Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee Joint Meeting September 10-11, 2020

Location: Please note that due to the impact of the COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online teleconferencing platform

Topic: The Committees discussed the results of required postmarketing studies (Postmarketing Requirements 3051-1, 3051-2, 3051-3, and 3051-4) that evaluated the effect of the reformulation of OXYCONTIN (oxycodone hydrochloride extended-release tablets, manufactured by Purdue Pharma L.P., NDA 022272) on abuse, misuse, and fatal and non-fatal overdose, associated with OXYCONTIN. The Committees discussed whether these studies, in concert with other information from the published literature, have demonstrated that the reformulated OXYCONTIN product has resulted in a meaningful reduction in these outcomes. The Committees also discussed the broader public health impact of OXYCONTIN's reformulation.

These summary minutes for the September 10-11, 2020 joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee of the Food and Drug Administration were approved on November 23, 2020.

I certify that I attended the September 10-11, 2020 joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Philip Bautista, PharmD	Sonia Hernandez-Diaz, MD, MPH
Designated Federal Officer, DSaRM	Chairperson, DSaRM

Final Summary Minutes of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) Joint Meeting
September 10-11, 2020

The Drug Safety and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on September 10-11, 2020. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Purdue Pharma L.P. The meeting was called to order by Sonia Hernandez-Diaz, MD, DrPH (Chairperson). The conflict of interest statement was read into the record by Philip Bautista, PharmD (Designated Federal Officer). There were approximately 361 people online. There were a total of six Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The Committees discussed the results of required postmarketing studies (Postmarketing Requirements 3051-1, 3051-2, 3051-3, and 3051-4) that evaluated the effect of the reformulation of OXYCONTIN (oxycodone hydrochloride extended-release tablets, manufactured by Purdue Pharma L.P., NDA 022272) on abuse, misuse, and fatal and non-fatal overdose, associated with OXYCONTIN. The Committees discussed whether these studies, in concert with other information from the published literature, have demonstrated that the reformulated OXYCONTIN product has resulted in a meaningful reduction in these outcomes. The Committees also discussed the broader public health impact of OXYCONTIN's reformulation.

Attendance:
DSaRM Members Present (Voting): Marie R. Griffin, MD, MPH; Sonia Hernandez-Diaz, MD, DrPH (Chairperson); Collin A. Hovinga, PharmD, MS, FCCP; Steve Meisel, PharmD, CPPS; Lewis S. Nelson, MD; Soko Setoguchi, MD, DrPH

DSaRM Members Not Present (Voting): Denise M. Boudreau, PhD, RPh; Karim Anton Calis, PharmD, MPH, FASHP, FCCP; Laurel A. Habel, MPH, PhD; Martin Kulldorff, PhD

DSaRM Member Present (Non-Voting): Reema J. Mehta, PharmD, MPH (Industry Representative)

AADPAC Members Present (Voting): Basavana G. Goudra, MD, FRCA, FCARSCI; Jennifer Higgins, PhD (Consumer Representative); Maryam Jowza, MD; Maura S. McAuliffe, CRNA, MSN, MSNA, PhD, FAAN; Abigail B. Shoben, PhD; Michael Sprintz, DO, DFASAM; Richard D. Urman, MD, MBA; Sherif Zaafran, MD, FASA; Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP

AADPAC Member Not Present (Voting): Lonnie Zeltzer, MD

AADPAC Member Present (Non-Voting): Jay Horrow, MD, MS, FACC (Industry Representative)

Temporary Members (Voting): Maryann Amirshahi, PharmD, MD, MPH, PhD; Brian T. Bateman, MD; Phillip O. Coffin, MD, MIA, FACP, FIDSA; Alex Davis, PhD; Dean Follmann, PhD; Adam J. Gordon, MD, MPH, FACP, DFASAM; Traci C. Green, PhD, MSc; Stefan G. Kertesz, MD, MSc; Erin E. Krebs, MD, MPH; Dermot P. Maher, MD, MS, MHS; Brandon D.L. Marshall, PhD; Joseph P. O'Brien, MBA (Patient Representative); Jon E. Zibbell, PhD

