

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) Meeting

March 13-14, 2017

**Postmarketing safety issues related to reformulated
Opana ER®**

Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the postmarketing safety issues related to reformulated Opana ER® to this Advisory Committee in order to gain the Committee's 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.

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FDA CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

MEMORANDUM

DATE: February 13, 2017

FROM: Judy Staffa, Ph.D., R.Ph.
Associate Director for Public Health Initiatives
Office of Surveillance and Epidemiology (OSE), CDER, FDA

TO: Chair, Members, and Invited Guests
Drug Safety and Risk Management Advisory Committee (DSaRM) Anesthetic
and Analgesic Drug Products Advisory Committee (AADPAC)

SUBJECT: Overview of the March 13-14, 2017, DSaRM/ AADPAC Meeting to Discuss
Postmarketing safety issues related to reformulated Opana ER

At this joint meeting of DSaRM and AADPAC, we will be discussing important safety issues that have emerged around the abuse of reformulated Opana ER (NDA 201655, oxymorphone hydrochloride extended-release tablets, Endo Pharmaceuticals), which was approved in December 2011. To understand the complexities of these safety data, it is important to review the background that has brought us to our current discussion.

The reformulation of Opana ER incorporates physicochemical properties that were designed to make it more difficult to defeat the extended-release properties, and to abuse by intranasal or injection routes. FDA issued a ‘complete response’ (i.e., did not approve) Endo’s supplemental application requesting approval of labeling describing these properties in May 2013.

Accordingly, these properties are not described in the Opana ER product labeling. **The regulatory history of Opana ER and reformulated Opana ER can be found in the memo from the Division of Anesthesia, Analgesia, and Addiction Products. In addition, documentation of the inclusion of reformulated Opana ER in the classwide Extended-Release/Long-Acting Opioid Analgesic Risk Evaluation and Mitigation Strategy (ER/LA REMS), and under the ER/LA Postmarketing Required Studies (PMRS) are included for your reference, along with the current product label.**

Beginning in February 2012, Endo Pharmaceuticals (Endo) gradually replaced distribution of original Opana ER with reformulated Opana ER over the subsequent three months. In August 2012, Endo submitted a citizen petition requesting that the FDA make a determination that original Opana ER was withdrawn for safety reasons. Such an action would result in the initiation of withdrawal proceedings for approved generic products referencing original Opana

ER. FDA denied this petition in 2013, citing among its reasons certain data suggesting that reformulated Opana can more easily be prepared for injection than original Opana ER. (**The FDA response to this petition is included in this background document**). The first generic oxymorphone ER product entered the market in July 2011, followed by additional generic oxymorphone ER product approvals in early 2013. The marketplace currently includes reformulated Opana ER, original immediate-release (IR) Opana, and multiple generic oxymorphone IR and ER products. Only reformulated Opana ER has a formulation designed to deter abuse via the intranasal or injection routes. **Recent utilization patterns for all the oxymorphone products are provided in the integrated OSE review.**

When issuing the decision to deny the citizen petition, FDA noted that, although the postmarketing data available at the time were inconclusive due to multiple deficiencies, there were suggestions that rates of abuse via injection might be higher and rates of abuse via insufflation might be lower for reformulated Opana ER than for the original Opana ER. Since then, it appears that several safety concerns, including a potentially fatal bleeding disorder resembling thrombotic thrombocytopenic purpura (TTP) and an unprecedented outbreak of Human Immunodeficiency Virus (HIV) in a rural Indiana county have been associated with the intravenous abuse of reformulated Opana ER. **The published investigations of these safety issues by the Centers for Disease Control (CDC) are included in this packet. In addition, the Division of Pharmacovigilance has provided information on reported cases of thrombotic microangiopathy (a broader case definition that includes TTP) associated with reformulated Opana ER as well as other comparator products in the integrated OSE review. Finally, a study by FDA's Center for Biologic Evaluation and Research (CBER), Blood Products Division has identified a mechanism through which polyethylene oxide (PEO), an excipient added to reformulated Opana ER to deter abuse, might cause TTP when injected. This publication has been included in this packet.**

With three full years of postmarketing data on abuse available (beyond an initial transition period) and the aforementioned safety concerns associated with reformulated Opana ER, FDA is convening this advisory committee meeting to discuss the data and to help determine whether regulatory action is warranted. Evaluating the effects of products with formulations designed to be abuse-deterrent, in both the pre-market and post-market settings, is a challenge on many levels. As a new area of regulatory science, standard approaches and methodologies are still being developed. In the postmarket setting, there is no single data source that captures all of the behavioral, clinical, and demographic aspects of drug abuse, along with information on abuse of specific products via specific routes. Further adding to the methodological difficulties is the use of a variety of definitions of misuse and abuse. The methods of identifying the abuse-related clinical outcomes of interest – addiction, overdose, and death – in available data sources await robust validation and linkages as well as the development of algorithms to effectively identify them in standard clinical healthcare datasets. These and other methodological considerations are discussed in **the Guidance for industry, Abuse-Deterrent Opioids — Evaluation and Labeling, which is included in this packet.**

In vitro studies and human abuse potential (HAP) studies were conducted by Endo on reformulated Opana ER and were reviewed by Agency staff. **The in vitro studies are discussed in the review by Dr. Englund, and the HAP studies are discussed in the review by CDER's**

Controlled Substances Staff (CSS). We believe these reviews will help the committees understand the performance of this product under conditions of manipulation for abuse. The review from CSS also integrates the findings of the manipulation and extraction studies with the known pharmacological properties of oxymorphone, providing insights to assist the committee in understanding the patterns of abuse seen in the epidemiologic postmarketing studies.

As suggested by FDA's guidance, Endo has provided information from a number of sources and perspectives in their attempts to determine if there were changes in the levels of abuse (particularly with regard to the route of abuse) of reformulated Opana ER, and, furthermore, if those changes were the result of the reformulation. The sponsor has conducted two formal postmarketing studies of reformulated Opana ER's abuse using the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO), and the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) Poison Center data to assess the post-market effects of reformulated Opana ER. They have also included supportive data from the RADARS Drug Diversion and Street Price study and the StreetRx Study. While the evidence that Endo presents is multi-faceted, it is also quite complex. Each of these data sources and methodologies has its own set of assumptions and limitations that render the results more or less relevant in determining the effect of the reformulated product on abuse, route of abuse, and therefore the safety issues that result from the different routes of abuse. These assumptions are generally neither quantifiable nor testable, although they may have a critical effect on the analysis results and interpretation. **The Office of Biostatistics' review discusses these assumptions and how their violation might affect the results. An extensive discussion of the findings from each study, and an overall interpretation of the totality of evidence is provided in OSE's integrated review.**

In addition to the general challenges of studying abuse and the impact of product-specific changes in formulation on rates of abuse by different routes, determining the patterns of abuse associated with reformulated Opana ER is further complicated by the potential for misclassification of reported drugs of abuse. This is because of the presence of multiple oxymorphone products, both immediate-release and extended-release, and generic and branded, in the marketplace. The ability of individuals abusing prescription opioid products to accurately report the specific product they abuse, and the ability of data collection systems to correctly capture that information are limited. It is necessary to review the abuse patterns of all oxymorphone products to provide context for understanding what might be occurring with reformulated Opana ER. An understanding of these issues is crucial for appropriately interpreting the patterns of abuse seen in the epidemiologic data in association with all oxymorphone products, and considering appropriate regulatory actions most likely to result in improved public health.

This summary memorandum outlines the information that we hope you will find helpful in preparing for the meeting. The documents included in this package are:

1. This introductory memorandum from the Office of Surveillance & Epidemiology
2. Product label for reformulated Opana ER
3. Guidance for Industry: Abuse-Deterrent Opioids — Evaluation and Labeling

4. The Regulatory History of Opana ER
5. FDA letter response to Endo Pharmaceuticals' 2012 citizen petition
6. Memo on inclusion of Opana ER in ER/LA Opioid Analgesic REMS
7. Memo on inclusion of Opana ER in ER/LA Opioid Analgesic classwide postmarketing study requirements (PMRS)
8. Summary of in vitro studies for abuse-deterrent properties
9. Review of human abuse liability studies from CDER's Controlled Substances Staff
10. Results of laboratory analyses from the Center for Biologic Evaluation and Research (Blood Products), and publication describing a mechanism for polyethylene oxide (PEO) to cause thrombotic thrombocytopenic purpura (TTP).
11. Publications describing Centers for Disease Control investigations of TTP outbreak in Tennessee and HIV outbreak in Indiana
12. Statistical Briefing Material from the Office of Biostatistics, Division of Biometrics VII
13. Integrated Review from the Office of Surveillance & Epidemiology (includes drug utilization, pharmacovigilance and epidemiology findings)

After reviewing the evidence and hearing both Endo's and FDA's presentations, in addition to hearing comments from the public, the committee will be asked to consider the following questions:

Please discuss the strengths and limitations of the experimental and epidemiologic data regarding reformulated Opana ER, including the apparent shift in abuse patterns from snorting to injection among those abusing this product and reports of a TTP-like illness and HIV transmission associated with abuse by injection. How do these data inform our understanding of the risk/benefit balance for Opana ER, in comparison to the other marketed oxymorphone ER products?

Please discuss the potential consequences of taking regulatory action related to Opana ER (e.g., product withdrawal, labeling changes), such as effects on abuse patterns or prescribing of other products.

Thank you in advance for your attention and participation in this meeting, and for providing us with your insights on this important public health issue.

OPANA ER Product Label

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OPANA® ER safely and effectively. See full prescribing information for OPANA® ER.

OPANA® ER (oxymorphone hydrochloride) extended-release tablets, for oral use, CII

Initial U.S. Approval: 1959

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES AND OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- OPANA ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow OPANA ER tablets whole to avoid exposure to a potentially fatal dose of oxymorphone. (5.2)
- Accidental ingestion of OPANA ER, especially by children, can result in fatal overdose of oxymorphone. (5.2)
- Prolonged use of OPANA 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).
- Instruct patients not to consume alcohol or any product containing alcohol while taking OPANA ER because co-ingestion can result in fatal plasma oxymorphone levels. (5.4)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.4, 7)

RECENT MAJOR CHANGES

Boxed Warning	12/2016
Dosage and Administration (2)	12/2016
Contraindications (4)	12/2016
Warnings and Precautions (5)	12/2016

INDICATIONS AND USAGE

OPANA 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 OPANA 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)
- OPANA ER is not indicated as an as-needed (prn) analgesic. (1)

DOSAGE AND ADMINISTRATION

- To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain. (2.1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1).
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Administer on an empty stomach, at least 1 hour prior to or 2 hours after eating. (2.1)
- OPANA ER tablets should be taken one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. (2.1, 17)

- For opioid-naïve and opioid non-tolerant patients, initiate treatment with 5 mg tablets orally every 12 hours. (2.2)
- To convert to OPANA ER from another opioid, use available conversion factors to obtain estimated dose. (2.2)
- Dose can be increased every 3 to 7 days, using increments of 5 to 10 mg every 12 hours (i.e., 10 to 20 mg per day). (2.3)
- Do not abruptly discontinue OPANA ER in a physically dependent patient. (2.4, 5.14)
- **Mild Hepatic Impairment:** For opioid-naïve patients, initiate treatment with 5 mg and titrate slowly. For patients on prior opioid therapy, reduce starting dose by 50% and titrate slowly. Monitor for signs of respiratory and central nervous system depression. (2.5)
- **Renal Impairment:** For opioid-naïve patients, initiate treatment with 5 mg and titrate slowly. For patients on prior opioid therapy, reduce starting dose by 50% and titrate slowly. Monitor for signs of respiratory and central nervous system depression. (2.6)
- **Geriatric Patients:** Initiate dosing with 5 mg, titrate slowly, and monitor for signs of respiratory and central nervous system depression. (2.7)

DOSE FORMS AND STRENGTHS

Extended-release tablets: 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- **Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients:** Monitor closely, particularly during initiation and titration. (5.5, 5.6)
- **Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions:** If symptoms occur, stop administration immediately, discontinue permanently, and do not rechallenge with any oxymorphone formulation. (5.6)
- **Adrenal Insufficiency:** If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.7)
- **Severe Hypotension:** Monitor during dose initiation and titration. Avoid use of OPANA ER in patients with circulatory shock. (5.9)
- **Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury or Impaired Consciousness:** Monitor for sedation and respiratory depression. Avoid use of OPANA ER in patients with impaired consciousness or coma. (5.10)
- **Difficulty in Swallowing:** Use with caution in patients who have difficulty in swallowing or have underlying GI disorders that may predispose them to obstruction. (5.11)

ADVERSE REACTIONS

Adverse reactions in ≥2% of patients in placebo-controlled trials: nausea, constipation, dizziness, somnolence, vomiting, pruritus, headache, sweating increased, dry mouth, sedation, diarrhea, insomnia, fatigue, appetite decreased, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Endo Pharmaceuticals Inc. at 1-800-462-3636 or FDA at 1-800 FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Serotonergic Drugs:** Concomitant use may result in serotonin syndrome. Discontinue OPANA ER if serotonin syndrome is suspected. (7)
- **Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics:** Avoid use with OPANA ER because they may reduce analgesic effect of OPANA ER or precipitate withdrawal symptoms. (7)
- **Monoamine Oxidase Inhibitors (MAOIs):** Can potentiate the effects of oxymorphone. Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping treatment with an MAOI. (7)

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** May cause fetal harm. (8.1)
- **Lactation:** Not Recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

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FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

OPANA 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 OPANA ER, and monitor all patients regularly for the development of these behaviors and conditions [see *Warnings and Precautions* (5.1)].

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of OPANA ER. Monitor for respiratory depression, especially during initiation of OPANA ER or following a dose increase. Instruct patients to swallow OPANA ER tablets whole; crushing, chewing, or dissolving OPANA ER tablets can cause rapid release and absorption of a potentially fatal dose of oxymorphone [see *Warnings and Precautions* (5.2)].

Accidental Ingestion

Accidental ingestion of even one dose of OPANA ER, especially by children, can result in a fatal overdose of oxymorphone [see *Warnings and Precautions* (5.2)].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of OPANA 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)].

Interaction with Alcohol

Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking OPANA ER. The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone [see *Warnings and Precautions* (5.4)]

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see *Warnings and Precautions* (5.4), *Drug Interactions* (7)].

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

1 INDICATIONS AND USAGE

OPANA 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 [see *Warnings and Precautions* (5.1)], reserve OPANA 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.
- OPANA ER is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

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

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see *Warnings and Precautions* (5.1)].

- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see *Warnings and Precautions (5.1)*].
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with OPANA ER and adjust the dosage accordingly [see *Warnings and Precautions (5.2)*].

Instruct patients to swallow OPANA ER tablets whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth [see *Patient Counseling Information (17)*]. Crushing, chewing, or dissolving OPANA ER tablets will result in uncontrolled delivery of oxymorphone and can lead to overdose or death [see *Warnings and Precautions (5.2)*].

Administer on an empty stomach, at least 1 hour prior to or 2 hours after eating.

OPANA ER is administered orally every 12 hours.

2.2 Initial Dosage

Use of OPANA ER as the First Opioid Analgesic

Initiate treatment with OPANA ER with the 5 mg tablet orally every 12-hours.

Use of OPANA ER in Patients who are not Opioid Tolerant

The starting dose for patients who are not opioid tolerant is OPANA ER 5 mg orally every 12 hours.

Patients considered opioid tolerant are those taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression.

Conversion from OPANA to OPANA ER

Patients receiving OPANA may be converted to OPANA ER by administering half the patient's total daily oral OPANA dose as OPANA ER, every 12 hours.

Conversion from Parenteral Oxymorphone to OPANA ER

The absolute oral bioavailability of OPANA ER is approximately 10%. Convert patients receiving parenteral oxymorphone to OPANA ER by administering 10 times the patient's total daily parenteral oxymorphone dose as OPANA ER in two equally divided doses (e.g., [IV dose x 10] divided by 2). Due to patient variability with regards to opioid analgesic response, upon conversion monitor patients closely to evaluate for adequate analgesia and side effects.

Conversion from Other Oral Opioids to OPANA ER

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

While there are useful tables of opioid equivalents readily available, there is substantial inter-patient variability in the relative potency of different opioid drugs and products. As such, it is preferable to underestimate a patient's 24-hour oral oxymorphone requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral oxymorphone requirements which could result in adverse reactions. In an OPANA ER clinical trial with an open-label titration period, patients were converted from their prior opioid to OPANA ER using Table 1 as a guide for the initial OPANA ER dose.

Consider the following when using the information in Table 1:

- This is **not** a table of equianalgesic doses.
- The conversion factors in this table are only for the conversion **from** one of the listed oral opioid analgesics **to** OPANA ER.
- This table **cannot** be used to convert **from** OPANA ER **to** another opioid. Doing so will result in an overestimation of the dose of the new opioid and may result in fatal overdose.

CONVERSION FACTORS TO OPANA ER	
Prior Oral Opioid	Approximate Oral Conversion Factor
Oxymorphone	1
Hydrocodone	0.5
Oxycodone	0.5
Methadone	0.5
Morphine	0.333

To calculate the estimated OPANA ER 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 conversion factor to calculate the approximate oral oxymorphone daily dose.
- For patients on a regimen of more than one opioid, calculate the approximate oral oxymorphone dose for each opioid and sum the totals to obtain the approximate total oxymorphone 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

Always round the dose down, if necessary, to the appropriate OPANA ER strength(s) available.

Example conversion from a single opioid to OPANA ER:

Step 1: Sum the total daily dose of the opioid oxycodone 20 mg BID

20 mg former opioid 2 times daily = 40 mg total daily dose of former opioid

Step 2: Calculate the approximate equivalent dose of oral oxymorphone based on the total daily dose of the current opioid using Table 1

40 mg total daily dose of former opioid x 0.5 mg Conversion Factor = 20 mg of oral oxymorphone daily

Step 3: Calculate the approximate starting dose of OPANA ER to be given every 12 hours. Round down, if necessary, to the appropriate OPANA ER TABLETS strengths available.

10 mg OPANA ER every 12 hours

Conversion from Methadone to OPANA 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.

2.3 Titration and Maintenance of Therapy

Individually titrate OPANA ER to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving OPANA 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, and 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.

If the level of pain increases, attempt to identify the source of increased pain, while adjusting the OPANA ER dose to decrease the level of pain. Because steady-state plasma concentrations are approximated within 3 days, OPANA ER dosage adjustments, preferably at increments of 5-10 mg every 12 hours, may be done every 3 to 7 days.

Patients who experience breakthrough pain may require a dose increase of OPANA 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 OPANA ER dose.

If unacceptable opioid-related adverse reactions are observed, the subsequent dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

2.4 Discontinuation of OPANA ER

When a patient no longer requires therapy with OPANA ER, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue OPANA ER [see *Warnings and Precautions (5.14), Drug Abuse and Dependence (9.3)*].

2.5 Dosage Modification in Patients with Mild Hepatic Impairment

OPANA ER is contraindicated in patients with moderate or severe hepatic impairment.

In opioid-naïve patients with mild hepatic impairment, initiate treatment with the 5 mg dose. For patients on prior opioid therapy, start OPANA ER at 50% lower than the starting dose for a patient with normal hepatic function on prior opioids and titrate slowly. Monitor patients closely for signs of respiratory or central nervous system depression [see *Warnings and Precautions (5.2), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

2.6 Dosage Modification in Patients with Renal Impairment

In patients with creatinine clearance rates less than 50 mL/min, start OPANA ER in the opioid-naïve patient with the 5 mg dose. For patients on prior opioid therapy, start OPANA ER at 50% lower than the starting dose for a patient with normal renal function on prior opioids and titrate slowly. Monitor patients closely for signs of respiratory or central nervous system depression [*see Warnings and Precautions (5.2), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)*].

2.7 Dosage Modification in Geriatric Patients

The steady-state plasma concentrations of oxymorphone are higher in elderly subjects than in young subjects. Initiate dosing with OPANA ER in patients 65 years of age and over using the 5 mg dose and monitor closely for signs of respiratory and central nervous system depression when initiating and titrating OPANA ER to adequate analgesia [*see Warnings and Precautions (5.2), Use in Specific Populations (8.5) and Clinical Pharmacology (12.3)*]. For patients on prior opioid therapy, start OPANA ER at 50% lower than the starting dose for a younger patient on prior opioids and titrate slowly.

3 DOSAGE FORMS AND STRENGTHS

Extended Release Tablets 5 mg: pink, round, film-coated, biconcave extended-release tablet debossed with an “E” on one side and a “5” on the other side.

Extended Release Tablets 7.5 mg: gray, round, film-coated, biconcave extended-release tablet debossed with an “E” on one side and a “7 ½” on the other side.

Extended Release Tablets 10 mg: light orange, round, film-coated, biconcave extended-release tablet debossed with an “E” on one side and a “10” on the other side.

Extended Release Tablets 15 mg: white, round, film-coated, biconcave extended-release tablet debossed with an “E” on one side and a “15” on the other side.

Extended Release Tablets 20 mg: light green, round, film-coated, biconcave extended-release tablet debossed with an “E” on one side and a “20” on the other side.

Extended Release Tablets 30 mg: red, round, film-coated, biconcave extended-release tablet debossed with an “E” on one side and a “30” on the other side.

Extended Release Tablets 40 mg: light yellow to pale yellow, round, film-coated, biconcave extended-release tablet debossed with an “E” on one side and a “40” on the other side.

4 CONTRAINDICATIONS

OPANA ER is contraindicated in patients with:

- Significant respiratory depression [*see Warnings and Precautions (5.2)*]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [*see Warnings and Precautions (5.5)*]
- Hypersensitivity to oxymorphone, (e.g. anaphylaxis) [*see Warnings and Precautions (5.6), Adverse Reactions (6)*]
- Moderate and severe hepatic impairment [*see Warnings and Precautions (5.8,) Clinical Pharmacology (12.3)*]
- Known or suspected gastrointestinal obstruction, including paralytic ileus [*see Warnings and Precautions (5.11)*]

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

OPANA ER contains oxymorphone, a Schedule II controlled substance. As an opioid, OPANA ER exposes users to the risks of addiction, abuse, and misuse. Because extended-release products such as OPANA 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 oxymorphone present [*see Drug Abuse and Dependence (9)*].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OPANA ER. 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 OPANA ER, and monitor all patients receiving OPANA ER for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as OPANA ER, but use in such patients necessitates intensive counseling about the risks and proper use of OPANA ER along with intensive monitoring for signs of addiction, abuse, and misuse.

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

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OPANA 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 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)*]. 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 OPANA ER, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within 24-72 hours of initiating therapy with and following dose increases of OPANA ER.

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

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

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of OPANA ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Patients must not consume alcoholic beverages or prescription or non-prescription products containing alcohol while on OPANA ER therapy. The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone [*see Clinical Pharmacology (12.3)*].

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

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

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

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

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

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

Patients with Chronic Pulmonary Disease: OPANA ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea even at recommended dosages of OPANA ER [*see Warnings and Precautions (5.2)*].

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [*see Warnings and Precautions (5.2)*].

Monitor such patients closely, particularly when initiating and titrating OPANA ER and when OPANA ER is given concomitantly with other drugs that depress respiration [*see Warnings and Precautions (5.2)*]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.6 Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions

Potentially life-threatening hypersensitivity reactions, including anaphylaxis and angioedema, have occurred in patients treated with OPANA ER in the postmarket setting. The most commonly described clinical features in these reports were swelling of the face, eyes, mouth, lips, tongue, hands, and/or throat; dyspnea; hives, pruritus, and/or rash; and nausea/vomiting. If anaphylaxis or other hypersensitivity occurs, stop administration of OPANA ER immediately, discontinue OPANA ER permanently, and do not rechallenge with any formulation of oxymorphone. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction [*see Patient Counseling Information (17)*].

5.7 Adrenal Insufficiency

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

5.8 Use in Patients with Hepatic Impairment

A study of OPANA ER in patients with hepatic disease indicated greater plasma concentrations than those with normal hepatic function [*see Clinical Pharmacology (12.3)*]. OPANA ER is contraindicated in patients with moderate or severe hepatic impairment. In patients with mild hepatic impairment reduce the starting dose to the lowest dose and monitor for signs of respiratory and central nervous system depression [*see Dosage and Administration (2.5)*].

5.9 Severe Hypotension

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

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

In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), OPANA ER may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with OPANA ER.

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

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

There have been post-marketing reports of difficulty in swallowing OPANA ER tablets. These reports included choking, gagging, regurgitation and tablets stuck in the throat. Instruct patients not to pre-soak, lick or otherwise wet OPANA 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.

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

5.12 Risks of Use in Patients with Gastrointestinal Conditions

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

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

5.13 Increased Risk of Seizures in Patients with Seizure Disorders

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

5.14 Withdrawal

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

When discontinuing OPANA ER, gradually taper the dosage [*see Dosage and Administration (2.4)*]. Do not abruptly discontinue OPANA ER.

5.15 Risks of Driving and Operating Machinery

OPANA ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of OPANA ER and know how they will react to the medication.

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- 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 Benzodiazepines or Other CNS Depressants [*see Warnings and Precautions (5.4)*]
- Anaphylaxis and angioedema [*see Warnings and Precautions (5.6)*]
- Adrenal Insufficiency [*see Warnings and Precautions (5.7)*]
- Severe Hypotension [*see Warnings and Precautions (5.9)*]
- Gastrointestinal Adverse Reactions [*see Warnings and Precautions (5.11, 5.12)*]
- Seizures [*see Warnings and Precautions (5.13)*]
- Withdrawal [*see Warnings and Precautions (5.14)*]

6.1 Clinical Trial Experience

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 clinical practice.

The safety of oxymorphone hydrochloride extended-release tablets was evaluated in a total of 2011 patients in open-label and controlled clinical trials. The clinical trials enrolled of patients with moderate to severe chronic non-malignant pain, cancer pain, and post surgical pain. The most common serious adverse events reported with administration of oxymorphone hydrochloride extended-release tablets were chest pain, pneumonia and vomiting.

Tables 1 and 2 list the most frequently occurring adverse reactions (in at least 5% of patients) from the placebo-controlled trials in patients with low back pain.

Table 1: Treatment-Emergent Adverse Reactions Reported in ≥5% of Patients During the Open-Label Titration Period and Double-Blind Treatment Period by Preferred Term —Number (%) of Treated Patients (12-Week Study In Opioid-Naïve Patients with Low Back Pain)

	Open-Label Titration Period	Double-Blind Treatment Period	
	Oxymorphone Hydrochloride Extended-Release Tablets	Oxymorphone Hydrochloride Extended-Release Tablets	Placebo
Preferred Term	(N = 325)	(N = 105)	(N = 100)
Constipation	26%	7%	1%
Somnolence	19%	2%	0%
Nausea	18%	11%	9%
Dizziness	11%	5%	3%
Headache	11%	4%	2%
Pruritus	7%	3%	1%

Table 2: Treatment-Emergent Adverse Reactions Reported in ≥5% of Patients During the Open-Label Titration Period and Double-Blind Treatment Period by Preferred Term —Number (%) of Treated Patients (12-Week Study In Opioid-Experienced Patients with Low Back Pain)

	Open-Label Titration Period	Double-Blind Treatment Period	
	Oxymorphone Hydrochloride Extended-Release Tablets	Oxymorphone Hydrochloride Extended-Release Tablets	Placebo
Preferred Term	(N = 250)	(N = 70)	(N = 72)
Nausea	20%	3%	1%
Constipation	12%	6%	1%
Headache	12%	3%	0%
Somnolence	11%	3%	0%
Vomiting	9%	0%	1%
Pruritus	8%	0%	0%
Dizziness	6%	0%	0%

The following table lists adverse reactions that were reported in at least 2% of patients in placebo-controlled trials (N=5).

Table 3: Adverse Reactions Reported in Placebo-Controlled Clinical Trials with Incidence ≥2% in Patients Receiving Oxymorphone Hydrochloride Extended-Release Tablets

MedDRA Preferred Term	Oxymorphone Hydrochloride Extended-Release Tablets (N=1259)	Placebo (N=461)
Nausea	33%	13%
Constipation	28%	13%
Dizziness (Excl Vertigo)	18%	8%
Somnolence	17%	2%
Vomiting	16%	4%
Pruritus	15%	8%
Headache	12%	6%
Sweating increased	9%	9%
Dry mouth	6%	<1%

Sedation	6%	8%
Diarrhea	4%	6%
Insomnia	4%	2%
Fatigue	4%	1%
Appetite decreased	3%	<1%
Abdominal pain	3%	2%

The common ($\geq 1\%$ to <10%) adverse drug reactions reported at least once by patients treated with oxymorphone hydrochloride extended-release tablets in the clinical trials organized by MedDRA's (Medical Dictionary for Regulatory Activities) System Organ Class and not represented in Table 1 were:

Eye disorders: vision blurred

Gastrointestinal disorders: diarrhea, abdominal pain, dyspepsia

General disorders and administration site conditions: dry mouth, appetite decreased, fatigue, lethargy, weakness, pyrexia, dehydration, weight decreased, edema

Nervous system disorders: insomnia

Psychiatric disorders: anxiety, confusion, disorientation, restlessness, nervousness, depression

Respiratory, thoracic and mediastinal disorders: dyspnea

Vascular disorders: flushing and hypertension

Other less common adverse reactions known with opioid treatment that were seen <1% in the oxymorphone hydrochloride extended-release tablets include the following: Bradycardia, palpitation, syncope, tachycardia, postural hypotension, miosis, abdominal distention, ileus, hot flashes, allergic reactions, hypersensitivity, urticaria, oxygen saturation decreased, central nervous system depression, depressed level of consciousness, agitation, dysphoria, euphoric mood, hallucination, mental status changes, difficult micturition, urinary retention, hypoxia, respiratory depression, respiratory distress, clamminess, dermatitis, hypotension.

6.2 Post-marketing Experience

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

Nervous system disorder: amnesia, convulsion, memory impairment

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

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

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in OPANA ER

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

7 DRUG INTERACTIONS

Table 4 includes clinically significant drug interactions with OPANA ER

Table 4: Clinically Significant Drug Interactions with OPANA ER

Alcohol	
<i>Clinical Impact:</i>	The concomitant use of alcohol with OPANA ER can result in an increase of oxymorphone plasma levels and potentially fatal overdose of oxymorphone.
<i>Intervention:</i>	Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on OPANA ER therapy [see <i>Clinical Pharmacology (12.3)</i>].
Benzodiazepines and other Central Nervous System (CNS) Depressants	
<i>Clinical Impact:</i>	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
<i>Intervention:</i>	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see <i>Warnings and Precautions (5.4)</i>].

Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue OPANA ER if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) [see <i>Warnings and Precautions (5.2)</i>].
Intervention:	The use of OPANA ER is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of OPANA ER and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Oxymorphone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of OPANA ER and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when OPANA ER is used concomitantly with anticholinergic drugs.
Cimetidine	
Clinical Impact:	Cimetidine can potentiate opioid-induced respiratory depression.
Intervention:	Monitor patients for respiratory depression when OPANA ER and cimetidine are used concurrently.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see *Warnings and Precautions (5.3)*]. Available data with OPANA ER in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, reduced postnatal survival of pups and an increased incidence of stillborn pups were observed following oral treatment of pregnant rats with oxymorphone during gestation and through lactation at doses 2.4 and 12 times the human daily dose of 20 mg/day (HDD), respectively. Reduced fetal weights were observed with oral administration of oxymorphone to pregnant rats and rabbits during organogenesis at exposures up to 4.9 and 48.8 times the HDD, respectively [see *Data*]. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinical recognized pregnancies is 2-4% and 14-20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes may cause fetal-neonatal physical dependence and neonatal withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, including poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly [see *Warning and Precautions (5.3)*].

Labor or delivery

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

Data

Animal data

Pregnant rats were treated with oxymorphone hydrochloride from Gestation Day 6 to 17 via oral gavage doses of 5, 10, or 25 mg/kg/day (2.4, 4.9, or 12.2 times the HDD based on body surface area, respectively). Reduced mean fetal weights were observed at 4.9 times the HDD. Maternal toxicity was noted in all treatment groups (reduced food consumption and body weights in all groups and mortality in the high dose group).

Pregnant rabbits were treated with oxymorphone hydrochloride from Gestation Day 7 to 20 via oral gavage doses of 10, 25, or 50 mg/kg/day (9.8, 24.4, or 48.8 times the HDD based on body surface area, respectively). Decreased mean fetal weights were noted at 48.8 times the HDD. Maternal toxicity was noted in all treatment groups (reduced food consumption and body weights).

Pregnant rats were treated with oxymorphone hydrochloride from Gestation Day 6 to Lactation Day 20 via oral gavage doses of 1, 5, 10, or 25 mg/kg/day (0.5, 2.4, 4.9, or 12.2 times the HDD based on body surface area, respectively). Increased neonatal death (postnatal day 0-1) was noted at 2.4 times the HDD. Decreased pup survival over the first week of life, reduced pup birth weight, and reduced postnatal weight gain were noted at 4.9 times the HDD. Maternal toxicity was noted in all treatment groups (reduced food consumption and body weights in all groups and mortality in the 10 and 25 mg/kg/day groups).

8.2 Lactation

In a published study, neural tube defects (exencephaly and cranioschisis) were noted following subcutaneous administration of 153 mg/kg oxymorphone hydrochloride (62.2 times the HDD) on Gestation Day 8 to pregnant hamsters. This dose also produced significant maternal toxicity (20% maternal deaths).

Risk Summary

There is no information regarding the presence of oxymorphone in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with OPANA ER.

Clinical Considerations

Monitor infants exposed to OPANA ER through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [*Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of OPANA ER in patients below the age of 18 years have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of oxymorphone hydrochloride extended-release tablets, 27% were 65 and over, while 9% were 75 and over. No overall differences in effectiveness were observed between these subjects and younger subjects. There were several adverse events that were more frequently observed in subjects 65 and over compared to younger subjects. These adverse events included dizziness, somnolence, confusion, and nausea. On average, age greater than 65 years was associated with an increase in oxymorphone AUC and C_{max} . Initiate dosing with OPANA ER in patients 65 years of age and over using the 5 mg dose and monitor closely for signs of respiratory and central nervous system depression when initiating and titrating OPANA ER. For patients on prior opioid therapy, start at 50% of the starting dose for a younger patient on prior opioids and titrate slowly.

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

8.6 Hepatic Impairment

Patients with mild hepatic impairment have an increase in oxymorphone bioavailability compared to the subjects with normal hepatic function. In opioid-naïve patients with mild hepatic impairment, initiate OPANA ER using the 5 mg dose and monitor closely for respiratory and central nervous system depression. OPANA ER is contraindicated for patients with moderate and severe hepatic impairment [*see Dosage and Administration (2.5), Contraindications (4), Warnings and Precautions (5.8), and, Clinical Pharmacology (12.3)*]. For patients on prior opioid therapy, start at the 50% of the dose for that a patient with normal hepatic function on prior opioids and titrate slowly.

8.7 Renal Impairment

Patients with moderate to severe renal impairment were shown to have an increase in oxymorphone compared to the subjects with normal renal function [*see Clinical Pharmacology (12.3)*]. Start opioid-naïve patients with the 5 mg dose of OPANA ER and titrate slowly while closely monitoring for respiratory and central nervous system depression [*see Dosage and Administration (2.6)*]. For patients on prior opioid therapy, start at 50% of the dose for a patient with normal renal function on prior opioids and titrate slowly.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

OPANA ER contains oxymorphone, a Schedule II controlled substance.

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

9.2 Abuse

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

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

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

Prescription drug abuse is the intentional non-therapeutic use of prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

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

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

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

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

Risks Specific to Abuse of OPANA ER

OPANA ER is for oral use only. Abuse of OPANA ER poses a risk of overdose and death. This risk is increased with concurrent abuse of OPANA ER with alcohol and other substances. Taking cut, broken, chewed, crushed, or dissolved OPANA ER enhances drug release and increases the risk of over dose and death.

With parenteral abuse, cases of thrombotic microangiopathy (a condition characterized clinically by thrombocytopenia and microangiopathic hemolytic anemia) have been reported; many cases resulted in hospitalization and treatment with plasmapheresis. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

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 dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

OPANA ER should not be abruptly discontinued [*see Dosage and Administration (2.3)*]. If OPANA ER is abruptly discontinued in a physically-dependent patient, withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [*see Use in Specific Populations (8.2)*].

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with OPANA ER can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations [*see Clinical Pharmacology (12.2)*].

Treatment of Overdose

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose.

For clinically significant respiratory or circulatory depression secondary to oxymorphone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxymorphone overdose.

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

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

11 DESCRIPTION

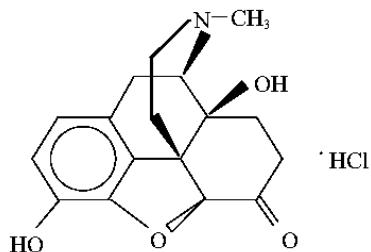
OPANA ER extended-release tablets are for oral use and contain oxymorphone, an opioid agonist. OPANA ER extended-release tablets are supplied in 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg tablet strengths for oral administration. The tablet strength describes the amount of oxymorphone hydrochloride per tablet.

The tablets contain the following inactive ingredients: hypromellose, polyethylene oxide, polyethylene glycol, α -tocopherol, citric acid, polyvinyl alcohol, titanium dioxide, macrogol and talc.

In addition, the 5 mg, 7.5 mg and 30 mg tablets contain iron oxide red. The 7.5 mg tablets contain iron oxide black, and iron oxide yellow. The 10 mg tablets contain FD&C yellow No. 6. The 20 mg tablets contain FD&C blue No. 1, FD&C yellow No. 6, and D&C yellow No. 10. The 40 mg tablets contain FD&C yellow No. 6, and D&C yellow No. 10.

The chemical name of oxymorphone hydrochloride is 4, 5 α -epoxy-3, 14-dihydroxy-17-methylmorphinan-6-one hydrochloride, a white or slightly off-white, odorless powder, which is sparingly soluble in alcohol and ether, but freely soluble in water. The molecular weight of oxymorphone hydrochloride is 337.80. The pKa1 and pKa2 of oxymorphone at 37°C are 8.17 and 9.54, respectively. The octanol/aqueous partition coefficient at 37°C and pH 7.4 is 0.98.

The structural formula for oxymorphone hydrochloride is as follows:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxymorphone is a full opioid agonist and is relatively selective for the mu-opioid receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of oxymorphone is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with [oxycodeoneoxymorphone \[editorial change\]](#). Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

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

12.2 Pharmacodynamics

CNS Depressant/Alcohol Interaction

Additive pharmacodynamic effects may be expected when OPANA ER is used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Effects on the Central Nervous System

Oxymorphone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation. Oxymorphone 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 origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and on Other Smooth Muscle

Oxymorphone causes a reduction in motility and is associated with an increase in 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 is increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Oxymorphone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Release of histamine can occur and may contribute to opioid-induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include, pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

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

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

Effects on the Immune System

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

Concentration-Efficacy Relationships

The minimum effective plasma concentration of oxymorphone ~~will vary~~ [editorial change] widely among patients, especially among patients who have been previously treated with agonist opioids. The minimum effective analgesic concentration of oxymorphone for any individual patient may increase over time due to an increase in pain, development of a new pain syndrome, and/or the development of analgesic tolerance [see *Dosage and Administration* (2.1, 2.2)].

Concentration–Adverse Reaction Relationships

There is a relationship between increasing oxymorphone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [see *Dosage and Administration* (2.1, 2.2, 2.3)].

12.3 Pharmacokinetics

Absorption

The absolute oral bioavailability of oxymorphone is approximately 10%.

Steady-state levels are achieved after three days of multiple dose administration. Under both single-dose and steady-state conditions, dose proportionality has been established for the 5 mg, 10 mg, 20 mg, and 40 mg doses of oxymorphone hydrochloride extended-release tablets, for both peak plasma levels (C_{max}) and extent of absorption (AUC) (see Table 4).

Table 4: Mean ($\pm SD$) Oxymorphone Hydrochloride Extended-Release Tablets Pharmacokinetic Parameters

Regimen	Dosage	C_{max} (ng/mL)	AUC_{0-12h} (ng·hr/mL)	$T_{\frac{1}{2}}$ (hr)
Single Dose	5 mg	0.27±0.13	4.54±2.04	11.30±10.81
	10 mg	0.65±0.29	8.94±4.16	9.83±5.68
	20 mg	1.21±0.77	17.81±7.22	9.89±3.21
	40 mg	2.59±1.65	37.90±16.20	9.35±2.94
Multiple Dose ^a	5 mg	0.70±0.55	5.60±3.87	NA
	10 mg	1.24±0.56	9.77±3.52	NA
	20 mg	2.54±1.35	19.28±8.32	NA
	40 mg	4.47±1.91	36.98±13.53	NA

NA = not applicable

^a Results after 5 days of q12h dosing.

Food Effect

Two studies examined the effect of food on the bioavailability of single doses of 20 and 40 mg of oxymorphone hydrochloride extended-release tablets in healthy volunteers. In both studies, after the administration of oxymorphone hydrochloride extended-release tablets, the C_{max} was increased by approximately 50% in fed subjects compared to fasted subjects. A similar increase in C_{max} was also observed with oxymorphone solution.

The AUC was unchanged in one study and increased by approximately 18% in the other study in fed subjects following the administration of oxymorphone hydrochloride extended-release tablets. Examination of the AUC suggests that most of the difference between fed and fasting conditions occurs in the first four hours after dose administration. After oral dosing with a single dose of 40 mg, a peak oxymorphone plasma level of 2.8 ng/ml is achieved at 1 hour in fasted subjects and a peak of 4.25 ng/ml is achieved at 2 hours in fed subjects and that beyond the 12 hour time point, there is very little difference in the curves. As a result, OPANA ER should be dosed at least one hour prior to or two hours after eating [see *Dosage and Administration* (2.1, 2.2)].

