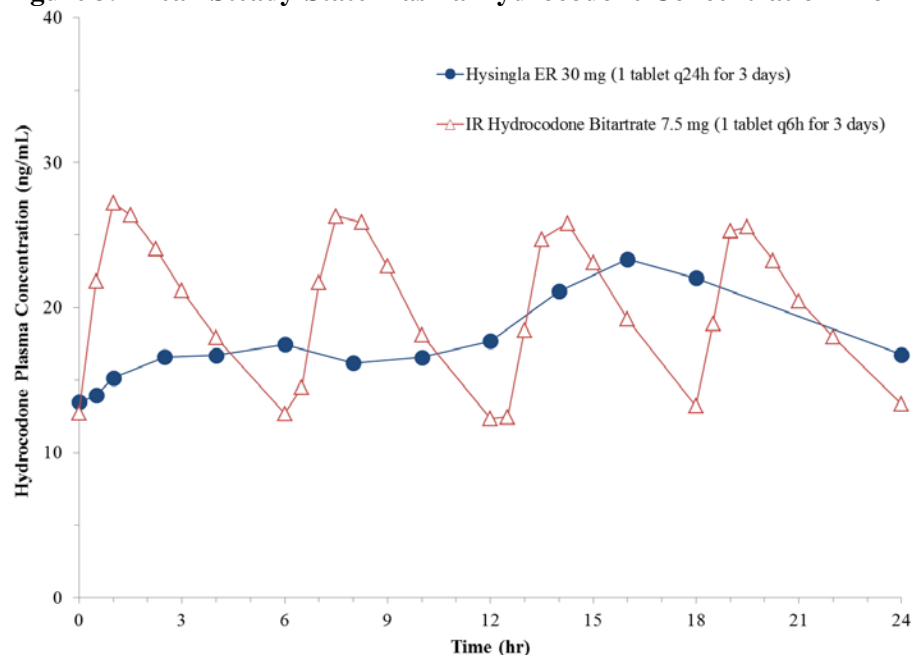
Table 5 Mean (SD) Single-Dose Pharmacokinetic Parameters of HYSINGLA ER

Dose Strength (mg)	AUC _{inf} (ng•h/mL)	C_{max} (ng/mL)	T_{max} * (h)
20	284 (128)	14.6 (5.5)	16 (6, 24)
40	622 (252)	33.9 (11.8)	16 (6, 24)
60	1009 (294)	53.6 (15.4)	14 (10, 30)
80	1304 (375)	69.1 (17.2)	16 (10, 24)
120	1787 (679)	110 (44.1)	14 (6, 30)

* median (minimum, maximum)

As compared to an immediate-release hydrocodone combination product, HYSINGLA ER at the same daily dose results in similar bioavailability but with lower maximum concentrations at steady state. (Figure 3).

Figure 3. Mean Steady-State Plasma Hydrocodone Concentration Profile



Steady-state plasma hydrocodone concentrations were confirmed on day 3 of once-daily dosing of HYSINGLA ER. The extent of accumulation of systemic exposure was 1.3 and 1.1 fold with respect to AUC and C_{max} at steady-state. The mean terminal half-life ($t_{1/2}$) at steady state was 7 hours. Median T_{max} values were 14 hours (range: 12 to 24 hours) on both Day 1 and Day 5 following once daily administration of HYSINGLA ER for five days. Daily fluctuation in peak to trough plasma levels of hydrocodone were higher at 80 mg and 120 mg doses of HYSINGLA ER compared to 30 mg dose (Table 6).

Table 6 Mean (SD) Steady-State Hydrocodone Pharmacokinetic Parameters

Regimen	AUC _{24,ss} (ng•h/mL)	$C_{max,ss}$ (ng/mL)	$C_{min,ss}$ (ng/mL)	%Fluctuation*
HYSINGLA ER				
30 mg q24h	443 (128)	26.4 (7.4)	16.7 (5.2)	61 (6.4,113)
80 mg q24h	1252 (352)	82.6 (25.7)	28.2 (12)	105 (36,214)
120 mg q24h	1938 (729)	135 (50)	63.6 (29)	97.9 (32, 250)

* Mean (minimum, maximum); Percentage fluctuation in plasma concentration is derived as $(C_{max,ss} - C_{min,ss}) * 100 / C_{avg,ss}$.

Food Effects

C_{\max} and AUC of HYSINGLA ER 120 mg tablets were similar under low fat conditions relative to fasting conditions (17% and 9% higher, respectively). C_{\max} was higher (54%) under high fat conditions relative to fasting conditions; however, AUC of HYSINGLA ER 120 mg tablets was only 20% higher when co-administered with a high fat meal. HYSINGLA ER may be administered without regard to meals.