FDA Participants (Non-Voting): Judy Staffa, PhD, RPh; Jana McAninch, MD, MPH, MS; Rigoberto Roca, MD; Mark Liberatore, PharmD, RAC; Josh Lloyd, MD; Silvia Calderon, PhD; Yueqin Zhao, PhD

Designated Federal Officer (Non-Voting): Philip Bautista, PharmD

Open Public Hearing Speakers: Sidney Wolfe (Public Citizen); Ed Thompson (Pharmaceutical Manufacturing Research Service, Inc.); Miguel de la Garza, MD (Florida Society of Interventional Pain Physicians); Richard Malamut, MD (Collegium Pharmaceutical); Andrew Kolodny, MD (Physicians for Responsible Opioid Prescribing); Adriane Fugh-Berman, MD (PharmedOut)

The agenda was as follows:

Day 1: Thursday, September 10, 2020

Call to Order	**Sonia Hernandez-Diaz, MD, MPH, DrPH** Chairperson, DSaRM
Introduction of Committee and Conflict of Interest Statement	**Philip Bautista, PharmD** Designated Federal Officer, DSaRM
FDA Opening Remarks	**Patrizia Cavazzoni, MD** Acting Director, CDER, FDA
OSE Introductory Remarks	**Judy Staffa, PhD, RPh** Associate Director for Public Health Initiatives Office of Surveillance and Epidemiology (OSE) CDER, FDA
In Vitro, Pharmacokinetic and Human Abuse Potential Evaluation of the Deterrent Properties of Reformulated OxyContin	**Silvia Calderon, PhD** Senior Pharmacologist Controlled Substance Staff Office of the Center Director, CDER, FDA

Reformulated OxyContin: Regulatory History of the Postmarketing Requirements (PMRs)	**Mark Liberatore, PharmD, RAC** LCDR, United States Public Health Service (USPHS) Deputy Director for Safety Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP) Office of Neuroscience (ON) Office of New Drugs (OND), CDER, FDA
A Systems Approach to Considering the Impacts of OxyContin Abuse Deterrent Formulation	**Sara Eggers, PhD** Director, Decision Support and Analysis Team Office of Program and Strategic Analysis (OPSA) Office of Strategic Programs (OSP), CDER, FDA
GUEST SPEAKER PRESENTATION	
Overview of Evaluating ADFs in the Community	**Nabarun Dasgupta, MPH, PhD** Senior Scientist Injury Prevention Research Center University of North Carolina at Chapel Hill
Clarifying Questions	
BREAK	
SPONSOR PRESENTATIONS	**Purdue Pharma, L.P.**
Introduction	**Craig Landau, MD** President and Chief Executive Officer Purdue Pharma L.P.
Overview and Results of Postmarketing Studies 1-4	**Alexander M. Walker, MD, DrPH** Principal World Health Information Science Consultants
LUNCH	
SPONSOR PRESENTATIONS (cont.)	
Real World Evidence for Opioid Analgesics with Abuse Deterrent Properties	**Richard C. Dart, MD, PhD** Director, Rocky Mountain Poison and Drug Safety Executive Director, RADARS System Professor, University of Colorado School of Medicine
Closing Remarks	**Craig Landau, MD**
Clarifying Questions	

FDA PRESENTATIONS

Utilization Patterns of Oxycodone Extended-Release Products	**Nabila Sadiq, PharmD, MPH** Drug Utilization Analyst Division of Epidemiology II (DEPI-II) Office of Pharmacovigilance and Epidemiology (OPE) OSE, CDER, FDA
Methodologic Considerations for Design and Interpretation of Reformulated OxyContin Postmarketing Studies	**Hana Lee, PhD** Staff Fellow Division of Biometrics VII (DB-VII) Office of Biostatistics (OB) Office of Translational Sciences (OTS), CDER, FDA

BREAK

FDA PRESENTATIONS (cont.)