Distribution

Formal studies on the distribution of oxymorphone in various tissues have not been conducted. Oxymorphone is not extensively bound to human plasma proteins; binding is in the range of 10% to 12%.

Elimination

Metabolism

Oxymorphone is highly metabolized, principally in the liver, and undergoes reduction or conjugation with glucuronic acid to form both active and inactive metabolites. The two major metabolites of oxymorphone are oxymorphone-3-glucuronide and 6-OH-oxymorphone. The mean plasma AUC for oxymorphone-3-glucuronide is approximately 90-fold higher than the parent compound. The pharmacologic activity of the glucuronide metabolite has not been evaluated. 6-OH-oxymorphone has been shown in animal studies to have analgesic bioactivity. The mean plasma 6-OH-oxymorphone AUC is approximately 70% of the oxymorphone AUC following single oral doses, but is essentially equivalent to the parent compound at steady-state.

Excretion

Because oxymorphone is extensively metabolized, <1% of the administered dose is excreted unchanged in the urine. On average, 33% to 38% of the administered dose is excreted in the urine as oxymorphone-3-glucuronide and less than 1% excreted as 6-OH-oxymorphone in subjects with normal hepatic and renal function. In animals given radiolabeled oxymorphone, approximately 90% of the administered radioactivity was recovered within 5 days of dosing. The majority of oxymorphone-derived radioactivity was found in the urine and feces.

Specific Populations

Geriatric Patients

The steady-state plasma concentrations of oxymorphone, 6-OH-oxymorphone, and oxymorphone-3-glucuronide are approximately 40% higher in elderly subjects (≥ 65 years of age) than in young subjects (18 to 40 years of age). On average, age greater than 65 years was associated with a 1.4-fold increase in oxymorphone AUC and a 1.5-fold increase in C_{max} . This observation does not appear related to a difference in body weight, metabolism, or excretion of oxymorphone [see *Use in Specific Populations* (8.5)].

Sex

The effect of sex was evaluated following single- and multiple-doses of oxymorphone hydrochloride extended-release tablets in male and female adult volunteers. There was a consistent tendency for female subjects to have slightly higher AUC_{ss} and C_{max} values than male subjects; however, sex differences were not observed when AUC_{ss} and C_{max} were adjusted by body weight.

Hepatic Impairment

The bioavailability of orally administered oxymorphone is markedly increased in patients with moderate to severe liver disease. The disposition of oxymorphone was compared in six patients with mild, five patients with moderate, and one patient with severe hepatic impairment and 12 subjects with normal hepatic function. The bioavailability of oxymorphone was increased by 1.6-fold in patients with mild hepatic impairment and by 3.7-fold in patients with moderate hepatic impairment. In one patient with severe hepatic impairment, the bioavailability was increased by 12.2-fold. The half-life of oxymorphone was not significantly affected by hepatic impairment.

Renal Impairment

Data from a pharmacokinetic study involving 24 patients with renal dysfunction show an increase of 26%, 57%, and 65% in oxymorphone bioavailability in mild (creatinine clearance 51-80 mL/min; n=8), moderate (creatinine clearance 30-50 mL/min; n=8), and severe (creatinine clearance <30 mL/min; n=8) patients, respectively, compared to healthy controls.

Drug Interaction Studies

Alcohol Interaction

An *in vivo* study of the effect of alcohol (40%, 20%, 4% and 0%) on the bioavailability of a single dose of 40 mg of oxymorphone hydrochloride extended-release tablets in healthy, fasted volunteers demonstrated a highly variable effect on C_{max} with concomitant administration of alcohol and oxymorphone hydrochloride extended-release tablets. The change in C_{max} ranged from a decrease of 50% to an increase of 270% across all conditions studied. Following administration of 240 mL of 40% ethanol, the C_{max} increased on average by 70% and up to 270% in individual subjects. Following the concomitant administration of 240 mL of 20% ethanol, the C_{max} increased on average by 31% and up to 260% in individual subjects. Following the concomitant administration of 240 mL of 4 % ethanol, the C_{max} increased 7% on average and by as much as 110% for individual subjects. After oral dosing with a single dose of 40 mg in fasted subjects, the mean peak oxymorphone plasma level is 2.4 ng/mL and the median T_{max} is 2 hours. Following co-administration of oxymorphone hydrochloride extended-release tablets and alcohol (240 mL of 40% ethanol) in fasted subjects, the mean peak oxymorphone level is 3.9 ng/mL and the median T_{max} is 1.5 hours (range 0.75 – 6 hours). The oxymorphone mean AUC was 13% higher after co-administration of 240 mL of 40% alcohol. The AUC was essentially unaffected in subjects following the co-administration of oxymorphone hydrochloride extended-release tablets and ethanol (240 mL of 20% or 4% ethanol).

In vitro studies have demonstrated that oxymorphone hydrochloride extended-release tablets does not release oxymorphone more rapidly in 500 mL of 0.1N HCl solutions containing ethanol (4%, 20%, and 40%).

Instruct patients to avoid use of alcohol when taking OPANA ER.

In vitro studies revealed little to no biotransformation of oxymorphone to 6-OH-oxymorphone by any of the major cytochrome P450 (CYP P450) isoforms at therapeutically relevant oxymorphone plasma concentrations.

No inhibition of any of the major CYP P450 isoforms was observed when oxymorphone was incubated with human liver microsomes at concentrations of $\leq 15.1 \mu\text{g/mL}$. An inhibition of CYP3A4 activity occurred at oxymorphone concentrations $\geq 45.3 \mu\text{g/mL}$. Therefore, it is not expected that oxymorphone, or its metabolites will act as inhibitors of any of the major CYP P450 enzymes *in vivo*.

Increases in the activity of the CYP 2C9 and CYP 3A4 isoforms occurred when oxymorphone was incubated with human hepatocytes. However, clinical drug interaction studies with oxymorphone hydrochloride extended-release tablets showed no induction of CYP450 3A4 or 2C9 enzyme activity, indicating that no dose adjustment for CYP 3A4- or 2C9-mediated drug-drug interactions is required.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No evidence of carcinogenic potential was observed in long-term animal studies in mice and rats. Oxymorphone hydrochloride was administered to Sprague Dawley rats (2.5, 5, and 10 mg/kg/day in males and 5, 10, and 25 mg/kg/day in females) for 2 years by oral gavage. Systemic drug exposure (AUC) at the highest doses tested in male and female rats was 4.8 times and 21.2 times the human exposure at a dose of 20 mg/day, respectively. Oxymorphone hydrochloride was administered to male and female CD-1 mice (10, 25, 75 and 150 mg/kg/day) for 2 years by oral gavage. Systemic drug exposure (AUC) at 150 mg/kg/day in male and female mice was 205 times and 243 times the human exposure at a dose of 20 mg/day, respectively.

Mutagenesis

Oxymorphone hydrochloride was not mutagenic when tested in the *in vitro* bacterial reverse mutation assay (Ames test), or in an *in vitro* mammalian cell chromosome aberration assay performed with human peripheral blood lymphocytes. Oxymorphone hydrochloride tested positive in both the rat and mouse *in vivo* micronucleus assays. An increase in micronucleated polychromatic erythrocytes occurred in mice given doses $\geq 250 \text{ mg/kg}$ and in rats given doses of 20 and 40 mg/kg. A subsequent study demonstrated that oxymorphone hydrochloride was not aneugenetic in mice following administration of up to 500 mg/kg. Additional studies indicate that the increased incidence of micronucleated polychromatic erythrocytes in rats may be secondary to increased body temperature following oxymorphone administration. Doses associated with increased micronucleated polychromatic erythrocytes also produce a marked, rapid increase in body temperature. Pretreatment of animals with sodium salicylate minimized the increase in body temperature and prevented the increase in micronucleated polychromatic erythrocytes after administration of 40 mg/kg oxymorphone.

Impairment of Fertility

Female rats were treated with oxymorphone hydrochloride beginning 14 days prior to mating through Gestation Day 7 via oral gavage doses of 5, 10, or 25 mg/kg/day (2.4, 4.9, or 12.2 times the human daily dose of 20 mg/day based on body surface area, respectively). Male rats were treated via oral gavage with the same oxymorphone hydrochloride doses beginning 28 days prior to and throughout mating. In female rats, an increase in the length of the estrus cycle and decrease in the mean number of viable embryos, implantation sites and corpora lutea were observed at 4.9 times the human dose of 20 mg/day. No adverse effects of oxymorphone on male reproductive function or sperm parameters were observed.

14 CLINICAL STUDIES

The efficacy and safety of oxymorphone hydrochloride extended-release tablets have been evaluated in double-blind, controlled clinical trials in opioid-naïve and opioid-experienced patients with moderate to severe pain including low back pain.

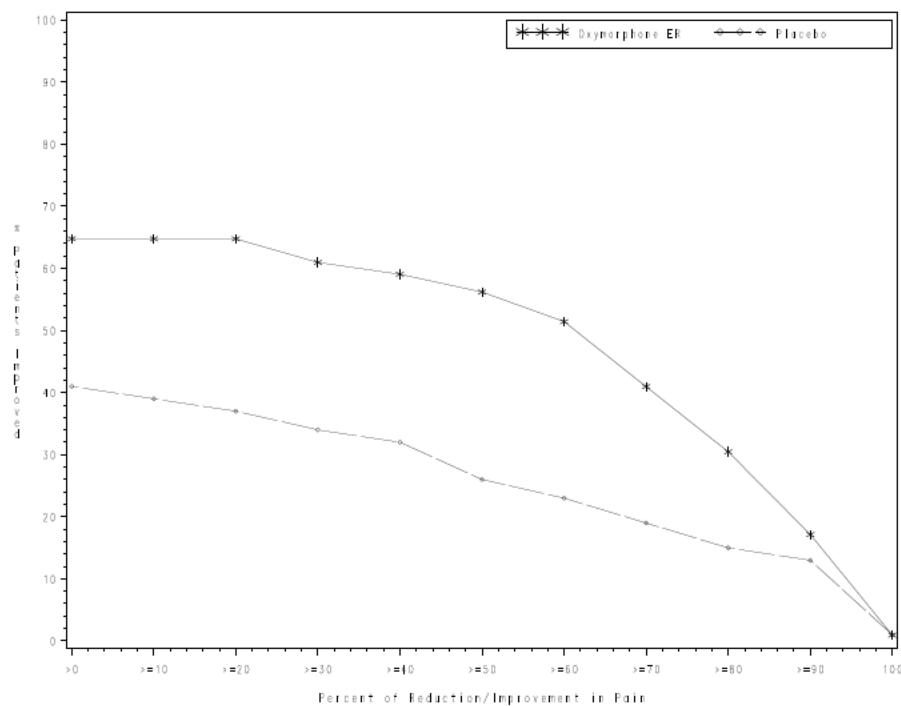
12-Week Study in Opioid-Naïve Patients with Low Back Pain

Patients with chronic low back pain who were suboptimally responsive to their non-opioid therapy entered a 4-week, open-label dose titration phase. Patients initiated therapy with two days of treatment with oxymorphone hydrochloride extended-release tablets 5 mg, every 12 hours. Thereafter, patients were titrated to a stabilized dose, at increments of 5 to 10 mg every 12 hours every 3 to 7 days. Of the patients who were able to stabilize within the Open-Label Titration Period, the mean \pm SD VAS score at Screening was 69.4 ± 11.8 mm and at Baseline (beginning of Double-Blind Period) were 18.5 ± 11.2 mm and 19.3 ± 11.3 mm for the oxymorphone ER and placebo groups, respectively. Sixty three percent of the patients enrolled were able to titrate to a tolerable dose and were randomized into a 12-week double-blind treatment phase with placebo or their stabilized dose of oxymorphone hydrochloride extended-release tablets. The mean \pm SD stabilized doses were 39.2 ± 26.4 mg and 40.9 ± 25.3 mg for the oxymorphone hydrochloride extended-release tablets and placebo groups, respectively; total daily doses ranged from 10 to 140 mg. During the first 4 days of double-blind treatment patients were allowed an unlimited number of OPANA, an immediate-release (IR) formulation of oxymorphone, 5 mg tablets, every 4-6 hours as supplemental analgesia; thereafter the number of OPANA was limited to two tablets per day. This served as a tapering method to minimize opioid withdrawal symptoms in placebo patients. Sixty-eight percent of patients treated with oxymorphone hydrochloride

extended-release tablets completed the 12-week treatment compared to 47% of patients treated with placebo. Oxymorphone hydrochloride extended-release tablets provided superior analgesia compared to placebo. The analgesic effect of oxymorphone hydrochloride extended-release tablets was maintained throughout the double-blind treatment period in 89% of patients who completed the study. These patients reported a decrease, no change, or a ≤ 10 mm increase in VAS score from Day 7 until the end of the study.

The proportion of patients with various degrees of improvement from screening to study endpoint is shown in Figure 1. The figure is cumulative, so that patients whose change from baseline is, for example, 30%, are also included at every level of improvement below 30%. Patients who did not complete the study were assigned 0% improvement.

Figure 1: Percent Reduction in Average Pain Intensity from Screening to Final Visit

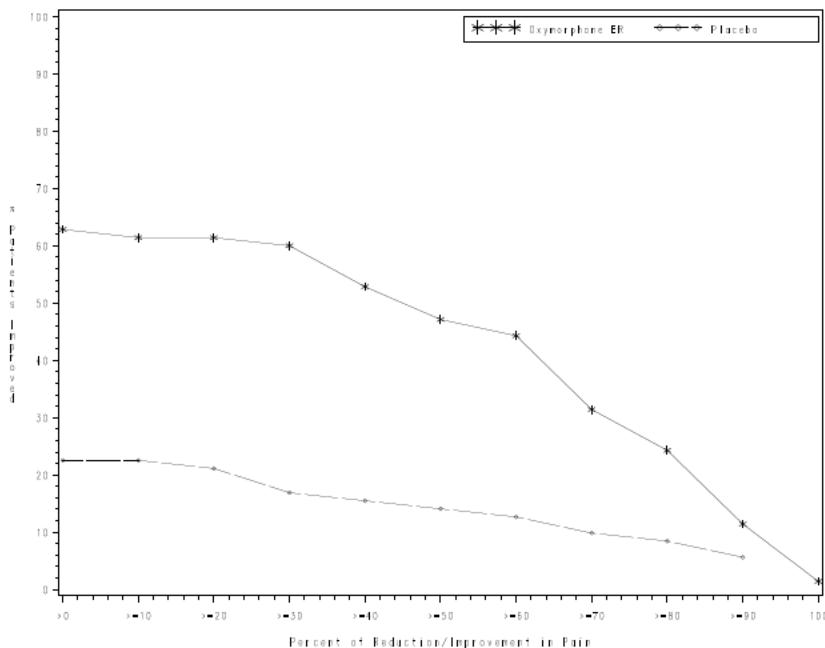


12-Week Study in Opioid-Experienced Patients with Low Back Pain

Patients on chronic opioid therapy entered a 4-week, open-label titration phase with oxymorphone hydrochloride extended-release tablets dosed every 12 hours at an approximated equianalgesic dose of their pre-study opioid medication. Of the patients who were able to stabilize within the Open-Label Titration Period, the mean \pm SD VAS score at Screening was 69.5 ± 17.0 mm and at Baseline (beginning of Double-Blind Period) were 23.9 ± 12.1 mm and 22.2 ± 10.8 mm for the oxymorphone ER and placebo groups, respectively. Stabilized patients entered a 12-week double-blind treatment phase with placebo or their stabilized dose of oxymorphone hydrochloride extended-release tablets. The mean \pm SD stabilized doses were 80.9 ± 59.3 mg and 93.3 ± 61.3 mg for the oxymorphone hydrochloride extended-release tablets and placebo groups, respectively; total daily doses ranged from 20-260 mg. During the first 4 days of double-blind treatment, patients were allowed an unlimited number of OPANA 5 mg tablets, every 4-6 hours as supplemental analgesia; thereafter the number of OPANA was limited to two tablets per day. This served as a tapering method to minimize opioid withdrawal symptoms in placebo patients. Fifty seven percent of patients were titrated to a stabilized dose within approximately 4 weeks of oxymorphone hydrochloride extended-release tablets dose titration. Seventy percent of patients treated with oxymorphone hydrochloride extended-release tablets and 26% of patients treated with placebo completed the 12-week treatment. Oxymorphone hydrochloride extended-release tablets provided superior analgesia compared to placebo. The analgesic effect of oxymorphone hydrochloride extended-release tablets was maintained throughout the double-blind treatment period in 80 % of patients who completed the study. These patients reported a decrease, no change, or a ≤ 10 mm increase in VAS score from Day 7 until the end of the study.

The proportion of patients with various degrees of improvement from screening to study endpoint is shown in Figure 2. The figure is cumulative, so that patients whose change from baseline is, for example, 30%, are also included at every level of improvement below 30%. Patients who did not complete the study were assigned 0% improvement.

Figure 2: Percent Reduction in Average Pain Intensity from Screening to Final Visit



16 HOW SUPPLIED/STORAGE AND HANDLING

OPANA ER extended-release tablets are supplied as follows:

5 mg

Pink, round, film-coated, biconcave extended-release tablets debossed with an "E" on one side and a "5" on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-812-60
Bottles of 100 with child-resistant closure	NDC 63481-812-70
Unit-Dose package of 20 tablets (2 blister cards of 10 tablets, not child-resistant, for hospital use only)	NDC 63481-812-20

7.5 mg

Gray, round, film coated, biconcave extended-release tablets debossed with an "E" on one side and a "7 ½" on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-813-60
Bottles of 100 with child-resistant closure	NDC 63481-813-70
Unit-Dose package of 20 tablets (2 blister cards of 10 tablets, not child-resistant, for hospital use only)	NDC 63481-813-20

10 mg

Light orange, round, film-coated, biconcave extended-release tablets debossed with an "E" on one side and a "10" on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-814-60
Bottles of 100 with child-resistant closure	NDC 63481-814-70
Unit-Dose package of 20 tablets (2 blister cards of 10 tablets, not child-resistant, for hospital use only)	NDC 63481-814-20

15 mg

White, round, film-coated, biconcave extended-release tablets debossed with an "E" on one side and a "15" on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-815-60
Bottles of 100 with child-resistant closure	NDC 63481-815-70
Unit-Dose package of 20 tablets (2 blister cards of 10 tablets, not child-resistant, for hospital use only)	NDC 63481-815-20

20 mg

Light green, round, film-coated, biconcave extended-release tablets debossed with an “E” on one side and a “20” on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-816-60
Bottles of 100 with child-resistant closure	NDC 63481-816-70
Unit-Dose package of 20 tablets (2 blister cards of 10 tablets, not child-resistant, for hospital use only)	NDC 63481-816-20

30 mg

Red, round, film-coated, biconcave extended-release tablets debossed with an “E” on one side and a “30” on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-817-60
Bottles of 100 with child-resistant closure	NDC 63481-817-70
Unit-Dose package of 20 tablets (2 blister cards of 10 tablets, not child-resistant, for hospital use only)	NDC 63481-817-20

40 mg

Light yellow to pale yellow, round, film-coated, biconcave extended-release tablets debossed with an “E” on one side and a “40” on the other side.

Bottles of 60 with child-resistant closure	NDC 63481-818-60
Bottles of 100 with child-resistant closure	NDC 63481-818-70
Unit-Dose package of 20 tablets (2 blister cards of 10 tablets, not child-resistant, for hospital use only)	NDC 63481-818-20

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

Dispense in tight container as defined in the USP, with a child-resistant closure (as required).

17 PATIENT COUNSELING INFORMATION

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

Addiction, Abuse, and Misuse

Inform patients that the use of OPANA 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 OPANA ER with others and to take steps to protect OPANA 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 OPANA ER or when the dosage 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 breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [*see Warnings and Precautions (5.2)*]. Instruct patients to take steps to store OPANA ER securely and to dispose of unused OPANA ER by flushing the tablets down the toilet.

Interactions with Benzodiazepines and other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if OPANA ER is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider [*see Warnings and Precautions (5.4), Drug Interactions (7)*].

Instruct patients not to consume alcoholic beverages, as well as prescription and over-the-counter products that contain alcohol, during treatment with OPANA ER. The co-ingestion of alcohol with OPANA ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone [*see Warnings and Precautions (5.4)*].

Anaphylaxis, Angioedema, and Other Hypersensitivity Reactions

Inform patients that anaphylaxis and other hypersensitivity reactions have been reported with ingredients contained in OPANA ER. Advise patients how to recognize such a reaction and when to seek medical attention [*see Contraindications (4), Warnings and Precautions (5.6), Adverse Reactions (6)*].

Serotonin Syndrome

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

MAOI Interaction

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

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [*see Warnings and Precautions (5.7)*].

Important Administration Instructions

Instruct patients how to properly take OPANA ER, including the following:

- OPANA ER is designed to work properly only if swallowed intact. Taking cut, broken, chewed, crushed, or dissolved OPANA ER tablets can result in a fatal overdose [*see Dosage and Administration (2.1)*].
- OPANA ER tablets should be taken one tablet at a time [*see Dosage and Administration (2.1)*].
- Do not pre-soak, lick or otherwise wet the tablet prior to placing in the mouth [*see Dosage and Administration (2.1)*].
- Take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth [*see Dosage and Administration (2.1)*].
- Occasionally, the inactive ingredients of OPANA ER may be eliminated as a soft mass in the stool that may resemble the original tablet. Inform patients that the active medication has already been absorbed by the time the patient sees the soft mass.
- Use OPANA ER exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression) [*see Dosage and Administration (2), Warnings and Precautions (2.1)*].
- Do not discontinue OPANA ER without first discussing the need for a tapering regimen with the prescriber [*see Dosage and Administration (2.4), Warnings and Precautions (5.14)*].

Hypotension

Inform patients that OPANA 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).

Anaphylaxis

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

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of OPANA 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), Use in Specific Populations (8.1)*].

Embryo-Fetal Toxicity

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

Lactation

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

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [see *Adverse Reactions* (6.2), *Use in Specific Populations* (8.3)].

Driving or Operating Heavy Machinery

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

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [see *Adverse Reactions* (6), *Clinical Pharmacology* (12.2)].

Disposal of Unused OPANA ER

Advise patients to flush the unused tablets down the toilet when OPANA ER is no longer needed.

Distributed by:

Endo Pharmaceuticals Inc.

Malvern, PA 19355

Manufactured by:

Pharmaceuticals Manufacturing Research Services Inc.

Horsham, PA 19044

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Medication Guide**OPANA® ER (O-pan-a) (oxymorphone hydrochloride) extended-release tablets, for oral use, CII****OPANA ER is:**

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

Important information about OPANA ER:

- **Get emergency help right away if you take too much OPANA ER (overdose).** When you first start taking OPANA 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.
- Taking OPANA ER with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone your OPANA ER. They could die from taking it. Store OPANA ER away from children and in a safe place to prevent stealing or abuse. Selling or giving away OPANA ER is against the law.

Do not take OPANA 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 OPANA ER, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

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

When taking OPANA ER:

- Do not change your dose. Take OPANA ER exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 12 hours at the same time every day on an empty stomach, at least 1 hour before or 2 hours after meals. Do not take more than your prescribed dose in 24 hours. If you miss a dose, take your next dose at your usual time.
- Swallow OPANA ER whole. Do not cut, break, chew, crush, dissolve, snort, or inject OPANA ER because this may cause you to overdose and die.
- To avoid choking on the tablet OPANA ER should be taken 1 tablet at a time. Do not pre-soak, lick, or wet the tablet before placing in your mouth.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking OPANA ER without talking to your healthcare provider.**
- After you stop taking OPANA ER, flush any unused tablets down the toilet.

While taking OPANA ER DO NOT:

- Drive or operate heavy machinery, until you know how OPANA ER affects you. OPANA 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 OPANA ER may cause you to overdose and die.

The possible side effects of OPANA ER:

- 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, or hands, hives, itching, rash, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of OPANA 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**

Distributed by: Endo Pharmaceuticals Inc., Malvern, PA 19355, www.endo.com or call 1-800-462-3636

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: December 2016

117836

**Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and
Labeling**

Abuse-Deterrent Opioids — Evaluation and Labeling

Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**Clinical Medical
April 2015**

Abuse-Deterrent Opioids — Evaluation and Labeling

Guidance for Industry

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**Clinical Medical
April 2015**

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Abuse-Deterrent Opioids — Evaluation and Labeling Guidance for Industry¹

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance explains FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties. The guidance makes recommendations about how those studies should be performed and evaluated and discusses how to describe those studies and their implications in product labeling.

This guidance is intended to assist sponsors who wish to develop opioid drug products with potentially abuse-deterrent properties and is not intended to apply to products that are not opioids or opioid products that do not have the potential for abuse.

This guidance also does not address issues associated with the development or testing of generic formulations of abuse-deterrent opioid products. FDA intends to address that topic in one or more future guidance documents.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Prescription opioid products are an important component of modern pain management. However, abuse and misuse of these products have created a serious and growing public health problem. One potentially important step towards the goal of creating safer opioid analgesics has

¹ This guidance has been prepared by the Division of Anesthesia, Analgesia, and Addiction Products, the Office of Regulatory Policy, the Office of Surveillance and Epidemiology, the Office of Biostatistics, and the Controlled Substance Staff in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

been the development of opioids that are formulated to deter abuse. FDA considers the development of these products a high public health priority.

Because opioid products are often manipulated for purposes of abuse by different routes of administration or to defeat extended-release (ER) properties, most abuse-deterrent technologies developed to date are intended to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding. It should be noted that these technologies have not yet proven successful at deterring the most common form of abuse—swallowing a number of intact capsules or tablets to achieve a feeling of euphoria. Moreover, the fact that a product has abuse-deterrent properties does not mean that there is no risk of abuse. It means, rather, that the risk of abuse is lower than it would be without such properties. Because opioid products must in the end be able to deliver the opioid to the patient, there may always be some abuse of these products.

For purposes of this guidance, *abuse-deterrent properties* are defined as those properties shown to meaningfully **deter** abuse, even if they do not fully **prevent** abuse. The term *abuse* is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect.² Abuse is not the same as *misuse*, which refers to the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse.³ This guidance uses the term *abuse-deterrent* rather than *tamper-resistant* because the latter term refers to, or is used in connection with, packaging requirements applicable to certain classes of drugs, devices, and cosmetics.⁴

The science of abuse deterrence is relatively new, and both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. Based on the evolving nature of the field, FDA intends to take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products. Methods for evaluating the abuse-deterrent properties of new molecular entities may have to be adapted based on the characteristics of those products and the anticipated routes of abuse. The development of an abuse-deterrent opioid product should be guided by the need to reduce the abuse known or expected to occur with similar products.

Because FDA expects that the market will foster iterative improvements in products with abuse-deterrent properties, no absolute magnitude of effect can be set for establishing abuse-deterrent characteristics. As a result, FDA intends to consider the *totality of the evidence* when reviewing the results of studies evaluating the abuse-deterrent properties of a product.

² Smith S M, Dart R C, Katz N P, et al. 2013. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. *Pain*, 154:2287-2296.

³ Ibid.

⁴ FDA's current Good Manufacturing Practice regulations include tamper-evident packaging requirements. See 21 CFR 211.132. There are also requirements for child resistant "special packaging" under the Poison Prevention Packaging Act and regulations adopted by the Consumer Protect Safety Commissioner (CPSC) in 16 CFR 1700.

As with all NDA products, FDA intends to consider opioids with abuse-deterrent properties within the context of available therapy. The standard against which each product's abuse-deterrent properties are evaluated will depend on the range of abuse-deterrent and non-abuse-deterrent products on the market at the time of that application.⁵

Abuse-deterrent properties can generally be established only through comparison to another product.

FDA encourages additional scientific and clinical research that will advance the development and assessment of abuse-deterrent technologies.

FDA believes it is critical to address the problem of opioid abuse while seeking to ensure that patients in pain have appropriate access to opioid products. Moreover, it is important that opioids without abuse-deterrent properties remain available for use in some clinical settings. For example, patients in hospice care and with difficulty swallowing may need access to opioid products that are in solution or that can be crushed.

The following section describes the categories of abuse-deterrent products. The premarket and postmarket studies that should be performed to assess the impact of a potentially abuse-deterrent product are discussed in subsequent sections. Finally, information is provided about labeling for abuse-deterrent products.

III. ABUSE-DETERRENT PRODUCTS

Opioid products can be abused in a number of ways. For example, they can be swallowed whole, crushed and swallowed, crushed and snorted, crushed and smoked, or crushed, dissolved and injected. Abuse-deterrent technologies should target known or expected routes of abuse relevant to the proposed product. As a general framework, abuse-deterrent formulations can currently be categorized as follows:

1. *Physical/chemical barriers* – Physical barriers can prevent chewing, crushing, cutting, grating, or grinding of the dosage form. Chemical barriers, such as gelling agents, can resist extraction of the opioid using common solvents like water, simulated biological media, alcohol, or other organic solvents. Physical and chemical barriers can limit drug release following mechanical manipulation, or change the physical form of a drug, rendering it less amenable to abuse.
2. *Agonist/antagonist combinations* – An opioid antagonist can be added to interfere with, reduce, or defeat the euphoria associated with abuse. The antagonist can be sequestered and released only upon manipulation of the product. For example, a drug product can be

⁵ For guidance on the evaluation of abuse potential for purposes of the Controlled Substances Act (CSA), we refer sponsors to FDA's draft guidance for industry *Assessment of Abuse Potential of Drugs*. This guidance is available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>. FDA guidances are available at <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

formulated such that the substance that acts as an antagonist is not clinically active when the product is swallowed, but becomes active if the product is crushed and injected or snorted.

3. *Aversion* – Substances can be added to the product to produce an unpleasant effect if the dosage form is manipulated or is used at a higher dosage than directed. For example, the formulation can include a substance irritating to the nasal mucosa if ground and snorted.
4. *Delivery System* (including use of depot injectable formulations and implants) – Certain drug release designs or the method of drug delivery can offer resistance to abuse. For example, sustained-release depot injectable formulation or a subcutaneous implant may be difficult to manipulate.
5. *New molecular entities and prodrugs* – The properties of a new molecular entity (NME) or prodrug could include the need for enzymatic activation, different receptor binding profiles, slower penetration into the central nervous system, or other novel effects. Prodrugs with abuse-deterrent properties could provide a chemical barrier to the in vitro conversion to the parent opioid, which may deter the abuse of the parent opioid. New molecular entities and prodrugs are subject to evaluation of abuse potential for purposes of the Controlled Substances Act (CSA).
6. *Combination* – Two or more of the above methods could be combined to deter abuse.
7. *Novel approaches* – This category encompasses novel approaches or technologies that are not captured in the previous categories.

IV. PREMARKET STUDIES

First and foremost, any studies designed to evaluate the abuse-deterrent characteristics of an opioid formulation should be scientifically rigorous. Important general considerations for the design of these studies include the appropriateness of positive controls⁶ and comparator drugs, outcome measures, data analyses to permit a meaningful statistical analysis, and selection of subjects for the study.

The evaluation of an abuse-deterrent formulation should take into consideration the known routes of abuse for the non-abuse-deterrent predecessor or similar products, as well as anticipate the effect that deterring abuse by one route may have on shifting abuse to other, possibly riskier route. For example, if a product is known to be abused using nasal and intravenous routes, developing deterrent properties for the nasal route in the absence of deterrent properties for the intravenous route risks shifting abusers from the nasal to the intravenous route, which is associated with a greater risk for the spread of infectious diseases.

Another concept that should be considered is whether the deterrent effects can be expected to have a meaningful impact on the overall abuse of the product. For example, immediate-release (IR) opioid and acetaminophen combination products are predominantly abused using the oral

⁶ For purposes of this guidance, a positive control is an opioid drug product or drug substance expected to result in a predictable opioid drug liking effect and has a known potential for, or history of, abuse.

route. Demonstrating a deterrent effect by the nasal route may not meaningfully reduce overall abuse of the product.

FDA is committed to retaining a flexible, adaptive approach to evaluating potentially abuse-deterrent opioid drug products. This flexibility is intended to permit a sponsor to tailor the development program to suit the abuse-deterrent characteristics of their product and the routes of abuse for that product. The adaptive aspect is intended to permit a sponsor to take into consideration the relevant products on the market at the time they are developing their product, so that appropriate non-abuse-deterrent and abuse-deterrent comparators can be used. For example, for some proposed products the appropriate comparator may be a conventional formulation. However, if there are similar approved products with abuse-deterrent properties described in labeling, the appropriate comparator should be one of those abuse-deterrent products.

The following sections describe three categories of premarket studies. Although, in general, any development program for studying abuse-deterrent technologies should include data from all three categories of studies, there may be exceptions. For example, a formulation with a sequestered antagonist may intentionally be formulated not to resist crushing, so testing the syringeability of the product may not be relevant. In most cases, however, to obtain a full and scientifically rigorous understanding of the impact of a technology or technologies on a product's abuse potential, data from each of the following three categories of premarket studies are appropriate:

1. Laboratory-based in vitro manipulation and extraction studies (Category 1)
2. Pharmacokinetic studies (Category 2)
3. Clinical abuse potential studies (Category 3)

The results of Category 1 studies may influence the design of Category 2 pharmacokinetic studies and Category 3 clinical abuse potential studies by suggesting the methods of manipulation that would yield the greatest release of opioid. The results of Category 2 studies may influence the need for Category 3 studies of clinical abuse potential and the designs and goals of these studies. For example, if the extended-release characteristics of an abuse-deterrent opioid formulation cannot be defeated and the pharmacokinetic profile remains unchanged following oral or nasal administration of the manipulated product, oral and nasal studies of abuse potential may not be necessary.

Additional studies (i.e., Category 4 studies) analyze postmarket data to assess the impact of an abuse-deterrent formulation on actual abuse. Nonclinical drug discrimination studies are useful in the evaluation of the abuse potential of a drug, but their utility in predicting the impact of abuse-deterrent properties on human behavior has not been established.⁷

⁷ See FDA draft guidance for industry, *Assessment of Abuse Potential of Drugs* see <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm198650.pdf>.

A. Laboratory Manipulation and Extraction Studies (Category 1)

The goal of laboratory-based Category 1 studies should be to evaluate the ease with which the potentially abuse-deterrent properties of a formulation can be defeated or compromised. This information should be used when designing Category 2 and Category 3 studies. These studies are critical to the understanding of product characteristics and performance.⁸

Methodologically, these studies should be designed with knowledge of the physicochemical properties of the product and the methods available to abusers to manipulate the product and should be conducted on the to-be-marketed formulation. Sponsors should consider both the mechanisms by which abusers can be expected to attempt to deliberately overcome the abuse-deterrent properties of the product as well as the ways that patients may alter the formulation (unintentionally or intentionally) that change the rate or amount of drug released (e.g., dose dumping may occur when taking the product with alcohol or when the product is cut, chewed, or crushed). Testing should provide information sufficient to fully characterize the product's abuse-deterrent properties, including the degree of effort required to bypass or defeat those properties. In some cases, when designing in vitro studies, it may be useful to obtain information from prescription opioid abusers about how they would manipulate and abuse an abuse-deterrent product.

In vitro studies should assess various simple and sophisticated mechanical and chemical ways a drug could be manipulated, such as by (1) defeating or compromising the controlled release of an opioid from ER formulations for purposes of abuse by different routes of administration; (2) preparing an IR formulation for alternative routes of administration; or (3) separating the opioid antagonist, if present, from the opioid agonist, thus compromising the product's abuse-deterrent properties. The goal of these studies is to manipulate the product to the point of defeating its abuse-deterrent properties. Once this goal is achieved, it is no longer necessary to continue experiments using more sophisticated methods. For example, if 90% of the opioid can be extracted under a set of conditions in 10 minutes, there is no need to test the same condition for 30 minutes.

The test product should be compared to appropriate comparator products for ease of mechanical manipulation. The ability to crush, cut, grate, or grind the product formulation using readily available items such as spoons, cutters, and coffee grinders should be assessed. Particular attention should be given to particle size distribution following each mode of physical manipulation because particle size may influence the rate of opioid extraction from manipulated product. The effect of heat and cold on mechanical manipulation should also be studied.

Extractability and solubility studies should be designed to determine whether any of the formulation components might be differentially solubilized and extracted, allowing an abuser to

⁸ This topic has been discussed at meetings of the Anesthetic & Life Support Drugs Advisory Committee and the Drug Safety & Risk Management Advisory Committee (*NDA 022272, OxyContin*, May 5, 2008, and September 24, 2009). Additional information on these meetings is available on FDA's web site at the following location: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM187082.pdf>.

bypass the drug's abuse-deterrent properties. In addition to extraction and solubility studies, an assessment should be made to determine if free-base opioid can be precipitated from solution by pH adjustment. After establishing how a product could be manipulated, chemical extraction of the opioid from the intact and the manipulated product should be assessed and compared to opioid extraction from the selected intact and similarly manipulated comparator products.

The ease of extracting the opioid from the intact and manipulated product should be determined using a variety of solvents that are commonly available (e.g., water, vinegar, ethanol, isopropanol, acetone, mineral spirits) and those that have potentially relevant solvent characteristics (e.g., pH, polarity, protic vs. aprotic). The effects of time, temperature, pH, and agitation on solvent extraction should also be determined. For products containing more than one drug substance, extractability and solubility studies should be designed to determine whether any of the active ingredients might be differentially solubilized and extracted. Sampling times should start early (e.g., 30 seconds) and continue until at least 80% of the opioid has been released, or 12 hours has been reached. The in vitro drug-release characteristics of the intact and manipulated product should also be compared using a discriminatory and robust dissolution method.

In addition to the general evaluation of the effects of physical and chemical manipulation on the product, there are important route-specific data that should be generated, as follows:

- For a product with potential for abuse by the nasal route, the particle size distribution following attempted manipulation by various methods should be established, and the method that provides the smallest particle size should be used in subsequent studies.
- For a product with potential for abuse by smoking, the amount of drug produced by vaporization at temperatures encompassing the range from the melting point of the active ingredient to its degradation point should be determined. Appropriate controls, such as pure active ingredient, both in salt and free-base form should be included in these assessments.
- For a product with potential for abuse by injection, the amount of opioid that can be obtained in a syringe should be based on studies of intact and manipulated test product and comparator(s) using small volumes of water (5-10 mL) at room temperature and at 90° C – 95° C with and without agitation. Extraction times should range from 30 seconds to 30 minutes. The amount of opioid extracted, the volume of solution collected and the viscosity of the samples should be recorded. The ability to get the sample into a syringe and expel the sample using needles of various gauges should also be explored.

The following examples illustrate the kinds of outcomes that in vitro studies should evaluate.

1. Characteristics of the product by crushing, grinding or melting, or by changing the intact formulation using other methods that would limit nasal administration of the manipulated product, and/or that would limit dissolution of the manipulated product and incorporation into a solvent that could then be injected by intravenous or subcutaneous routes.

2. Quantity of the opioid extracted from the product following the various methods attempted that could be used for injection by intravenous or subcutaneous routes and a description of any barriers resulting from attempts at dissolution for drawing the drug into a syringe.
3. Quantity of opioid antagonist released from an agonist/antagonist combination when it is manipulated for administration by ingestion, nasal administration, or injection.
4. Quantity of opioid product following in vitro manipulation of the prodrug.

B. Pharmacokinetic Studies (Category 2)

The goal of the clinical pharmacokinetic studies, Category 2, should be to understand the in vivo properties of the formulation by comparing the pharmacokinetic profiles of the manipulated formulation with the intact formulation and with manipulated and intact formulations of the comparator drugs through one or more routes of administration. Even though the same routes of administration should be studied for the new product and comparators, if specific circumstances prevent this approach, the study design should be discussed with FDA. The method of manipulation used for the pharmacokinetic studies should be based on the methods explored during in vitro testing that can be expected to result in the greatest drug release. The routes of administration chosen should be relevant to the proposed product, and likely will be based on what is known about the abuse of similar products. Note that, for some development programs, it may be preferable to combine measures of pharmacokinetic parameters for Category 3 studies, in which case separate Category 2 studies may not be necessary.

In general, the pharmacokinetic profile for the oral route of administration should be studied. Appropriate study subjects for Category 2 studies include healthy volunteers as long as naltrexone is used to block the pharmacodynamic effects of the opioids.

Depending on the product, it may be important to evaluate the pharmacokinetic profile for the nasal route of administration as well. For nasal pharmacokinetic studies, it is important to weigh the risk to the subject based on the excipients in the formulation. Only subjects with a history of nasal abuse of opioids should be recruited for these studies. As with the oral route of administration, it may be possible to combine the pharmacokinetic assessment and the pharmacodynamic assessment in one clinical abuse potential study with sampling for the pharmacokinetic analysis.

Relevant pharmacokinetic parameters for the opioid drug and any psychoactive metabolites that should be measured in these studies include the following.

- Maximum concentration (C_{max})
- Time to maximum concentration (T_{max})
- Area under the curve (AUC_{0-t} and $AUC_{0-\infty}$)
- Relevant partial AUC, including early time points such as AUC_{0-30} minutes or AUC_{0-2} hours, the period of time when C_{max} is expected
- Terminal elimination half-life ($T_{1/2}$)

Traditional pharmacokinetic study designs should be employed (e.g., crossover designs), and the results should be analyzed using bioequivalence methods. The rate of rise of drug concentration should be assessed when possible because it is thought to contribute to differential abuse potential among drugs, formulations, and routes of administration.⁹ To support these analyses, it is important to have specimen collection and analysis time points sufficient to cover the onset, peak, and offset of the effects of both IR and ER formulations, in both the intact and manipulated conditions. In addition, these data are necessary to calculate the relevant partial area under the curve, which should capture the time to maximum concentration of the opioid.

If food and alcohol alter the pharmacokinetic parameters of the formulation, data should be provided to characterize those effects.¹⁰ If food significantly increases systemic exposure of the intact formulation, the underlying mechanism for the food effect should be established by assessing whether the effect is based on the drug substance or the formulation and whether the effect is present with intact product as well as with manipulated product. When food is expected to increase exposure, subsequent abuse potential studies of the oral route should be conducted in the fed state to maximize the potential systemic exposure.