Distribution

Following administration of HYSINGLA ER, the typical (70 kg adult) value of apparent volume of distribution (V/F) is 402 L, suggesting extensive tissue distribution. The extent of *in vivo* binding of hydrocodone to human plasma proteins was minimal with a mean % bound at 36%.

Elimination

Metabolism

Hydrocodone exhibits a complex pattern of metabolism, including *N*-demethylation, *O*-demethylation, and 6-keto reduction to the corresponding 6- α - and 6- β -hydroxy metabolites. CYP3A4 mediated *N*-demethylation to inactive norhydrocodone is the primary metabolic pathway of hydrocodone with a lower contribution from CYP2B6 and CYP2C19. The minor metabolite hydromorphone (<3% of the circulating parent hydrocodone) was mainly formed by CYP2D6 mediated *O*-demethylation with a smaller contribution by CYP2B6 and CYP2C19. Hydromorphone may contribute to the total analgesic effect of hydrocodone.

Excretion

Hydrocodone and its metabolites are cleared primarily by renal excretion. The percent of administered dose excreted unchanged as hydrocodone in urine was 6.5% in subjects with normal renal function, and 5.0%, 4.8%, and 2.3% in subjects with mild, moderate, and severe renal impairment, respectively. Renal clearance (CL_r) of hydrocodone in healthy subjects was small (5.3 L/h) compared to apparent oral clearance (CL/F, 83 L/h); suggesting that non-renal clearance is the main elimination route. Ninety-nine percent of the administered dose is eliminated within 72 hours. The mean terminal half-life ($t_{1/2}$) was similar for all HYSINGLA ER dose strengths ranging from approximately 7 to 9 hours across the range of doses.

Specific Populations

Elderly (≥ 65 years)

Following administration of 40 mg HYSINGLA ER, the pharmacokinetics of hydrocodone in healthy elderly subjects (65 to 77 years) are similar to the pharmacokinetics in healthy younger subjects (20 to 45 years). There were no clinically meaningful increase in C_{\max} (16%) and AUC (15%) of hydrocodone in elderly as compared with younger adult subjects [see *Use in Specific Populations (8.5)*].

Gender

Systemic exposure of hydrocodone (C_{\max} and AUC) was similar between males and females.

Hepatic Impairment

After a single dose of 20 mg HYSINGLA ER in subjects (8 each) with normal hepatic function, mild, moderate or severe hepatic impairment based on Child-Pugh classifications, mean hydrocodone C_{\max} values were 16, 15, 17, and 18 ng/mL, respectively. Mean hydrocodone AUC values were 342, 310, 390, and 415 ng.hr/mL for subjects with normal hepatic function, mild, moderate or severe hepatic impairment, respectively. Mean hydrocodone C_{\max} values were -6%, 5%, and 5% and AUC values were -14%, 13%, and 4% in patients with mild, moderate or severe hepatic impairment, respectively.

The mean *in vivo* plasma protein binding of hydrocodone across the groups was similar, ranging from 33% to 37% [see *Use in Specific Populations (8.6)*].

Renal Impairment

After a single dose of 60 mg HYSINGLA ER in subjects (8 each) with normal renal function, mild, moderate, or severe renal impairment based on Cockcroft-Gault criteria and end stage renal disease patients, mean hydrocodone C_{max} values were 40, 50, 51, 46, and 38 ng/mL, respectively. Mean hydrocodone AUC values were 754, 942, 1222, 1220, and 932 ng.hr/mL for subjects with normal renal function, mild, moderate or severe renal impairment and ESRD, respectively. Hydrocodone C_{max} values were 14%, 23%, 11% and -13% and AUC values were 13%, 61%, 57% and 4% higher in patients with mild, moderate or severe renal impairment or end stage renal disease, respectively [see *Use in Specific Populations* (8.7)].

Drug Interaction Studies

CYP3A4

Co-administration of HYSINGLA ER (20 mg single dose) and CYP3A4 inhibitor ketoconazole (200 mg BID for 6 days) increased mean hydrocodone AUC and C_{max} by 135% and 78%, respectively [see *Warnings and Precautions* (5.11) and *Drug Interactions* (7.1)].