FDA Review of PMR 3051-1 & 3051-3: Treatment Center Data to Assess the Impact of OxyContin Reformulation on Non-Oral and Overall Abuse of OxyContin	**Celeste Mallama, PhD, MPH** Epidemiologist DEPI-II, OPE, OSE, CDER, FDA
FDA Review of PMR 3051-2 & 3051-4: Poison Control Center Study and Opioid Overdose Study Using Administrative Claims Data	**Alex Secora, PhD** Epidemiologist DEPI-II, OPE, OSE, CDER, FDA
Clarifying Questions	

ADJOURNMENT

Day 2: Friday, September 11, 2020

Call to Order	**Sonia Hernandez-Diaz, MD, MPH, DrPH** Chairperson, DSaRM
Introduction of Committee	**Philip Bautista, PharmD** Designated Federal Officer, DSaRM
FDA Introductory Remarks	**Judy Staffa, PhD, RPh**

NATIONAL INSTITUTE ON DRUG ABUSE (NIDA) PRESENTATION

U.S. Opioid Crisis	**Wilson Compton, MD, MPE** Deputy Director, NIDA
Clarifying Questions	

FDA PRESENTATIONS

Literature Review: Impact of Reformulated OxyContin on Abuse and Opioid-related Morbidity and Mortality	**Christina Greene, PhD** Epidemiologist DEPI-II, OPE, OSE, CDER, FDA
FDA Summary of Postmarketing Findings on OxyContin ADF Effectiveness and Public Health Impact	**Jana McAninch, MD, MPH, MS** Senior Medical Epidemiologist DEPI-II, OPE, OSE, CDER, FDA
Clarifying Questions	

LUNCH

OPEN PUBLIC HEARING

Charge to the Committee	**Judy Staffa, PhD, RPh**
Questions to the Committee/Committee Discussion	

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss whether the evidence shows that OxyContin's reformulation with abuse-deterrent properties has meaningfully reduced its abuse (by one or more routes, or overall) and related adverse outcomes, including overdose. Please share the scientific rationale for your opinion, including what you believe to constitute a meaningful reduction.

   Committee Discussion: *Overall, the majority of the committee members agreed that the evidence shows that OxyContin's reformulation with abuse-deterrent properties reduced abuse by one or more non-oral routes. The committee members were not able to come to a consensus on what constitutes a meaningful reduction. In their discussion of what might constitute a meaningful reduction, some committee members noted that post-marketing requirement (PMR) study 3051-1 demonstrated up to 50% reduction in non-oral abuse, which they found compelling. One member also suggested that perhaps evidence of a 25% reduction in non-oral abuse could represent a meaningful reduction. Another committee member suggested the need for a higher standard of 40% reduction in overdose deaths within three years, consistent with the National Institutes of Health's HEALing Communities Study, and acknowledged that this standard has not been met by the current evidence. One member remarked that there was no evidence to suggest that someone prescribed the*

reformulated product was less likely to abuse the drug. Overall. the committee members also agreed that there was not enough evidence to demonstrate that the reformulation reduced related adverse outcomes, including overdose. Multiple committee members commented that the term "abuse-deterrent formulation" is problematic because people conflate abuse with addiction and think all forms of abuse are deterred (providing a false sense of security), and that the term "abuse" is pejorative and stigmatizing. Please see the transcript for details of the Committees' discussion.

2. **VOTE:** Does the available evidence demonstrate that the reformulation of OxyContin meaningfully reduced abuse of this product, relative to the original formulation, by one or more non-oral routes?

    a. If you answer YES, please explain:
        i. Which route(s) of abuse you believe have been meaningfully deterred by OxyContin's abuse-deterrent properties?
        ii. In which population(s) you believe this effect has been demonstrated?
        iii. How would you rate the strength of this evidence supporting your opinion, and which evidence did you find most compelling?

    b. If you answer NO, please explain:
        i. Whether you think the available data are sufficient to answer this question.
            1. If so, how would you rate the strength of this evidence supporting your opinion, and which evidence did you find most compelling?
            2. If not, what additional information do you think would be necessary to answer this question?