In addition to the pharmacokinetic profile of the opioid, for agonist/antagonist combinations , the pharmacokinetic characteristics of the antagonist should be defined for the intact product as well as for the manipulated formulation.

As with all clinical studies, adverse events should be collected, and those that can provide additional insight about the abuse-deterrent effects are especially important. For example, if the manipulated formulation is abused by snorting, it would be important to assess adverse events related to intranasal tolerability.

C. Clinical Abuse Potential Studies (Category 3)

In addition to their use by FDA to formulate its scheduling recommendation under the CSA for drug products containing a controlled substance, clinical studies of abuse potential, Category 3, are important for assessing the impact of potentially abuse-deterrent properties. As discussed in

⁹ References suggesting that drugs associated with a rapid onset of action are associated with greater abuse potential include:

Abreu M E, Bigelow G E, Fleisher L, and Walsh S L. 2001. Effect of intravenous injection speed on responses to cocaine and hydromorphone in humans. *Psychopharmacology*, 154:76-84.

de Wit H, Bodker B, and Ambre J. 1992. Rate of increase of plasma drug level influences subjective responses in humans. *Psychopharmacology*, 107:352-358.

de Wit H, Didish S, and Ambre J. 1993. Subjective and behavioral effects of diazepam depend on its rate of onset. *Psychopharmacology*, 112: 324-330.

¹⁰ FDA has issued a draft guidance on this topic (*Assessment of Abuse Potential of Drugs*). Once finalized, it will represent FDA's current thinking on this topic.

FDA's guidance on that topic,¹¹ the preferred design is a randomized, double-blind, placebo-controlled and positive controlled crossover study. These studies generally are conducted in a drug-experienced, recreational user population. The use of a pre-qualification phase (see section 2 below) to identify subjects who can reproducibly distinguish active drug from placebo is a common enrichment strategy used to improve the power of the study to establish a difference between treatments.

Additional considerations applicable to clinical abuse potential studies used to assess potentially abuse-deterrent properties are discussed below. For products that are not susceptible to manipulation based on Category 1 and 2 testing, study designs for Category 3 testing should be discussed with FDA.

1. Blinding

Clinical studies of abuse potential should use a randomized, double-blind, placebo-controlled and positive controlled crossover design. Because study subjects are recreational drug users and familiar with the effects of the drug substances being studied, the double-dummy technique or other techniques should be used to ensure the blinding of all tests when possible. However, alternative designs may be suitable when the blinding of the study drug and the positive control cannot be maintained and treatment by period interactions may lead to sequence effects in a crossover design. For example, a parallel design may be useful when studying the intranasal route of administration, where subjects may be able to see the differences in volume or color between test drug and placebo or positive control, or when it is not possible to create similar results from manipulation, such as particle size from crushing. In these circumstances, early discussion with FDA is recommended.

For clinical abuse potential studies in which the subjects will snort test samples, administration of the samples in a narrow neck, opaque container with a pre-inserted straw may help facilitate blinding. However, even though subjects might not be able to see the sample, un-blinding may still occur due to the physical properties of samples with similar particle size distribution. In some formulations, higher crushed tablet/capsule volume or larger particle size may inhibit complete intranasal administration thereby contributing to the deterrence effects. To be able to evaluate these effects, it may be necessary to maintain differences in tablet/capsule volume between the potentially abuse-deterrent formulation and the comparator. To facilitate blinding and maintain the crossover design, placebos matched to each of the differing weights or particle sizes may be useful. The details of the preparation of the samples should be provided in the study protocol.

2. Pre-qualification Phase

The purpose of the pre-qualification phase is to increase the power of a study to detect differences in the abuse potential of the various formulations of drug and placebo.¹² In general,

¹¹ Ibid.

¹² An additional advantage of a pre-qualification phase is that it helps familiarize subjects with and train them in the use of various scales and questionnaires that measure subjective effects.

the pre-qualification phase should ensure that subjects can distinguish between placebo and a conventional IR formulation of the same opioid being developed in an abuse-deterrent formulation, using the same route of administration as planned for the assessment phase. There is little value in having subjects unable to distinguish placebo from active drug continue in the study. The positive control should include a strength that is at least equal to the lowest strength selected for the assessment during the clinical phase. An important aspect of the pre-qualification phase is assessing the ability of subjects to tolerate the study dose. If the dose used in the pre-qualification phase is lower than the lowest strength planned for the assessment phase, some subjects may not be able to tolerate the higher dose that will be administered in the assessment phase. Thus, when tolerability may be an issue, particularly if more than one dose is planned for the assessment phase, a pre-qualification dose that is no lower than the lowest dose planned may be the most efficient choice to establish that the subject can distinguish active drug from placebo and can tolerate the study drug in the range to be tested. For example, a 30 mg or 45 mg dose of opioid could be used in the pre-qualification phase when a 30 mg and 60 mg doses will be assessed in the clinical phase.

Qualifying criteria that help identify subjects with an acceptable placebo response and an acceptable response for the positive control should be pre-specified in the study protocol. After a range for an acceptable placebo response is set, a minimum value for the maximum effect (E_{max}) for the positive control should be defined. The minimum E_{max} for the positive control may vary from measure to measure, and from study to study. However, an acceptable response for the positive control should not overlap with the acceptable range for placebo response.

3. Assessment Phase

The potentially abuse-deterrent product should be compared to a positive control, and the positive control should be compared to placebo to validate the study. For an IR product with potentially abuse-deterrent properties, the positive control should be an IR formulation of the same opioid. For an ER formulation with potentially abuse-deterrent properties, the positive control could be an IR formulation of the same opioid or an ER formulation of the same opioid. In general, these studies should include one strength of the positive control which is associated with high levels of drug liking. However, when assessing drug liking through the intranasal route, the use of two strengths of the positive control may be helpful to both identify a strength of the positive control associated with high drug liking scores and to validate the study.

If there are no approved products with the same drug substance, the positive control should be a drug that, based on pharmacological profile or nonclinical data, can be expected to have similar pharmacodynamic effects. Selection of the positive control in this setting should be discussed with FDA.

4. Subjects

Studies should be conducted in opioid-experienced, recreational drug users who have experience with the particular route of abuse being studied. Subjects should generally not be physically dependent and should not be currently seeking or participating in treatment for drug abuse such that participating in the study could make them vulnerable to relapse. Depending on the

formulation being studied, however, clinical abuse potential studies can be conducted in physically dependent subjects. For example, if the deterrent product contains an opioid antagonist, clinical abuse potential studies in a physically dependent population may provide information not only on the drug liking of the product, but on the ability of the antagonist to precipitate withdrawal in this population.

Detailed characteristics of the study population with respect to past and current drug use and abuse should be captured (e.g., drugs abused, drug of choice, duration of abuse or abstinence).

5. Route of Administration, Dose Selection, Manipulation Mode, and Sample Preparation

The selection of the route(s) of administration should be based on epidemiological data showing that a selected route is a relevant route of abuse. For NMEs, the sponsor should review the relevant routes of abuse for products similar to the test product and discuss the selected routes with FDA. For each relevant route of administration, the potentially abuse-deterrent product and comparator should be manipulated based on the results of Category 1 studies to cause the highest release of the opioid and the highest plasma levels. The dose of the opioid selected for the study should be known to produce high levels of liking in non-tolerant opioid-experienced recreational users.

For studies using the intranasal route of administration, the preparation of the samples is extremely important. The potentially abuse-deterrent product and comparator study drug should be produced with similar particle size distribution based on a detailed protocol for the preparation of the samples, even if different methods are necessary to do so.¹³ With some formulations, a high volume of the crushed tablet/capsule or larger particle size may inhibit complete intranasal administration and, thereby, contribute to deterrence effects. To evaluate these effects, it may be necessary to maintain differences in tablet/capsule volume between the potentially abuse-deterrent product and the comparator.

For studies using the intravenous route of administration, the oral formulations may not be safe for intravenous use depending on the excipients used in the formulation. In place of the manipulated oral formulation, a solution for injection should be prepared using approved, commercially available parenteral products when available, or products suitably formulated for the study. The amount of the opioid and that of the antagonist, when relevant, should be based on extrapolation from in vitro extraction studies of manipulated solid formulations.

6. Outcome Measures and Data Interpretation

In abuse potential studies, the primary method for evaluating the subjective effects of drugs should be through the use of standardized instruments.

¹³ Available safety-related information on the use of the various excipients through the intranasal route should be provided. Additionally, some sponsors have conducted intranasal tolerability studies before the abuse potential studies to evaluate irritation of the nasal cavity, nasal congestion, and discharge, among other measures.

In typical abuse potential studies, several instruments have been used to measure subjective responses predictive of the likelihood of abuse. These instruments include:

- Visual Analogue Scales (VAS) – used for drug liking, good effects, bad effects, and other drug abuse-related effects
- Profile of Mood States

The VAS should be the primary measure for drug liking because it appears to correlate most directly with potential for abuse. Other measures of particular interest include assessment of likelihood to take the drug again and assessment of overall drug liking.¹⁴

These measures can be assessed using either a unipolar or bipolar scale, and a rationale should be provided for the choice for a particular scale. In general, FDA recommends using a bipolar scale for the primary measure of drug liking. Unipolar scales have been used to measure other drug effects, such as good and bad effects. Regardless of whether a unipolar or bipolar scale is selected, FDA recommends that for purposes of training subjects, the same scale be used in the pre-qualification and assessment phases.

7. *Data Interpretation*

For clinical studies of abuse potential conducted on potentially abuse-deterrent opioid drug products, the primary analysis should be the difference in means of the E_{max} ¹⁵ for the primary measure(s) based on the population of study completers. A statistical analysis plan (SAP) should be included in the study protocol or submitted as a separate document before un-blinding the study. The sponsor should provide data and dropout information for non-completers. To ensure adequate power, the sponsor should take into account that there will be subjects who drop out of the study early and plan the sample size calculation accordingly. Proper planning should avoid any need to replace subjects who discontinue without completing the study.

Additional pharmacodynamic measures, including positive subjective effects other than drug liking (e.g., take drug again, high, overall drug liking) and other subject-rated assessments, are generally considered secondary endpoints. Other subject-rated assessments of interest include: alertness; drowsiness; nausea; and, when the intranasal route is used, intranasal irritation, burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal congestion.

Some sponsors provide descriptive statistics including mean, standard error, median, and interquartile range, calculated for all pharmacodynamic endpoints by time and treatment.¹⁶ What

¹⁴ Overall drug liking measures the user's retrospective assessment of a drug, whereas VAS for drug liking measures the user's immediate assessment.

¹⁵ In general, the primary endpoint of interest is drug liking, and the E_{max} is captured within 8 hours after dosing. However, the timeframe of measuring the maximum response will be determined by the pharmacokinetic and pharmacodynamic parameters of the formulations studied.

¹⁶ See Statistical Analysis Section for further guidance.

constitutes a clinically significant difference in drug liking, between the manipulated and intact versions of the potentially abuse-deterrent product and positive control, is an area requiring further research and will be evaluated on a case-by-case basis. Analysis of postmarket data on abuse levels associated with the potentially abuse-deterrent product being studied may help to support the findings from abuse potential studies.

In addition, when interpreting results from clinical abuse potential studies, attention should be given to the profile of subjective effects produced by the manipulated and intact formulation in terms of onset, peak duration of activity, and offset. The rate of rise of drug onset for the intact and manipulated potentially abuse-deterrent product should be given appropriate weight in the overall analysis of the abuse-deterrent properties. A more rapid onset of action or a shorter time-to-reach peak effect is generally associated with greater abuse potential. Regarding the duration of effect, it may be difficult to interpret the abuse potential of a formulation that produces a sustained liking effect when taken intact or after manipulation, though lower than that produced by the positive control formulation.

The overall assessment of abuse potential should be based on the pattern of findings across all of the measures. In addition, qualitative aspects of the findings, such as the steepness of the drug liking response and duration of the liking effects associated with manipulated formulations, should be taken into consideration, along with other positive effects and negative effects.

8. *Statistical Analysis*

a. *Background*

The overall goal of a clinical study of abuse potential is to assess a number of abuse potential outcome measures (e.g., drug liking VAS) in the potentially abuse-deterrent product (T) relative to a formulation of the drug without abuse-deterrent properties (C), or a newly formulated opioid product (positive control). Substantial decreases in the responses for the potentially abuse-deterrent formulation compared to the positive control are evidence of deterrence.

A clinical study of abuse potential should be validated by comparing the responses to C with those of placebo (P). Thereafter, the assessment of the abuse-deterrence properties of T is of primary interest. This can be achieved by comparing the difference in means between C and T with a *margin* for abuse potential measures and comparing the difference between C and T relative to C in drug liking on a bipolar VAS.

The statistical analysis of the data in a clinical study should begin with descriptive statistics making up tabulations and graphs that include tables of the mean, standard error, and other summary statistics: minimum, Q1, median, Q3, and maximum of the responses of interest for each treatment and for each paired difference among treatments.

Useful graphs include mean time course profiles, heat-maps,¹⁷ and continuous responder profiles.

The next subsection describes the statistical test that sponsors should use for the primary analysis of E_{max} on the VAS for drug liking. An analysis of the percent reduction in drug liking for T relative to C on the individual level in subsection c is recommended as a secondary analysis.

b. Primary analyses

The primary analysis of abuse-deterrent effects should be based on the comparison of means¹⁸ between crushed, chewed, or otherwise modified T and C with an abuse deterrence margin on drug liking VAS. That is, test

$$H_0 : \mu_C - \mu_T \leq \delta_1 \text{ versus } H_a : \mu_C - \mu_T > \delta_1$$

where $\delta_1 = \delta^*(\mu_C - 50)$, and $0 < \delta^* < 1$. Because C is an opioid drug, the validation test also needs a margin, say δ_2 . That is,

$$H_0 : \mu_C - \mu_P \leq \delta_2 \text{ versus } H_a : \mu_C - \mu_P > \delta_2$$

where $\delta_2 \geq 15$.

The significant level for both tests is 2.5%.

The actual value of δ_1 is related to μ_C , hence, it may vary according to abuse potential measures and the route of drug administration. The δ^* should be pre-specified in the protocol. We also suggest the use of 95% confidence intervals to assess both the differences $\mu_C - \mu_T$ and $\mu_C - \mu_P$.

c. Secondary analyses

In addition to the primary analysis, an analysis should be performed of the percent reduction for the potentially abuse-deterrent product T relative to C from each individual study subject for drug liking VAS on a bipolar scale from 0 to 100. One definition for percent reduction for individual subjects is as follows:

$$\%reduction = \frac{c_i - t_i}{c_i - p_i} \times 100\%, i = 1, 2, \dots, n,$$

where c_i , t_i and p_i are the E_{max} values for C , T , and P from the i th subject, respectively; n is the sample size.

¹⁷ Chen L and Wang Y. 2012. Heat map displays for data from human abuse potential crossover studies. *Drug Information Journal*, 46:701:707.

¹⁸ If a nonparametric method is necessary, analysis of the median difference in E_{max} may be appropriate.

However, this definition is problematic because for two subjects having the same E_{\max} values for T and C ($t_1 = t_2$ and $c_1 = c_2$), the larger the placebo response, the greater the percent reduction. A more appropriate definition of percent reduction can be derived by replacing p_i by the neutral score 50 on a bipolar scale; that is,

$$\% \text{ reduction} = \frac{c_i - t_i}{c_i - 50} \times 100\%, i = 1, 2, \dots, n$$

where we assume that $c_i > 50$. In case some subjects have $c_i \leq 50$, define % reduction = 0.

Note that even though most abuse potential studies have a pre-qualification phase, approximately 10% of subjects still have placebo responses p_i over 65, with 5% over 75 in the assessment phase. Consequently, it may be necessary to penalize subjects with large values of p_i in computing percent reduction. For example, the percent reduction could be multiplied by an adjustment factor that equals 1 when p_i is around 50 or less and decreases from 1 when p_i is large. Sponsors should discuss with FDA the need for an adjustment factor in computing percent reduction and an appropriate formula for defining the penalty to be applied before finalizing the study protocol.

Two approaches for assessing the deterrent effects using percent reduction for crossover design studies are provided below. Note that when a parallel design is used, the percent reduction for individual subjects is not applicable, and the primary analysis may also serve the purpose for assessing the percent reduction based on $\mu_C - \mu_T$ related to $\mu_C - 50$.

- Responder Analysis

A *responder* is defined as a subject who had at least $\delta^* 100\%$ of reduction, in E_{\max} for T relative to C. To ensure that a majority of subjects are responders, a proportion test can be used to test the null hypothesis that 50% or fewer subjects are responders. That is, test

$$H_0 : p^* \leq 50\% \text{ versus } H_a : p^* > 50\%$$

at the 2.5% significance level where p^* denotes the percentage of responders. The 95% confidence interval of p^* can also be calculated.

- Analysis of the Median Percent Reduction

The median of the percent reduction (ptr) is a descriptive measure of central tendency of ptr . At most 50% of subjects have ptr less than the median, and at most 50% of subjects have ptr greater than the median. If the median of ptr is equal to 30%, for example, it means that approximately 50% of subjects have greater than or equal to a 30% reduction.

For assessing deterrent effects, we can test

$$H_0 : \text{median}(\text{ptr}) \leq DR\% \text{ versus } H_a : \text{median}(\text{ptr}) > DR\%$$

at the 2.5% significance level, where DR denotes deterrent reduction. To be consistent with the responder analysis, we recommend $DR\% = \delta^* 100\%$. If the distribution of ptr is symmetric, the Wilcoxon-signed rank test can be used to test the null hypothesis that $\text{median}(\text{ptr}) \leq DR\%$, and a 95% confidence interval for the median based on this test can be readily calculated using standard methods. Otherwise, the sign test should be used or an alternate method of this test can be pre-specified in the SAP.

Sponsors should pre-specify one of the two analysis methods for the percent reduction in their SAP in addition to the primary analysis in their clinical studies and discuss with FDA the definition of a responder in the responder analysis or the value of DR% used in the analysis of the median percent reduction before finalizing the study protocol.

d. Multiplicity

Whether or not an adjustment for multiplicity is needed for claiming significant results on the primary or key secondary endpoints varies from study to study. Sponsors should refer to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance *E9 Statistical Principles for Clinical Trials*¹⁹ for statistical principles regarding the multiplicity adjustment.

V. POSTMARKET STUDIES (CATEGORY 4)

Premarket studies focus on assessing the potentially abuse-deterrent properties of a product under controlled conditions. The goal of postmarket²⁰ studies, Category 4, is to determine whether the marketing of a product with abuse-deterrent properties results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting. As more abuse-deterrent products are approved, it is possible that the amount of reduction observed in an epidemiologic study may also change. Consequently, a reduction that is deemed meaningful at one time may not be meaningful at another. Given the changing landscape, a numerical threshold cannot define what would be considered a meaningful reduction.

Currently, data on the impact of an abuse-deterrent product on drug abuse in the U.S. population are limited, and thus the optimal data sources, study variables, design features, analytical

¹⁹ ICH guidelines are available on FDA's guidance webpage at <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

²⁰ FDA requires postmarket studies for all opioids with abuse-deterrent labeling claims. For more information on postmarket requirements, see <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/ucm070766.htm>.

techniques, and outcomes of interest of postmarket epidemiologic studies are not fully established.

Postmarket evaluations of abuse deterrence fall into two categories—formal studies and supportive information. Sponsors should submit protocols to FDA for all formal studies of abuse deterrence. Supportive information can also be submitted to FDA, but cannot substitute for formal studies.

A wide range of interrelated behavioral, clinical, and societal factors contribute to drug abuse; therefore, the effects of an abuse-deterrent formulation can manifest in a variety of ways.

Understanding the actual impact of a particular abuse-deterrent formulation may require using a variety of study designs to examine different abuse-related outcomes in given populations of interest. Generally, multiple formal studies using a variety of data sources should be conducted to provide insights into product-specific abuse and the effect of an abuse-deterrent product on the outcomes of interest for other opioid drug products. The use of multiple study designs will also generally help with assessment of the impact of abuse-deterrent products on the full spectrum of abuse-related outcomes (i.e., addiction, overdose, and death) and to characterize and quantify the relevant clinical events that are associated with these outcomes.

Recognizing that the current thinking in this area may change, the following subsections provide recommendations for designing postmarket epidemiologic studies that are capable of detecting a change in the occurrence of abuse as a result of a drug product's abuse-deterrent properties.

A. Formal Studies

1. General Characteristics

Formal studies have the following characteristics:

1. They are hypothesis-driven, population-based, observational evaluations that follow good epidemiological practices^{21,22} and use outcomes that provide meaningful measures of abuse deterrence.
2. They capture one or more outcomes that can be used to assess meaningful reductions in misuse, abuse, addiction, overdose, and death.
3. They produce estimates of abuse and related clinical outcomes that are nationally representative, or are based on data from multiple large geographic regions that can reasonably be generalized to the national level. In the absence of nationally generalizable

²¹ See FDA guidance *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*, available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm243537.pdf>.

²² International Society for Pharmacoepidemiology and Risk Management, Guidelines for Good Practices and Pharmacoepidemiologic Studies, available at http://www.pharmacoepi.org/resources/guidelines_08027.cfm, accessed January 25, 2015.

data, smaller or regional studies may be informative, but must be accompanied by a clear explanation of their representativeness and generalizability for appropriate interpretation.

4. They assess overall and route-specific (i.e., injected, snorted, smoked) changes in abuse levels that are associated with an abuse-deterrent product.
5. They are sufficiently powered statistically to assess meaningful changes in drug abuse and are of sufficient duration to examine trends in abuse following the marketing of the abuse-deterrent product. The necessary duration of the studies will depend on a variety of factors, including drug utilization and market share, early postmarket abuse deterrence data, and changes in the prescription opioid or illicit drug market.

2. Study Design Features

The epidemiologic methods and data sources that underlie formal postmarket studies to evaluate the effect of abuse-deterrent formulations are evolving, and best practices have not been established. In addition, characterizing the relevant clinical events that are most useful for understanding the actual impact of a product on abuse-related adverse events is also an evolving science. Based on the current state of this field, we provide below some basic guidelines on recommended study design features that will enable FDA to evaluate the results of formal studies.

1. The study hypothesis and its relationship to assessing abuse deterrence should be clearly stated. The study hypothesis should also include the route(s) of abuse that will be studied.
2. An understanding of each data source is important to the design and interpretation of the study. A description of each data source should be provided in the protocol and should include if and how the data source captures drugs, study outcomes, drug formulation, and route of abuse. The sampling methods, study population, or catchment area for the data source should be clearly described.²³
3. The choice of population(s) in each study should be carefully considered. The populations included in the study should be described in the protocol. At least one study should include a high-risk population, such as a population of known drug abusers, but formal studies should not be limited to only high-risk populations.
4. The protocol and study reports should thoroughly define the study outcomes. The choice of the outcome measure(s) should be justified. Formal studies should, as a group, capture all relevant outcomes: misuse, abuse, addiction, overdose, and death, as well as misuse and abuse clinical outcomes. Overall and route-specific misuse and abuse estimates should include prevalence and frequency of abuse. Clinical outcomes should include, when possible, an assessment of severity of abuse outcomes (e.g., addiction or overdose).

²³ See FDA guidance *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*.

5. Both population- and drug utilization-based estimates should be included in the study protocol.²⁴ Drug utilization-based estimates should use multiple denominators. The denominators are generally the number of prescriptions and the number of extended units (e.g., tablets or capsules). The catchment area for drug utilization data should be specified, particularly for sub-national or regional populations.
6. Sponsors should list all proposed opioid comparators and describe the rationale behind their inclusion. When branded and generic versions of a comparator are marketed, all should be included in the study when possible because many data sources used in abuse studies can identify only active ingredients and do not distinguish between branded and generic products or among multiple generic products. Information should be provided on the ability of data sources and study participants to accurately discriminate among different opioid products and formulations. The choice of comparator is critical for determining if a reduction in drug abuse is the result of a product's abuse-deterrent properties or the result of other factors (e.g., educational programs, prescription drug monitoring programs, changes in law enforcement policies, and the availability of other drugs) or secular trends. The choice of comparators will depend on the particular abuse-deterrent product studied and the opioid market environment at the time the study is initiated. Multiple comparators should be used to achieve the most complete picture of the impact of a product's abuse-deterrent properties. For the purposes of hypotheses, some comparators should be selected and justified as primary comparators in the study protocol before data collection, with additional comparators providing context. The following are examples of several potential abuse-deterrent study comparator scenarios.

If an abuse-deterrent formulation of a previously marketed product is introduced to the market, the primary comparators should include historical and currently available non-abuse-deterrent formulations of the products (including branded and generic whenever possible). Additional individual opioid products should be included as well and should be agreed upon with FDA and identified before the start of the study.

If a new abuse-deterrent product does not have an historical or currently available non-abuse-deterrent version of the same opioid, an appropriate group of comparators should be identified before the start of the study through mutual agreement with FDA. Examples of appropriate primary comparators include immediate release non-abuse-deterrent products with the same active moiety and/or a non-abuse-deterrent product with a relatively stable market share and abuse estimates captured at baseline during the postmarket period. Larger groupings of products can also serve as comparators and can help determine secular trends.

When available, a product that has the same active moiety, but has a different abuse-deterrent property, can serve as a comparator.

²⁴ Secora A, Dormitzer C, Staffa J, and Dal Pan G. 2014. Measures to quantify the abuse of prescription opioids: a review of data sources and metrics. *Pharmacoepidemiology and Drug Safety*, 23(12):1227-37.

7. Understanding the background rates of drug abuse is important for protocol design and interpretation of study results. A baseline assessment of the prevalence of drug abuse for formulations of the same opioid that lack abuse-deterrent properties should be conducted and the baseline time period should be justified.
8. Submissions should include the SAP. The plan should include parameter definitions, unit of analysis, model specification, power and sample size calculations, and any additional variables or predictors. Assessment of the abuse outcome measures should consider both average levels of abuse comparing pre- and post-periods to currently available product (means analysis) and trend analysis.
9. Statistical models should include variables that may affect how the product is used and also other related confounders (e.g., geographic variability and demographic characteristics).
10. Exposure and outcome measures that include self-reported assessments should be validated before the start of the study.
11. The precision of outcome measures will also influence the observational period. Outcome measures with large uncertainty (due to bias or variability) in the exposure or study variable measures, for example, may warrant longer observational periods.
12. Interim analyses are encouraged, but results should be considered tentative in light of their preliminary nature.

B. Supportive Information

Information is considered supportive if it can be used to provide additional context on societal, behavioral, and clinical aspects of abuse and abuse-deterrance. Supportive information may be qualitative or descriptive, and it may rely on sources that capture drug utilization or prescribing patterns, diversion events, attitudes and practices (e.g., tampering) of abusers and other information that may not directly be considered abuse (e.g., data concerning the street value of prescription drugs, information about drug use and misuse from social websites). Investigations that provide supportive information may also include investigations that are conducted in smaller populations or subgroups, and that while perhaps not broadly generalizable, may contribute to the totality of the evidence relating to abuse deterrence.

As is the case for formal studies, best practices for collecting and submitting supportive information are still evolving. However, below are some basic recommendations relating to supportive information.

1. Supportive information should be clearly stated, and the rationale for how the supportive information contributes to a sponsor's portfolio of abuse-related studies should be clearly identified.
2. How supportive information is representative of the population from which it is derived or sampled should be clearly described.

3. How the exposure and outcome are measured should be clearly described along with the relationship between the outcomes measured and the primary outcomes of interest: misuse, abuse, addiction, overdose, and death.
4. Collections of supportive information that include populations of particular interest or geographically diverse settings is strongly encouraged. Overlapping geographic areas between formal and supportive information should be considered.

VI. LABELING

Including information about a product's abuse-deterrent properties in labeling is important to inform health care professionals, the patient community, and the public about a product's abuse potential. Accordingly, FDA encourages sponsors to propose labeling that sets forth the results of in vitro, pharmacokinetic, clinical abuse potential and formal postmarket studies and appropriately characterizes the abuse-deterrent properties of a product.

There are several important concepts about the state of the science of pre- and postmarket studies of abuse deterrence that should be considered as these are reflected in labeling. First, as stated earlier in the guidance, abuse-deterrent does not mean abuse-proof. Therefore, labeling should reflect a product's abuse-deterrent properties, as supported by the data, but should include a caveat that abuse is still possible. Next, premarket studies are intended to demonstrate properties that are predictive of a meaningful abuse-deterrent effect for a particular route of administration. FDA has limited data correlating the abuse-deterrent properties of certain opioid drug products, as demonstrated by premarket studies, with the impact of those properties on abuse or adverse events associated with abuse in the post-approval setting. Even though postmarket studies have the potential to demonstrate such effects, the findings of postmarket studies are not available at the time of initial product approval. Labeling should reflect the predictive quality of premarket studies and include results of relevant completed postmarket studies.

When premarket data show that a product's abuse-deterrent properties can be expected to result in a meaningful reduction in that product's abuse, these data, together with an accurate characterization of what the data mean, should be included in product labeling.²⁵ When postmarket data become available that demonstrate a meaningful reduction in abuse by one or more routes of administration, these data should be added to the product labeling. However, if these postmarket data fail to confirm that the abuse-deterrent properties result in a reduction in abuse, or demonstrate a shift in routes of abuse that represent a greater risk (e.g., a shift from oral and nasal abuse to intravenous abuse), FDA may determine that labeling revisions are needed.

Labeling language regarding abuse deterrence should describe the product's specific abuse-deterrent properties as well as the specific routes of abuse that the product has been developed to deter. For example, a formulation that limits an abuser's ability to crush a tablet and to extract the opioid can be described as limiting manipulation for the purpose of snorting or injection if

²⁵ Abuse-deterrence information in labeling should be presented in the DRUG ABUSE AND DEPENDENCE section under 9.2 Abuse.

the data support such a statement. For this characterization to be accurate and not misleading, however, appropriate caveats are likely to be necessary as described above. For example, a product's labeling should explain that the product's abuse-deterrent properties only make abuse more difficult, not impossible, and that these properties provide no deterrence against other potential forms of abuse.

As noted at the outset of this guidance, FDA will take a flexible, adaptive approach to the evaluation and labeling of abuse-deterrent opioid products. FDA expects sponsors to update their formulations to take advantage of technological improvements and further expects to allow labeling statements related to abuse deterrence commensurate with those advances.

Furthermore, FDA expects sponsors to compare their formulations against approved abuse-deterrent versions of the same opioid. The comparisons should be based on the relevant categories of testing. For instance, if a proposed product is less resistant to manipulation than an approved product, the proposed product may not be eligible for labeling regarding abuse-deterrent properties.

FDA is concerned that, with time, abusers may adapt to abuse-deterrent technologies and discover methods to defeat them. If and when abusers can overcome a technology such that it no longer has a meaningful effect in deterring abuse, FDA may require labeling revisions.

As discussed below, the nature of information in labeling on abuse deterrence for a particular product will depend on the types of studies performed and the result of those studies. Because it cannot provide specific guidance on the magnitude of effect that would be sufficient to support each type of claim, FDA will assess the appropriateness of all proposed labeling statements about abuse deterrence based on the data provided.

Information describing the results of the evaluation of abuse-deterrent properties can be used to support labeling statements based on the three premarket categories (i.e., in vitro data, pharmacokinetic data, and clinical abuse potential studies) and the fourth category (postmarket data) once it is available.

The data necessary to support abuse-deterrent labeling will depend on the characteristics of the product that impart the abuse deterrence and the route of abuse. In general, most abuse-deterrent information included in product labeling will be based on data from more than one category.

Key elements of the study design and conduct should be summarized in the product labeling. Category 1 studies can be described in general terms to avoid creating a *road map* for defeating the product's abuse-deterrent properties. However, the design, conduct, and results of Category 2 and 3 studies should be described in sufficient detail, including the primary outcome measure data from Category 3 studies, to support clear labeling regarding a product's abuse-deterrent properties.

The following are examples of information for inclusion in labeling for different types of abuse-deterrent effects based on various types of premarket studies performed.

- Category 1

For this product, in vitro data demonstrated that an abuse-deterrent product cannot be crushed and dissolved or extracted in a small volume of solution suitable for injection. In this case, Category 1 in vitro data may be sufficient to support a statement in labeling about abuse deterrence for the intravenous route of abuse (See Section IV Premarket Studies). Possible labeling text:

In vitro physical and chemical tablet manipulation studies were performed to evaluate the ability of different extraction methods to defeat the formulation. Results support that Tradename resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some extended-release properties despite manipulation.

These in vitro data demonstrate that Tradename has physical and chemical properties that are expected to deter intravenous abuse. However, abuse of this product is still possible by the oral and nasal routes.

- Category 1 and Category 2

For this product, in vitro and pharmacokinetic data from study of the oral and nasal routes of administration demonstrated that no changes occurred in the extended-release properties of the opioid after crushing or dissolution in a variety of solvents. These data may be sufficient to support statements in labeling about abuse deterrence for the nasal and intravenous routes of abuse. Possible labeling text:

In vitro physical and chemical tablet manipulation studies were performed to evaluate the ability of different extraction methods to defeat the formulation, and pharmacokinetic studies of the oral and intranasal routes were performed to determine the effect of manipulation on drug release. Results support that Tradename resists crushing, breaking, and dissolution using a variety of tools and solvents and retains its extended-release properties despite manipulation.

The in vitro data demonstrate that Tradename has physical and chemical properties that are expected to deter oral, nasal and intravenous abuse. However, abuse of intact product is still possible by the oral route.

- Category 2 and Category 3

For this product, pharmacokinetic and clinical abuse potential studies demonstrated the release of an antagonist from an opioid and antagonist combination product following crushing and that the presence of the antagonist resulted in less drug liking compared to a similar amount of opioid alone when administered by the oral and intranasal routes. In

addition, an additional clinical abuse potential study simulating intravenous abuse using the amounts of opioid and antagonist found to be released from the crushed product also demonstrated reduced drug liking.

The pharmacokinetic data demonstrate that crushing Tradename results in the simultaneous release and rapid absorption of opioid and antagonist.

These data along with the results from oral and intranasal clinical abuse potential studies and a clinical abuse potential study of intravenous opioid and antagonist to simulate crushed Tradename indicate that Tradename has properties that are expected to deter abuse via the oral, intranasal, and intravenous routes. However, abuse of Tradename by these routes is still possible.

All of these statements based on Categories 1, 2, or 3 testing should be followed by a statement that data from laboratory and clinical studies may not fully predict abuse potential in the post-approval setting.

As discussed in Section V, postmarket data from a variety of sources can demonstrate that a product's abuse-deterring properties result in persistent and relevant abuse deterrence. These data can result from appropriately designed, conducted, and analyzed formal postmarket studies and from supportive information on the abuse of the product.

FDA is currently considering formal studies plus a variety of supportive information (e.g., data concerning the street value of prescription drugs) as sources that may be acceptable to provide evidence that a product's formulation has had an actual impact on reducing its abuse. FDA anticipates that data from some or all three of the premarket categories along with data from postmarket studies (including both formal studies and supportive information) would be needed to support a statement in labeling that the product has been shown to reduce abuse. The combined results from all of these studies would be described in the product labeling, including specific study designs, conduct, analyses, and study data.

An example of labeling for a product with evidence of a reduction in abuse is:

These data demonstrated a reduction in the abuse of Tradename in the community setting compared to the levels of abuse, overdose, and death that occurred when only formulations of the same opioid without abuse-deterring properties were available. This reduction in abuse appears to be attributable to the product's formulation, which deters abuse by injection or snorting of the manipulated product. However, such abuse of this product is still possible, and the product's abuse deterrence properties do not deter abuse associated with swallowing the intact formulation.

VII. ADDITIONAL RESEARCH NEEDS

As discussed above, the science of abuse deterrence is relatively new. Both the technologies involved and the analytical, clinical, and statistical methods for evaluating those technologies are

rapidly evolving. For these reasons, FDA will take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent opioid products. Additionally, there is considerable room for additional scientific work that could advance the development and assessment of abuse-deterrent products. In particular, FDA encourages additional research on the following topics:

- The quantitative link between changes in the pharmacokinetics of opioids in different formulations and results of a clinical abuse potential study with those same formulations.
- The best assessment methods to employ when analyzing a clinical study of abuse potential.
- The quantitative link between the outcomes from a clinical study of abuse potential comparing formulations and the effect on those same formulations on abuse in the community.
- Further understanding of the best study methods to employ to assess the effect of a product with abuse-deterrent properties on the rates of abuse in the community.
- Development of a communication tool (e.g., a simple graph or chart) to inform prescribers of the relative impact the product has on the different routes of abuse.

Progress on these topics could facilitate the ability of sponsors to propose and FDA to approve labeling that would give a more complete picture of the anticipated effect of products with abuse-deterrent properties. Ultimately, progress in these areas could facilitate product development by reducing the amount of information that is needed to accurately assess a product with abuse-deterrent properties and predict its impact on abuse in the community.

Regulatory History of OPANA ER



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS**

M E M O R A N D U M

DATE: February 1, 2017

FROM: Ellen Fields, MD, MPH, Deputy Director, DAAAP

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

RE: Open Session Background Document: Regulatory History of Opana ER

Oxymorphone is a semisynthetic opioid analgesic, first approved in 1959 as Opana (Endo NDA 011707, oxymorphone 1mg/mL), a parenteral formulation indicated for the relief of moderate-to-severe pain, preoperative medication, support of anesthesia, obstetrical analgesia, and for relief of anxiety in patients with dyspnea associated with pulmonary edema secondary to acute left ventricular dysfunction. A rectal suppository, Numorphan (Endo NDA 011738), was approved in 1960. Both of these NDAs have been withdrawn and these products are not marketed. The first oral formulations of oxymorphone were approved in June, 2006, and included immediate-release tablets, Opana (Endo NDA 21611), indicated for the relief of moderate-to-severe acute pain, and extended-release tablets, Opana ER (Endo's NDA 21610), indicated for the management of moderate-to-severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

Opana ER is a member of the class of extended-release/long-acting (ERLA) opioid analgesics. It is a full opioid agonist and is relatively selective for the mu-opioid receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of oxymorphone is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

To support the initial approval, the efficacy of Opana ER was demonstrated in two twelve-week double-blind, controlled clinical trials, one each in opioid naïve and opioid-experienced patients with moderate-to-severe chronic low back pain. The safety of Opana ER was assessed in more

than 2000 patients with a variety of chronic pain conditions requiring opioid analgesia. The initial approval included 5 mg, 10 mg, 20 mg, and 40 mg strength tablets for every twelve hour administration. Due to a large increase in exposure to oxymorphone in the fed state, Opana ER was labeled to be dosed on an empty stomach, at least one hour prior to or two hours after eating. The approved labeling stated that the product should be swallowed whole, and warned that crushing, chewing, snorting, or injecting the dissolved product will result in uncontrolled delivery and pose significant risk that could result in overdose and death. The product was not formulated to deter abuse, and approved labeling did not include language on abuse-deterrent properties. As part of the original approval, a Risk Minimization Action Plan was included to mitigate the risks associated with Opana ER.

In 2008, a supplemental new drug application provided for addition of 7.5-mg, 15-mg, and 30-mg tablets that were within the range of the already approved range of strengths for Opana ER.

In July, 2010, Endo submitted a new drug application for reformulated Opana ER. The stated intention was to make the formulation resistant to physical and chemical manipulation for the purposes of abuse. Reformulated Opana ER was designed with a polyethylene oxide matrix intended to make the tablets more difficult to crush, and to form a viscous gel when in contact with liquids, making the product more difficult to abuse by the intranasal and intravenous routes of administration. Endo's application included data from in vitro and in vivo studies designed to assess the potentially abuse-deterrent properties of the new formulation, and Endo sought to include language describing these properties in the product labeling. Although FDA approved the application on December 9, 2011, because it concluded that reformulated Opana ER was safe and effective, FDA did not approve labeling describing abuse-deterrent properties because it concluded that the available data were inadequate to support such labeling. Endo replaced original Opana ER with reformulated Opana ER during the first half of 2012. However, generic products based on the original formulation continue to be marketed. Included in the approval of this product was a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use that included a Medication Guide, voluntary prescriber education, and a schedule of REMS assessments. This product would subsequently become a part of the shared REMS for all extended-release/long-acting opioid analgesics.

In July, 2012, the class-wide extended-release/long-acting opioid analgesic Risk Evaluation and Mitigation Strategy (ERLA REMS) was approved. This REMS uses a single, shared system, and includes all ERLA opioid analgesics, including Opana ER. The ERLA REMS includes a Medication Guide, voluntary prescriber education, and a schedule for REMS assessments. The details of the REMS are described in another document in this background package.

Two safety labeling changes have been issued by FDA for opioid analgesics, both of which apply to Opana ER. In 2014, the Agency approved a safety labeling change for all ERLA opioid analgesics in order to augment labeling language to ensure safe use of these products, proper prescribing and patient selection, and to more clearly describe the serious risks associated with this class of medication, including misuse, abuse, hyperalgesia, addiction, overdose, death, and neonatal opioid withdrawal syndrome. This labeling change also included a revision of the indication for all ERLA opioid analgesics, including Opana ER, to, "TRADENAME 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.”

A second class-wide safety labeling change was approved in December, 2016, which included all ERLA and immediate-release opioid analgesics. This change included the addition of a warning pertaining to the risks of concomitant use of opioid analgesics with benzodiazepines or other central nervous system depressants. The labeling change also added information regarding the risks of serotonin syndrome with concomitant use of serotonergic drugs; adrenal insufficiency; androgen deficiency; and anaphylaxis, angioedema, and other hypersensitivity reactions.