CYP2D6

The 90% confidence interval (CI) of the geometric means for hydrocodone AUC_{inf} (98 to 115%), AUC_t (98 to 115%), and C_{max} (93 to 121%) values were within the range of 80 to 125% when a single dose of HYSINGLA ER 20 mg was co-administered with CYP2D6 inhibitor paroxetine (20 mg treatment each morning for 12 days). No differences in systemic exposure of hydrocodone were observed in the presence of paroxetine.

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Hydrocodone was evaluated for carcinogenic potential in rats and mice.

In a two-year bioassay in rats, doses up to 25 mg/kg in males and females were administered orally and no treatment-related neoplasms were observed (exposure is equivalent to 0.2-fold the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons). In a two-year bioassay in mice, doses up to 200 mg/kg in males and 100 mg/kg in females were administered orally and no treatment-related neoplasms were observed (exposure is equivalent to 3.5-fold and 3.0-fold, respectively, the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons).

Mutagenesis

Hydrocodone was genotoxic in the mouse lymphoma assay in the presence of rat S9 metabolic activation but not in the absence of rat metabolic activation. However, hydrocodone was not genotoxic in the mouse lymphoma assay with or without human S9 metabolic activation. There was no evidence of genotoxic potential with hydrocodone in an *in vitro* bacterial reverse mutation assay with *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation or in an *in vivo* mouse bone marrow micronucleus test with or without metabolic activation.

Impairment of Fertility

No effect on fertility or general reproductive performance was seen with oral administration of hydrocodone to male and female rats at doses up to 25 mg/kg/day (approximately 0.06-fold and 0.08-fold, respectively, the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons).

14 CLINICAL STUDIES

The efficacy and safety of HYSINGLA ER was evaluated in a randomized double-blind, placebo-controlled, multi-center, 12-week clinical trial in both opioid-experienced and opioid-naïve patients with moderate to severe chronic low back pain.

14.1 Moderate to Severe Chronic Lower Back Pain Study

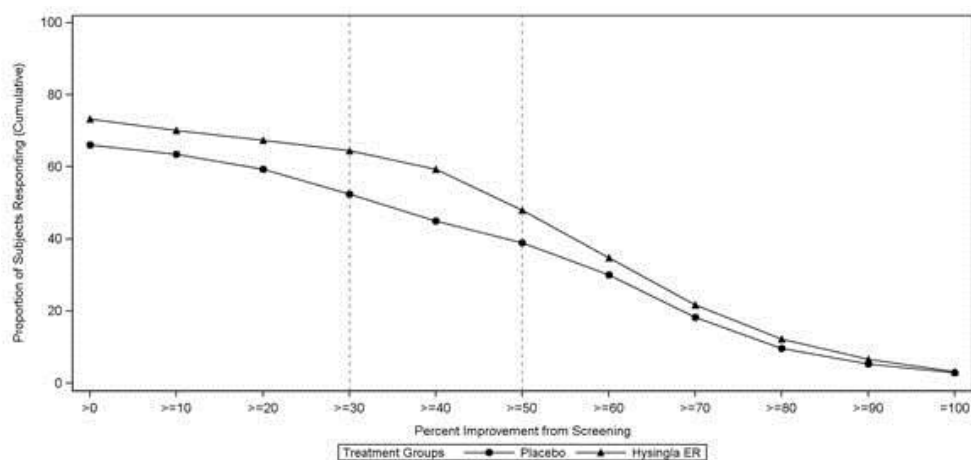
A total of 905 chronic low back pain patients (opioid naive and opioid-experienced) who were not responsive to their prior analgesic therapy entered an open-label conversion and dose-titration period for up to 45 days with HYSINGLA ER. Patients were dosed once daily with HYSINGLA ER (20 to 120 mg). Patients stopped their prior opioid analgesics and/or nonopioid analgesics prior to starting HYSINGLA ER treatment. Optional use of rescue medication (immediate-release oxycodone 5 mg) up to 2 doses (2 tablets) was permitted during the dose titration period. For inadequately controlled pain, HYSINGLA ER dose was allowed to be increased once every 3–5 days until a stabilized and tolerable dose was identified. During the dose-titration period, 65% of the patients achieved a stable HYSINGLA ER dose and entered the double-blind treatment period. The remaining subjects discontinued from the dose-titration period for the following reasons: adverse events (10%); lack of therapeutic effect (5%); confirmed or suspected diversion (3%); subject's choice (5%); lost to follow-up (2%); administrative reasons (2%); and failure to achieve protocol-defined reduction in pain score (7%).