Vote Result: Yes: 20 No: 7 Abstain: 1

Committee Discussion: *The majority of the committee members voted "Yes", agreeing that the available evidence demonstrates that the reformulation of OxyContin meaningfully reduced abuse of the product, relative to the original formulation, by one or more non-oral routes. These members agreed that the data most strongly demonstrated reduction of abuse via intranasal and intravenous routes, and that this effect has been demonstrated mostly in patients with moderate to severe opioid use disorder. These committee members generally rated the quality of data to be moderate and found PMR study 3051-1 to be the most compelling. Some committee members stated that the consistency in results from PMR study 3051-2 and the published literature provided additional support. The committee members who voted "No" noted that the evidence was not compelling and was too weak in quality and magnitude to determine that the abuse-deterrent formulation had meaningfully reduced non-oral abuse of the product. These members argued that the data were confounded by changing prescribing patterns and other secular changes (e.g., shifts to illicit opioids) during the timeframes of the studies. One of these members stated that there were a number of other data sources (e.g., syringe services programs) that could have been utilized to better answer this question; another member stated that a prospective registry would have been needed to address this question. Another one of these members highlighted that PMR study 3051-1 studied patients with substance abuse disorder and is not generalizable to chronic pain*

patients (for whom this drug is intended). The one member who abstained stated that they could not vote "Yes" based on the quality of evidence from these types of retrospective "database" studies, and could not vote "No" as they were unsure of the most feasible study design to answer this question. Please see the transcript for details of the Committees' discussion.

3. **VOTE:** Does the available evidence demonstrate that the reformulation of OxyContin meaningfully reduced overall abuse of this product, relative to the original formulation?

    a. If you answer YES, please explain:
        i. In which population(s) you believe this effect has been demonstrated?
        ii. How would you rate the strength of this evidence supporting your opinion, and which evidence did you find most compelling?

    b. If you answer NO, please explain:
        i. Whether you think the available data are sufficient to answer this question.
            1. If so, how would you rate the strength of this evidence supporting your opinion, and which evidence did you find most compelling?
            2. If not, what additional information do you think would be necessary to answer this question?

Vote Result: Yes: 2 No: 26 Abstain: 0

Committee Discussion: *A majority of the committee members voted "No", that the available evidence does not demonstrate that the reformulation of OxyContin meaningfully reduced overall abuse of this product, relative to the original formulation. There was no consensus among these members as to whether there was sufficient evidence or whether additional information is still needed. Some of these members stated that their decision was based on PMR study 3051-2, PMR study 3051-1, and published literature by Cicero et al. Other members rated the supporting evidence as weak. One member who voted "No" added that the studies provided weak evidence when taken on an individual basis, but as a whole provided a reasonable amount of evidence to suggest no meaningful reduction in overall abuse. Several committee members agreed that the studies were plagued by confounders (such as concurrent public health efforts and secular trends) that weakened the overall strength of evidence, particularly when comparing only to the previous formulation of the same product. Several members further added that it would be difficult to control for these confounders in studies and suggested instead using prospective or randomized designs. Regarding additional information that would be necessary to answer this question, overall, the committee members highlighted the difficulty of designing a study that would permit causal inference, particularly with regard to changes in utilization of the product. One member suggested studying initiation of abuse in a population previously not engaging in*

these behaviors. One member opined that reducing overall abuse of the product was not the intent of the abuse-deterrent formulation and it would be difficult to meet this target. Another member recognized the difficulty in designing a study to better answer this question given the previous formulation is no longer on the market. One member who voted "Yes" said that the evidence suggests that the new reformulation worked as intended as there was an observed shift from non-oral abuse to oral abuse. The other member who voted "Yes" stated that misuse of the reformulated product via intranasal and intravenous routes is of more concern than oral abuse and was demonstrated to be meaningfully reduced. Please see the transcript for details of the Committees' discussion.

4. **VOTE:** Does the available evidence demonstrate that OxyContin's reformulation meaningfully reduced the risk of opioid overdose, relative to the original formulation?

    a. If you answer YES, please explain:
        ii. In which population(s) you believe this effect has been demonstrated?
        iii. How would you rate the strength of this evidence supporting your opinion, and which evidence did you find most compelling?

    b. If you answer NO, please explain:
        i. Whether you think the available data are sufficient to answer this question.
            1. If so, how would you rate the strength of this evidence supporting your opinion, and which evidence did you find most compelling?
            2. If not, what additional information do you think would be necessary to answer this question?