On February 15, 2013, Endo submitted a supplemental new drug application (sNDA) requesting that FDA approve labeling describing reformulated Opana ER’s purported abuse-deterrent properties. In support of the supplement, Endo submitted: (1) the same studies on which it had previously sought to rely, and the results of which were determined previously to be inadequate by FDA; and 2) preliminary post-marketing data. FDA did not approve this application (May 2013). At that time, FDA also determined that original Opana ER was not withdrawn for safety or effectiveness reasons because there was insufficient data to conclude that original Opana ER posed an increased risk of abuse compared to reformulated Opana ER. Endo resubmitted the sNDA on January 29, 2016, including epidemiologic data on the abuse patterns of Opana ER. The Division planned to bring this data to an advisory committee to obtain input on the epidemiologic data, patterns of abuse of Opana ER, and reports of serious illness associated with intravenous (IV) abuse of Opana ER. Endo withdrew their supplement on August 11, 2016, resulting in the cancellation of the planned advisory committee meeting to discuss this product.

**FDA RESPONSE to ENDO PHARMACEUTICAL CITIZEN
PETITION**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 10 2013

Robert Barto
Vice President, Regulatory Affairs
Endo Pharmaceuticals Inc.
1400 Atwater Drive
Malvern, PA 19355

Re: Docket No. FDA-2012-P-0895

Dear Mr. Barto:

This letter responds to a citizen petition (the Petition) you submitted on behalf of Endo Pharmaceuticals Inc. (Endo). The Petition, received on August 13, 2012, requests that the Food and Drug Administration (FDA): (1) determine that Opana ER (oxymorphone hydrochloride) Extended-Release Tablets approved under new drug application (NDA) 21-610 were discontinued for reasons of safety, (2) refuse to approve any pending abbreviated new drug application (ANDA) for a generic version of Opana ER approved under NDA 21-610, and (3) suspend and withdraw the approval of any ANDA referencing Opana ER approved under NDA 21-610 as the reference listed drug (RLD) (Petition at 1).

We have carefully considered the Petition, supplements, and comments to the Petition docket. For the reasons summarized below, the Petition is denied.¹ FDA has determined that Opana ER approved under NDA 21-610 was not withdrawn from sale for reasons of safety or effectiveness. Accordingly, this product will remain listed in the "Discontinued Drug Product List" section of *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book).² As a result, ANDAs referencing NDA 21-610 may be approved as long as they meet all other legal and regulatory requirements for the approval of ANDAs, and we will not begin procedures to suspend or withdraw approval of ANDAs that reference NDA 21-610.

¹ Endo's submissions contain attachments marked "confidential." Endo also states in a supplement to its Petition (April 23, 2013, p.6) that it submitted in support of NDA 201-655 (the reformulated Opana ER NDA) studies demonstrating that reformulated Opana ER is resistant to crushing, and notes these studies are described in another citizen petition submitted by Endo on August 31, 2012 (Docket No. FDA-2012-P-0951). Because of potential disclosure implications, this response discusses these data and our assessment of the data only in general terms.

² The "Discontinued Drug Product List" includes products that have been discontinued from marketing for reasons other than safety or effectiveness.

I. BACKGROUND

A. Original and Reformulated Opana ER

Opana ER (oxymorphone hydrochloride) Extended-Release Tablets (OP) are the subject of NDA 21-610, held by Endo and initially approved by FDA on June 22, 2006. The approved labeling stated that the product should be swallowed whole, and warned that crushing, chewing, snorting, or injecting the dissolved product will result in uncontrolled delivery and pose significant risk that could result in overdose and death.

In December 2010, FDA approved two ANDAs that reference OP. One entered the market in July 2011;³ the other entered the market in January 2013.⁴

A reformulated version of OP, also called Opana ER (oxymorphone hydrochloride) Extended-Release Tablets (OPR), is the subject of NDA 201-655, also held by Endo and initially approved by FDA on December 9, 2011. Endo's original NDA for OPR included data from studies designed to assess the potentially abuse-deterrent properties of the new formulation. Although FDA approved the application in December 2011 because it concluded that OPR was safe and effective, the approved labeling did not describe any abuse-deterrent properties.⁵ To date, the "abuse potential" subsection of the "Warnings and Precautions" section and "Drug Abuse and Dependence" section of the OPR and OP product labeling are virtually identical.⁶

³ See *Actavis U.S. Launches Oxymorphone Hydrochloride Extended-Release Tablets, CII*, available at http://www.actavis.com/en/media+center/PressReleases/articles/oxymorphone_hcl_extended_release_us.htm.

⁴ See *Press Release: Impax Laboratories Launches Oxymorphone Hydrochloride Extended-Release Tablets*, available at <http://investors.impaxlabs.com/Media-Center/Press-Releases/Press-Release-Details/2013/Impax-Laboratories-Launches-Oxymorphone-Hydrochloride-Extended-Release-Tablets1132511/default.aspx>.

⁵ See Summary Review for Regulatory Action NDA 21-655(January 7, 2011) at (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000MedR.pdf); Summary Review for Regulatory Action NDA 201-655 (Dec. 9, 2011) at (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000SumR.pdf) ("While the new formulation has demonstrated a minimal improvement in resistance to tampering by crushing, thereby limiting the likelihood of abuse by crushing followed by ingestion, and by insufflation (snorting) to some degree, it can still be . . . cut . . . rendering it readily abusable by ingestion and intravenous injection, and possibly still by insufflation; although whether . . . tablets can be snorted was not studied. Of more concern, when chewed . . . the new formulation essentially dose dumps like an immediate-release formulation."); Cross-Discipline Team Leader Review for NDA 201-655 (second review cycle) (November 30, 2011) at (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000CrossR.pdf; See also product labeling for NDA 201-655 (December 9, 2011) at (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201655lbl.pdf).

⁶ Compare most current product labeling for OP (NDA 21-610/S-13; July 9, 2012) (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021610s013lbl.pdf) and most current product labeling for OPR (NDA 201-655/S-04; January 14, 2013) (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/201655s004lbl.pdf).

B. Relisting Petition and Lawsuit

Endo withdrew the 7.5 mg and 15 mg strengths of OP from sale in March 2011.⁷ On May 31, 2012, Endo notified FDA that it had ceased shipping all strengths of OP. In August 2012, Endo submitted the Petition, which asks FDA to determine that OP was withdrawn for safety reasons (Petition at 1, 6, 10).

Endo sued FDA on November 30, 2012, alleging that FDA had improperly failed to decide in a timely manner whether OP was withdrawn from sale for safety or effectiveness reasons and asking the court to order FDA to make this determination by December 31, 2012.⁸ FDA asked the court to dismiss Endo's complaint, noting that under the relevant section of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), the agency was not required to determine whether Endo had withdrawn OP from sale for safety or effectiveness reasons until May 10, 2013.⁹ The Court dismissed Endo's complaint on December 19, 2012.

Endo supplemented its Petition on November 13, 2012 and March 21, 2013 with preliminary postmarketing data and analysis concerning abuse of OP, generic versions of OP, and OPR. Endo further supplemented its Petition on April 23, 2013.

C. Summary of Legal Framework

In the 1980's, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products (commonly referred to as "generic drugs") under an abbreviated procedure. ANDA applicants must show that the drug for which they are seeking approval has the same active ingredient, route of administration, dosage form, strength and, with certain exceptions, labeling as and is bioequivalent to the "listed drug," which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA) (505(j) of the FD&C Act).

Under section 505(j)(7) of the FD&C Act (21 U.S.C. 355(j)(7)), FDA is required to publish a list of all approved drugs. FDA publishes this list as part of the *Approved Drug Products With Therapeutic Equivalence Evaluations*, which is known generally as the *Orange Book*.

⁷ FDA determined that Opana ER (oxymorphone HCl) extended-release tablets, 7.5 mg and 15 mg, were not withdrawn from sale for reasons of safety or effectiveness. See 76 Fed. Reg. 53,908 (August 30, 2011).

⁸ See Complaint for Mandatory, Declaratory, and Injunctive Relief, *Endo Pharmaceuticals Inc. v. FDA et al*, Civil Action 12-1936 (D.D.C. 2012).

⁹ See Consolidated Memorandum in Support of Federal Defendants' Motion to Dismiss and in Opposition to Plaintiff's Motion for a Preliminary Injunction, *Endo Pharmaceuticals Inc. v. FDA et al*, Civil Action 12-1936 (D.D.C. 2012).

Drugs are removed from the list if the Agency determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (505(j)(7)(C) of the FD&C Act; 21 CFR 314.162). In addition, if the listed drug has been withdrawn from sale for safety or effectiveness reasons, the approved ANDAs that refer to the listed drug must be withdrawn or suspended (505(j)(6)(C) of the FD&C Act).

A person may petition the Agency to determine (or the Agency may determine on its own initiative) whether a listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.161). Under section 505(w) of the FD&C Act, FDA must issue a final, substantive determination on such a petition “no later than 270 days after the date the petition is submitted” (21 U.S.C. 355(w)).¹⁰ Further, FDA must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness before approving any ANDAs that refer to the listed drug or if any approved ANDAs refer to the listed drug (21 CFR 314.161(a)).

The NDA holder’s stated reasons for withdrawing the drug are not determinative. 57 Fed. Reg. at 17971 (Apr. 28, 1992). The agency “will...consider other factors...such as increases in the number of adverse drug reactions reported on the drug and published or unpublished studies of the drug questioning its safety or effectiveness.” 54 Fed. Reg. at 28907 (July 10, 1989).

FDA has long considered the abuse potential of a drug in numerous regulatory contexts. Where appropriate, FDA may take abuse potential into account when weighing a drug’s benefits and risks. The agency has also recognized that a drug’s benefit/risk profile can change due to the availability of alternative products.¹¹ Recently, the agency considered the increased potential for abuse of original OxyContin (oxycodone hydrochloride) Extended-Release Tablets relative to reformulated OxyContin (oxycodone hydrochloride) Extended-Release Tablets in determining that original OxyContin was withdrawn for safety or effectiveness reasons.¹²

¹⁰ This provision was added by section 1134(a) of the Food and Drug Administration Safety and Innovation Act (Public Law 112-144, 126 Stat. 1075).

¹¹ For example, FDA determined that the 10 mg presentation of Halflytely and Bisocodyl Tablets Bowel Prep Kit was withdrawn for safety reasons because the 5 mg presentation had “comparable effectiveness to the 10 mg product and...a safety advantage over the 10 mg product[.]” 76 Fed. Reg. 51037 (Aug. 17, 2011).

¹² Determination that the OXYCONTIN (Oxycodone Hydrochloride) Drug Products Covered by New Drug Application 20-553 Were Withdrawn From Sale for Reasons of Safety or Effectiveness, 78 Fed. Reg. 23,273 (April 18, 2013).

II. DISCUSSION

A. The Available Data Do Not Support Endo's Conclusions Regarding Purported Safety Advantages of OPR Relative to OP.

Endo contends that OPR offers "safety advantages" over OP because OPR "is resistant to crushing by common methods and tools employed by abusers of prescription opioids ... [and] is less likely to be chewed or crushed even in situations where there is no intent for abuse, such as where patients inadvertently chew the tablets, or where caregivers attempt to crush the tablets for easier administration with food or by gastric tubes, or where children accidentally gain access to the tablets" (Petition at 8). In its April 2013 supplement, Endo states that it submitted in support of NDA 201-655 in vitro manipulation and extraction studies, pharmacokinetic studies, and clinical studies demonstrating that OPR is resistant to crushing compared to OP for purposes of intranasal or injectable use. Endo notes that these studies are described in a separate citizen petition Endo submitted on August 31, 2012, and can be found in NDA 201-655 (Docket No. FDA-2012-P-0951). Endo contends that preliminary postmarketing data show a significant reduction in overall and non-oral OPR abuse rates compared to baseline OP abuse rates, as well as a significant increase in the overall and non-oral abuse rates of generic versions of OP following the replacement of OP with OPR in the market.¹³

We disagree with Endo's conclusions about OPR's alleged safety advantages. While there is an increased ability of OPR to resist crushing relative to OP, data from in vitro and pharmacokinetic studies show that OPR's extended-release features can be compromised, causing the product to "dose dump," when subjected to other forms of manipulation such as cutting, grinding, or chewing, followed by swallowing.^{14,15} It also

¹³ See November 13, 2012, Supplement to Petition at 2-7; March 21, 2013, Supplement to Petition at 3, 6-12.

¹⁴ Although it is possible that OPR's crush-resistance may deter some misuse, such as improper crushing for administration with food or through a feeding tube, OPR appears to remain susceptible to other types of therapeutic or unintentional misuse, such as causing the product to "dose dump" by cutting or chewing and then swallowing. Inclusion of language regarding reduced crushability in the labeling could be misleading and result in health care practitioners or patients thinking that OPR is safer than OP, and that it is safe to chew OPR; or that it is safe to give OPR to vulnerable populations (e.g., cognitively impaired) who may chew the product if not adequately supervised. See Summary Review for Regulatory Action (January 7, 2011) at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000MedR.pdf.

¹⁵ Although Endo states that it submitted bioavailability data demonstrating that attempted crushing of OPR with a commercial pill crusher had no effect on relative bioavailability and extended-release profile of OPR (April 2013 supplement cross-referencing August 31, 2012 Petition pp. 8-9), other data, as noted in the text, show that other forms of manipulation can compromise OPR's extended release features causing it to dose dump. See e.g., Summary Review for Regulatory Action (January 7, 2011) at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000MedR.pdf; Summary Review for Regulatory Action (December 9, 2011) at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201655lbl.pdf. Endo's Petition and supplements make other assertions regarding crushing, but do not address chewing, cutting, and grinding.

appears that OPR can be prepared for insufflation (snorting) using commonly available tools and methods.¹⁶ OPR can be readily prepared for injection, despite Endo's claim that OPR tablets have "resistance to aqueous extraction (i.e., poor syringeability)" (Petition at 4).¹⁷ In addition, certain data suggest that OPR can more easily be prepared for injection than OP.¹⁸

Moreover, the data from the postmarketing investigations Endo relies on are inconclusive and, as the company repeatedly acknowledges, "preliminary."¹⁹ They include only 2 to 3 quarter-years of data following introduction of OPR, and suffer from significant additional deficiencies (including small sample sizes, likely misclassification of drug exposure, and possibly artificially elevated OP baseline abuse rates²⁰), such that it is not possible to draw meaningful conclusions based on them.²¹

¹⁶ In particular, as noted in the Summary Review for Regulatory Action (January 7, 2011) and a Discipline Review Letter (January 4, 2011), OPR can be ground for possible insufflation. Accordingly, FDA recommended that a study be conducted to determine whether ground OPR could be administered intranasally, if such a study could be conducted safely. See (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000MedR.pdf); see also (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000AdminCorres.pdf). Endo's Petition and supplements do not discuss such a study and only refer to manipulation using simple tools such as a hammer, pill crusher, and two spoons, which are not sufficient to fully assess whether OPR is suitable for insufflation or to assess clinical preference for insufflation by experienced drug users. Endo states (April 2013 Supplement cross-referencing August 31, 2012 Petition, pp. 7-8) that (1) users in a particular study were largely unwilling to snort the resulting broken materials made from OPR; and (2) that approximately 96% of subjects were willing to snort tampered OP compared with 11% of subjects for OPR. But subjects in that study largely attempted to tamper with OPR using tools and methods other than grinding. See Vosburg et al, Assessment of a formulation designed to be crush-resistant in prescription opioid abusers. 126 Drug Alcohol Depend. pp. 206-15 (2012), available at <http://dx.doi.org/10.1016/j.drugalcdep.2012.05.013>. Accordingly, this study does not provide adequate data with which to assess possible intranasal abuse of ground OPR.

¹⁷ Endo also claims that OPR "gradually forms a viscous hydrogel" when "subjected to an aqueous environment" (April 23 Supplement to Petition at 3).

¹⁸ See e.g., Summary Review for Regulatory Action (January 7, 2011) at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000MedR.pdf.

¹⁹ See, e.g., March 21, 2013 Supplement to Petition at 2, 4, 6.

²⁰ The investigations Endo relies upon use OP abuse rates from 2011 as the baseline comparator against which OPR abuse rates are measured. Endo states that 2011 saw an increase in OP abuse from 2010, and it states that this increase may be caused by the launch of reformulated OxyContin (which was designed to be difficult to manipulate for purposes of abuse and was determined by FDA to have certain abuse-deterrent properties). It is too early to say whether the 2011 OP abuse rates represent the appropriate baseline risk or an aberration.

²¹If one were to treat the available data as a reliable indicator of abuse rates despite the data limitations noted above, one of the postmarketing investigations suggests the troubling possibility that a higher (and rising) percentage of OPR abuse is occurring via injection than was the case with OP. Abuse via injection is highly dangerous, and injection of OPR in particular has been associated with a serious thrombotic thrombocytopenic purpura (TTP)-like illness. See "FDA warns about serious blood disorder resulting from misuse of Opana ER," dated October 11, 2012, and updated on November 1, 2012; available at <http://www.fda.gov/Drugs/DrugSafety/ucm322432.htm>; Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report, Vol. 62, No. 1, January 11, 2013. TTP is a serious blood disorder

While FDA considers the development of abuse-deterrent formulations a high public health priority, such properties must be supported by adequate data.

B. Endo's Assertion that OPR and Reformulated OxyContin have "Virtually Identical" Abuse-Deterrent Properties is Misplaced and Without Merit.

In its April 2013 supplement, Endo contends that FDA should make the same determination regarding OP as it did regarding original OxyContin (OC) because OPR and reformulated OxyContin (OCR) "have virtually identical abuse-deterrent properties...[as] demonstrated through the data Endo submitted in support of NDA No. 201655, post-marketing epidemiology data, and the similar physicochemical properties between both [OPR] and [OCR]."²²

We disagree. The abuse-deterrent properties of OPR and OCR and the resulting regulatory implications have been the subject of independent, extensive consideration by Agency experts over the course of many months.²³ Our decisions take into account the totality of the evidence for the particular drug at issue, and must be made on a case-by-case basis. Accordingly, any attempt by Endo to draw parallels between OCR and OPR and thereby make assumptions regarding the regulatory implications for OP is misplaced.

Nonetheless, we note that there are differences in the products and the available data such that it is reasonable to draw different conclusions. Based on in vitro, pharmacokinetic, clinical abuse potential, and post-marketing data, we were able to conclude that OC posed an increased potential for intranasal abuse compared to OCR. In vitro data showed that OCR required more effort, time, experience, and tools to create a fine powder for intranasal abuse than OC. A clinical abuse potential study showed that most study subjects liked finely ground OCR less than finely ground OC following attempted snorting. Pharmacokinetic and post-marketing data were also supportive of our conclusions regarding intranasal abuse of OCR.

While the available data show that there is an increased ability of OPR to resist crushing relative to OP, OPR still can be prepared for insufflation (snorting) using commonly available tools and methods. Endo's Petition and supplements do not describe a clinical abuse potential study to assess the ability to insufflate or clinical preferences.²⁴ Further,

characterized by microangiopathic hemolytic anemia and thrombocytopenia. FDA's review has not revealed this association with any other opioid analgesic.

²² April 23 Supplement to the Petition at 6.

²³ For OxyContin, see Dr. Throckmorton Memo re: Purdue's reformulated OxyContin (oxycodone hydrochloride) extended release tablets (April 16, 2013) at (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022272Orig1s014_ODMemo.pdf); Determination that the OXYCONTIN (Oxycodone Hydrochloride) Drug Products Covered by New Drug Application 20-553 Were Withdrawn From Sale for Reasons of Safety or Effectiveness, 78 Fed. Reg. 23,273 (April 18, 2013).

²⁴ See footnote 16.

the preliminary data from the Opana ER post-marketing investigations have significant limitations and are not as mature as the OxyContin postmarketing investigations, which themselves were only supportive, and not conclusive, of reduced intranasal abuse.

Based on in vitro and post-marketing data, we were able to conclude that OC posed an increased potential for abuse via injection compared to OCR. The in vitro data showed that OCR has physicochemical properties expected to make abuse by injection difficult. When subjected to an aqueous environment, OCR gradually forms a viscous hydrogel that resists passage through a needle such that it prevents oxycodone from being drawn into a syringe to any meaningful extent. Postmarketing data were supportive of our conclusions regarding abuse of OCR via injection. In contrast, OPR can be readily prepared for injection and preliminary data from the Opana ER post-marketing investigations have significant limitations, as discussed above.²⁵

In sum, while there were sufficient data to conclude that OC posed an increased potential for abuse by certain routes of administration compared to OCR, there currently are *not* sufficient data to conclude that OP poses an increased potential for abuse compared to OPR.

C. OP Was Not Withdrawn for Safety or Effectiveness Reasons.

We have conducted an extensive review of the issues raised by Endo and have concluded that while OPR and OP have the same therapeutic benefits, there is insufficient evidence that OP has an increased potential for abuse compared to OPR. Based on the totality of the data and information available to the Agency, FDA has determined that OP's benefits continue to outweigh its risks. Therefore, OP was not withdrawn from sale for reasons of safety or effectiveness.

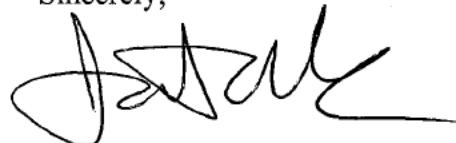
The Agency will continue to list OPANA ER (oxymorphone HCl) extended-release tablets approved under NDA 21-610 in the "Discontinued Drug Product List" section of the Orange Book. FDA will not begin procedures to withdraw approval of ANDAs that refer to these drug products. Additional ANDAs that refer to Opana ER (oxymorphone HCl) extended-release tablets may be approved by the Agency as long as they meet all other legal and regulatory requirements for the approval of ANDAs. FDA plans to publish a notice announcing this determination in the *Federal Register*.

²⁵ If one were to treat the available post-marketing data from the Opana ER investigations as a reliable indicator of abuse rates despite these limitations, these data appear to suggest that a greater (and rising) percentage of Opana ER abusers are abusing Opana ER via injection since the replacement of OP with OPR in the market. This suggestion would be consistent with in vitro data showing that while it may be more difficult to prepare OPR for insufflation using certain tools (although it is possible to do so using other tools) it may actually be *easier* to prepare OPR for injection. Taken together, these data suggest the troubling possibility that the reformulation may be shifting a non-trivial amount of Opana ER abuse from snorting to even more dangerous abuse by intravenous or subcutaneous injection.

III. CONCLUSION

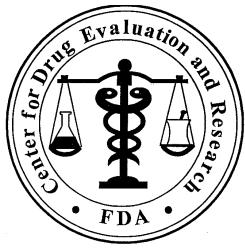
For the reasons explained above, the Petition is denied.

Sincerely,

A handwritten signature in black ink, appearing to read "Janet Woodcock".

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

**Extended-Release Long-Acting Opioid Analgesic Risk Evaluation
and Mitigation Strategy (ER/LA OA REMS) Memo**



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

Date: February 1, 2017

To: Judy Staffa, PhD, RPh
*Associate Director for Public Health Initiatives
Office of Surveillance and Epidemiology (OSE)*

From: Cynthia LaCivita, Pharm.D., Director
Division of Risk Management
Office of Medication Error Prevention and Risk Management
OSE

Drug Name: Opana ER (oxymorphone hydrochloride) extended-release tablets

Application Numbers: NDA 201655 (reformulated)
NDA 021610 (original)

Subject: Extended-Release and Long-Acting (ER/LA) Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

Opana ER (original) was approved on June 22, 2006 with a Risk Minimization Action Plan (RiskMAP). Opana ER (reformulated) was approved on December 9, 2011 with a risk evaluation and mitigation strategy (REMS). On July 9, 2012 the FDA approved the REMS for the extended-release (ER) and long-acting (LA) opioid analgesics. The ER/LA Opioid Analgesics REMS is a class-wide shared system REMS. In the interest of public health and to minimize the burden on the health care delivery system of having multiple unique REMS programs, Opana ER (original) and Opana ER (reformulated) were subject to the ER/LA Opioid Analgesics REMS requirements since approval of the ER/LA Opioids Analgesics REMS.

The ER/LA Opioid Analgesic REMS was approved to ensure the benefits of ER/LA opioid analgesics outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. The ER/LA Opioid Analgesic REMS is part of a multi-agency Federal effort to address the growing problem of prescription drug abuse and misuse.

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

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.

**Extended-Release Long-Acting Opioid Analgesic Postmarketing
Required Studies (ER/LA OA PMRS) Memo**

Postmarketing Requirements for Extended-Release/Long-Acting (ERLA) Opioid Analgesics and ERLAs Labeled with Abuse-Deterrent Properties

The following PMRs are required for all approved ERLA opioid analgesics. The Agency has determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death associated with the long-term use of ERLA opioid analgesics. We have encouraged sponsors to work together on these studies to provide the best information possible. The milestone dates reflect those that were specified at the time the study requirements were issued for the class of ERLA opioid analgesics.

1. A prospective, observational study designed to quantify the serious risks of misuse, abuse, and addiction associated with long-term use of opioid analgesics for management of chronic pain among patients prescribed ER/LA opioid analgesics.

This study must address at a minimum the following specific objectives:

- a. Estimate the incidence of misuse, abuse, and addiction associated with long-term use of opioid analgesics for chronic pain. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, and addiction.
- b. Evaluate and quantify other risk factors for misuse, abuse, and addiction associated with long-term use of opioid analgesics for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships.

The following timetable is the schedule for this study:

Final Protocol Submission:	11/2015
Interim Report (Cumulative Enrollment of 470 patients)	05/2017
Interim Report (Cumulative Enrollment of 1,042 patients)	09/2017
Interim Report (Cumulative Enrollment of 1,609 patients)	01/2018
Interim Report (Cumulative Enrollment of 2,300 patients)	06/2018
Study Completion:	10/2019
Final Report Submission:	03/2020

2. An observational study designed to measure the incidence and predictors of opioid overdose and death (OOD), as well as opioid abuse/addiction, using patient health records, insurance claims, and death records.

This study must address at a minimum the following specific objectives:

- a. Estimate the incidence of abuse/addiction, overdose, and death associated with long-term use of opioid analgesics for chronic pain. Stratify overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of abuse/addiction, overdose, and death.
- b. Evaluate and quantify other risk factors for abuse/addiction, overdose, and death associated with long-term use of opioid analgesics for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify overdose by intentionality wherever possible.

The following timetable is the schedule for this study:

Final Protocol Submission: 11/2014

Study Completion: 04/2019

Final Report Submission: 09/2019

3. A prospective observational study designed to assess the content validity and patient interpretation of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). Patient understanding of the concepts of misuse and abuse will also be obtained.

The following timetable is the schedule for this study:

Final Protocol Submission: 04/2015

Study Completion: 10/2015

Final Report Submission: 01/2016

4. An observational study to evaluate the validity and reproducibility of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), which will be used to identify opioid abuse and misuse behaviors among participants who have chronic pain which requires long-term opioid analgesic use.

The following timetable is the schedule for this study:

Final Protocol Submission: 04/2015
Study Completion: 10/2016
Final Report Submission: 02/2017

5. An observational study to validate measures of prescription opioid Substance Use Disorder and addiction in patients who have received or are receiving opioid analgesics for chronic pain.

The following timetable is the schedule for this study:

Final Protocol Submission: 04/2015
Study Completion: 12/2016
Final Report Submission: 05/2017

6. An observational study to develop and validate an algorithm using coded medical terminologies and other electronic healthcare data to identify opioid-related overdose and death.

The following timetable is the schedule for this study:

Final Protocol Submission: 11/2014
Study Completion: 09/2016
Final Report Submission: 12/2016

7. An observational study to develop and validate an algorithm using coded medical terminologies to identify patients experiencing prescription opioid abuse or addiction, among patients receiving an ER/LA opioid analgesic.

The following timetable is the schedule for this study:

Final Protocol Submission: 11/2014
Study Completion: 10/2016
Final Report Submission: 01/2017

8. An observational study using coded medical terminologies and other electronic healthcare data to define and validate doctor and/or pharmacy shopping outcomes by examining their association with abuse and/or addiction.

The following timetable is the schedule for this study:

Final Protocol Submission: 03/2015
Study Completion: 10/2017
Final Report Submission: 01/2018

9. An observational study using a validated patient survey to evaluate the association between doctor/pharmacy shopping outcomes and self-reported misuse and abuse.

The following timetable is the schedule for this study:

Final Protocol Submission: 03/2015
Study Completion: 09/2018
Final Report Submission: 12/2018

10. An observational study using medical record review to evaluate the association between doctor/pharmacy shopping outcomes and patient behaviors suggestive of misuse, abuse and/or addiction.

The following timetable is the schedule for this study:

Final Protocol Submission: 03/2015
Study Completion: 03/2017
Final Report Submission: 06/2017

The Agency has determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of hyperalgesia associated with the class of ER/LA opioid analgesics, of which TRADENAME is a member.

11. Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following the long-term use of high-dose ER/LA opioid analgesics for at least one year to treat chronic pain. Include an assessment of risk relative to efficacy.

The following timetable is the schedule for this trial:

Final Protocol Submission: 11/2014
Trial Completion: 02/2019
Final Report Submission: 08/2019

Summary of In Vitro Studies



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

MEMORANDUM

DATE: January 30, 2017

FROM: Erika E. Englund, Ph.D.
Julia Pinto, Ph.D.

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

RE: Open Session Background Document: In Vitro Studies of Proposed Abuse-Deterrent Properties, NDA 201655 Opana (oxymorphone HCl) ER Tablets

Overview of the Proposed Product Abuse-Deterrent Features (ADFs):

The drug product is an extended-release formulation of oxymorphone HCl in seven dosage strengths: 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg tablets.

Summary of In Vitro Studies

In vitro abuse-deterrent studies were conducted to assess the relative difficulty and effectiveness of various potential manipulation methods to defeat the drug product's purported abuse-deterrent properties. The abuse-deterrent properties of Opana ER include the tablet hardness to deter grinding or crushing; and gelling to form a hydrogel to make the API difficult to extract and abuse. The comparators included original Opana ER, OxyContin abuse-deterrent formulation (ADF), and generic formulations of oxymorphone HCl ER from Activis and Impax. Note that not all comparators were used in all studies. Only the studies and results that reflect the most probable abuse approaches and that pose the most challenges to the drug product under evaluation are summarized below.

Physical Manipulation (Size Reduction)

Particle size reduction is a common first step abusers employ to increase the release rate of a product. Several simulated common techniques that are used by abusers to manipulate the drug product through crushing and grinding were studied. Relative to comparators, Opana ER tablets were either comparable or more resistant to crushing and grinding. The oxymorphone HCl generic comparators could be crushed using Tools A, B, or T. In comparison, Opana ER could not be crushed with tools A and B. Tools N-S, T, and V could reduce the particle size of Opana ER. The particle size reduction of Opana ER and OxyContin were similar with tool V, which was the most effective tool at the particle size reduction of Opana ER. Pre-treating the tablets with conditions P3, P4 and P6 did not significantly alter the particle size reduction of Opana ER with tool V.

Large Volume Extraction Studies

Large volume extraction studies evaluated the extraction potential of oxymorphone HCl from intact or [redacted] (b) (4) tablets in 30 mL of solvent with shaking. The percent of oxymorphone HCl released from [redacted] (b) (4) tablets increased in solvents a, b, e, and j at temperature T2. All of these solvents at temperature T2 extracted nearly 80% of oxymorphone HCl within 1 hour. The tablets were not pre-treated prior to these conditions.

The dissolution profile of intact, [redacted] (b) (4) and [redacted] (b) (4) tablets cut was also evaluated. The dissolution rate increased with an increase in the number of tablet pieces. The dissolution of the [redacted] (b) (4) tablet was the fastest.

Small Volume Extraction Studies

Small volume extractions were conducted to assess the potential for syringability and injectability of the manipulated product. Most small volume extraction studies were performed with either solvent 'a' or 'e' at temperatures T1 and T2. Pre-treatment conditions were also studied.

Opana ER forms a hydrogel under some conditions which can make syringability difficult. The hydrogel which formed from the [redacted] (b) (4) tablet in [redacted] (b) (4) of solvent A at temperature T2 restricted the syringability of the mixture. The extract could be syringed from intact, [redacted] (b) (4) and [redacted] (b) (4) tablets. The [redacted] (b) (4) tablets were extracted with 5 mL of solvent at temperature T2. 26-40% of the API was extracted with these conditions and the mixture was withdrawn with an N3 needle. The cut tablets were extracted 5 times with 2 mL of solvent at temperature T2. 39% of the API was extracted with these conditions and the mixture was withdrawn with an N1 needle.

Endo also evaluated the impact of heat pre-treatment of the [redacted] (b) (4) tablets prior to the small volume extraction. Conditions P3, P4, P6, P7 and P8 were studied. 5 mL and 10 mL of solvents 'a' and 'e' were used for these studies and the mixtures were heated to T2 for 5 min. 50% of the API was filtered and extracted through an N3 needle in 10 mL of solvent a following pre-treatment P4 conditions.

The FDA laboratories studied intact and [redacted] (b) (4) Opana ER tablets. The tablets were studied at temperatures T1 and T3, and in 2 or 5 mL of solvent 'a'. The extraction times were either 5 or 30

min. All extracts could be withdrawn with a N5 needle. At temperature T3 in 5 mL solvent a, 44% of the API was extracted after 30 min.

The FDA laboratories also studied the impact of heat pre-treatment with condition P4. At temperature T3 in 5 mL solvent a, 79% of the API was extracted after 30 min following pre-treatment P4 conditions.

Summary of Human Abuse Potential Studies



M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: February 2, 2017

To: Judy Staffa, Ph.D., RPh
Associate Director for Public Health Initiatives
Office of Surveillance and Epidemiology (OSE)

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Silvia Calderon, Ph.D., Pharmacologist
James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: OPEN SESSION BACKGROUND DOCUMENT on NDA 201-655 for OPANA ER. Prepared for the FDA Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety & Risk Management Advisory Committee Meeting, March 13-14, 2017.

Background Document

Under NDA 201-655 Endo Pharmaceuticals conducted two human abuse potential studies in support of reformulated OPANA ER (Oxymorphone HCl) Tablets. One was an intranasal dose-ranging pilot study designated EN3288-113. The second study was a pivotal intranasal study designated EN3288-114. These types of studies are used to assess the potential abuse-deterrent effects of pharmaceutical products. Both studies are described below followed by a discussion of routes of abuse for oxymorphone containing products including OPANA ER.

Study EN3288-113 entitled: "A Double-Blind, Dose-Ranging, Pilot Study to Evaluate the Safety, Subjective Effects, and Pharmacokinetics of Oxymorphone Hydrochloride in Healthy Subjects Who Recreationally Administer Opioids Intranasally."

Description of Study EN3288-113

Study EN3288-113 served as a pilot study to determine the safety and the dose response relationship of intranasal oxymorphone HCl powder for producing subjective reinforcing effects (i.e., Drug Liking). The results of this study were used to select a dose of OPANA ER to be used in a pivotal intranasal human abuse potential study (EN3288-114). Study EN3288-113 utilized a

randomized, double-blind, ascending-dose, placebo-controlled design in healthy, non-dependent recreational opioid users with experience in using opioids intranasally. Each subject participated in a screening visit, a qualification phase and a treatment phase.

Some of the important measures in the Qualification and Treatment Phases include obtaining the subjective responses of subjects on Drug Liking by Visual Analog Scale (VAS), High VAS, Take Drug Again VAS, and Overall Drug Liking VAS.

Drug Liking VAS is scored using a 0-100 point bipolar VAS anchored, on the left with "strong disliking" (score of 0), in the center with a neutral anchor of "neither like nor dislike" (score of 50) and on the right with "strong liking" (score of 100). Subjects completed the statement "At this moment, my liking for this drug is."

High VAS was scored using a 0 to 100 point unipolar VAS anchored on the left by "Not at all" (score of 0) and on the right by "Extremely" (score of 100). Subjects rated the statement "At this moment, I am feeling high."

Take Drug Again VAS was scored using a 0-100 point bipolar VAS anchored on the left with "definitely not" (score of 0); "Indifferent" (score of 50); and anchored on the right with "Definitely so" (score of 100). Subjects responded to the statement "Overall, I would take this drug again.

Overall Drug Liking VAS was scored using a 0 to 100 point bipolar VAS anchored on the left with "Strong disliking" (score of 0); "Neither like nor dislike" (score of 50) in the middle; and anchored on the right with "Strong liking" (score of 100). Subjects completed the statement "Overall, my liking for this drug is:"

In the Qualification Phase, subjects were required to distinguish (discriminate) oral treatment with OPANA ER 30 mg from placebo. To advance to the Treatment Phase, subjects were required to satisfy the following criteria:

Oral administration of OPANA ER 30 mg resulting in maximum response of at least 65 on the 100-point VAS for Drug Liking with at least a 15-point difference between the maximum response of OPANA 30 mg and placebo with appropriate time course of responses.

Appropriate placebo responses following oral OPANA ER 30 mg ranging from 40 to 60 on the 100-point VAS for Drug Liking.

During the Treatment Phase, subjects were divided into Cohort 1 and Cohort 2, containing 10 and 9 subjects, respectively. Cohort 1 received in ascending order intranasal doses of 2.5 mg and 7.5 mg oxymorphone HCl. Cohort 2 received in ascending order intranasal doses of 5 mg and 10 mg oxymorphone. Placebo powder was insufflated by 12 subjects. Each of the four oxymorphone HCl doses was insufflated by 6 subjects.

Pharmacodynamic measures used in the Treatment Phase included but were not limited to the primary measure of Drug Liking VAS, as well as the secondary measures of High VAS, Take

Drug Again VAS, and Overall Drug Liking VAS. Specific pharmacodynamic parameters measured included but were not limited to the maximum drug effect (Emax) and the time to achieve maximum drug effect (TEmax).

Pharmacokinetic parameters evaluated for plasma oxymorphone included but were not limited to the maximum oxymorphone plasma concentration (Cmax) and the time to achieve Cmax (Tmax).

Findings from Study EN3288-113

- 1) Insufflation of 5 mg oxymorphone HCl caused an increase in the mean Emax values for Drug Liking (76.2 mm), High (62.8 mm), Take Drug Again (77.2 mm), and Overall Drug Liking (74.8 mm).
- 2) With insufflation of 7.5 mg oxymorphone HCl, the mean maximum scores of Drug Liking, High, Take Drug Again, and Overall Drug Liking were 96.3 mm, 98.8 mm, 90.7 mm, and 89.0 mm, thereby approaching the maximum scores possible using these measures.
- 3) Increasing the intranasal dose to 10 mg oxymorphone HCl, resulted in roughly similar scores for the four subjective measures as produced by the 7.5 mg dose of oxymorphone HCl.
- 4) Based on study results, 7.5 mg OPANA ER was selected for use in the pivotal study EN3288-114.

Study EN3288-114 entitled “A Randomized, Double-Blind, Single-Dose, Placebo-Controlled, Four-Period, Crossover Study to Evaluate the Subjective Effects and Systemic Exposure of Manipulated OPANA ER Administered Intranasally Compared With Oxymorphone Hydrochloride Powder Administered Intranasally in Healthy, Non-Dependent Subjects Who Recreationally Administer Opioids Intranasally.”

Description of Study EN3288-114

This study utilized a randomized, double-blind, single-dose, placebo-controlled, 4-period, crossover design. Each subject participated in a screening visit, a qualification phase, and a treatment phase. Primary objective was to evaluate the subjective effects of manipulated OPANA ER (reformulated) 7.5 mg insufflated compared with Oxymorphone HCl powder 7.5 mg (positive control) insufflated in healthy non-dependent subjects with experience in using opioids intranasally..

In total, 104 subjects were enrolled in the study and, based on the outcome of the naloxone challenge and check-in safety procedures, 98 subjects were randomized into the Qualification Phase. Subjects in the Qualification Phase were each administered single intranasal doses of oxymorphone HCl powder (7.5 mg) and placebo powder. Forty-nine subjects qualified for and were randomized into the Treatment Phase and 38 completed the study.

In the Qualification Phase, subjects insufflated oxymorphone HCl powder 7.5 mg or placebo (lactose powder) in a randomized, double-blind, crossover manner. In order to be eligible for the Treatment Phase, subjects were required to meet the following criteria:

- Demonstrate an oxymorphone HCl powder 7.5 mg maximum effect (Emax) of at least 75 on the Drug Liking VAS with at least a 15-point difference between the Emax of oxymorphone HCl powder 7.5 mg and placebo.
- Demonstrate appropriate placebo responses ranged from 40 to 60 (inclusive) on the Drug Liking VAS.
- Demonstrate acceptable responses to oxymorphone HCl powder 7.5 mg and placebo on VAS for Overall Drug Liking, VAS for High, VAS for Good Effects, and VAS for Take Drug Again, as judged by the Investigator.
- Demonstrate tolerance to oxymorphone HCl powder 7.5 mg, as judged by the Investigator.

During the Treatment Phase, each treatment period was determined by a randomization schedule. Treatments were administered under fasted conditions and separated by at least a 4-day washout period. Treatments insufflated included:

- A. OPANA ER 7.5 mg – manipulated
- B. OPANA ER placebo tablets – manipulated
- C. Oxymorphone HCl powder 7.5 mg
- D. Placebo powder (Lactose Powder)

With manipulation of OPANA ER 7.5 mg tablets, approximately 41% of the weight consisted of particles less than 0.5 mm. In contrast, the percentage weight retained constituting particles less than 0.5 mm was 71.9% and 91.4% for oxymorphone HCl API and lactose monohydrate, respectively.

Subjects were given up to 5 minutes to insufflate each treatment using a short straw and a dosing bottle. Any powder not insufflated was documented.

Pharmacodynamic measures conducted at selected times post-dosing included the primary measure of Drug Liking VAS as well as the secondary measures of High VAS, Take Drug Again VAS, and Overall Drug Liking VAS (identical scale structure as previously described). Parameters determined included maximum drug effect, designated Emax, and the time to maximum drug effect, designated TEmax. Statistical analyses of the pharmacodynamic measures were conducted using the pharmacodynamics population (N = 38 subjects) by the FDA CDER/OTS Office of Biostatistics using a mixed-effects model in which period, sequence and treatment were fixed effects and subjects nested within sequence as a random effect.