Following the dose titration period, 588 patients (65%) were randomized at a ratio of 1:1 into a 12-week double-blind treatment period with their fixed stabilized dose of HYSINGLA ER (or matching placebo). These patients met the study randomization criteria of adequate analgesia (pain reduction of at least 2 points to a score of 4 or less on a 0-10 numerical rating scale) and acceptable tolerability of HYSINGLA ER. Patients randomized to placebo were given a blinded taper of HYSINGLA ER according to a pre-specified tapering schedule, 3 days on each step-down dose (reduced by 25-50% from the previous dose). Patients were allowed to use rescue medication (immediate-release oxycodone 5 mg) up to 6 doses (6 tablets) per day depending on their randomized HYSINGLA ER dose. During the double-blind period, 229 treated patients (77%) completed the 12-week treatment with HYSINGLA ER and 210 patients (72%) completed on placebo. Overall, 10% of patients discontinued due to lack of therapeutic effect (5% in HYSINGLA patients and 15% in placebo patients); 5% of patients discontinued due to adverse events (6% in HYSINGLA ER treated patients and 3% in placebo patients).

HYSINGLA ER provided greater analgesia compared with placebo. There was a statistically significant difference in the weekly average pain scores at Week 12 between the two groups.

The percentage of patients (responders) in each group who demonstrated improvement in their weekly average pain scores at Week 12, as compared with screening is shown in Figure 4. The figure is cumulative, so that patients whose change from screening is, for example, 30%, are also included at every level of improvement below 30%. Patients who did not complete the study were classified as non-responders. Treatment with HYSINGLA ER resulted in a higher proportion of responders, defined as patients with at least a 30% and 50% improvement, as compared with placebo.

Figure 4. Percent Improvement in Pain Intensity



16 HOW SUPPLIED/STORAGE AND HANDLING

HYSINGLA ER (hydrocodone bitartrate) extended-release tablets 20 mg are round, green-colored, bi-convex tablets printed with “HYD 20” and are supplied in child-resistant closure, opaque plastic bottles of 60 (NDC 59011-271-60).

HYSINGLA ER (hydrocodone bitartrate) extended-release tablets 30 mg are round, yellow-colored, bi-convex tablets printed with “HYD 30” and are supplied in child-resistant closure, opaque plastic bottles of 60 (NDC 59011-272-60).

HYSINGLA ER (hydrocodone bitartrate) extended-release tablets 40 mg are round, grey-colored, bi-convex tablets printed with “HYD 40” and are supplied in child-resistant closure, opaque plastic bottles of 60 (NDC 59011-273-60).

HYSINGLA ER (hydrocodone bitartrate) extended-release tablets 60 mg are round, beige-colored, bi-convex tablets printed with “HYD 60” and are supplied in child-resistant closure, opaque plastic bottles of 60 (NDC 59011-274-60).

HYSINGLA ER (hydrocodone bitartrate) extended-release tablets 80 mg are round, pink-colored, bi-convex tablets printed with “HYD 80” and are supplied in child-resistant closure, opaque plastic bottles of 60 (NDC 59011-275-60).

HYSINGLA ER (hydrocodone bitartrate) extended-release tablets 100 mg are round, blue-colored, bi-convex tablets printed with “HYD 100” and are supplied in child-resistant closure, opaque plastic bottles of 60 (NDC 59011-276-60).

HYSINGLA ER (hydrocodone bitartrate) extended-release tablets 120 mg are round, white-colored, bi-convex tablets printed with “HYD 120” and are supplied in child-resistant closure, opaque plastic bottles of 60 (NDC 59011-277-60).

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Dispense in tight, light-resistant container, as defined by the USP.

CAUTION

DEA FORM REQUIRED

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Addiction, Abuse, and Misuse

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

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting HYSINGLA ER or when the dose is increased, and that it can occur even at recommended doses [see *Warnings and Precautions (5.2)*]. Advise patients how to recognize respiratory depression and to seek medical attention if they are experiencing breathing difficulties.

Accidental Consumption

Inform patients that accidental exposure, especially in children, may result in respiratory depression or death [see *Warnings and Precautions (5.2)*]. Instruct patients to take steps to store HYSINGLA ER securely and to dispose of unused HYSINGLA ER in accordance with local state guidelines and/or regulations.

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that chronic use of HYSINGLA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [see *Warnings and Precautions (5.3)*].

Interaction with Alcohol and other CNS Depressants

Inform patients that the concomitant use of alcohol with HYSINGLA ER can increase the risk of life-threatening respiratory depression [see *Warnings and Precautions (5.4)*]. Instruct patients not to consume alcoholic beverages, as well as prescription and over-the-counter products that contain alcohol, during treatment with HYSINGLA ER. Inform patients that potentially serious additive effects may occur if HYSINGLA ER is used with alcohol or other CNS depressants, and not to use such drugs unless supervised by a health care provider.