Vote Result: Yes: 1 No: 26 Abstain: 1

Committee Discussion: *The majority of the committee members voted "No", that the available evidence does not demonstrate that OxyContin's reformulation meaningfully reduced the risk of opioid overdose, relative to the original formulation. The committee members who voted "No" stated that PMR 3051-4 did not provide compelling evidence to demonstrate a meaningful reduction. These committee members highlighted methodology concerns with PMR 3051-4, including lost to follow-up, censoring, confounders, and the possibility of patients switching to other products due to the OxyContin reformulation. The committee members discussed the desirability of prospective studies again. One committee member noted the difficulty in determining cause of death and overdose from poison control data, medical examiner data, and coded data, such as in PMR study 3051-4. One member stated that overdose is usually a polypharmacy issue and highlighted that it is unlikely that the reformulation of one product would have a meaningful effect. The one member who voted "Yes" stated that the reformulated product has decreased the potential for overdose from abuse via intranasal and intravenous routes, asserting that decreasing abuse by these routes would likely decrease fatal overdose. The committee member who abstained highlighted the*

studies' data quality issues and lack of confirmatory toxicology data. Please see the transcript for details of the Committees' discussion.

5. **DISCUSSION:** Discuss whether the available evidence indicates that the reformulation of OxyContin had any important unintended adverse consequences.

    a. If so, please explain what these unintended consequences were, in which population(s) you believe they occurred, and what evidence you found most compelling

    b. If not, please explain whether you believe the available data are sufficient to answer this question, and if they were not, what additional information would be necessary to answer this question

    Committee Discussion: *Overall, the committee members agreed that the available evidence suggests that the reformulation of OxyContin likely had important unintended adverse consequences, such as the substitution of heroin and other opioid products with less predictable dosing, leading to adverse consequences. However, committee members agreed that while there is likely a relationship between OxyContin's reformulation and the rise in heroin overdose rates, definitively establishing causality is very difficult in the context of the evolving opioid epidemic. Please see the transcript for details of the Committees' discussion.*

6. **DISCUSSION**: Considering the totality of evidence, discuss the overall public health impact of the reformulation of OxyContin. Explain what evidence you found most compelling, and what additional information, if any, you think is needed to address this question.

    Committee Discussion: *The committee members agreed that assessing the overall public health impact of the reformulation of OxyContin is challenging but critical. They discussed several public health issues that the data suggest may have resulted from the reformulation of OxyContin. These included the substitution of heroin or other opioid products, increase in HIV and Hepatitis C that may have resulted from circumventing the abuse deterrent technology, and the potential misperception of increased safety with the use of "abuse deterrent" (vs. "crush-resistant" or "tamper-resistant") terminology to describe the technology/formulation. Some committee members stated that the new formulation provided positive public health benefits in its deterrence of dose dumping, conferring a safety benefit and reflecting the original intent of the reformulation. Other committee members suggested that the motivation for reformulating OxyContin is now outdated as drug use has become more polysubstance in nature. Some committee members highlighted the need for more data on patient and provider perceptions regarding abuse deterrent formulations. Other committee members highlighted the difficulty in answering this question from the perspective of one drug or one formulation as part of a much broader, more complex and evolving public health crisis. The committee members suggested that FDA needs to go beyond improving specific product safety and partner with other relevant HHS agencies to ensure positive*

public health impact of its regulatory actions. Please see the transcript for details of the Committees' discussion.

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

   Committee Discussion: *Overall, the committee members agreed that it is important to convey the continued risks for addiction with reformulated OxyContin to clinicians, patients and the public. They also agreed that it should be communicated that reformulated OxyContin only appears to deter abuse via non-oral routes and has not been shown to reduce overall abuse or the risk of addiction (based on post-marketing evidence). One member suggested that clinicians should be informed that some patients who become addicted may switch to heroin. The committee members added that it is important for prescribing clinicians to have the knowledge and skills to identify when their patients abuse opioids as well as how to treat and/or refer them for substance use disorder treatment. The committee members also strongly suggested making a summary of this advisory committee discussion and data available to the public. Please see the transcript for details of the Committees' discussion.*

The meeting was adjourned at approximately 5:05 p.m. Eastern Time on September 10, 2020 and 5:40 p.m. Eastern Time on September 11, 2020.