Nasal tolerability was assessed using a numerical rating scales (0 to 5) for the following nasal symptoms: “Burning,” “Itching,” “Need to Blow Nose,” “Runny Nose/Nasal Discharge,” “Facial Pain/Pressure,” and “Nasal Congestion.”

Blood samples were periodically taken in order to evaluate plasma levels of oxycodone as a function of time. Pharmacokinetic parameters for plasma oxycodone included Cmax and Tmax.

Findings from EN3288-114

- 1) Insufflation of the comparator, oxymorphone HCl 7.5 mg, resulted in statistically significantly greater ($p<0.0001$) VAS scores compared to insufflation of placebo for Drug Liking VAS, High VAS, Take Drug Again VAS, and Overall Drug Liking VAS, thereby validating these pharmacodynamic measures.
- 2) Insufflation of OPANA ER 7.5 mg resulted in a mean Emax of Drug Liking VAS of 70.32 mm that was statistically significantly less than ($p<0.0001$) the mean Emax of 87.82 mm following Oxymorphone HCl 7.5 mg, but greater ($p<0.0001$) than the mean Emax of Drug Liking following OPANA ER placebo (53.32 mm). Median times to achieve Emax of Drug Liking were 2 hours and 1 hour following intranasal OPANA ER 7.5 mg and Oxymorphone HCl 7.5 mg, respectively. These data support a possible deterrent effect of OPANA ER to intranasal abuse; however, some positive subjective effects were reported following insufflation of OPANA ER.
- 3) Insufflation of OPANA ER 7.5 mg and Oxymorphone HCl 7.5 mg resulted in mean Emax values for High VAS of 45.29 mm and 83.00 mm, respectively. This reduction in maximum High following OPANA ER was statistically significant ($p<0.0001$) and supports a deterrent effect of OPANA ER to abuse by insufflation.
- 4) Insufflation of OPANA ER 7.5 mg resulted in a mean Emax of Take Drug Again of 59.79 mm that was statistically significantly less than ($p<0.0001$) the mean Emax of 81.66 mm following insufflation of oxymorphone HCl 7.5 mg. This reduction suggests that, if given the opportunity again, subjects would have a greater willingness to insufflate oxymorphone HCl powder versus OPANA ER. This supports a deterrent effect of OPANA ER on abuse by insufflation.
- 5) The Overall Drug Liking experience was significantly less ($p<0.0001$) following insufflation of OPANA ER 7.5 mg (mean Emax of 60.66 mm), compared to following insufflation of Oxymorphone HCl 7.5 mg (mean Emax of 81.79 mm). This provides additional support for a deterrent effect of OPANA ER to abuse by insufflation.
- 6) Insufflation of the comparator, Oxymorphone HCl 7.5 mg, compared to insufflation of OPANA ER 7.5 mg was associated with a more rapid rise (median Tmax of 0.25 hours versus 1.5 hours) and greater maximum oxymorphone plasma level (mean Cmax of 6.03 ng/mL versus 2.84 mg/mL).
- 7) Results of the nasal tolerability assessment suggest that all four insufflation treatments were well tolerated.

Routes of Abuse of Oxymorphone

Results of studies EN3288-113 and EN3288-114 coupled with results from Category 1 physical manipulation and extraction studies, as well as the pharmacological properties of oxymorphone provide support for the abuse of OPANA ER and other oxymorphone containing formulations through the intranasal (IN) and intravenous (IV) routes, as observed in epidemiological studies. Broadly speaking, epidemiological studies indicate that OPANA ER, oxymorphone ER generics, and oxymorphone IR products are commonly abused by non-oral routes. Among individuals being assessed for substance abuse treatment, insufflation was the predominant route of abuse of oxymorphone ER generic products, although these products were also commonly abused by

injection. In contrast to the oxymorphone ER generic products, the predominant route of abuse of OPANA ER was by intravenous injection, with a lower incidence of abuse by insufflation. In this population, oral abuse of all these oxymorphone products was very low, whereas the proportion of oxycodone ER and oxycodone IR single entity abusers who reported abuse via the oral route was much higher (Data discussed in the Integrated Review of Postmarketing Data by Jana McAninch, Corinne Woods and Chaitali Patel).

To understand possible reasons underlying the difference in reported frequency of oral abuse for oxymorphone compared to oxycodone, the relative oral bioavailability of the active opioid from the drug products was evaluated, along with the reinforcing effects of different doses of the two drugs. The oral bioavailability of oxymorphone in humans is only approximately 10% (Endo 2011) compared to an intravenous dose of the same amount. In contrast, the oral bioavailability of oxycodone is 60% to 87% (Purdue 2016). As a result, oral administration of oxymorphone will result in lower plasma drug levels than oral administration of an equivalent amount of oxycodone and could contribute to the oral route being less preferred by individuals who abuse oxymorphone. However, Babalonis et al. (2016) recently evaluated the subjective reinforcing effects of equal oral doses of immediate-release oxycodone and oxymorphone (Babalonis et al., 2016). This study showed that at doses of 20 mg and 40 mg oxycodone produced significant increases in ratings of drug liking and high compared to placebo. Oxymorphone, at a dose of 40 mg but not 20 mg, produced peak ratings significantly greater than that of placebo and that were comparable with oxycodone in a subset of subjective measures that include drug liking, good drug effect, high and overall effect. The fact that 40 mg oxymorphone produces significant levels of reinforcing subjective effects similar to those produced by an equal dose of oxycodone, in spite of its limited oral bioavailability, may be indicative of the high potency of oxymorphone in mediating reinforcing subjective effects predictive of abuse, and why there is still some oral abuse of oxymorphone even with the lower oral bioavailability.

In the pivotal intranasal study EN3288-114, OPANA ER demonstrated an abuse-deterrent effect for the intranasal route of administration. This deterrent effect may help explain the lower frequency of abuse of reformulated OPANA ER via insufflation observed in the epidemiological data. Important factors likely contributing to this deterrent effect include the fact that reformulated OPANA ER tablets are difficult to crush into a fine powder and that they contain a high molecular weight gelling agent. In contrast, studies conducted by the Endo showed that, for selected oxymorphone ER generic products, there was no resistance to crushing, allowing abuse by insufflation. Taken together, the low oral bioavailability of oxymorphone and the difference among formulations in resisting crushing may explain the higher levels of abuse by insufflation associated with oxymorphone ER generic products. Although oxymorphone ER generic formulations contain excipients that can gel upon contact with water, it is not known to what extent these excipients may impact abuse of these products by insufflation.

Epidemiological data indicate that intravenous injection is an important route of abuse for reformulated OPANA ER. The difficulties associated with abuse of OPANA ER by oral administration and insufflation, as described above, may contribute to a higher proportion of individuals abusing reformulated OPANA ER by injection than the other routes. An additional factor contributing to the intravenous abuse of reformulated OPANA ER tablets upon manipulation is the feasibility of obtaining suitable solutions for injection upon manipulation of

the reformulated OPANA ER tablets. To date, no studies have been identified that examine the dose-response relationship of intravenously injected oxymorphone to subjective reinforcing effects such as Drug Liking or High. Indirect evidence of a reinforcing intravenous dose can be taken from the data provided by the pilot study EN3288-113, which demonstrated that the intranasal administration of oxymorphone HCl at a dose of 7.5 mg into non-dependent, opioid experienced subjects resulted in high levels of Drug Liking and High. Although the bioavailability of oxymorphone in humans following insufflation is not known, it is likely less than 100%. Based on this assumption, intravenous injection of a solution containing 7.5 mg and possibly lower amounts may be expected to produce subjective reinforcing effects.

Data from Category 1 studies conducted by the Office of Pharmaceutical Quality in CDER have shown that under certain experimental conditions of extraction, around 17.6 mg (44 %) mg of oxymorphone was extracted in a small volume of ^{(b) (4)} from one manipulated Opana 40 mg tablet. Taking a conservative approach by considering an approximate intravenous reinforcing dose of 7.5 mg of oxymorphone, individuals using the same methods may be able to extract approximately a little over two reinforcing doses of intravenous oxymorphone.

In conclusion, the intrinsic properties of a drug, such as bioavailability through different routes of administration, and the feasibility of obtaining reinforcing opioid doses upon manipulation of a formulation may play a role in the way an opioid formulation is abused.

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**Center for Biologic Evaluation and Research (CBER) Division of
Blood Products – research abstract and publication**



M E M O R A N D U M

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

DATE: February 9, 2017

FROM: Ryan Hunt, M.D.
Chava Kimchi-Sarfaty, Ph.D.
Paul Buehler, Ph.D.

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

RE: Open Session Background Document: Thrombotic microangiopathy associated with intravenous Opana ER abuse

Background

A 2013 CDC Morbidity and Mortality Weekly Report first described the occurrence of a “TTP-like illness” of unclear etiology in individuals injecting adulterated tablets of reformulated Opana ER. Subsequent case reports have described such patients as having microangiopathic hemolytic anemia, thrombocytopenia and renal failure, with thrombotic microangiopathy (TMA) in kidney biopsies. The mechanistic basis for these cases of TMA associated with Opana ER abuse was unclear. CBER initiated a study to better understand the pathogenic mechanisms and toxicities of Opana ER associated TMA.

Findings

Guinea pigs intravenously administered the inert ingredients in reformulated Opana ER were found to develop dose-dependent intravascular hemolysis coincident with the appearance of fragmented red blood cells in the peripheral blood—two hallmark features of thrombotic microangiopathy. Signs of acute renal injury (increased serum creatinine, urinary albumin, renal cortex NGAL expression) were also found in animals given repeated injections of the inert ingredients, which was accompanied by histologic evidence of tubular and glomerular damage.

Conclusions

- The occurrence of thrombotic microangiopathy is a rare but serious consequence of the intravenous abuse of reformulated Opana ER and can be associated long term sequelae.
- Animal studies implicate the inert ingredients in the reformulated Opana ER tablet as a causal factor in the development of thrombotic microangiopathy.
- The pathogenesis appears to be driven by the impact of high molecular weight polyethylene oxide (HMW PEO) in the microvasculature.

References

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Regular Article

THROMBOSIS AND HEMOSTASIS

A mechanistic investigation of thrombotic microangiopathy associated with IV abuse of Opana ER

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Key Points

- The inert ingredients in Opana ER tablets can elicit TMA in the setting of IV abuse and stems from the impact of HMW PEO.

Since 2012, a number of case reports have described the occurrence of thrombotic microangiopathy (TMA) following IV abuse of extended-release oxymorphone hydrochloride (Opana ER), an oral opioid for long-term treatment of chronic pain. Here, we present unique clinical features of 3 patients and investigate IV exposure to the tablet's inert ingredients as a possible causal mechanism. Guinea pigs were used as an animal model to understand the hematopathologic and nephrotoxic potential of the inert ingredient mixture (termed here as PEO+) which primarily contains high-molecular-weight polyethylene oxide (HMW PEO). Microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury were found in a group of 3 patients following recent injection of adulterated extended-release oxymorphone tablets. Varying degrees of cardiac involvement and retinal ischemia occurred, with TMA evident on kidney biopsy. A TMA-like state also developed in guinea pigs IV administered PEO+. Acute tubular and glomerular renal injury was accompanied by nonheme iron deposition and hypoxia-inducible factor-1 α upregulation in the renal cortex. Similar outcomes were observed following dosing with HMW PEO alone. IV exposure to the inert ingredients in reformulated extended-release oxymorphone can elicit TMA. Although prescription opioid abuse shows geographic variation, all physicians should be highly inquisitive of IV drug abuse when presented with cases of TMA. (*Blood*. 2017;129(7):896-905)

Introduction

Prescription opioids are effective analgesics in the setting of severe and chronic pain but carry a high potential for dependency and abuse. In geographically defined areas of the United States, the prevalence of abuse has reached epidemic proportions and represents a serious public health concern.¹ The adulteration of prescription opioids commonly involves crushing, heating, and liquid extraction of tablets followed by nasal inhalation or injection. A 2013 Centers for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report first described the occurrence of a "thrombotic thrombocytopenic purpura (TTP) like illness" of unclear etiology in patients who had recently injected adulterated tablets of extended release oxymorphone hydrochloride.² A number of case reports have subsequently emerged describing patients with microangiopathic hemolytic anemia, thrombocytopenia, and renal failure,³⁻⁸ with thrombotic microangiopathy (TMA) observed in kidney biopsies. These individuals commonly present with sequelae related to injection drug abuse. Soft tissue, musculoskeletal, and blood borne infection have been diagnosed even in the absence of overt TMA. A 2015 outbreak of HIV in rural Indiana,

where a majority of infected persons reported injecting "melted" tablets of extended release oxymorphone, speaks to this trend.⁹

Syndromes of TMA include a variety of pathogenic mechanisms with unique approaches to care.¹⁰ TTP arises through a severe deficiency of ADAMTS13, the von Willebrand Factor (VWF) cleaving protease.¹¹⁻¹³ The accumulation of ultra large VWF multimers promotes the deposition of platelet rich thrombi within the microcirculation.¹⁴ Other TMA syndromes arise independent of changes to ADAMTS13 and encompass complement, toxin and drug mediated syndromes. Significant deficiencies of ADAMTS13 have not been found in patients with TMA associated with IV abuse of extended release oxymorphone, although not all individuals were tested. Approaches to treatment have ranged from early plasma exchange therapy to aggressive supportive care alone,⁴ but the mechanistic basis for these cases of TMA remains unclear.

In early 2012, Endo Pharmaceuticals reformulated tablets of extended release oxymorphone to contain a crush resistant ingredient mixture. The formulation is chiefly composed of high molecular weight

Submitted 31 August 2016; accepted 7 November 2016. Prepublished online as *Blood First Edition* paper, 18 November 2016; DOI 10.1182/blood.2016.08736579.

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The online version of this article contains a data supplement.

There is an Inside *Blood* Commentary on this article in this issue.

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polyethylene oxide (HMW PEO; \sim 7 000 000 Da) in addition to smaller amounts of hypromellose, macrogol, α tocopherol, and citric acid; herein collectively referred to as PEO+. The US Food and Drug Administration (FDA) determined that the reformulated tablet may indeed “resist crushing relative to the original formulation” but can be “readily prepared for injection.”¹⁵ The true epidemiologic impact of the reformulation remains uncertain, and the tablet currently does not have abuse deterrent labeling. The hematotoxic potential of IV HMW PEO has received limited attention. An abrupt lethal effect of IV HMW PEO was described in animals shortly after the first synthesis of the polymer¹⁶ and rats administered IV or intraperitoneal HMW PEO have been reported to develop hemolytic anemia.¹⁷

Here, we describe illustrative cases of TMA in patients exposed to PEO+ during IV abuse of extended release oxymorphone tablets. We next evaluate the dose dependent effects of IV PEO+ administration in guinea pigs. We show that the inert ingredients generate acute hematotoxicity and kidney injury, consistent with a mechanistic link between the tablet’s constituents and cases of TMA following its IV abuse in humans.

Methods

In vivo administration of IV PEO+

Male Hartley guinea pigs (Charles River Laboratories) were maintained in the animal facility of the FDA Center for Biologics Evaluation and Research (CBER) Animal Care Facility. Animals were 8 to 10 weeks old and weighed 650 to 850 g before surgery. Animal protocols were approved by the FDA CBER Institutional Animal Care and Use Committee, and all experimental procedures were performed in compliance with the National Institutes of Health guidelines on the use of experimental animals. The inert ingredient mixture was provided by Endo Pharmaceuticals under a research collaborative agreement. The bulk PEO+ powder was dissolved in 1× phosphate buffered saline by heating to 45°C with gentle agitation to achieve a 1 mg/mL stock solution. To achieve solution consistency, the solubilized material was centrifuged at 10 000g for 20 minutes to remove large undissolved aggregates. Bolus injections were administered via an indwelling jugular catheter. Blood samples were obtained at baseline, 4, 8, 24, and 48 hours and animals were euthanized at 24 or 48 hours after initial injection for tissue collection and histopathologic examination.

Hematological analysis

Blood samples were collected into heparin containing tubes at indicated time points via an indwelling jugular catheter. Peripheral blood smears were prepared and red blood cell (RBC) count, hematocrit, and platelet count were determined using a Cell Dyn 3700 hematology analyzer (Abbott Diagnostics) in veterinary mode; a manual white blood cell (WBC) count and differential were performed. Plasma was prepared by centrifugation of whole blood at 1500g for 10 minutes and stored at -80°C .

Analysis of acute kidney injury

NGAL quantitative RT-PCR. Total RNA was isolated from guinea pig kidney cortical tissue using a TRIzol isolation protocol followed by complementary DNA synthesis (Applied Biosystems). Quantitative real time polymerase chain reaction (RT PCR) was performed on a LightCycler 480 (Roche) using TaqMan Universal PCR Master Mix and the following TaqMan primer/probes for guinea pig Lcn2 (neutrophil gelatinase associated lipocalin [NGAL]) (forward, 5' GTCCCACCACTGAGCAAGAT 3'; reverse, 5' GTCATCTTCAGCCGTAGG 3'; TaqMan probe, 5' CAAGACAAGT TCCAGGGAA 3') and 18S ribosomal RNA (Mm03928990_g1). Samples were assayed in triplicate. Crossing point (Cp) values were obtained and $\Delta\Delta\text{Cp}$ values were calculated using 18S as the reference gene. Statistical analysis was performed on raw ΔCp data.

Urinary albumin determination. Albumin content in urine was measured using a commercially available guinea pig albumin enzyme linked immunosorbent assay (ELISA) kit (MyBioSource).

Plasma creatinine measurement. Plasma creatinine levels were determined by a colorimetric assay kit (Abcam).

Sodium dodecyl sulfate–polyacrylamide gel electrophoresis/Western blot

Tissue lysates were resolved on NuPAGE Novex 4% to 12% Bis Tris gels (Thermo Fisher), transferred to nitrocellulose membranes, and blocked for 1 hour with 5% nonfat dry milk solution. Membranes were incubated overnight at 4°C in primary antibody solution. Primary antibodies used were mouse anti hemeoxygenase 1 (Enzo Lifescience), mouse anti β actin (Abcam), goat anti hypoxia inducible factor 1 α (HIF 1 α ; R&D Systems). Membranes were incubated with horseradish peroxidase (HRP) conjugated goat anti mouse (Thermo Fisher) or bovine anti goat (Santa Cruz Biotechnology) antibodies for 1 hour at room temperature. A chemiluminescent signal was developed using SuperSignal West Pico chemiluminescent substrate (Pierce) and visualized using an Image Station 4000MM Pro (Carestream). Densitometry analysis was performed using Kodak molecular imaging software (Carestream).

Spectrophotometric determination of plasma hemoglobin

Hemoglobin in plasma was measured in semimicro cuvettes using a Cary 60 UV Vis spectrophotometer (Agilent Technologies). Absorbance was measured between 350 and 650 nm. Spectra were deconvoluted against standard extinction curves of pure substances using a nonnegative least square algorithm.

Measurement of HMW PEO in plasma

The concentration of PEO within plasma of guinea pigs was determined using a Life Diagnostics ELISA kit that recognizes the PEO backbone.

RBC ektacytometry

RBC deformability was measured using ektacytometry (RheoScan AnD 300; Rheomeditech). The elongation index was evaluated from 0 to 20 Pa and compared at 3 to 9 Pa, which is relevant to shear stress experienced by circulating RBCs.

Tissue iron measurements

Iron content within renal cortex tissue was determined by a ferrozine based assay as previously described.¹⁸

Histopathology

Kidney and spleen were fixed in 10% formalin for 24 hours and stored in 100% isopropanol. Tissue was embedded in paraffin, and 2 to 5 μm sections were prepared. Hematoxylin and eosin (H&E) and Perls diaminobenzidine (DAB) staining were performed as previously described.¹⁹ Patient kidney biopsy sections were routinely processed for light microscopy with H&E, periodic acid Schiff, and Jones silver staining, immunofluorescence for immunoglobulins IgG, IgA, IgM, κ , λ , and complements C3 and C1q, and for electron microscopy, with selected sections viewed and glomeruli selected for thin sectioning and viewed in a Philips Morgagni electron microscope.

Immunohistochemistry

Sections were dewaxed and rehydrated. Citrate buffer antigen retrieval was performed by microwave heat treatment of 15 minutes and cooling for 30 minutes at room temperature. Slides were incubated with 3% H_2O_2 for 20 minutes to quench endogenous peroxidase activity. Sections were blocked with 2.5% normal horse serum (Vector Laboratories) for 1 hour at room temperature before overnight incubation at 4°C in primary antibody (mouse anti polyethylene glycol [clone 3F12 1; Life Diagnostics] or rabbit anti fibrinogen (Abcam)). After washing, a peroxidase conjugated anti mouse IgG reagent or alkaline phosphatase conjugated anti rabbit IgG reagent (Vector Laboratories) was added to each slide for 30 minutes at room temperature.

Table 1. Clinical characteristics in 3 patients treated for TMA following IV abuse of extended-release oxymorphone

	Patient 1	Patient 2	Patient 3
Age, y	24	28	48
Sex	Female	Male	Female
Presenting symptoms	Numbness of extremities, vision loss	Angina, dyspnea, abdominal pain, vision loss	Angina, dyspnea, abdominal pain, diarrhea, numbness of extremities, vision loss
Treatment	5 times plasma exchange	9 times plasma exchange	5 times plasma exchange

The peroxidase signal was developed using 3, 3' DAB or red alkaline phosphatase substrate (Vector Laboratories) and counterstained with Gill II hematoxylin.

VWF multimer analysis

Guinea pig plasma samples or control guinea pig platelet lysate were electrophoresed on a 0.6% agarose sodium dodecyl sulfate (SDS) gel in a horizontal gel apparatus at 4°C. Electrophoresis was performed until the dye front migrated ~9 cm. Protein was transferred overnight onto an Immobilon P polyvinylidene difluoride membrane (Millipore) at 100 mA in a *trans* blot cell tank (Bio Rad) at 4°C. After blocking in 5% nonfat milk for 1 hour, the membrane was incubated at room temperature for 2 hours with a rabbit anti VWF polyclonal antibody (Abcam) followed by a HRP conjugated goat anti rabbit secondary antibody (Lifespan Bio) for 1 hour. The chemiluminescent signal was developed using SuperSignal West Pico chemiluminescent substrate (Pierce) and visualized using an Image Station 4000MM Pro (CAREstream).

VWF antigen and collagen-binding activity

VWF antigen (Abcam) and collagen binding activity (Technoclone) were determined using commercially available ELISA kits.

Endothelial cell culture

Primary human umbilical vein endothelial cells (HUVECs; Thermo Fisher) were cultured in media supplemented with various amounts of PEO+ or 1 µg/mL lipopolysaccharide (Sigma Aldrich) for 24 hours. The amount of soluble VCAM (sVCAM) was quantified by ELISA (R&D Systems).

Statistical analysis

Data are presented as mean ± standard error of the mean (SEM) unless otherwise noted. A 1 way analysis of variance (ANOVA) was used to compare means among groups with a Tukey corrected posttest for between group comparisons. $P < .05$ was considered statistically significant. All statistical analyses were performed using GraphPad Prism (version 6.02).

Results

TMA following IV abuse of extended-release oxymorphone in humans

Two female and 1 male patient presented to the emergency department of Erlanger Medical Center in Chattanooga, TN with complaints of chest pain, dyspnea, and varying degrees of visual impairment. Two patients were found to be in acute renal failure and all 3 had anemia and thrombocytopenia. Laboratory data also revealed elevated lactate dehydrogenase (LDH) and undetectable serum haptoglobin levels (Tables 1 and 2). Examination of peripheral blood smears showed microspherocytosis, schistocytosis (>10%), and markedly reduced platelets: features consistent with microangiopathic hemolytic anemia. At presentation, 2 of 3 patients had reductions in C3 and C4 serum complements. Troponin levels were elevated in all 3 patients and an electrocardiogram in the male patient revealed diffuse ST segment elevation and PR segment depression, consistent with acute pericarditis. An echocardiogram in this patient showed reduced left ventricular

and right ventricular function (ejection fraction of 30%) but no overt pericardial effusion. Percutaneous coronary intervention was not performed due to the likelihood of a microvascular disease process. Dyspnea was associated with diffuse alveolar infiltrates on chest radiograph.

Based upon these findings, the patients were initiated on plasma exchange therapy until ADAMTS13 levels could be determined. The male patient also required acute hemodialysis throughout his hospitalization. Gelatinous material within patient plasma was found to occlude the dialysis catheter, pheresis tubing, and bedside drain. Upon further questioning, all 3 patients reported recent IV abuse of extended release oxymorphone tablets. According to the account of the male patient, as many as 10 extractions had been performed on a single tablet with the last injection occurring ~6 hours prior to presentation. Kidney biopsies were performed in 2 patients and showed TMA, dominantly affecting arterioles and interlobular arteries with focal endothelial swelling involving larger arteries, accompanied by extensive acute tubular injury (Figure 1A-B). There were no immune complexes seen by immunofluorescence. Transmission electron microscopy showed increased lamina rara interna, podocyte foot process effacement, and cellular vacuolization with no deposits (Figure 1C-D). The clearance of gelatinous material continued through the first 3 plasma exchange sessions and then began to diminish. Plasma exchange was continued through at least 5 cycles, and all patients demonstrated complete or partial recovery of renal function prior to discharge. Over the first 3 days, the loss of vision worsened in all 3 patients with the male patient developing near total blindness in the left eye and marked reduction of visual acuity in the right. An ophthalmologic examination and fluorescence angiography revealed diffuse occlusive disease of retinal arterioles (Figure 1E). The male patient was discharged with chronic renal disease (serum creatinine, 2.3 mg/dL) and unfortunately continued to IV abuse Opana ER tablets. He was admitted a second time with TMA and became hemodialysis dependent. With continued abuse, he eventually died ~18 months after his initial presentation. The other 2 patients were not readmitted and lost to follow up.

The potential for excipients in extended-release oxymorphone to cause TMA when IV administered to guinea pigs

To guide our investigation, we first determined the amount of inert ingredients (termed here PEO+) that would be extracted and delivered through a typical adulteration process. Tablets (40 mg) were cut into 4 to 5 pieces and heated together on a spoon in 2 mL of water to the point of boiling with a propane torch. When the volume was reduced by ~50%, the remaining liquid was collected. Through 5 extractions of a single 40 mg tablet, the total mass of the dried excipients was ~14 mg. Assuming complete distribution within the plasma volume of a 70 kg adult, the resulting plasma concentration of PEO+ would be ~5 µg/mL.

To account for variation in injection frequency and adulteration method, we sought to achieve a range of PEO+ levels within blood by establishing 4 IV dosing schemes: 0.1 mg/kg or 0.3 mg/kg bolus

Table 2. Laboratory abnormalities in 3 patients treated for TMA following IV abuse of extended-release oxymorphone

Test result	Patient 1		Patient 2		Patient 3	
	Presentation	Peak or nadir	Presentation	Peak or nadir	Presentation	Peak or nadir
WBC, $4.5 \times 10^9/L$	12.6	12.8	23.3	30.2	WNL	WNL
Hemoglobin, 13.5 g/dL	11.2	9.9	7.7	4.7	7.7	6.9
Hematocrit, 35% 50%	31.9	27.8	22.8	14.3	23.3	20.4
Platelet count, $150 \times 10^9/L$	43	41	18	13	20	20
Creatinine, 0.6–1.3 mg/dL	WNL	WNL	2.2	5.3	1.6	1.7
LDH, 140–280 U/L	1507	1507	1981	4418	2584	2854
Haptoglobin, 30–200 mg/dL	Undetectable		Undetectable		Undetectable	
ADAMTS13	66%		64%		ND	
D dimer, $\leq 0.5 \mu\text{g/mL}$	0.97	0.97	ND		ND	
C3, 88–252 mg/dL	45	44	WNL	22	73	69
C4, 12–75 mg/dL	6	6	WNL	5	10	6
CH 50, 31–60 U/mL	24	24	WNL	13	WNL	WNL
Troponin I, <0.01 ng/mL	6.14	6.14	4.95	27.2	12.83	22.53
Hepatitis B antibody	Negative		Negative		Negative	
Hepatitis C antibody	13.73		Negative		Negative	
Echocardiography	EF 55%		EF 30%, mild RV and LV dilation		EF 20%, global hypokinesis, moderate RA dilation	

EF, left ventricular ejection fraction; LV, left ventricular; ND, not determined; RA, right atrial; RV, right ventricular; WNL, result within reference range.

injections of freshly solubilized PEO+ administered once or repeatedly (5 times at 1.5 hour intervals). The plasma level of HMW PEO, the main constituent of the inert ingredient mixture, was determined over

time. Single injections of 0.1 mg/kg and 0.3 mg/kg PEO+ resulted in a peak plasma PEO concentration of 3 $\mu\text{g/mL}$ and 5 $\mu\text{g/mL}$, respectively, which was followed by a slow elimination of PEO from

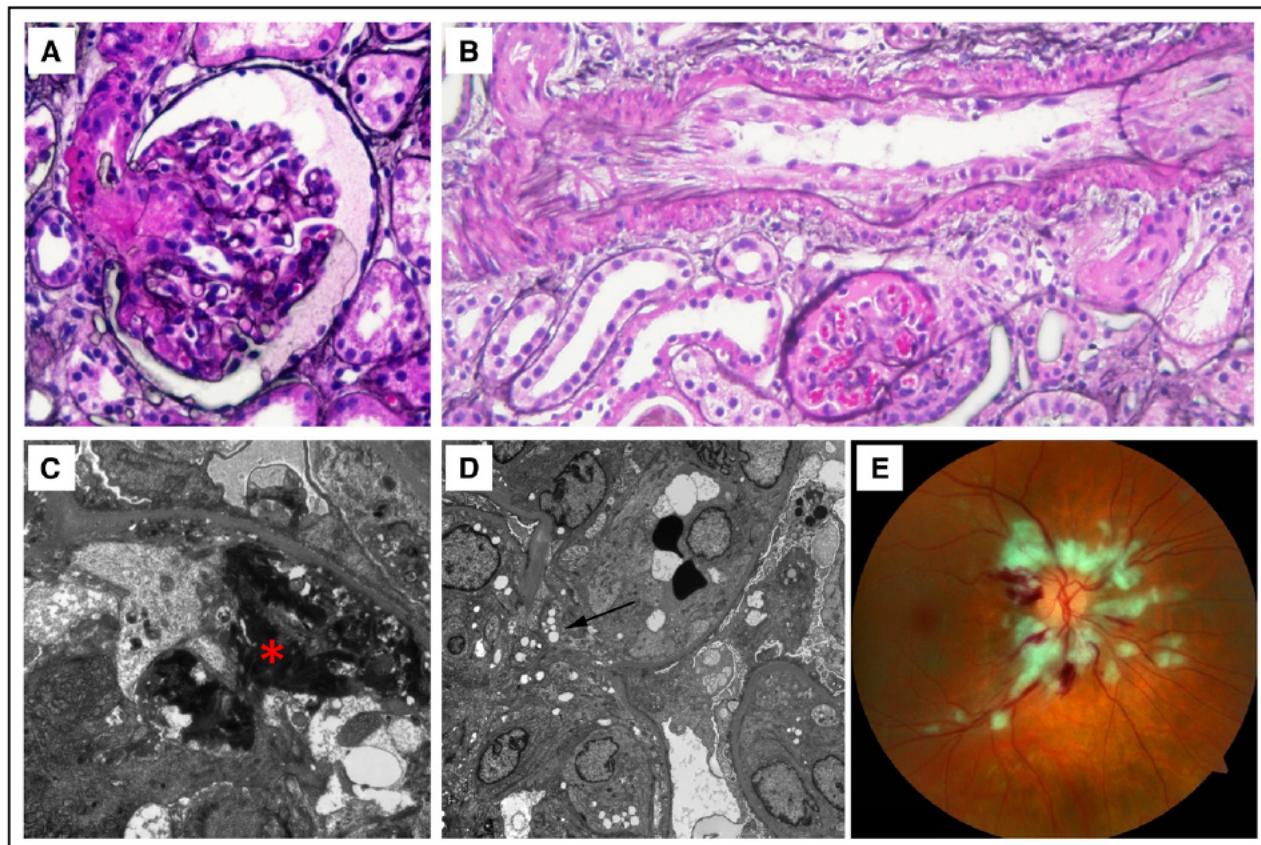


Figure 1. Renal biopsy findings and retinal fundus photograph from patients following IV abuse of extended-release oxymorphone tablets. (A) TMA involving the arteriole with fibrinoid necrosis, extending into the vascular pole of the glomerulus (Jones silver stain, original magnification $\times 200$). (B) Large artery showing endothelial swelling and partial lumen occlusion, with congested glomerulus below (Jones silver stain, original magnification $\times 100$). (C) Fibrin tactoids (red asterisk) underneath swollen endothelium with overlying podocyte foot process effacement, without immune complex deposition (transmission electron microscopy, original magnification $\times 7100$). (D) Swollen endothelium nearly occluding capillary lumen, with RBC fragments (dark black material) and overlying podocyte foot process effacement, without immune complexes. Clear vacuolated areas (black arrow) are found in endothelium and other cells, possibly representing particulate matter from adulterated tablets (transmission electron microscopy, original magnification $\times 2800$). (E) Retinal fundus photograph in a patient experiencing loss of vision following IV abuse of extended release oxymorphone, demonstrating numerous cotton wool spots and microhemorrhages.

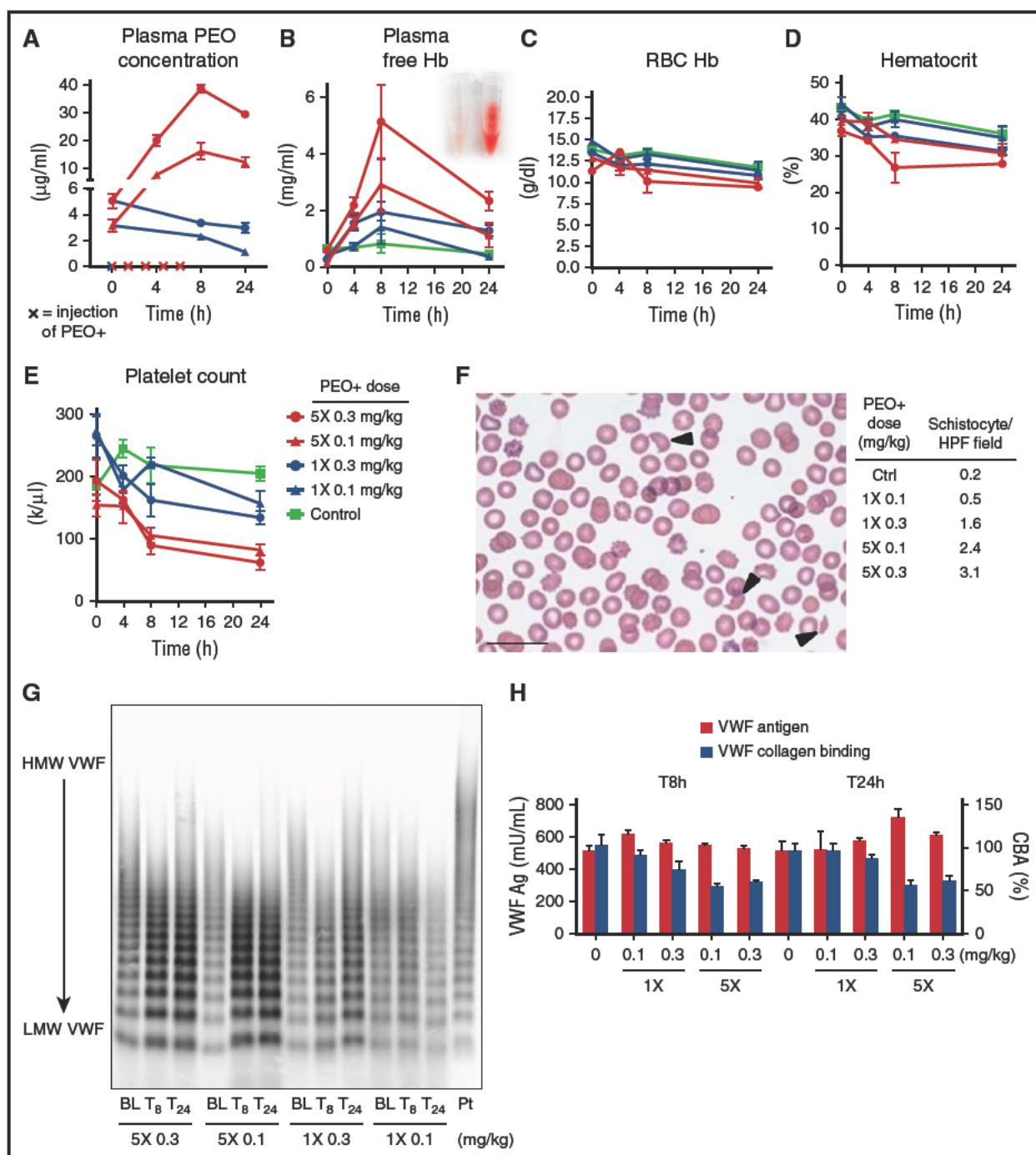


Figure 2. IV PEO+ results in intravascular hemolysis, declines platelet count and the appearance of schistocytes in the peripheral blood accompanied by increased LMW VWF multimers. (A) The plasma PEO concentration of all PEO+ treated groups over time. Multidosed (5 times [5×]) guinea pigs were injected repeatedly with PEO+ at 1.5 hour intervals (as designated on x axis). (B-E) Hematologic changes in cell free plasma hemoglobin, total RBC hemoglobin, hematocrit, and platelet count in guinea pigs after a single (1×) or repeated (5×) injections of 0.1 and 0.3 mg/kg PEO+. The inset in panel B provides a visualization of the extent of plasma hemoglobin in maximally dosed guinea pigs vs control. (F) Appearance of schistocytes in the peripheral blood 24 hours postinjection is presented as number per high power field. (G) The molecular weight distribution of VWF multimers in PEO+ treated guinea pig plasma samples was assessed by low resolution (0.6%) SDS agarose gel electrophoresis at baseline (BL), 8 hours (T₈) and 24 hours (T₂₄) after injection. Platelet lysate (Pt) prepared from normal guinea pig blood was used as a reference for minimally proteolyzed HMW VWF. (H) VWF antigen and VWF collagen binding activity in plasma collected at 8 and 24 hours after injection with PEO+. All data displayed as mean values \pm SEM ($n = 4$ per group). Ag, antigen; CBA, collagen binding activity; Ctrl, control; Hb, hemoglobin; HPF, high powered field; LMW, low molecular weight.

the circulation through 48 hours (Figure 2A). Five injections at 1.5 hour intervals resulted in the accumulation of PEO in plasma through the last injection, reaching a maximal concentration of $\sim 15 \mu\text{g}/\text{mL}$ (5 times, 0.1 mg/kg) and $\sim 40 \mu\text{g}/\text{mL}$ (5 times, 0.3 mg/kg) at 8 hours,

respectively, followed by a decline in plasma PEO concentration over time.

Following IV administration of PEO+, we observed an abrupt, dose dependent increase in free hemoglobin in the plasma accompanied

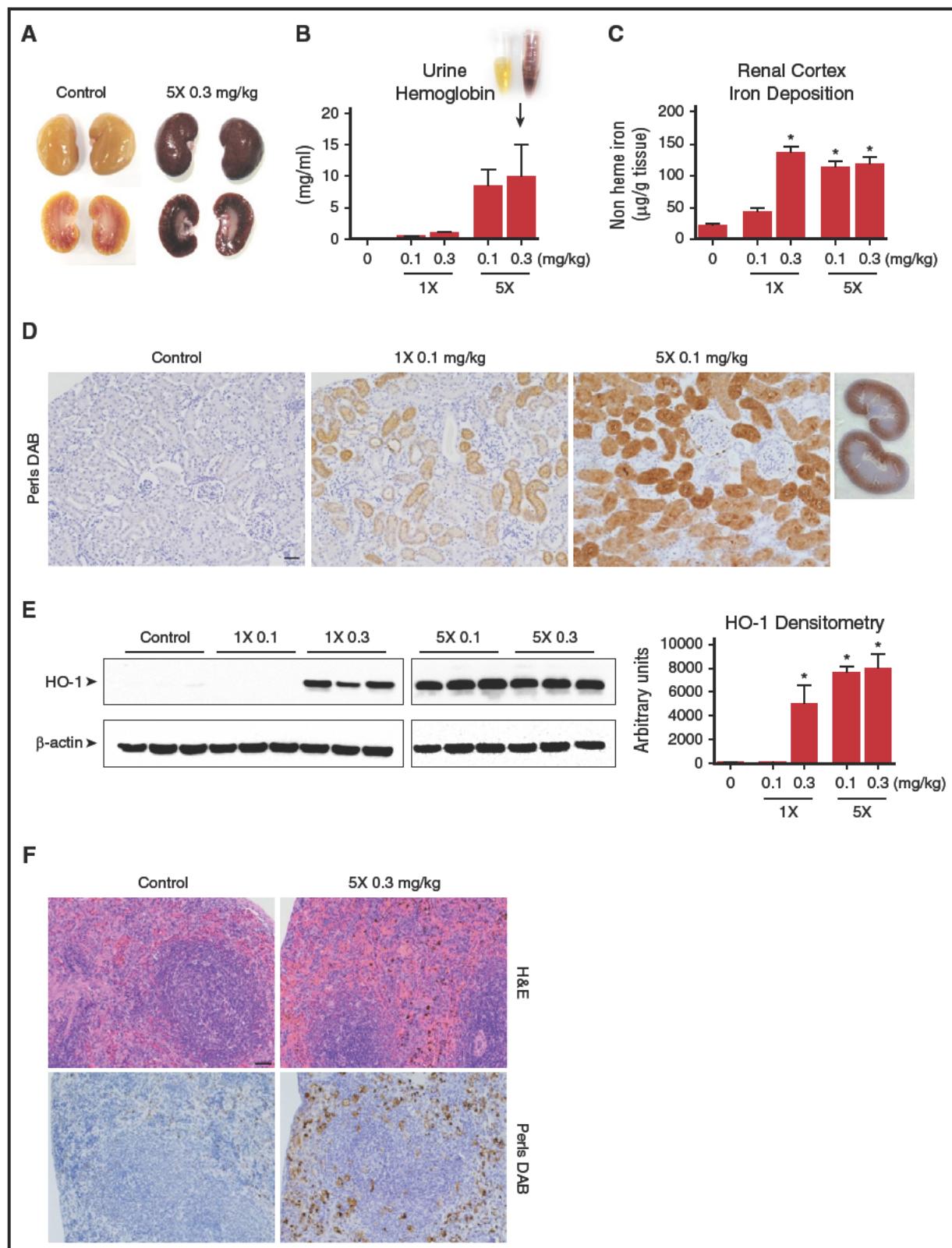


Figure 3. Tissue iron deposition secondary to PEO+ induced hemolysis. (A) High levels of cell free hemoglobin result in macroscopic discoloration of kidneys after exposure to IV PEO+. (B) Quantitation of T_{24h} urine hemoglobin. (C) Quantitation of nonheme bound iron accumulation in the renal cortex of PEO+ injected animals measured by a colorimetric ferrozine based assay at the study end point. (D) Iron deposition within the renal cortex highlighted by Perls DAB staining. Renal cortical areas are shown from control, single (1X), and multidosed (5X) animals (scale bar, 50 μ m), demonstrating the tendency for iron to deposit within the proximal tubule. (E) Western blot of HO 1 expression in kidney tissue and its quantitative densitometric analysis. β actin was probed as a loading control. (F) Splenic sections stained with H&E and Perls DAB from a multidosed (5X) and control animal (scale bar, 50 μ m), demonstrating increased hemosiderin deposition and red cell engorgement. Data displayed as mean values \pm SEM ($n = 4$ per group). * $P < .05$ (1 way ANOVA).