Important Administration Instructions

Instruct patients how to properly take HYSINGLA ER, including the following:

- The tablets must be swallowed whole and must not be chewed, crushed, or dissolved. Taking chewed, crushed or dissolved HYSINGLA ER tablets or contents can lead to rapid release and absorption of a potentially fatal dose of hydrocodone.
- Use HYSINGLA ER exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression).
- Contact prescriber if pain control is not adequate or if there are adverse reactions occurring during therapy.
- Do not discontinue HYSINGLA ER without first discussing the need for a tapering regimen with the prescriber.
- HYSINGLA ER tablets should be taken one tablet at a time.
- Do not pre-soak, lick or otherwise wet the tablet prior to placing in the mouth which may result in difficulty swallowing HYSINGLA ER tablets.
- Take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth.

Hypotension

Inform patients that HYSINGLA ER 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).

Driving or Operating Heavy Machinery

Inform patients that HYSINGLA ER may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Blood levels of hydrocodone, in some patients, may be high at the end of 24 hours after repeated dose administration. Advise patients not to perform such tasks until they know how they will react to the medication.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention. Instruct patients to monitor their analgesic response following the use of strong laxatives and to contact the prescriber if changes are noted.

QT interval prolongation

Inform patients that QT prolongation has been observed with HYSINGLA ER [see *Clinical Pharmacology* (12.2)]. HYSINGLA ER should be avoided in patients with congenital long QT syndrome. Instruct patients with a history of congestive heart failure or bradyarrhythmias, and patients at risk for electrolyte abnormalities or who are taking other medications known to prolong the QT interval that periodic monitoring of electrocardiograms and electrolytes may be necessary during therapy with HYSINGLA ER.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in HYSINGLA ER. Advise patients how to recognize such a reaction and when to seek medical attention.

Pregnancy

Advise female patients that HYSINGLA ER may cause fetal harm and to inform the prescriber if they are pregnant or plan to become pregnant.

Nursing Mothers

Advise female patients that HYSINGLA ER passes into human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue drug [See *Use in Specific Populations* (8.3)]

Disposal of unused HYSINGLA ER

Advise patients to dispose of any unused tablets from a prescription as soon as they are no longer needed in accordance with local state guidelines and/or regulations.

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: 6,488,963; 6,733,783; 8,309,060; 8,361,499; 8,529,948; 8,551,520; 8,647,667 and 8,808,740.

Medication Guide

HYSINGLA ER (hye-SING-luh)

(hydrocodone bitartrate) extended-release tablets, CII

HYSINGLA ER is:

- A strong prescription pain medicine that contains an opioid (narcotic). It 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.

Important information about HYSINGLA ER:

- Get emergency help right away if you take too much HYSINGLA ER (overdose). When you first start taking HYSINGLA ER, 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.
- Never give anyone else your HYSINGLA ER. They could die from taking it. Store HYSINGLA ER away from children and in a safe place to prevent stealing or abuse. Selling or giving away HYSINGLA ER is against the law.

Do not take HYSINGLA ER if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking HYSINGLA ER, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- heart rhythm problems (long QT syndrome)
- 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 HYSINGLA ER during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** HYSINGLA ER passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking HYSINGLA ER with certain other medicines can cause serious side effects and could lead to death.

When taking HYSINGLA ER:

- Do not change your dose. Take HYSINGLA ER exactly as prescribed by your healthcare provider.
- Take your prescribed dose every 24 hours, at the same time every day. Do not take more than your prescribed dose in 24 hours. If you miss a dose, take your next dose at your usual time the next day.
- Swallow HYSINGLA ER whole. Do not cut, break, chew, crush, dissolve, snort, or inject HYSINGLA ER because this may cause you to overdose and die.
- HYSINGLA ER should be taken 1 tablet at a time. Do not pre-soak, lick, or wet the tablet before placing it 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 HYSINGLA ER without talking to your healthcare provider.**
- After you stop taking HYSINGLA ER, flush any unused tablets down the toilet.

While taking HYSINGLA ER, DO NOT:

- Drive or operate heavy machinery until you know how HYSINGLA ER affects you. HYSINGLA ER 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 HYSINGLA ER may cause you to overdose and die.

The possible side effects of HYSINGLA ER 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, or you are feeling faint.

These are not all the possible side effects of HYSINGLA ER. 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.

Issue: MM/YYYY