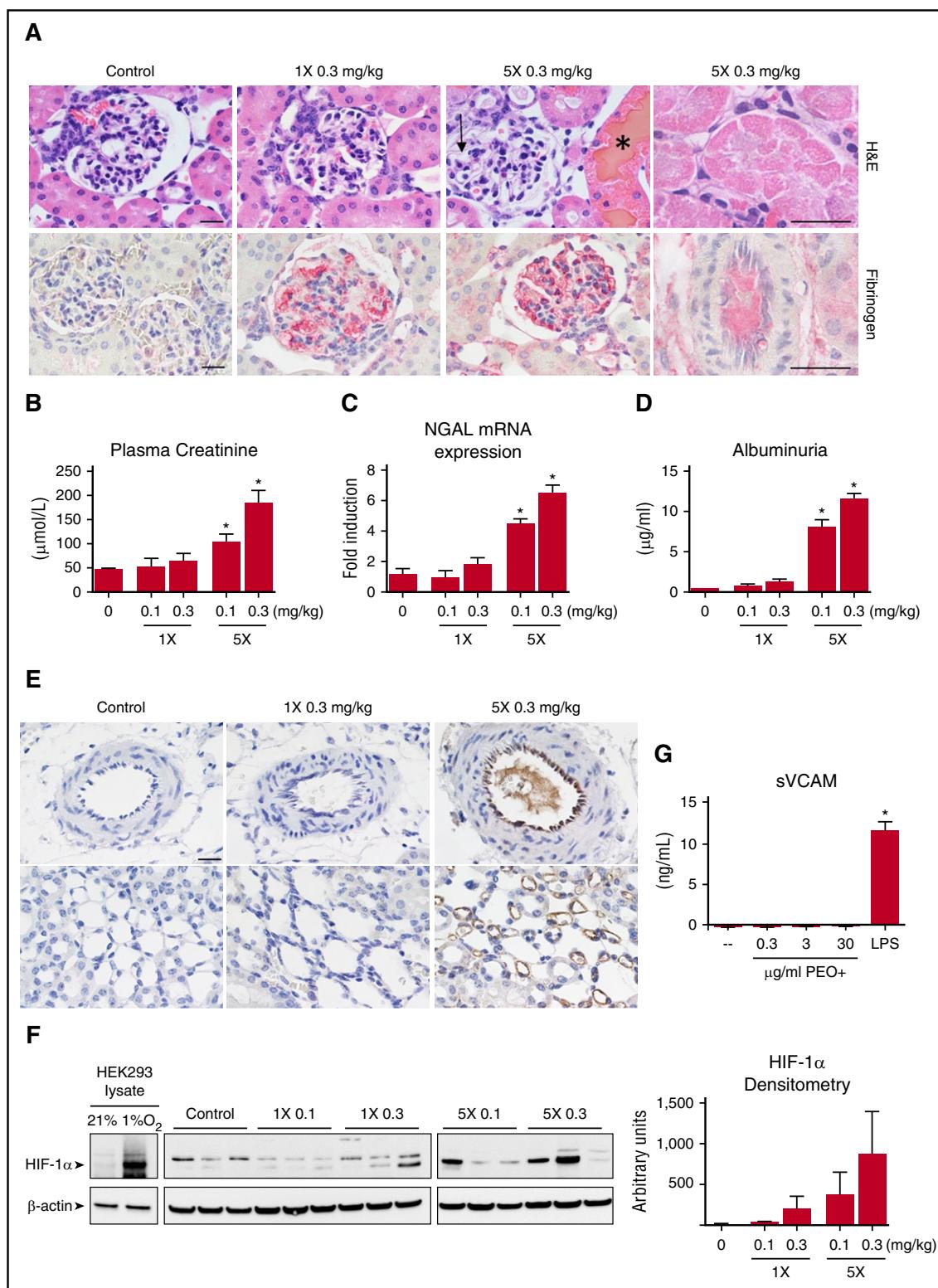


Figure 4. PEO+ induced acute kidney injury and identification of HWM PEO in the microvasculature. (A) Representative kidney sections stained with H&E (top panel) and for fibrinogen by immunohistochemistry (NovaRed, bottom panel) (scale bar, 20 μm). Multidosed (5×) animals demonstrate glomerular capillary swelling (arrow), patchy necrosis of proximal tubule cells with widespread eosinophilic intracellular inclusions (rightmost panel), and hemoglobin laden tubular casts (*). A dose dependent increase in fibrin deposition within the glomerular capillaries of PEO+ treated animals could be found. (B-D) Quantitation of T_{24h} plasma creatinine levels, renal cortex mRNA NGAL levels, and urinary albumin after PEO+ administration (n = 4 per group). (E) Kidney sections of control, single (1X) and multidosed (5X) PEO+ animals were immunohistochemically stained for PEO using a monoclonal antibody against the polyethylene backbone with DAB development. Interlobular arteries (top panel) and vasa recta lining the loop of Henle (bottom panel) are shown (scale bar, 20 μm). (F) Western blot for HIF 1α expression in the renal cortex of representative animals. β actin was probed as a protein loading control. Cell lysates of hypoxic (8 hours at 1% O₂) and normoxic (21% O₂) HEK293 cells served as a reference of the HIF 1α specific upregulated band. (G) HUVECs were cultured for 24 hours in the presence of various concentrations of PEO+ or activated with 1 μg/mL lipopolysaccharide. The amount of sVCAM released into the cell culture supernatant was quantified by ELISA. *P < .05 (1 way ANOVA).

by modest declines in total RBC hemoglobin, hematocrit, and platelet count (Figure 2B E). Maximum plasma free hemoglobin levels were reached 8 hours after the first injection in both single and repeatedly dosed guinea pigs. Peripheral blood smears prepared from PEO+ treated animals revealed the existence of schistocytes, which appeared in the peripheral blood in a dose dependent manner (Figure 2F). Hemolysis could not be recapitulated by directly spiking PEO+ into control blood subjected to end over end mixing, arguing against a direct hemolytic effect (data not shown). Measurements of RBC deformability by ektacytometry were also unaffected by the presence of PEO+ (data not shown). Although a small increase in total leukocyte count was observed in animals injected with the highest dose of PEO+ over control animals ($7.1 \text{ vs } 4.3 \times 10^9/\text{L}$ at 24 hours), the leukocyte count of all animal groups remained within reference ranges.²⁰

With evidence of microangiopathic hemolytic anemia and decreased platelet counts, we next characterized the VWF multimer distribution using SDS agarose gel electrophoresis. Hyperreactive, ultra large multimers of VWF accumulate during the remission phases of ADAMTS13 deficiency mediated TTP.¹⁴ The plasma of animals injected with PEO+ showed no evidence of increased HMW VWF species (Figure 2G). Increased quantities of low molecular weight VWF species were instead seen in multidosed animals, reflected by decreased VWF collagen binding activity to antigen ratios (Figure 2H). This VWF profile supports a state of TMA^{21,22} and high shear stress in the microcirculation,^{23–25} which can promote Weibel Palade body release,²⁶ platelet VWF interaction,^{27,28} and proteolysis of VWF.²² No significant differences in D dimer and complement C3 levels among control and PEO+ injected animals were found, arguing against the occurrence of disseminated intravascular coagulation or complement activation (data not shown).

End-organ changes following IV PEO+ dosing: hemolysis, tissue iron deposition, and response to heme stress

The kidneys of multidosed PEO+ animals were macroscopically found to have a dark brown discoloration of renal cortical tissue (Figure 3A), which is consistent with high levels of hemoglobinuria (Figure 3B). The iron content within the renal cortex tissue of single dose and multidosed animals was significantly elevated (Figure 3C), depositing primarily within the proximal and distal tubules (Figure 3D). In response to elevated hemoglobin/heme mediated oxidative stress, the expression of heme oxygenase 1 (HO 1) was found to be significantly upregulated (Figure 3E). The spleen of multidosed animals likewise showed engorgement of the red pulp with red cells and red cell fragments in H&E stained sections, accompanied by widespread iron/hemosiderin deposits (Figure 3F).

Kidney sections from multidosed animals demonstrated signs of glomerular and tubular damage. Proximal tubular epithelial cells showed hyaline droplet deposition and patchy necrosis, resulting in the filling of tubular lumens with cellular debris and protein casts. Ectatic glomerular capillary loops were frequently seen (Figure 4A top panel). These outcomes were mostly absent in animals given a single injection of PEO+. A dose dependent increase in glomerular capillary fibrinogen content was also identified by immunohistochemistry (Figure 4A bottom panel). Glomeruli did not stain positively for VWF or platelet antigen (data not shown). These histological findings support the capacity for IV PEO+ to mediate a unique constellation of tubular and glomerular damage with a strong dose dependency (ie, minimal changes with single injections of PEO+ vs overt kidney injury following repeated injections).

To better define the extent of kidney damage, common markers of acute kidney injury were quantified (Figure 4B D). Only repeatedly dosed groups (5 times, 0.1 mg/kg; and 5 times, 0.3 mg/kg) were found to have significant elevations of plasma creatinine, with twofold and fourfold increases over control at 24 hours, respectively. NGAL (or Lcn2) is rapidly induced and secreted from renal distal tubules following ischemic or nephrotoxic injury.^{29,30} The level of NGAL messenger RNA (mRNA) transcript within the renal cortex of multidosed animals (5 times, 0.1 mg/kg; and 5 times, 0.3 mg/kg) was increased by fourfold and sevenfold over control, respectively, whereas guinea pigs receiving single doses of PEO+ showed no significant NGAL upregulation. Significant albuminuria was also observed in repeatedly dosed animals, indicating impaired glomerular permeability function, which may occur secondary to podocyte injury and/or lack of tubular reabsorption of filtered albumin.

Identification of HMW PEO within the renal microvasculature

The distribution of HMW PEO within the kidney following its IV administration was evaluated by immunohistochemistry using an antibody that recognizes the PEO backbone. The endothelium of interlobular arteries as well as the vasa recta (straight capillaries of the medulla) showed positive staining for PEO (Figure 4E top and bottom right panels). The intraluminal appearance of PEO+ material within the small arteries of multidosed animals raised the possibility that microvascular flow or oxygenation may be compromised. We therefore probed the renal cortical tissue by western blot for HIF 1 α expression, a transcription factor that mediates adaptive cellular responses to hypoxia. Variable but prominent HIF 1 α expression was detected in the renal cortex of multidosed animals, with low levels of HIF 1 α expression seen in animals injected with a single 0.3 mg/kg dose (Figure 4F). These results suggest that IV PEO+ may lead to varying degrees of diminished tissue oxygenation. Although this may result in endothelial activation or injury in vivo, the presence of the inert ingredients in the culture medium of HUVECs did not directly stimulate release of sVCAM, a marker of endothelial activation (Figure 4G).

Discussion

Microangiopathic hemolytic anemia, thrombocytopenia, renal injury, and vision loss have been described in prior published cases of TMA associated with extended release oxymorphone abuse. However, this report introduces the first descriptions of cardiac involvement and atypical clinical features of TMA (eg, pulmonary involvement, dyspnea). Although serum complements were found to be normal in at least 1 other case report,⁷ the patients described here were found to have decreasing levels across the course of hospitalization. These declines in complement did not occur concomitant with the onset of disease and, therefore, complement activation/consumption is likely to be of secondary consequence in lieu of a primary mechanism.^{31–33} Evidence of foreign material within the plasma of affected individuals was also found. We therefore sought to understand whether the tablet's reformulated inert ingredients could elicit TMA when IV administered to guinea pigs.

IV infusion of the solubilized inert ingredient mixture elicited hallmark features of TMA. Microangiopathic hemolytic anemia, declines in platelet count, and renal injury were all observed with dose dependence in our animal model. These findings speak to the utility of the guinea pig model, which are increasingly recognized for their nephrotoxic sensitivity to hemoglobin^{19,34} and also confirm the inert ingredients as a causal factor in the development of TMA.

The injection of HMW PEO ($\sim 7\,000\,000$ Da) alone, the main constituent in PEO+ by mass, can recapitulate many of the effects of IV PEO+ at comparable doses (supplemental Figure 1, available on the *Blood* Web site). HMW polymers can decrease disordered motion of RBCs and promote more laminar blood flow.³⁵ HMW PEO has therefore been investigated as a drag reducing therapeutic polymer.³⁶⁻³⁸ However, recent work has shown that HMW PEO decreases the thickness of the cell free plasma layer that naturally abuts the microvascular wall, directing RBC traffic more proximal to the vessel wall, thereby generating increased wall shear stress.³⁹ Our observation of mechanical damage to RBCs and increased proteolysis of VWF support a state of high shear stress in the microvasculature of guinea pigs injected with PEO+. Infusion rate and polymer concentration may be influential in determining the impact of IV HMW PEO, which is reflected in the stepwise gradient of pathology seen in the current animal study. Although shear driven hemolysis appeared in all animal groups in a dose dependent manner, end organ damage was only observed in animals given repeated doses. This may also explain why only a minority of individuals (approximately one third at Wake Forest Baptist Medical Center; P.M., unpublished clinical observations) who seek medical treatment after injecting tablets of extended release oxymorphone show signs of fulminant TMA.

Renal injury, although seen in many forms of TMA, is also a recognized consequence of acute and chronic hemolysis.⁴⁰⁻⁴³ Brisk hemolysis overwhelms endogenous mechanisms to scavenge free hemoglobin and heme from the circulation,⁴⁴ and glomerular filtration becomes a primary mechanism to clear hemoglobin and its decay products. Once outside of the confines of an erythrocyte, hemoglobin can extravasate into tissue compartments where it becomes oxidized and denatured, resulting in heme loss and iron release.^{19,45} Hemoglobin degradation products trigger proinflammatory and pro oxidative cascades^{46,47} and cause cytotoxicity through oxidative damage and mitochondrial dysfunction.^{46,48-50} Extracellular hemoglobin also readily reacts with numerous small biologic molecules within plasma. Its scavenging of nitric oxide, a potent vasodilator within the microcapillary bed, can result in hypertension and endothelial dysfunction.^{50,51} Kidney injury in these cases of TMA is likely a consequence of free hemoglobin toxicity, compromised tissue oxygenation and endothelial injury.

The long term consequences for renal function in humans have ranged from complete recovery to chronic renal insufficiency necessitating renal replacement therapy. Although the supporting body of evidence is limited, initial plasma exchange therapy has been applied in several cases and may be appropriate in the setting of severe TMA. However, the resolution of symptoms in patients managed with supportive care alone is noteworthy, which may stem from the natural degradation of PEO polymers under flow.^{52,53}

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Abuse deterrent formulations are an important mechanism to limit prescription opioid misuse and are part of the FDA's comprehensive action plan to address the public health crisis of opioid addiction, abuse, and overdose.⁵⁴ However, the present study demonstrates a potential for HMW PEO based deterrent formulations to cause hematotoxicity, TMA, and end organ injury in the setting of IV misuse. Other oral prescription opioids formulated with HMW PEO have only recently been linked with TMA.^{55,56} The reasons for such varying incidence may partially stem from shifting patterns and methods of abuse, but are poorly understood. Although injection abuse of prescription opioids is highly concentrated in certain regions of the United States, particularly in rural Appalachia,⁵⁷ all physicians should be highly inquisitive of IV drug abuse when presented with cases of TMA.

Acknowledgments

The authors thank Dan Mellon and Judith Racoosin (Division of Anesthesia, Analgesia, and Addiction Products/Center for Drug Evaluation and Research) for their insightful comments and guidance.

Authorship

Contribution: R.H., A.Y., T.S., A.W., P.W.B., and C.K. S. designed the study; R.H., A.Y., J.H.B., E.W., and P.W.B. performed experiments; J.T. and P.M. provided case reports and clinical insight; A.B.F. and H.Y. prepared and interpreted human kidney biopsies; and R.H., A.Y., J.T., A.B.F., P.M., P.W.B. and C.K. S. wrote the manuscript.

Conflict of interest disclosure: E.W. is employed by Quest Diagnostics. The remaining authors declare no competing financial interests.

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doi:10.1182/blood-2016-08-736579 originally published online November 18, 2016

A mechanistic investigation of thrombotic microangiopathy associated with IV abuse of Opana ER

Ryan Hunt, Ayla Yalamanoglu, James Tumlin, Tal Schiller, Jin Hyen Baek, Andrew Wu, Agnes B. Fogo, Haichun Yang, Edward Wong, Peter Miller, Paul W. Buehler and Chava Kimchi-Sarfaty

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Statistical Review of Postmarketing Studies

STATISTICAL BRIEFING DOCUMENT

OPANA OBSERVATIONAL STUDIES

Joint Meeting of the Drug Safety and Risk Management Advisory Committee
and the Anesthetic and Analgesic Drug Products Advisory Committee Meeting

March 13–14, 2017

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Abbreviations

ASI-MV	Addiction Severity Index - Multimedia Version
ER	Extended release
IR	Immediate release
P1	Time period that was before OxyContin reformulation 2009Q1–2010Q2 in NAVIPPRO study 2009Q1–2010Q3 in RADARS study
P2	Time period that was after OxyContin reformulation and before Opana ER reformulation 2010Q3–2011Q4 in NAVIPPRO study 2010Q4–2011Q4 in RADARS study
P12	Time period that was before Opana ER reformulation 2009Q1–2011Q4 in NAVIPPRO study
P3	Time period that was after Opana ER reformulation 2013Q3–2016Q2 in NAVIPPRO and RADARS study
ROA	Route of administration
Rx	Prescriptions
SE	Single entity
Tb	Tablets

1 EXECUTIVE SUMMARY

This document addresses two questions. First, can the submitted data be used to assess the extent of overall abuse of Opana ER, whether in absolute or relative terms, in the underlying population? Second, can the data be used to assess whether there was a shift in the route of abuse of Opana ER from snorting to injection in the underlying population after it was reformulated? We reviewed two observational studies submitted by the sponsor. The results from these studies suggested that the extent of overall abuse of Opana ER was potentially high in relative terms, and there might be a shift from abuse through snorting to abuse through injection after the reformulation of Opana ER. However, there are statistical issues that complicate the findings of these studies. This document discusses statistical aspects of the two observational studies. Four main considerations that are important to make valid conclusions about Opana ER's abuse deterrence in the community are: data quality, estimability, causality, and interpretability.

With respect to data quality, it is important that the data measure what they are intended to measure. For example, a reported abuse based on a pre-specified definition should actually be an abuse. An exposure to a particular opioid should actually be an exposure to that opioid. If the data is incorrect, this is a misclassification problem. Misclassification, of either exposure (specific opioids) or outcome (abuse and route of administration), can bias the results, i.e. either exaggerate or diminish the actual change in an abuse metric. The direction and magnitude of bias may be difficult to quantify.

The estimability issue is caused by the fact that the data are captured by passive surveillance systems, and these data may not necessarily represent the underlying population of interest. In particular, the data are not a random sample of the population. In order to make valid statements about changes in overall abuse from the pre-reformulation period (pre period) to the post-reformulation period (post period) in the population, one of the following assumptions have to hold:

- Selection into the sample is independent of the substance being abused;
- If selection into the sample depends on the substances being abused, then the nature of the dependence does not change over time;
- If selection into the sample depends on the substances being abused, and the nature of the dependence changes over time, then the change in the dependence is the same for Opana ER and the comparator opioid.

In order to make valid statements about changes in route-specific abuses, similar assumptions have to hold with regard to the route of abuse, instead of substances being abused. Violations

of these assumptions may cause the sample data to show results that are different from what is taking place in the underlying population.

The causality issue occurs when comparing changes in Opana ER abuse from the pre period to the post period with those of comparator opioids. The goal of such comparisons is to separate the effect due to the reformulation of Opana ER from those due to secular trends and make causal statements about the effects of the reformulation. However, for such comparisons to be valid, we have to assume that Opana ER is similar to comparators, and different only in the sense that Opana ER has abuse-deterring formulation while comparators do not. For both the pre and the post periods, Opana ER and the comparators used in each study should be similar in terms of how they are affected by external factors, such as Drug Enforcement Administration (DEA), state and local law enforcement and education efforts to reduce opioid abuse, FDA efforts such as risk evaluation and mitigation systems, and social trends such as availability and cost of substitutable drugs. It is difficult to know from the data whether the external factors affect each opioid in different ways. When external factors differentially affect each opioid class, it is difficult to disentangle the effect due to reformulation from that due to secular trends.

Given the issues in data quality, estimability, and causality, caution is needed when interpreting the results from these two observational studies.

2 INTRODUCTION

In December 2016, Endo (the sponsor) submitted to FDA three postmarketing observational studies in support of an sNDA requesting abuse deterrent labeling for reformulated Opana ER:

- National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO)—Post Market Epidemiology Study to Evaluate Abuse of Opana ER (oxymorphone HCl) Extended-Release Tablets - Final Report (formal study);
- Analysis of Reformulated Opana Extended-Release (ER) using the RADARS System Poison Center Program (formal study);
- Analysis of Reformulated Opana Extended Release (ER) using the RADARS System Drug Diversion Program (supportive study).

According to FDA's Guidance for Industry [3], formal studies are hypothesis-driven, population-based observational studies that follow good epidemiological practices. Supportive studies may rely on sources that capture drug utilization or prescribing patterns that may not directly be considered abuse. In this document, we focus on the two formal studies—the NAVIPPRO study and the RADARS poison center study. This review does not discuss the RADARS drug diversion

study because it is a supportive study. For convenience, we refer to the NAVIPPRO ASI-MV surveillance system as NAVIPPRO, and the RADARS Poison Center Program as RADARS.

Two important statistical issues arose in the course of reviewing these observational studies:

- Can the data be used to make assess the extent of overall abuse of Opana ER in the underlying population, in absolute or relative terms?
- Can the data be used to assess whether there is a shift in the pattern of Opana ER abuse from the nasal route to the intravenous route following the reformulation?

Before addressing these questions, it is useful to discuss some statistical considerations for evaluating the data from the two observational studies. To be specific, the main considerations are for determining the utility of the submitted data are the following four points:

- Data quality: Does the data measure what it is supposed to measure?
- Estimability: Can the data be used to make inference about the population?
- Causality: Can the estimated effects be attributed to the reformulation?
- Interpretability: How do we interpret the observed effects?

Section 3 provides an overview of the study designs, statistical methods and analyses results of the two observational studies. Section 4 discusses the statistical considerations. Section 5 summarizes the study findings in context of these statistical considerations.

3 OBSERVATIONAL STUDIES

3.1 NAVIPPRO

The objective of this postmarketing observational study is to assess changes in abuse patterns of Opana ER including overall abuse and abuse via specific routes of administration (ROA), before and after the reformulation of Opana ER. The study period spans January 1, 2009 to June 30, 2016, and was divided into the following time periods for comparison:

- pre period, before the reformulation of Opana ER (P12): 2009Q1–2011Q4, which can be divided into two sections:
 - before the reformulation of OxyContin (P1): 2009Q1–2010Q2;
 - after the reformulation of OxyContin (P2): 2010Q3–2011Q4;

-
- transition period (excluded from all analyses): 2012Q1–2013Q2;
 - post period, after the reformulation of Opana ER (P3): 2013Q3–2016Q2.

Please refer to the briefing document from the Office of Surveillance and Epidemiology, Section 2.3.2.1.1 for the NAVIPPRO data source information.

3.1.1 Outcome Definition and Abuse Metrics

The study investigated changes in abuse patterns using three abuse outcome definitions:

- overall abuse—any non-medical use of a prescription opioid within the past 30 days prior to assessment;
- abuse through alternate routes—abuse via route of administration (ROA) associated with tampering, i.e. abuse via all routes combined excluding swallowed whole;
- ROA-specific abuse—abuse via injection, oral route, and snorting.

Two metrics are used to assess the changes in abuse patterns of Opana ER over time:

- Prevalence: per 100 assessments within the ASI-MV study sample;
- Tb rate: per 10,000 dosage units (tablets/pills) dispensed.

The ASI-MV assessments are obtained from adults within a network of inpatient and residential/outpatient abuse treatment centers, and criminal justice settings. During the assessment, individuals who indicate substance abuse during the past 30-day are guided to a computer screen with product names and pictures of the pharmaceutical products, where they click on the pictures of drugs they have used. An individual may report abusing multiple drugs through multiple ROA.

Dosage unit numbers are obtained from IMS Health, which covers 70% of prescription activity in the United States. These data are collected nationwide from retail outlets, mail order channels and long-term care facilities. The database produces projected total number of prescription units at various levels of aggregation, including state and 3-digit zip code for all opioid products. The IMS data is then matched to the 3-digit zip code of assessed subjects' residences. Because the assessed could come from different zip codes at different time points, the catchment area of drug utilization in NAVIPPRO may vary over time.

3.1.2 Data Analyses

Five comparator opioids were included in the study—generic resistant oxymorphone ER, oxymorphone IR, oxycodone IR single-entity (SE), morphine ER (excluding Embeda), and oxycodone ER. The primary analyses compared abuse patterns of Opana ER over time and between Opana ER and comparators with the following methods:

1. post (P3) versus pre (P12) for Opana ER—for each outcome (overall abuse, alternate route abuse, and ROA-specific abuse), and each metric of abuse (prevalence and rate). For example, the study compared the prevalence of abuse through snorting in the post period to that in the pre period for Opana ER;
2. comparisons between Opana ER and comparator opioids in the post period (P3)—for each outcome (overall abuse, alternate route abuse, and ROA-specific abuse), and each metric of abuse (prevalence and rate). For example, the study compared the overall abuse in the post period of Opana ER to that of generic oxymorphone ER.

Comparisons were estimated based on quarterly data. Generalized mixed effect models were used to estimate the differences with log-binomial regression for prevalences, and log-Poisson regression for rates. In each model, within-subject correlation was adjusted for using a compound symmetric structure in the analyses as long as the model converges. All significance is determined at a two-sided 0.05 level without adjustments for multiplicity.

Additional sensitivity analyses were conducted. First, to account for the dynamic nature of the ASI-MV system, a sensitivity analysis was conducted using data from a fixed set of sites in the ASI-MV network which contributed data in each quarter of the total study period. The goal of the fixed-site analysis was to approximate a stable population over time. Second, to account for the possible effect of reformulated oxycodone ER on Opana ER's abuse, a sensitivity pre period was defined as the 18-month period after introduction of reformulated OxyContin and before reformulation of Opana ER (July 2010 to December 2011). The abuse rate of Opana ER in the sensitivity pre period was compared to the abuse rate of reformulated Opana ER in the post period, overall and through specific ROA. Third, to account for geographic difference in opioid abuse, a sensitivity analysis stratifies the comparisons according to ASI-MV sites in Tennessee and sites excluding Tennessee.

3.1.3 Results

During the study period, there were a total of 459,240 assessments from 40 states [2, p.37], of which 206,466 assessments (from 36 states) in the pre period and 168,078 assessments (from 37 states) in the post period. Among these assessed individuals, there were 99,484 prescription

opioid abusers, of which 39,808 were assessed in the pre period and 41,317 were assessed in the post period.

Table 1: Number (percentage) of assessments in states that contributed more than 10% of ASI-MV data in the pre and the post period in NAVIPPRO study

State	Pre Period	Post Period
	N = 206,417	N = 168,078
Missouri	11,869 (5.75)	24,818 (14.77)
North Carolina	33,679 (16.31)	20,246 (12.05)
New Mexico	56,667 (27.45)	5,038 (3.00)
Oklahoma	18,815 (9.11)	22,105 (13.15)
Tennessee	4,724 (2.29)	20,294 (12.07)

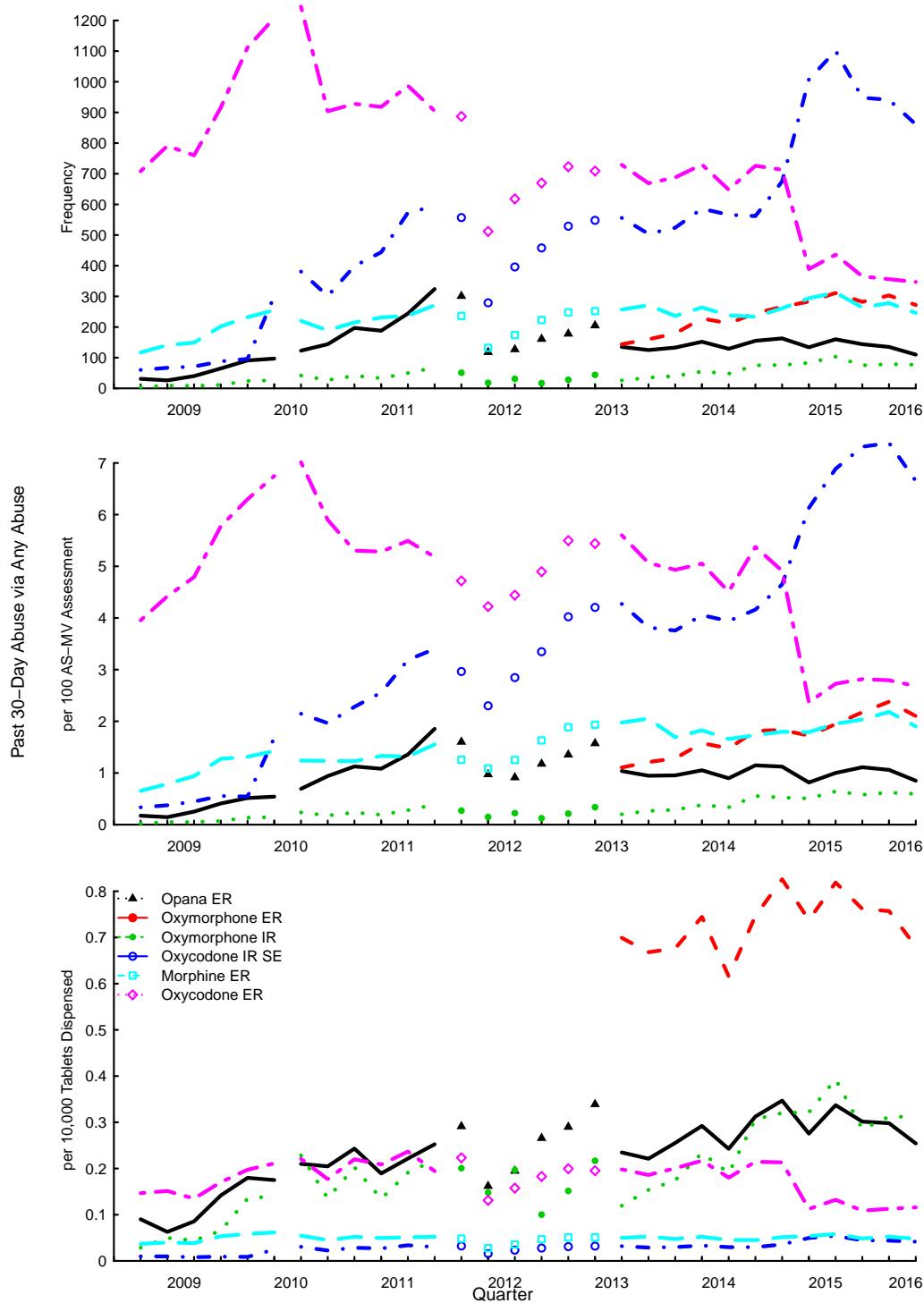
Source: Created by reviewer using the ASI-MV data submitted by the sponsor.

Table 1 showed the number of assessments in the pre and the post period for states that contributed more than 10% of the total number of assessments in either time period. Also, the number of assessment in each state varied dramatically from the pre to the post period. For example, the percentage of contribution from Tennessee increased from 2.29% in the pre period to 12.07% in the post period, while the contribution from New Mexico decreased from 27.45% to 3%.

Figures 1 to 5 showed the quarterly trend of frequencies, prevalences and rates of abuse, overall and via specific ROA, for Opana ER and comparator opioids.

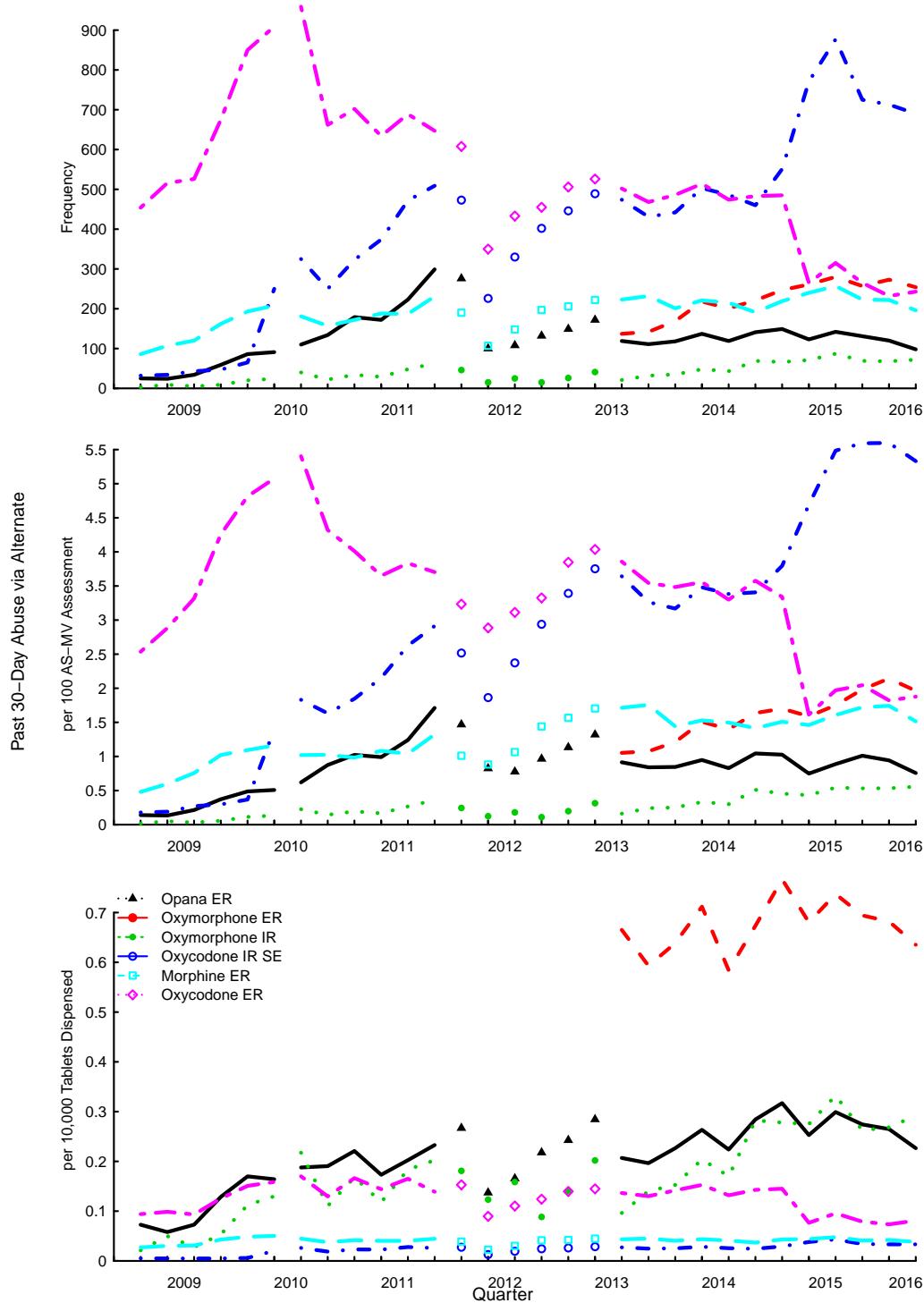
Figure 6 summarized some key findings:

- The overall abuse of reformulated Opana ER was significantly higher in the post period compared to that of original Opana ER in the pre period across both study denominators.
- While reformulated Opana ER demonstrated statistically significant reductions in abuse via snorting during the post period relative to the pre period, there was a significant increase in injection from the pre to the post period. This pattern was evident across both study denominators.



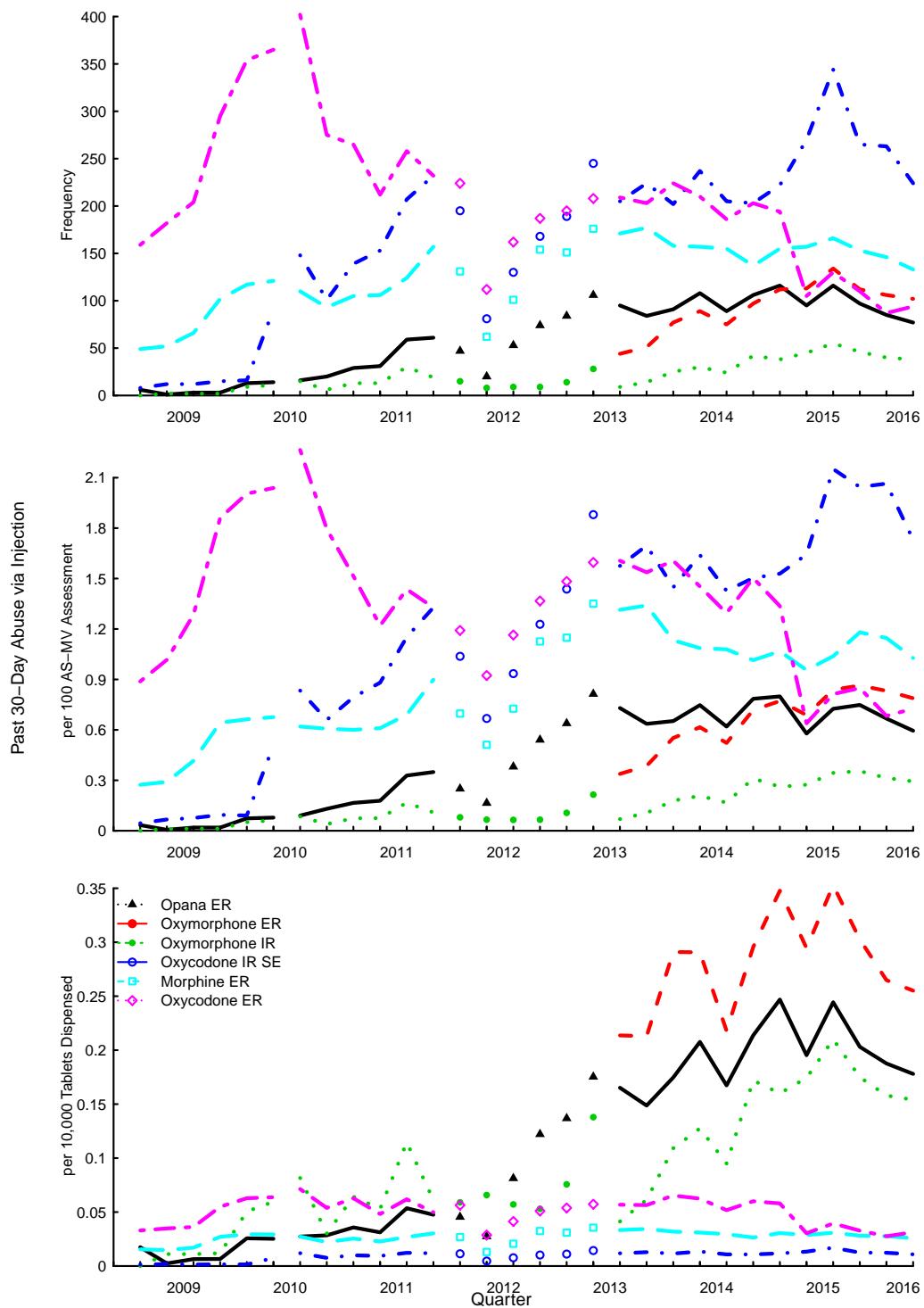
Source: Created by reviewer using ASI-MV data submitted by the sponsor.

Figure 1: Quarterly trend of frequencies and prevalence rate of overall abuse for Opana and comparator opioids in NAVIPPRO study. Trends are denoted as segments of lines in period P1, P2 and P3, and as dots in the transition period.



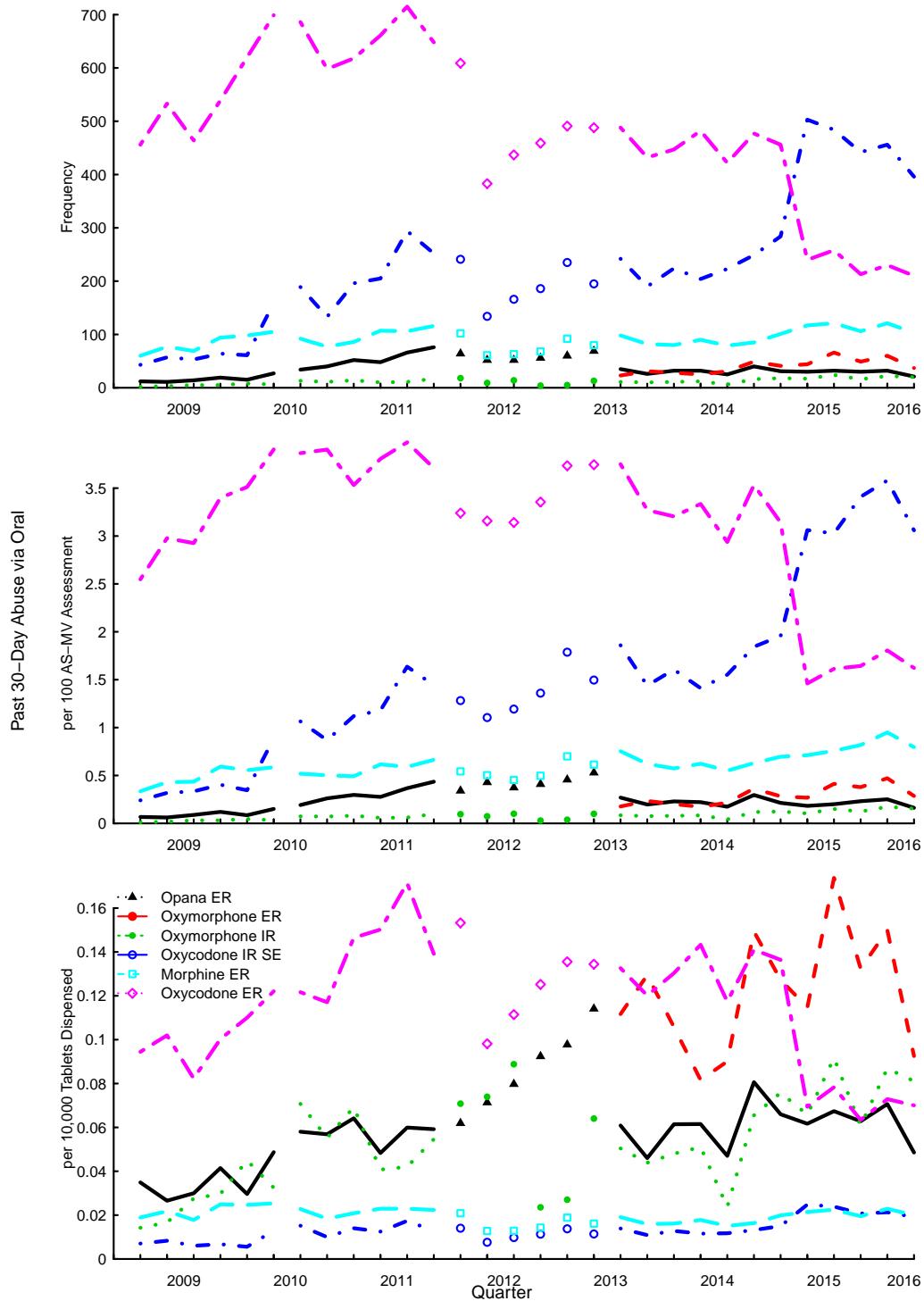
Source: Created by reviewer using ASI-MV data submitted by the sponsor.

Figure 2: Quarterly trend of frequencies and prevalence rate of abuse via alternate routes for Opana and comparator opioids in NAVIPPRO study. Trends are denoted as segments of lines in period P1, P2 and P3, and as dots in the transition period.



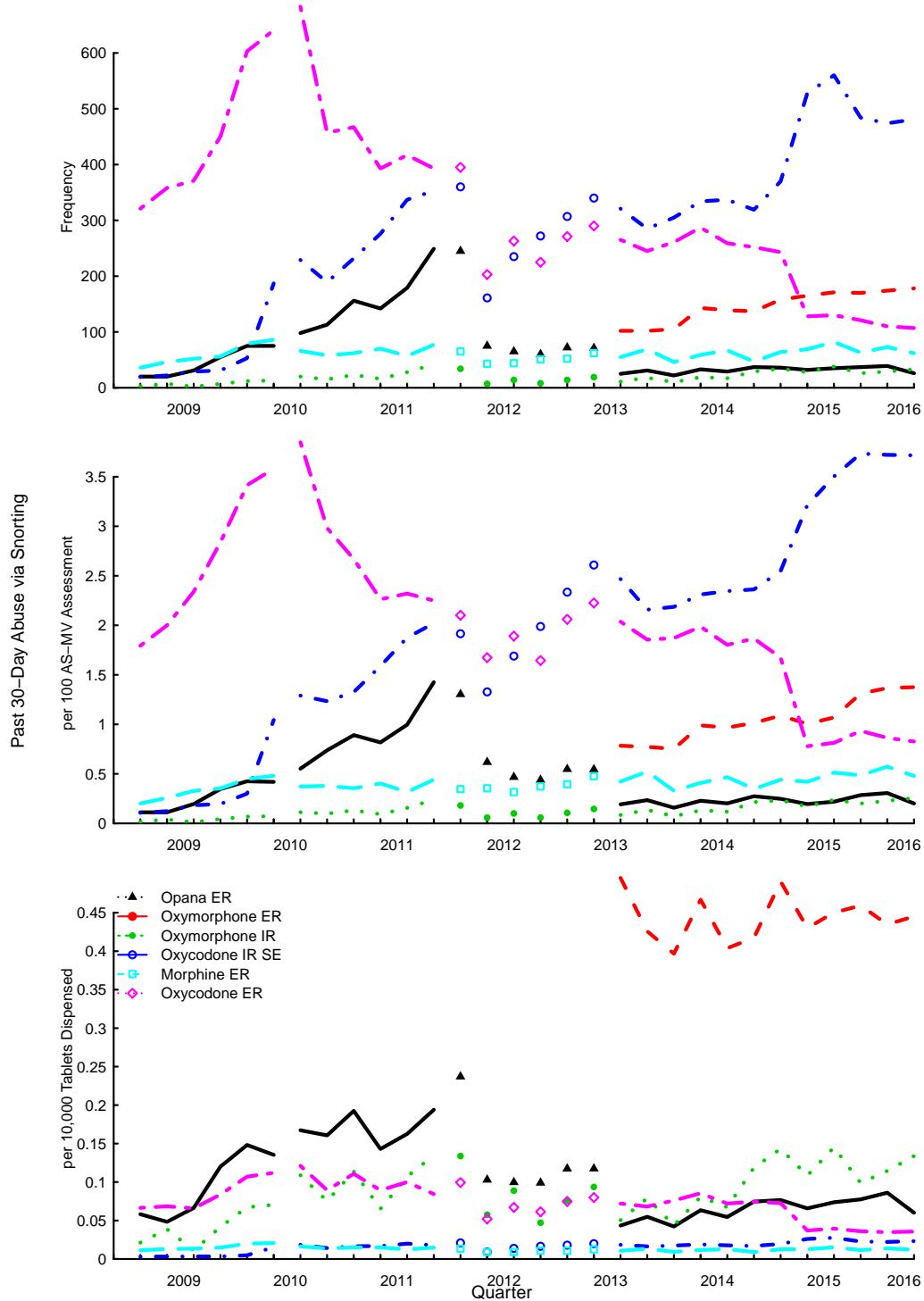
Source: Created by reviewer using ASI-MV data submitted by the sponsor.

Figure 3: Quarterly trend of frequencies and prevalence rate of abuse via injection for Opana and comparator opioids in NAVIPPRO study. Trends are denoted as segments of lines in period P1, P2 and P3, and as dots in the transition period.



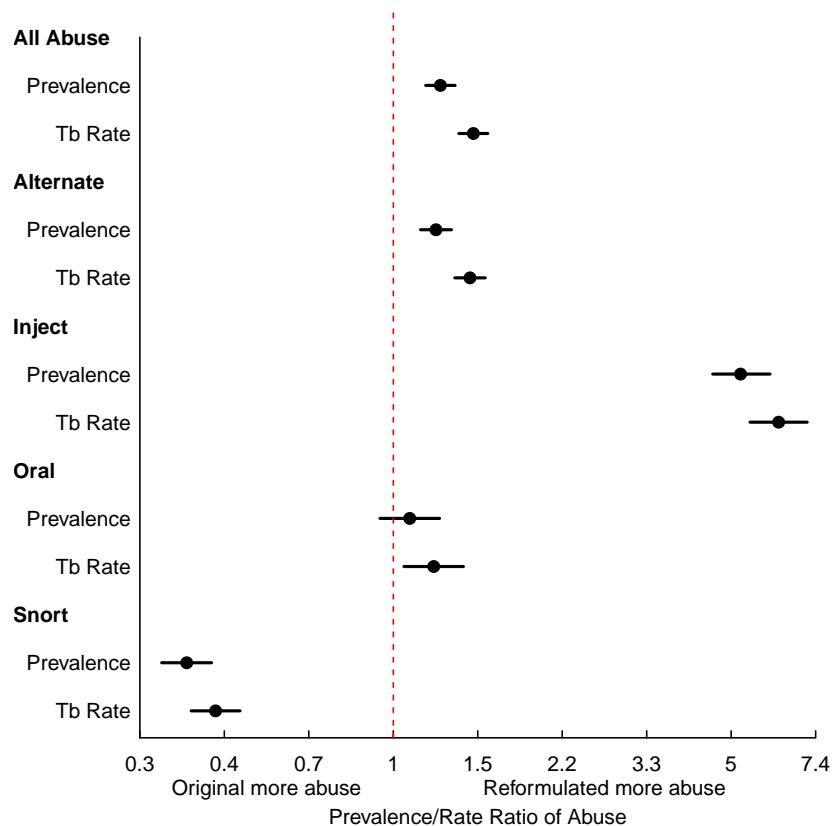
Source: Created by reviewer using ASI-MV data submitted by the sponsor.

Figure 4: Quarterly trend of frequencies and prevalence rate of abuse via oral route for Opana and comparator opioids in NAVIPPRO study. Trends are denoted as segments of lines in period P1, P2 and P3, and as dots in the transition period.



Source: Created by reviewer using ASI-MV data submitted by the sponsor.

Figure 5: Quarterly trend of frequencies and prevalence rate of abuse via snorting for Opana and comparator opioids in NAVIPPRO study. Trends are denoted as segments of lines in period P1, P2 and P3, and as dots in the transition period.



Source: Created by reviewer using results from NAVIPPRO [2, Appendix C, F].

Figure 6: Prevalence/rate ratio of past 30-day all abuse and abuse through specific ROA comparing reformulated Opana ER in the post period to Opana ER in the pre period in NAVIPPRO study using each of the two metrics: prevalence and Tb-adjusted rate.

3.2 RADARS Poison Center Study

This study used data from the Research Abuse, Diversion, and Addiction Related Surveillance (RADARS) System Poison Center Program to determine whether the intentional abuse, major medical outcomes/death, and overdoses declined following the reformulation of Opana ER. The study defined the following time periods for comparison:

- before the reformulated OxyContin and before the reformulated Opana ER (P1): 2009Q1–2010Q3;
- after the reformulated OxyContin and before the reformulated Opana ER (P2): 2010Q4–2011Q4;
- transition period (excluded from all analyses): 2012Q1–2013Q2;
- after the reformulated OxyContin and after the reformulated Opana ER (P3): 2013Q3–2016Q2.

Please refer to the briefing document from the Office of Surveillance and Epidemiology, Section 2.3.3.1.1 for the RADARS Poison Center data source information.

3.2.1 Outcome Definition and Abuse Metrics

The outcomes of interest were intentional abuse exposures, major medical outcomes/deaths, and overdose with the following definitions [1, p.10]:

- intentional abuse exposures—exposures 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;
- major medical outcomes/death—life-threatening medical outcomes or medical outcomes that resulted in significant residual disability or disfigurement;
- overdose—the total of intentional exposures, therapeutic errors and unintentional general exposures. Intentional exposures are defined as those resulting from a purposeful action, including suspected suicide, intentional misuse and abuse. Therapeutic errors are 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.

Three metrics are used to assess the changes in abuse patterns of Opana ER over time:

- prevalence: per 100,000 population, which was extrapolated from the 2000/2010 United States Census data;
- Rx rate: per 1,000 prescriptions dispensed, which was obtained from IMS Health data;
- Tb rate: per 100,000 dosing units (tablets), which was obtained from IMS Health data.

The numerators of these metrics are the sums of unique opioid product mentioned in each quarter of each year for intentional abuse exposure, major medical outcomes/deaths, and overdose. Each poison control center in RADARS system covered a distinct geographical area represented by 3-digit zip codes. U.S. Census data and IMS data are matched to RADARS data by quarter of the year and 3-digit zip codes covered by the participating poison centers.

3.2.2 Data Analyses

For each outcome, the study used quarterly data to compute the change in abuse metrics from the pre to the post period using log-Poisson regression models to adjust for population, total number of prescription, and tablets. The regression models included covariates of drug, period, and the interaction between drug and period. All significance is determined at a two-sided 0.05 level without adjustments for multiplicity. The change for each comparator opioid (oxymorphone SE IR and morphine ER) is then compared to the change for Opana ER.

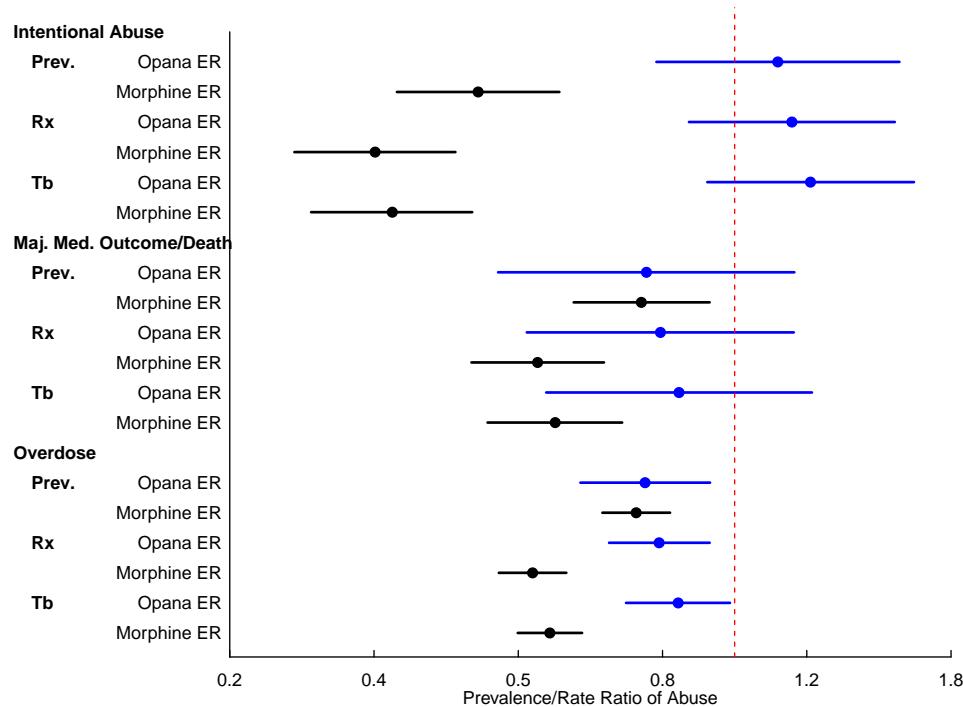
The primary analysis used data from 3-digit zip codes covered by poison centers that participated through the entire study period. A sensitivity analysis was conducted using data from all 3-digit zip codes covered by the Poison Center Program [1, p. 13].

3.2.3 Results

During the whole study period, the number of intentional abuse exposure cases was 696 for Opana ER, 784 for morphine ER, and 42 for oxymorphone IR SE (calculated by reviewer using the RADARS data submitted by the sponsor). The study results (Figure 7) show that

- The mean of intentional abuse increased in the post period compared to the pre period. The increase was not statistically significant, but was consistent across three denominators (population, prescriptions, tablets).
- The mean of major medical outcome and death decreased in the post period compared to the pre period. The decrease was not statistically significant, but was consistent across three denominators (population, prescriptions, tablets).

- The mean of overdose significantly decreased in the post period compared to the pre period. The decrease was consistent across three denominators (population, prescriptions, tablets).



Source: Created by reviewer using results from RADARS study reports [1, p. 19, 22, 25]

Figure 7: Summary of mean differences comparing the post period to the pre period by opioid group, outcome, and denominator (prevalence, Rx-adjusted and Tb-adjusted rate) in RADARS study.

4 STATISTICAL CONSIDERATIONS

In this section, we evaluate the statistical issues associated with the design and analyses of the NAVIPPRO and RADARS studies and discuss the implications of these issues on whether the regulatory questions can be answered. We categorize the main statistical concerns into four points: data quality, estimability, causality, and interpretability.

4.1 Data Quality

It is difficult for any study to make valid inferences if the data cannot reliably capture the required information. It is essential for an observational study to have valid and reliable information about outcomes and exposures of interest. It requires clear and meaningful definition of abuse and routes of abuse. It requires that the survey (ASI-MV or telephone calls) correctly records what drugs (name and class) were actually abused. For example, subjects assessed by NAVIPPRO have to identify the pills that they took, and distinguish the original Opana ER from the reformulated Opana ER among other drugs. When the data are not correctly recorded, we have misclassification. Misclassification, of either exposure (specific opioids) or outcome (abuse and ROA), can bias the results, i.e. either exaggerate or diminish the actual change in an abuse metric. The direction and magnitude of bias may be difficult to quantify. Please refer to the briefing document prepared by the Office of Surveillance and Epidemiology for additional discussion about data quality.

4.2 Estimability

4.2.1 Overview

In this section, we address the following questions:

- Can the data be used to assess the extent of overall abuse of Opana ER, in absolute or relative terms, in the underlying population?
- Can the data be used to assess whether there is a shift in abuse of Opana ER from snorting to injection, following its reformulation?

To address these questions, we first make the distinction between the population and the sample. We then define measures for overall and route-specific abuses whose values in the population we are interested in. We then raise the estimability question, a term we use to describe the phenomenon of whether the sample can be used to estimate certain quantities in the population.

4.2.2 Populations and Samples

To better understand the estimability issue, it is useful to make the distinction between the population and the sample. The population is an underlying set of individuals in the US to which inferences are to be made; for example, we are interested in learning about the prevalence or rate of abuse of Opana ER. This set could be the entire US or some subset thereof. If we could count the number of individuals who abuse opioids (and correctly identify which drugs

they abused) and the number of individuals in the underlying population, then we could compute population abuse prevalences of Opana ER and their change from the pre to the post period. Furthermore, if we could count the total number of tablets dispensed in the population, then we could also compute tablet-adjusted rates of Opana ER abuse and their change over time.

Unfortunately, we do not have access to information of either the population or a random sample of the population. All we have access to are non-random samples captured by the NAVIPPRO and RADARS surveillance systems. Because not all opioid abusers in the underlying population interact with the substance abuse treatment centers/sites in the NAVIPPRO network, and because not all opioid abuses result in calls to poison control centers, abuse data captured by these surveillance systems represent only a fraction of the opioid abusers in the underlying population. More importantly, the fraction captured by NAVIPPRO and RADARS are not random. Certain type of abusers, or abusers of certain drugs might be more or less likely to interact with the surveillance systems. Because the sample represents only a non-random fraction of the population, this raises the estimability question: can the data be used to make inferences about Opana ER abuse in the underlying population?

Note that if the data were well-defined samples, then sampling methods could be used to estimate population quantities. Unfortunately, the NAVIPPRO and RADARS surveillance systems possess neither of these characteristics; that is, the underlying sampling mechanism giving rise to these data is unknown and not random. For this reason, it is important to discuss the estimability issue. From here on, we simply refer to the surveillance sample as sample unless specified otherwise.

4.2.3 Population and Sample Quantities

We now address the question of whether the data can be used to assess the extent of overall abuse of Opana ER, in absolute or relative terms, in the underlying population. We first define population quantities whose values we would like to learn about. Refer to Appendix A for a detailed discussion about the sample and population quantities and the derivation of the assumptions.

Prevalence Define Opana ER abuse prevalence in the population as follows, with upper-case P :

- pre period

$$P_0 = \frac{\text{no. of Opana ER abusers in the population in the pre period}}{\text{no. of individuals in the population in the pre period}}$$

- post period

$$P_1 = \frac{\text{no. of Opana ER abusers in the population in the post period}}{\text{no. of individuals in the population in the post period}}$$

The corresponding prevalences in the sample are as follows, with lower-case p :

- pre period

$$p_0 = \frac{\text{no. of Opana ER abusers in the sample in the pre period}}{\text{no. of individuals in the sample in the pre period}}$$

- post period

$$p_1 = \frac{\text{no. of Opana ER abusers in the sample in the post period}}{\text{no. of individuals in the sample in the post period}}$$

For the prevalences in the sample to be useful estimates of the prevalences in the population, we need the following assumption.

Assumption 1. *Selection into the sample is independent of the substance being abused.*

In other words, an Opana ER abuser must have approximately the same chance of getting assessed by ASI-MV, or call into RADARS Poison Centers, as abusers of generic oxymorphone ER or any other drug, or any non-abuser.

Rates We define similar population and sample quantities for the utilization-adjusted abuse rates. For convenience of illustration, utilization-adjusted abuse rates are defined using the number of prescriptions as the denominator. For tablet-adjusted abuse rates, the denominator is replaced with the number of tablets. Points raised in the context of prescription-adjusted rates also apply to tablet-adjusted rates. Similar to the prevalence part above, we use upper-case R to denote population rates and lower-case r to denote sample rates for Opana ER.

- population pre period

$$R_0 = \frac{\text{no. of Opana ER abusers in the population in the pre period}}{\text{no. of Opana ER Rx in the population in the pre period}}$$

- population post period

$$R_1 = \frac{\text{no. of Opana ER abusers in the population in the post period}}{\text{no. of Opana ER Rx in the population in the post period}}$$

- sample pre period

$$r_0 = \frac{\text{no. of Opana ER abusers in the sample in the pre period}}{\text{no. of Opana ER Rx in the population in the pre period}}$$

- sample post period

$$r_1 = \frac{\text{no. of Opana ER abusers in the sample in the post period}}{\text{no. of Opana ER Rx in the population in the post period}}$$

Note that the number of prescriptions in the population is used as the denominator for both population and sample rates. The reasons of using the population prescription numbers in the sample rates are:

- first, the prescription numbers for the specific sample were not collected,
- second, the population prescription number represents some sort of availability of the opioid in the underlying population.

Because only a small fraction of Opana ER abusers in the population are captured in the sample, the sample abuse rates can never estimate the population abuse rates, but will be useful when estimating population ratios.

4.2.4 Post-Pre Comparison

Although the sample abuse prevalences and rates do not necessarily estimate the corresponding population quantities, an important question for FDA to consider is whether we can at least estimate the change in the population abuse prevalences and rates using the change in the sample abuse prevalences and rates, respectively.

For the outcome metrics defined above, we define change from the pre to the post period as follows:

- population,
 - relative prevalence $RP = P_1/P_0$;
 - relative rate $RR = R_1/R_0$;
- sample,
 - relative prevalence $rp = p_1/p_0$;
 - relative rate $rr = r_1/r_0$.

For the relative sample quantities to estimate the relative population quantities, we require either Assumption 1 or the following assumption:

Assumption 2. *If selection into the sample depends on the substances being abused, then the nature of the dependence does not change over time.*

4.2.5 Ratio-Ratio Comparison

When selection into the sample depends on the substances being abused and when this dependence varies over time, the post-versus-pre period change observed in the sample is not a valid estimate of the corresponding change in the underlying population. In this case, an important question to consider is whether we can estimate the relative change in the population abuse prevalences/rates from the pre to post periods between Opana ER and some comparator opioid using the relative change in the sample abuse prevalence/rates?

This comparison might be useful in the following sense. If abuse of Opana ER increased but the increase is substantially less than the increase observed in the comparator, then under certain conditions, it could suggest a positive public health impact due to the reformulation. Such a comparison can be accomplished by taking the ratio of two ratios, referred to here as the ratio-ratio comparison. Formally,

- population
 - ratio-ratio of prevalences between comparator d and Opana ER: $RRP_d = RP_d/RP_{Op}$
 - ratio-ratio of rates between comparator d and Opana ER: $RRR_d = RR_d/RR_{Op}$
- sample
 - ratio-ratio of prevalences between comparator d and Opana ER: $rrp_d = rp_d/rp_{Op}$
 - ratio-ratio of rates between comparator d and Opana ER: $rrr_d = rr_d/rr_{Op}$

For the sample ratio-ratio comparisons to be useful for the population, we need either Assumption 1 or Assumption 2. If neither of these conditions hold, then the sample ratio-ratio comparison is still valid under the following assumption:

Assumption 3. *If selection into the sample depends on the substances being abused, and the nature of the dependence changes over time, then the change in the dependence is the same for Opana ER and the comparator opioid.*

4.2.6 ROA Proportion Comparison

The second question from FDA is whether the data show a shift of Opana abuse from snorting to injection. If the sample is to be used to address this question of shift in ROA in the underlying population, it is important to understand how the sampling probability is related to the specific ROA. Similar to what was discussed in the previous sections, one of the following assumptions has to hold for the ROA change in the sample to reflect relevant ROA change in the underlying population:

1. Selection into the sample is independent of the ROA;
2. If selection into the sample depends on the ROA, then the nature of the dependence does not change over time.

For ratio-ratio comparison, we need a third assumption if the above two assumptions do not hold:

- 3 If selection into the sample depends on the ROA and the nature of the dependence changes over time, then the change in the dependence is the same for Opana ER and the comparator opioid.

Even if the above three assumptions are satisfied, we still cannot use the data to make inference for the second question. For the data to show a shift of Opana abuse from snorting to injection, one of the following three situations should be observed regarding Opana abuse:

- a The overall abuse was constant, the abuse through injection increased and the abuse through snorting decreased from the pre to the post period;
- b The overall abuse increased, the abuse through injection increased more than the abuse through snorting did from the pre to the post period;
- c The overall abuse decreased, the abuse through injection decreased less than the abuse through snorting did from the pre to the post period.

Note that the same metric of abuse (prevalence or rate) should be used when evaluating these situations.

4.2.7 Sample Plausibility

In the above sections, we discussed conditions under which the data could provide valid estimates of the underlying population quantities. Now, we discuss possible scenarios in the NAVIPPRO and RADARS samples that may violate these conditions.

Assumption 1: Selection into the sample is independent of the substance being abused.

If individuals who abuse Opana ER tend to interact more with substance abuse treatment centers or poison control centers relative to individuals who abuse comparator opioids, Assumption 1 does not hold, and the sample abuse prevalences do not necessarily estimate the population abuse prevalences.

Assumption 2: If selection into the sample depends on the substances being abused, then the nature of the dependence does not change over time.

One violation of Assumption 2 could be that policies changed over time, encouraging or discouraging people to be assessed by the NAVIPPRO system in the post period, which is possible in some states given the dramatic change in the number of assessments from the pre to the post period (Table 1). Another example would be that in the NAVIPPRO system, sites were added or dropped from the surveillance system in the post period in areas with more or less Opana ER abuse. In RADARS Poison Center data, it has been suggested that there is a decline in total exposure call volume and that the decline has been apparent from mid-2007 to 2013 [4, p.32]. This decline essentially refers to the change in the sampling fraction. However, it is unclear how the decline in sampling fraction differs among opioid classes.

Assumption 3: If selection into the sample depends on the substances being abused, and the nature of the dependence changes over time, then the change in the dependence is the same for Opana ER and the comparator opioid.

In the NAVIPPRO system, the number of assessments in some states changed dramatically from the pre to the post period (Table 1). If abuse prevalences of different opioids vary among these states, then the change in the state-level sampling fraction is likely to result in a change in the overall sampling fraction. As a result, this overall change is likely to be different across opioids. Therefore, Assumption 3 does not hold for the sample.

4.3 Causality

4.3.1 Overview

In Section 4.2, we identified the conditions under which the data can be used to make statements about the population. In this section, we suppose that those conditions are met, and that the population quantities are estimable using the sample. We ask the question of causality—if we observe a change in Opana ER abuse from the pre to the post period, can we attribute the change to the reformulation?

To evaluate the above question, we must consider secular trends—the external forces, other than the reformulation, that may explain the observed change in abuse. During the study period, many factors may affect the abuse pattern of Opana ER in the community. For example,

- DEA efforts to reduce opioid abuse;
- state and local law enforcement efforts to reduce opioid abuse;

- state and local education efforts;
- FDA efforts such as risk evaluation and mitigation systems;
- social trends such as availability and cost of substitutable drugs.

Given that these external factors may influence abuse patterns of Opana ER over time, how do we disentangle the effect due to the reformulation from the effects due to these external forces?

Comparing the abuse rate changes of Opana ER to those of comparators has the potential to overcome this problem. However, the use of comparators alone is not sufficient for making causal statements. In addition, we require that the opioids being compared are similar to each other, in some sense. In clinical trials, similarity between groups is achieved by randomization. A well-designed observational study lacks randomization but contains features that provide a reasonable basis for making causal statements:

- study is conducted at patient level;
- each cohort is well-defined and similar at baseline;
- the cohorts are followed over time and the outcomes of interest are recorded;
- confounding is reasonably controlled.

However, the two formal studies in this submission do not have these features. Of note is the lack of fixed cohorts in the pre period, which should be defined by collections of individuals exposed to specific classes of opioids that can be followed over time. The lack of cohorts lead to the lack of fixed catchment area for the drug utilization data. Because drug utilization data was matched to the study data based on 3-digit zip code, neither study captures the total number of prescriptions or tablets dispensed in the US. In the NAVIPPRO study, the IMS data is matched to the assessed subject's residence zip code. As assessed subjects come from different zip codes at different time points, the catchment area of drug utilization in NAVIPPRO may vary over time. In the RADARS study, the IMS data is matched to the 3-digit zip codes covered by the participating poison centers. Therefore, the catchment area in RADARS drug utilization data may not reflect the geographic area of those who called into the Poison Control Center. These limitations make it very difficult to assess whether the opioids being compared are similar.

Ideally, similarity should exist in both the pre and the post period. In Section 4.3.2 we discuss some reasonable metrics for assessing similarity in the pre period and examine whether the data enable us to conclude similarity between opioids based on these metrics. In Section 4.3.3, we define what we mean by similarity in the post period and discuss the possible ways that similarity in the post period can be broken, even if we have similarity in the pre period.

4.3.2 Similarity in Pre Period

Ideally, Opana ER and comparators should be similar in the pre period for assessment of abuse change due to reformulation. But for NAVIPPRO and RADARS, it is impossible to assess similarity by comparing risk factor distributions between cohorts of comparators, because there is no well-defined cohort in these studies. However, it might be reasonable to assess similarity between the classes of opioids in the following manner:

- compare abuse rates;
- compare abuse rate trends;
- compare abuse through specific ROA.

These comparisons may help us understand the magnitude and trend of abuse rates for each opioid in the pre period, and provide a basis for concluding whether two opioids are similar.

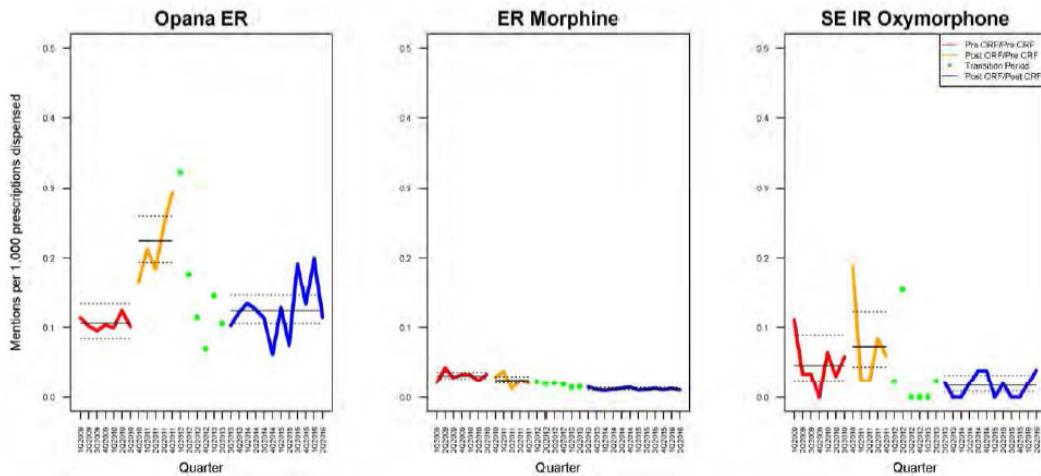
Figure 1 shows the rate of overall abuse for each opioid over time in the NAVIPPRO study. We focus on the pre period in this section. Note the variation in the magnitude of the rates of abuse per 10,000 tablets during the pre period (2009Q1–2011Q4). For overall abuse, Tb rates showed that both Opana ER and oxymorphone IR were highly abused and had similar trends. Morphine ER and oxycodone IR SE shared similar trends and had lower abuse rates. For abuse through alternate routes, oral and snorting (Figure 2, 4 and 5), again, Opana ER and oxymorphone IR were similarly highly abused, and morphine ER and oxycodone IR SE were similarly less abused. Figure 3 shows that the injection rate was higher for oxymorphone IR, and lower for other opioids during the period.

Figure 8 shows the prescription-adjusted rate of intentional abuse for each opioid over time in RADARS study. Note the abuse rate increase from P1 to P2 for Opana ER, which is absent for morphine ER and oxymorphone IR SE.

Based on these figures, it is not clear which drug is similar to Opana ER in terms of magnitudes and trends of abuse rates in the pre period.

4.3.3 Similarity in Post Period

The evolving nature of external factors on the opioid market adds to the challenge. Law enforcement may be under greater pressure to control the abuse epidemic and efforts to contain the problem may intensify. Availability of heroin, for example, may provide an avenue for prescription opioid abusers to switch in the presence of law enforcement restrictions. These evolving external factors may have different effects on each of the opioids causing different trajectories of abuse rates in the post period. Because of the potential for differential effects of these external



Source: Figure 4.1.1.2 in RADARS Poison Center study report [1, p. 21]

Figure 8: Intentional abuse exposure rate per 1,000 prescriptions dispensed in RADARS study

factors on opioid abuse rates, even if we have comparability at baseline, it is very difficult to disentangle the effects of reformulation (if any) from those due to external factors.

4.4 Interpretability

4.4.1 Overview

The purpose of this section is to make a salient point that whether we are looking at Opana ER's pre to post period changes or comparing Opana ER's changes with those of comparator opioids, these quantities must be interpreted within the context of data quality, estimability and causality. In other words, if there were issues with data quality, estimability or causality, do we have a sense of how much is reflected in the observed quantities? In the following sections, we present results of primary analyses from the NAVIPPRO and RADARS studies. We then connect the estimates of abuse rate changes with the issues of data quality, estimability and causality.

Table 2 and 3 summarize the results shown in the submitted study reports of NAVIPPRO and RADARS. Abuse prevalence/rate changes comparing post to the pre period are shown in Table 2 for Opana ER, and in Table 3 for comparator opioids.

4.4.2 Interpretation of NAVIPPRO Results

Note that the magnitude and direction of change in abuse metrics varies depending on the outcome. Consider, for example, the tablet-adjusted rate (Tb rate). Table 2 shows that, in the post period, the Opana ER's Tb rate increased 46.1% for overall abuse, increased 520.1% for abuse

Table 2: Changes in Opana ER abuse prevalences and rates comparing the post to the pre period in NAVIPPRO and RADARS studies

Route	Prevalence*		Tb Rate	Rx Rate
	% Change (95% CI)	% Change (95% CI)	% Change (95% CI)	% Change (95% CI)
NAVIPPRO[†]				
Overall	25.0 (16.6, 34.0)	46.1 (36.4, 56.5)		NA
Alternate	22.4 (13.8, 31.7)	43.8 (33.8, 54.6)		NA
Injection	417.9 (353.9, 495.4)	520.1 (441.6, 610.0)		NA
Oral	8.1 (-6.1, 24.5)	21.1 (5.2, 39.4)		NA
Snorting	-62.4 (-66.6, -57.7)	-56.9 (-61.6, -51.6)		NA
RADARS[‡]				
Intentional	12.7 (-19.5, 57.9)	23.4 (-7.3, 64.4)	17.2 (-11.9, 55.9)	

Source: Created by reviewer using results from NAVIPPRO [2, Appendix C, F] and RADARS study reports [1, p. 19, 22, 25].

* Prevalence uses number of ASI-MV assessments in NAVIPPRO, and projected U.S. population in RADARS.

[†] Percent change comparing P3 to P12 in the NAVIPPRO study.

[‡] Percent change comparing P3 to P1 in the RADARS study.

through injection, and decreased 56.9% for abuse through snorting. Given our previous discussions about data quality, estimability and causality, it is important to keep in mind that these observed changes are confounded by the effects of misclassification, the underlying sampling process, and the secular trends. How much of the change is due to each of these components is unknown.

As discussed in Section 4.3, one possible approach for addressing secular trends is to compare Opana ER to other opioid classes. Suppose we wanted to compare Opana ER to oxycodone ER. Table 3 shows that from the pre to the post period, the Tb rate for oxycodone ER decreased 11% for overall abuse, decreased 9% for injection, and decreased 35.4% for snorting. If we assume that there are no issues related to data quality and estimability, then these numbers suggest that Opana ER's Tb-rate increases are substantially larger than those of oxycodone ER, regarding overall abuse, abuse through injection and snorting.

Note however that such between-opioid comparison is hard to interpret unless the opioids being compared are similar in the sense that we have described (Sections 4.3.2 and 4.3.3) in both the pre period and the way they are affected by external factors over time.

In the case of oxycodone ER (or any comparator in NAVIPPRO), it is difficult to determine whether these could be viewed as reasonable comparators. Furthermore, if they could be viewed as reasonable comparators, an additional complication is introduced by the fact that the change

Table 3: Changes in comparator opioids abuse prevalences/rates comparing post to the pre period in NAVIPPRO and RADARS studies

Route	Prevalence*		Tb Rate	Rx Rate
	% Change (95% CI)	% Change (95% CI)	% Change (95% CI)	
NAVIPPRO[†] Oxymorphone IR				
Overall	172.2 (139.5, 209.4)	87.4 (65.0, 112.8)		NA
Alternate	168.2 (134.1, 207.3)	85.3 (61.9, 112.0)		NA
Injection	296.5 (223.0, 386.8)	117.1 (126.3, 239.2)		NA
Oral	117.0 (70.6, 176.0)	45.1 (14.1, 84.4)		NA
Snorting	89.9 (58.1, 128.2)	29.3 (7.7, 55.3)		NA
NAVIPPRO Oxycodone IR SE				
Overall	206.8 (195.0, 219.1)	67.0 (60.5, 73.8)		NA
Alternate	205.0 (191.9, 218.7)	66.9 (59.7, 74.4)		NA
Injection	194.5 (174.8, 215.7)	61.2 (50.5, 72.7)		NA
Oral	176.1 (160.9, 192.3)	45.8 (37.7, 54.3)		NA
Snorting	190.0 (175.2, 205.7)	56.5 (48.5, 64.9)		NA
NAVIPPRO Morphine ER				
Overall	53.6 (45.6, 62.1)	1.1 (-4.1, 6.6)		NA
Alternate	57.9 (48.8, 67.6)	4.5 (-1.4, 10.7)		NA
Injection	83.1 (69.9, 97.3)	22.3 (13.7, 31.5)		NA
Oral	34.6 (23.8, 46.2)	-14.2 (-21.0, -6.9)		NA
Snorting	23.9 (11.8, 37.4)	-20.0 (-27.7, -11.5)		NA
NAVIPPRO Oxycodone ER				
Overall	-26.9 (-29.0, -24.7)	-11.0 (-13.6, -8.3)		NA
Alternate	-30.2 (-32.6, -27.6)	-14.2 (-17.2, -11.1)		NA
Injection	-26.4 (-30.6, -22.0)	-9.0 (-14.0, -3.7)		NA
Oral	-25.0 (-27.8, -22.2)	-10.3 (-13.6, -6.8)		NA
Snorting	-46.9 (-49.4, -44.3)	-35.4 (-38.4, -32.2)		NA
RADARS[‡] Oxymorphone IR SE				
Intentional	-44.8 (-77.0, 32.5)	-64.0 (-85.7,-9.5)	-64.2 (-85.7,-10.2)	
RADARS Morphine ER				
Intentional	-50.9 (-60.8,-38.5)	-61.3 (-69.1,-51.7)	-63.1 (-70.5,-53.9)	

Source: Created by reviewer using results from submitted NAVIPPRO [2, Appendix C, F] and RADARS study reports [1, p. 19, 22, 25].

* Prevalence uses number of ASI-MV assessments in NAVIPPRO, and projected U.S. population in RADARS.

[†] Percent change comparing P3 to P12 in NAVIPPRO study.

[‡] Percent change comparing P3 to P1 in RADARS study.

in abuse metrics for these comparator opioids vary dramatically. For example, Tb-adjusted abuse rates for morphine ER show decreases in the oral and snorting outcomes while the prevalences show increases.

Given the similarity requirement, generic oxymorphone ER might be a good comparator, since it is bioequivalent to Opana ER. In this sense, generic oxymorphone ER could be considered as a counterfactual version of Opana ER, which might represent the abuse pattern of Opana ER if the reformulation had not occurred. An appropriate analysis would be contrasting the post-versus-pre prevalence/rate ratios of Opana ER to those of generic oxymorphone ER. However, the generic oxymorphone ER does not exist in the pre period. It could be argued that the pre period data for Opana ER could be viewed as a surrogate for generic oxymorphone in the pre period. For such a comparison to be appropriate, the following assumption must hold besides the assumptions we mentioned in Section 4.2.

Assumption 4. *The abuse pattern of generic oxymorphone ER in the pre period, if it existed, should have been exactly or approximately the same as the abuse pattern of Opana ER in the pre period.*

Assume that we have a good comparator. It is important to use statistical methods that can disentangle the effect of Opana ER’s reformulation from the effect of external factors. The ratio-ratio comparison might be helpful if external factors affects the abuse pattern of all comparators similarly over time. However, Figure 1 indicates an increase in the abuse of Opana ER and oxymorphone IR from P1 to P2 in NAVIPPRO, which is not observed for other comparators. It is possible that this increase in Opana ER’s abuse from P1 to P2 is associated with the reformulation of OxyContin. To avoid this possible confounding, we use the time period before OxyContin reformulation as the pre period in the following analyses. Recall that ratio-ratio comparison contrasts two ratios:

- the ratio of post versus pre abuse prevalence/rates for a comparator d , rr_d or rpd ;
- the ratio of post versus pre abuse prevalence/rates for Opana ER, rr_{Op} or rpo_p .

Table 4 and 5 show the ratio-ratio comparison results for overall abuse and abuse through specific routes, respectively. The value “% C_{ratio}” represents the change in abuse that might be attributed to Opana ER’s reformulation, assuming that there is no data quality, estimability and causality issues. The column “% C_{ratio}” is positive if Opana ER’s abuse pattern improved during the post period, which means one of the following three situations:

1. abuse for both Opana ER and the comparator opioid increased in the post period, and the increase was smaller for Opana ER compared to the other opioid;

-
2. abuse increased for the comparator opioid, and decreased for Opana ER in the post period;
 3. abuse for both Opana ER and the comparator opioid decreased in the post period, and the decrease in Opana ER was larger.

Negative “% C_{ratio}” implies that Opana ER abuse pattern worsened in the post period, which means one of the following three situations:

1. abuse for both Opana ER and the comparator opioid increased in the post period, and the increase was larger for Opana ER compared to the other opioid;
2. abuse decreased for the comparator opioid, and increased for Opana ER in the post period;
3. abuse for both Opana ER and the comparator opioid decreased in the post period, and the decrease in Opana ER was smaller.

Note that because generic oxymorphone ER does not exist in the pre period, the abuse pattern of Opana ER in the pre period is used as a surrogate for generic oxymorphone ER, the validity of which depends on the assumption that the abuse pattern of generic oxymorphone ER in the pre period, if it existed, was exactly the same as the abuse pattern of Opana ER in the pre period. However, there is no way for us to verify this assumption.

The overall abuse for Opana ER seems to have improved over time compared to oxycodone IR SE, oxymorphone IR and generic oxymorphone ER, and worsened over time compared to morphine ER and oxycodone ER. To be specific, for prevalence and tablet-adjusted rate respectively, generic oxymorphone ER’s overall abuse was worse than Opana ER by 72% and 162%, while morphine ER’s overall abuse rate was better than Opana ER by 38% and 53% (Table 4). The pattern of abuse through injection became worse for Opana ER in the post period compared to other opioids. For prevalence and tablet-adjusted rate respectively, morphine ER’s injection rate was better than Opana ER by 87% and 90% (Table 5).

4.4.3 Interpretation of RADARS Results

Table 6 shows counts during each time period of each comparator opioid when each opioid was mentioned in a telephone call to a Poison Control Center as having been intentionally abused. The low counts for oxymorphone IR SE raise concerns about data quality, and sampling probabilities for comparator opioid and how comparable they are to Opana ER. Even if the data quality and sampling issues were trivial, the low counts of oxymorphone IR SE result in estimates with high variances; in other words, the estimates are unstable. Add on to the unstable estimates is the issue of causality, which makes it extremely difficult to interpret the result of

Table 4: Ratio-ratio comparison of comparator opioids' P3-versus-P1 ratio relative to that of Opana ER for overall abuse in NAVIPPRO study

Comparator	% C _{ratio} [‡]	95% CI
Morphine ER		
Prevalence	-38.2	(-45.9, -29.4)
Tb Rate	-52.7	(-58.7, -46)
Oxycodone IR SE		
Prevalence	172.2	(137.3, 212.3)
Tb Rate	39.6	(21.5, 60.4)
Oxycodone ER		
Prevalence	-72.8	(-75.9, -69.4)
Tb Rate	-54.9	(-60, -49.1)
Oxymorphone IR		
Prevalence	103.5	(57.7, 162.7)
Tb Rate	52.0	(17.7, 96.1)
Generic Oxymorphone ER [†]		
Prevalence	71.6	(61.3, 82.6)
Tb Rate	162.1	(146.8, 178.4)

Source: Created by reviewer using ASI-MV data submitted by the sponsor.

[†] Using Opana ER pre period abuse pattern as a surrogate for the abuse pattern of generic oxymorphone ER in the pre period

[‡] Percent change of comparators's P3-versus-P1 ratio compared to that of Opana ER.

Table 5: Ratio-ratio comparison of comparator opioids' P3-versus-P1 ratio relative to that of Opana ER for abuse through specific routes in NAVIPPRO study

Comparator	Alternate Routes			Injection			Oral Route			Snorting		
	% C _{ratio} [‡]	95% CI	% C _{ratio} [‡]	95% CI	% C _{ratio} [‡]	95% CI						
Morphine ER												
Prevalence	-34.1	(-42.8, -24.0)	-86.9	(-90.5, -81.8)	-36.1	(-50.0, -18.4)	59.3	(30.2, 94.8)				
Tb Rate	-49.9	(-56.6, -42.2)	-90.0	(-92.8, -86.1)	-50.5	(-61.3, -36.7)	20.9	(-1, 47.6)				
Oxycodone IR SE												
Prevalence	223.0	(177.9, 275.4)	-34.1	(-53.5, -6.70)	137.4	(86.2, 202.6)	909.7	(735.7, 1120.0)				
Tb Rate	65.3	(41.9, 92.6)	-66.8	(-76.7, -52.7)	23.4	(-3.3, 57.5)	425.3	(334.5, 535.1)				
Oxycodone ER												
Prevalence	-73.1	(-76.3, -69.5)	-95.4	(-96.6, -93.7)	-64.0	(-71.3, -54.9)	-34.5	(-44.4, -22.7)				
Tb Rate	-55.6	(-60.9, -49.5)	-92.4	(-94.5, -89.6)	-38.5	(-51.0, -22.8)	10.7	(-6.1, 30.4)				
Oxymorphone IR												
Prevalence	113.2	(62.2, 180.4)	-43.8	(-66, -7.1)	71.5	(9.5, 168.7)	391.8	(245.2, 600.6)				
Tb Rate	59.0	(20.9, 109.1)	-58.4	(-74.9, -30.9)	30.5	(-16.8, 104.8)	270.4	(160.3, 427.0)				
Generic Oxymorphone ER[†]												
Prevalence	75.6	(64.5, 87.4)	-4.1	(-11.9, 4.4)	32.4	(15.5, 51.7)	347.4	(299.4, 401.2)				
Tb Rate	168.4	(152, 186)	46.0	(34.5, 58.5)	101.3	(75.7, 130.5)	594.8	(522.0, 676.1)				

Source: Created by reviewer using ASI-MV data submitted by the sponsor.

[†] Using Opana ER pre period abuse pattern as a surrogate for the abuse pattern of generic oxymorphone ER in the pre period

[‡] Percent change of comparator's P3-versus-P1 ratio compared to that of Opana ER.

such comparison. Therefore, we only compare Opana ER to morphine ER in the following discussion.

Table 6: Counts of outcomes in RADARS study by period for each opioid comparator

Count	Opana ER	Morphine ER	Oxymorphone IR SE
Intentional abuse			
P1	93	247	10
P2	243	161	16
Transition	170	156	6
P3	190	220	10
Major Medical Outcome and Death			
P1	43	185	1
P2	77	134	5
Transition	58	145	2
P3	61	259	3
Overdose			
P1	444	2354	42
P2	623	1717	45
Transition	500	1884	35
P3	628	3248	52

Source: Created by reviewer using RADARS data submitted by the sponsor.

It is important to emphasize that for a comparison to be appropriate, two comparators have to share some similarity in the pre period and the post period. The similarity assures that external factors impact the two comparators in the same manner, and hence, the difference between the changes from the pre to the post period of two comparators can be ascribed to the reformulation of Opana ER. Figure 8 shows that the trajectory of Rx-adjusted abuse rate of Opana ER is similar to morphine ER in P1 (before OxyContin reformulation) and P3 (after Opana ER reformulation), and different in P2. During P2, the Rx rate of Opana ER increased rapidly over time and is much higher than the rate in P1, while the rate for morphine ER is comparatively stable over time following the same trend as in P1. Therefore, it is reasonable to use P1 as the pre period and P3 as the post period for the comparison.

Table 7 shows the result of post-versus-pre comparison and ratio-ratio comparison for intentional abuse. Column “% Change” is the percent change of abuse prevalences/rates comparing P3 to P1. As it shows, the abuse of Opana ER increased by 12.7% to 23.4%, while morphine ER’s abuse decreased over time by 50.9% to 64.2%. Column “% C_{ratio}” is the percent change of

morphine ER's post-pre ratio compared to that of Opana ER, which reflects the abuse change that could be attributed to the reformulation of Opana ER if there were no issues about data quality, estimability and causality. These results imply that, using morphine ER as a comparator, the reformulation of Opana ER increased the intentional abuse by 56.4% in prevalence, 68.5% in Rx-adjusted rate, and 68.7% in Tb-adjusted rate.

Table 7: Comparisons of intentional abuse prevalences/rates of Opana ER and morphine ER in RADARS study

	% Change [†]	95% CI	% C _{ratio} [‡]	95%CI
Prevalence				
Opana ER	12.7%	(-20.1%, 59.0%)	--	--
Morphine ER	-50.9%	(-60.9%, -38.2%)	-56.4%	(-71.2%, -34.1%)
Rx Rate				
Opana ER	17.2%	(-12.4%, 56.7%)	--	--
Morphine	-63.1%	(-70.7%, -53.7%)	-68.5%	(-78.3%, -54.5%)
Tb Rate				
Opana ER	23.4%	(-7.9%, 65.4%)	--	--
Morphine	-61.3%	(-69.2%, -51.4%)	-68.7%	(-78.4%, -54.6%)

Source: Created by reviewer using RADARS data submitted by the sponsor.

[†] Percent change comparing abuse prevalences/rates in P3 to those in P1.

[‡] Percent change of morphine ER's P3-versus-P1 ratio compared to that of Opana ER.

We are not able to compare the ROA-specific abuse and make inference about the shift of abuse from snorting to injection using RADARS data because the intentional abuse counts are small, which means that the counts of abuse through specific ROA will be even smaller. The small counts will result in estimates with large variation, which is more vulnerable to any confounding caused by data quality and estimability issues. Any slight amount of misclassification or any small change in sampling fraction over time might cause the data to show opposite results in comparing the abuse rates.

5 SUMMARY

The NAVIPPRO study showed that the abuse rates for Opana ER increased during the post period for all abuse routes except for abuse through snorting. The increase is consistent across two metrics (prevalence and Tb-adjusted rate). The rate for abuse through snorting decreased for Opana ER, and the decrease was consistent across two metrics. In order to separate the effects

of reformulation apart from the effects of secular trends, Opana ER's abuse rate changes are compared to several comparator opioids' abuse rate changes, which is the ratio-ratio comparison we discussed in Section 4.2.5. For abuse through injection, the magnitude of increase in the abuse rate of Opana ER is consistently larger than all comparators across two metrics. For abuse through snorting, the magnitude of decrease in the abuse rate of Opana ER is consistently larger than all comparators across two metrics. For overall abuse, abuse through alternate routes and oral route, the increase of abuse rates of Opana ER is not larger than comparators. However, the relationship is not consistent across the two metrics (prevalence and Tb-adjusted rate).

The RADARS study showed that the intentional abuse rate increased for Opana ER, while decreased for comparators in the post period.

While addressing the two questions regarding high abuse of Opana ER and the shift of abuse from snorting to injection, there are several issues that are important to make valid conclusions about Opana ER's abuse deterrence in the community: data quality, estimability, causality, and interpretability.

With respect to data quality, it is important that the data measure what they are supposed to measure. For example, a reported abuse based on a pre-specified definition should actually be an abuse. An exposure to a particular opioid should actually be an exposure to that opioid. If the data is incorrect, then we have a misclassification problem. Misclassification, of either exposure (specific opioids) or outcome (abuse and ROA), can bias the results, i.e. either exaggerate or diminish the actual change in an abuse metric. The direction and magnitude of bias are difficult to quantify.

The estimability issue is caused by the fact that the data are captured by passive surveillance systems, and these data may not necessarily represent the underlying population because they are neither a random sample nor a probability sample. In order to make valid statement about overall abuse changes from pre to post period in the population, one of the following assumptions have to hold:

- Selection into the sample is independent of the substance being abused;
- If selection into the sample depends on the substances being abused, then the nature of the dependence does not change over time;
- If selection into the sample depends on the substances being abused, and the nature of the dependence changes over time, then the change in the dependence is the same for Opana ER and the comparator opioid.

In order to make valid statement about route-specific abuse changes, one of the following assumptions have to hold:

- Selection into the sample is independent of route of abuse;
- If selection into the sample depends on route of abuse, then the nature of the dependence does not change over time;
- If selection into the sample depends on the route of abuse, and the nature of the dependence changes over time, then the change in the dependence is the same for Opana ER and the comparator opioid.

Some violation of the assumptions may cause the sample data to show results that are different from what is taking place in the underlying population.

The causality issue occurs when comparing Opana ER abuse rate changes with those of comparators. The goal of such comparisons is to separate the effect due to reformulation from those due to secular trends, and make causal statements about reformulated Opana ER. However, for such comparisons to be valid, we have to assume that Opana ER is similar to comparators, and different only in the sense that Opana ER has abuse-deterrent formulation while comparators do not. For both the pre and the post period, Opana ER and comparators should be similar in terms of how they are affected by external factors, such as DEA, state and local law enforcement and education efforts to reduce opioid abuse, FDA efforts such as risk evaluation and mitigation systems, and social trends such as availability and cost of substitutable drugs. It is difficult to know from the data whether the external factors affect each opioid in different ways. When external factors differentially affect each opioid class, it is difficult to disentangle the effect due to reformulation from that due to secular trends.

Given the issues in data quality, estimability, and causality, caution is needed when interpreting the results from these two observational studies.

Appendix

A Estimability Concepts

Let

- D be Opana ER indicator; $D = 1$ if an individual abused Opana ER and $D = 0$ otherwise;
- T denote time period: $T = 0$ for the pre period and $T = 1$ for the post period;
- S denote the sampling status: $S = 1$ if an individual is included in the surveillance sample and $S = 0$ otherwise;

Using the notation of Section 4.2.3, it can be shown that

$$\begin{aligned} p_t &= \frac{P(S = 1|D = 1, T = t)}{P(S = 1|T = t)} P_t \\ &= \pi_t P_t; \quad t = 0, 1 \end{aligned}$$

For example, the Opana ER abuse prevalence in the pre period is given by $p_0 = \pi_0 P_0$. This expression says that the sample prevalence (left-hand-side) in the pre period do not estimate the population prevalence in the pre period. Instead, the sample prevalence estimates a quantity that is a confounding between the true population prevalence P_0 and the sampling ratio given by the expression $\pi_0 = P(S = 1|D = 1, T = 0)/P(S = 1|T = 0)$. The numerator of this ratio is the sampling fraction with which abusers of Opana ER in the population in the pre period got recruited into the sample. Similarly, the denominator is the sampling fraction with which individuals in the population in the pre period get recruited in the sample. Under Assumption 1 whereby selection into the sample is independent of the substances being abused, the numerator in the expression for π_0 equals the denominator so that $\pi_0 = 1$.

For the rate metric, the relationship between the sample rates and the population rates can be characterized by:

$$\begin{aligned} r_t &= P(S = 1|D = 1, T = t) R_t \\ &= \rho_t R_t \end{aligned}$$

Under any condition, $\rho_t \neq 1$ so that the sample abuse rate at time t can never equal the population abuse rate at time t .

From these relationships, the within-drug post-pre comparison in the sample is related to that in the population as follows:

- prevalence

$$rp = \frac{p_1}{p_0} = \left(\frac{\pi_1}{\pi_0} \right) \frac{P_1}{P_0}$$

- rate

$$rr = \frac{r_1}{r_0} = \left(\frac{\rho_1}{\rho_0} \right) \frac{R_1}{R_0}$$

Under Assumption 1, $\pi_1 = \pi_0 = 1$ so that $rp = RP$. When selection into the sample depends on the substances being abused but that dependence does not change over time (Assumption 2), $\pi_1/\pi_0 = 1$ (even though $\pi_1 \neq 1$ and $\pi_0 \neq 1$) so that we also have $rp = RP$. For rates, we know that $\rho_t \neq 1$. But $\rho_1 = \rho_0$ if Assumption 2 is satisfied.

For the between-drug post-pre comparison, referred to in the text as the ratio-ratio comparison, Assumptions 1 and 2 ensure $\pi_1 = \pi_0$ and $\rho_1 = \rho_0$ so that between-drug post-pre comparison in the sample is valid for that in the population. When these assumptions are not met, we need Assumption 3 so that π_1/π_0 and ρ_1/ρ_0 for the comparator are equal to those for Opana ER, in which case the sample ratio-ratio comparison is valid for that in the population.

In the evaluation of ROA, if we define

$$P_t = \frac{\text{no. of injection among abusers of Opana ER in period } t \text{ in the population}}{\text{no. of abusers of Opana ER in period } t \text{ in the population}}$$

and

$$p_t = \frac{\text{no. of injection among abusers of Opana ER in period } t \text{ in the sample}}{\text{no. of abusers of Opana ER in period } t \text{ in the sample}}$$

then it can be shown that

$$p_t = \pi_t P_t$$

where

$$\pi_t = \frac{P(S = 1 | ROA = 1, D = 1, T = t)}{P(S = 1 | D = 1, T = t)}$$

where $ROA = 1$ could be used to denote injection or some other ROA. Similar reasonings as above could then be used to discuss the question of shift, estimability issues, and required assumptions. These assumptions were enumerated in Section 4.2.6 in the body of the text.

References

- [1] Endo. Analysis of reformulated Opana Extended Release (ER) using the RADARS system poison center program. *NDA 201655*, 2016.
- [2] Endo. Post market epidemiology study to evaluate abuse of Opana ER (oxymorphone HCl) extended-release tablets - final report. *NDA 201655*, 2016.

- [3] FDA. Abuse-deterrent opioids—evaluation and labeling. *Guidance for Industry*, 2015. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf>.
- [4] JB Mowry, DA Spyker, LR Cantilena Jr, N McMillan, and M Ford. 2013 annual report of the American Association of Poison Control Centers National Poison Data System (NPDS): 31st annual report. *Clinical Toxicology*, 52(10):1032–1283, 2014. <http://dx.doi.org/10.3109/15563650.2014.987397>.

Drug Utilization, Pharmacovigilance and Epidemiologic Review of Post-marketing Studies

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

Integrated Review of Postmarketing Data

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Drug Name(s): Opana[®] ER (oxymorphone hydrochloride)

Application Type/Number: NDA 201655

Applicant/sponsor: Endo Pharmaceuticals

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ABBREVIATIONS

ADF – Abuse-Deterrent Formulation
ASI-MV® – Addiction Severity Index–Multimedia Version®
CDC – U.S. Centers for Disease Control and Prevention
CI – Confidence Interval
CP – Citizen Petition
CRF – Crush Resistant Formulation (of Opana ER)
DEA – U.S. 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
ER/LA – Extended-Release/Long-Acting
FDA – U.S. Food and Drug Administration
FAERS – FDA Adverse Event Reporting System
HIV – Human Immunodeficiency Virus
HUS – Hemolytic Uremic Syndrome
IR – Immediate-Release
LDH – Lactate Dehydrogenase
MAHA – Microangiopathic Hemolytic Anemia
NAVIPPRO® – National Addictions Vigilance Intervention and Prevention Program®
NDA – New Drug Application
NPA – IMS Health's National Prescription Audit™
OP – Original Opana ER
OPR – Reformulated Opana ER
ORF – Reformulated OxyContin
PCC – Poison Control Center
PCP – Poison Center Program
PDMP – Prescription Drug Monitoring Program
PMR – Postmarketing Requirement
RADARS® PC – Researched Abuse, Diversion and Addiction-Related Surveillance®
Poison Center study
REMS – Risk Evaluation and Mitigation Strategy
SE – Single-Entity
SD – Standard Deviation
TMA – Thrombotic Microangiopathy
TTP – Thrombotic Thrombocytopenic Purpura

REVIEW SUMMARY

Background

Opana ER (oxymorphone hydrochloride extended-release) is a schedule II, extended-release (ER), single entity (SE) opioid analgesic developed by Endo Pharmaceuticals Inc. (Endo; Sponsor) and initially approved by the United States Food and Drug Administration (FDA) on June 22, 2006. Original Opana ER (OP) was formulated with a polysaccharide matrix to control release of the active drug into the gastrointestinal tract by forming a gel when exposed to water. OP was not specifically formulated to deter abuse, and approved labeling did not include language on abuse-deterrent properties. Endo's reformulated version of Opana ER, also called Opana ER (OPR), was initially approved by FDA on December 9, 2011. OPR was designed with a proprietary polyethylene oxide-containing matrix (INTAC®) to make the tablets more difficult to crush, thereby intending to deter abuse through the crush-and-snort route. Additionally, OPR contained gelling properties intended to make it difficult to dissolve the drug in solution and draw into a syringe, thereby intending to deter abuse through the injection route as well. FDA approved the application because OPR was determined to be safe and effective; however, approved labeling did not include language on abuse-deterrent properties.¹

Beginning in February 2012, Endo gradually replaced distribution of OP with OPR during the subsequent three months. In August 2012, Endo submitted a citizen petition (CP) requesting that FDA determine that OP was withdrawn for safety reasons and suspend or withdraw the approval of generic products referencing OP. FDA denied the petition, citing among its reasons data indicating that OPR can be readily prepared for injection and certain data suggesting that OPR can more easily be prepared for injection than original OP.² In its response, FDA also noted that the postmarketing data submitted by the sponsor had multiple deficiencies and were inconclusive. However, the response also noted that if one were to treat the available data as a reliable indicator of abuse rates despite these limitations, "one of the postmarketing investigations suggested the troubling possibility that a higher (and rising) percentage of OPR abuse is occurring via injection than was the case with OP." The first generic oxymorphone ER products (without properties intended to deter abuse) entered the market in July 2011, and the full range of dosage forms of generic oxymorphone ER entered the market in early 2013.

In addition to the broader national crisis of opioid abuse, addiction, and overdose, several specific concerns have emerged involving abuse of Opana ER via the intravenous route. The first was a 2012 outbreak of a potentially fatal bleeding disorder resembling thrombotic thrombocytopenic purpura (TTP) linked to intravenous abuse of OPR.³ TTP is a rare coagulation disorder that causes microscopic clots to form in small blood vessels. More broadly, the term, thrombotic microangiopathy (TMA), encompasses a spectrum of clinical syndromes leading to microvascular thrombosis, including TTP and others such as hemolytic uremic syndrome (HUS). Following a full review, FDA issued a warning about the risk of TTP with intravenous abuse of Opana ER,⁴ and the risk of TMA with intravenous abuse was added to the Abuse section (9.2) of Opana ER product labeling. The second event was an unprecedented outbreak of Human Immunodeficiency Virus

(HIV) in a rural Indiana county, in which a large majority of affected individuals reported injecting Opana ER.⁵

In January 2016, Endo re-submitted its supplemental NDA requesting an update of OPR labeling to include a claim of intranasal abuse deterrence and a description of studies supporting these abuse-deterrent properties (in 2013 FDA declined to approve this supplemental NDA following its original submission in 2012). Several postmarketing epidemiologic study reports, as well as spontaneous adverse event reports, were included in this submission. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Office of Surveillance and Epidemiology (OSE), requesting a review of these data. While the submission was under FDA review, Endo withdrew the supplement, and plans for an FDA Advisory Committee meeting were cancelled. However, based on preliminary review, FDA was concerned that some of these data suggested that OPR may be less safe than OP, and that other oxymorphone products may also have significant abuse-related safety concerns. Endo subsequently agreed to participate in an FDA Advisory Committee meeting to publically discuss the abuse-related safety concerns surrounding Opana ER and other oxymorphone products, following submission and FDA review of an additional year of postmarketing data.

The overarching purpose of this review is to critically evaluate the postmarketing data to determine what the impact of Opana ER's reformulation was on abuse of this product in post-approval settings, both overall and via specific routes of administration, and to interpret these findings within the context of abuse rates and patterns for comparator opioids, including generic oxymorphone ER and additional selected opioid analgesics. Although the postmarketing data were originally submitted to support a request for abuse-deterrence labeling, the current OSE review evaluates these data from a safety perspective, with the goal of understanding the overall risk-benefit balance of OPR relative to that of OP, other oxymorphone products, and other selected opioid analgesics.

This review includes the following sections:

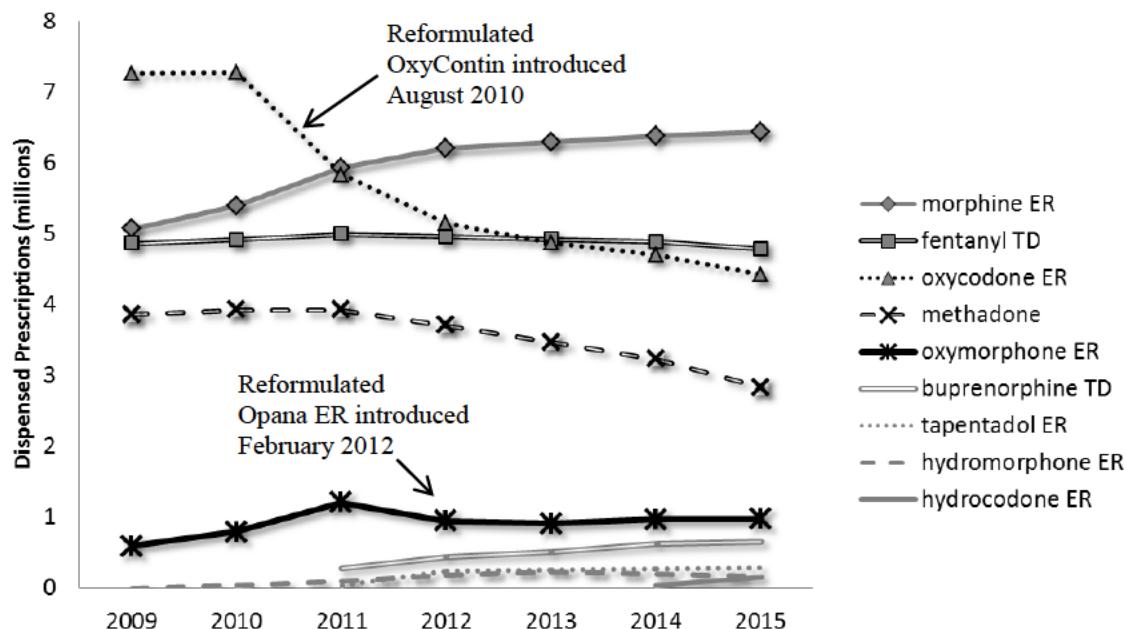
1. FDA analyses of drug utilization patterns for Opana ER and comparator opioids, as these provide context regarding the marketing history, prescribing trends, and settings of use for Opana ER and comparator opioid products.
2. An FDA analysis of spontaneous postmarketing adverse event reports related to Opana ER, focusing on reports of non-oral abuse, TMA, and HIV and viral hepatitis infection.
3. A review of epidemiologic study reports submitted by Endo, focusing primarily on the two formal investigations—the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®), and the Researcher Abuse, Diversion and Addiction-Related Surveillance® (RADARS®) Poison Center studies. We also review two supportive studies—the RADARS® Drug Diversion and Street Price study and the StreetRx study.

Summary of key review findings

1. Drug utilization

Figure E1 below shows the nationally estimated number of ER/LA opioid analgesic prescriptions dispensed annually from U.S. outpatient retail pharmacies from 2009 through 2015. Approximately 21-22 million ER/LA opioid analgesic prescriptions were dispensed annually from 2009 through 2015, representing approximately 10% of the overall opioid analgesic market.⁶ In 2015, morphine ER accounted for 31% of the total ER/LA prescriptions dispensed, followed by fentanyl transdermal (TD, 23%) and oxycodone ER (21%). Oxymorphone ER prescriptions accounted for approximately 5% of the total ER/LA prescriptions dispensed in 2015.

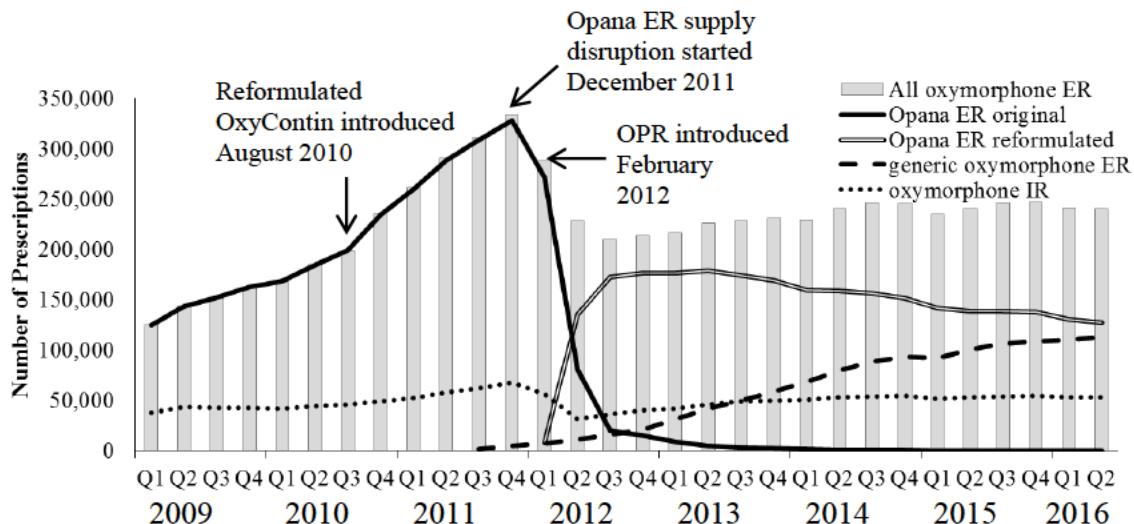
Figure E1. Nationally Estimated Number of Dispensed Prescriptions for Extended Release/Long Acting Opioid Analgesics from U.S. Outpatient Retail Pharmacies, 2009 through 2015, Annually.



Source: IMS Health, National Prescription Audit™. 2009-2015. Extracted September 2016. File: NPA ER_LA opioids yearly 2009-2015.xlsx.

Figure E2 below focuses in on trends in the nationally estimated number of prescriptions for OP, OPR, generic oxymorphone ER, and oxymorphone IR dispensed from U.S. outpatient retail pharmacies from January 2009 through June 2016, quarterly. Prescription volume for OP increased between the first quarter of 2009 and the fourth quarter of 2011, followed by a sharp decline during the market transition from the original to the reformulated product. Prescription volume for OPR increased between the first quarter of 2012 and the second quarter of 2013, followed by a steady decline through the second quarter of 2016. Prescription volume for generic oxymorphone ER products increased steadily from the third quarter of 2011 through the second quarter of 2016. Prescription volume for oxymorphone immediate release (IR) consistently remained lower than the oxymorphone ER products combined, comprising approximately 18% of the total oxymorphone market in 2015.

Figure E2. Nationally Estimated Number of Dispensed Prescriptions for Opana ER Original, Opana ER Reformulated, Generic Oxymorphone ER, and Oxymorphone IR (Brand and Generic) from U.S. Outpatient Retail Pharmacies, January 2009 through June 2016, Quarterly.



Source: IMS Health, National Prescription Audit™. January 2009 - June 2016. Extracted September 2016. File: NPA oxymorpha_ER_quarterly_2009-2016.xlsx.

Possibly affecting the utilization of OP and OPR, a voluntary stoppage of OP production occurred in December 2011, followed by limited production of this product through February 2012. During this supply disruption, Endo invoked strictly limited marketing of the product, indicating to physicians that they should not start new patients on OPR, but rather should ensure that existing supplies go to currently treated patients. Shipments of OPR began in February 2012 and dispensing of this product increased thereafter. Endo Pharmaceuticals nonetheless cited spot shortages of OP/OPR in the U.S. during the first half of 2012.⁷ During this time, oxymorphone IR and generic 7.5 mg and 15 mg oxymorphone ER were available from other manufacturers.

2. Spontaneous Postmarketing Adverse Events

Non-oral abuse:

DPV conducted a search in the FDA Adverse Event Reporting System (FAERS) from June 22, 2006 through June 1, 2016 for adverse events reported with Opana ER, specifically focusing on reports of non-oral abuse, TMA^a, and HIV and viral hepatitis infections. As shown in **Table E1**, after exclusions were applied, 117 cases of non-oral abuse of Opana ER with event dates were identified. In total, FAERS received 36 reports of non-oral abuse prior to approval of OPR and 81 reports of non-oral abuse after

^a FAERS was searched for reports of TMA to capture all potential cases of TTP-like illness described with injection of specific opioids, recognizing that individual cases may report signs and symptoms of TMA but not a specific diagnosis.

approval of OPR. Abuse via the nasal route was primarily reported during the time OP was marketed. In 2012, reports of intravenous abuse emerged, coinciding with the introduction of OPR and withdrawal of OP from the market. As noted above, generic oxymorphone ER products were first introduced to the market in July 2011, gradually increasing in market share. Although no cases of non-oral abuse of generic oxymorphone products were identified in FAERS, this finding should not be considered evidence that generic oxymorphone products are not being abused by non-oral routes. There are important limitations of spontaneous adverse event data (e.g., FAERS) that make it difficult to identify reports for specific products, particularly generic products.

Table E1. FAERS Cases of Non-Oral Abuse of Opana ER with Event Dates, that also Report the Terms, *chew, inhal, insuffl, nasal, smoke, snort, inject, or intravenous* in the Narrative from June 22, 2006 to June 1, 2016 (N=117)

Date of Event*	Route of Abuse			
	Chew†	Insufflate	Intravenous	Total cases
2006		1		1
2007	1	7		8
2008	2	7		9
2009		7		7
2010	1	1		2
2011‡	1	8		9
2012	4	3	31	38
2013			30	30
2014			8	8
2015			3	3
2016			2	2
Total Cases	9	34	74	117

* Reports were included in this analysis only if they provided an event date or year in the FAERS report. The date or year of event is not a required data element; therefore, it can be assumed this list may not be inclusive of all reports of non-oral abuse associated with Opana ER in FAERS.
 †Chewing, which may indicate oral abuse, was included in our analysis assuming OPR with properties to deter crushing, could have affected abuse by this route.
 ‡Reformulated Opana ER was approved December 9, 2011 and was marketed beginning February 2012. It is expected that there would be a time period where both formulations were available to patients; however, the duration of overlap is uncertain.

Thrombotic microangiopathy (TMA):

DPV's 2013 review of intravenous abuse of Opana ER and TMA⁸ evaluated 29 cases received from December 9, 2011 through March 26, 2013. Most of the cases were from a single rural county in northeast Tennessee. This review provides an update to the 2013 review, assessing cases reported to FAERS from March 27, 2013 through June 1, 2016. Thirty additional cases of TMA were identified. In total, 59 cases of TMA associated with intravenous abuse of Opana ER have been identified in FAERS from December 9, 2011 through June 1, 2016. DPV also searched for TMA cases associated with other opioids (i.e., OxyContin, Hysingla ER, Zohydro ER, Nucynta ER) formulated with a polyethylene oxide (PEO) polymer matrix intended to resist crushing and dissolving in solution. DPV identified three foreign TMA cases associated with intravenous abuse of

OxyContin. DPV did not identify any TMA cases associated with intravenous abuse of Hysingla ER, Zohydro ER, or Nucynta ER. Further, DPV did not identify any TMA cases that suggested intravenous abuse of generic oxymorphone ER products, which are not known to contain PEO.

3. Epidemiologic Studies

Methods summary and considerations:

The NAVIPPRO® study examined changes in self-reported past 30-day abuse of Opana ER and comparators, both overall and via specific routes of administration, in samples of individuals being assessed for substance abuse disorders. The study compares the 3-year time period before market introduction of OPR to a 3-year post-period, following a 6-quarter market transition period. Some analyses separately examine a 6-quarter pre-period prior to the introduction of reformulated OxyContin in the 3Q 2010 and a 6-quarter “sensitivity” pre-period following reformulated OxyContin’s introduction but before the introduction of OPR.

The NAVIPPRO® ASI-MV® surveillance system collects data from computerized assessments at sites in 40 states, including drug and alcohol treatment centers, corrections facilities, and other settings. Sites join and leave the network each quarter, resulting in changes in the geographic distribution and the distribution of assessment settings over time. As abuse patterns vary widely across different settings and geographic regions, the dynamic nature of this sample may bias pre-post comparisons of abuse rates. To mitigate this potential bias, our review focused primarily on analyses using a consistent sampling frame of “fixed” sites that contributed data in every quarter of the pre- and post-periods. This restricted analytic sample included 120,081 assessments from 53 sites located in 15 states. Sensitivity analyses also analyzed sites within Tennessee separately from non-Tennessee sites, as an attempt to control for confounding due to substantially higher Opana ER abuse prevalence in Tennessee sites and an increase in the proportion of total assessments being from Tennessee sites during the post-period compared to the pre-period. These stratified analyses are discussed in the body of this review. Of note, two Tennessee sites were included in the fixed site analyses that are the focus of the Review Summary.

Misclassification is another consideration in this study. The NAVIPPRO® study analyses defined Opana ER abuse cases during the post-period as only those specifically reporting abuse of “reformulated” Opana ER. However, approximately one fourth of post-period Opana ER abuse reports were for “original” Opana ER, raising the concern that substantial product misclassification might have occurred in this study, despite the use of pill photos in the assessment tool.

The RADARS® Poison Center (PC) study, examined changes in rates of drug exposure calls to U.S. poison centers, primarily those where the exposure was determined to be the result of intentional abuse involving the product. Similar to the NAVIPPRO® study, the RADARS® PC study examined abuse rates across pre- and post-reformulation time periods, as defined below for most analyses:

- a. Pre-ORF/Pre-CRF^b: 1Q2009 - 3Q2010; pre-period prior to introduction of reformulated OxyContin (ORF) in August 2010
- b. Post-ORF/Pre-CRF: 4Q2010 - 4Q2011; pre-period after ORF introduced but prior to introduction of reformulated Opana ER (CRF)
- c. Transition: 1Q2012 - 2Q2013; 6-quarter market transition period
- d. Post-ORF/Post-CRF: 3Q2013 - 2Q2016; three-year post period

Route of exposure information is also collected for each case and included in these analyses; however, in multi-substance exposures involving multiple routes, it may not always be possible to determine route of abuse (ROA) for each individual drug mentioned. As in the NAVIPPRO® study, product misclassification is a concern, particularly among the various oxymorphone products available. Notably, there were only six intentional abuse calls for generic oxymorphone ER during the 3-year post-period, despite prescription volume for these products nearing that of OPR by the end of this time period, suggesting the possibility that generic oxymorphone products may sometimes not be specifically identified in this data source.

In interpreting results from these studies, one question that we attempted to answer was “What happened to Opana ER abuse rates and patterns compared to what *would have* happened without the reformulation?” Although we cannot answer this question directly, trend analyses and comparators can help to disentangle the effect of the reformulation itself from secular trends and the effects of other interventions that may affect prescription opioid prescribing and abuse more broadly. Because it is bioequivalent to OP (although it may have different inactive ingredients and different prescribing patterns, cost, etc.), generic oxymorphone ER may offer a particularly valuable clue to what might have happened to Opana ER abuse patterns had it not been reformulated.

We considered both population-adjusted and utilization-adjusted abuse rates in comparing abuse rates over time and across products. Population-adjusted rates indicate the number of abuse cases identified as a proportion of the total study population (e.g., per 100 individuals surveyed or per 100,000 population covered by participating poison control centers). Utilization-adjusted abuse rates indicate the number of abuse cases for a given amount of drug dispensed from pharmacies within the study coverage area—here, per 100,000 tablets dispensed. As the number of tablets dispensed increases, so do opportunities for diversion and abuse. Prescription volume has been shown to be correlated with abuse rates,⁹ although the exact nature of this relationship has not been fully characterized. Utilization-adjusted rates facilitate comparisons across drugs with very different levels of prescription volume as well as comparisons over time that account for changes in the opioid analgesic market. Many factors can influence opioid prescribing trends over time—for example, drug shortages, advertising or detailing practices, availability of generic products, reimbursement policies, prescribing guidelines and regulations, law enforcement initiatives (e.g., “pill mill” crackdowns), and use of prescription drug monitoring programs (PDMPs)—and it is of course possible that

^b In the RADARS® study, reformulated OxyContin is referred to as ORF and reformulated Opana ER as CRF (“crush-resistant formula”)

changes in a product's prescription volume after reformulation might be due in part to a drug's reduced desirability for diversion or abuse.

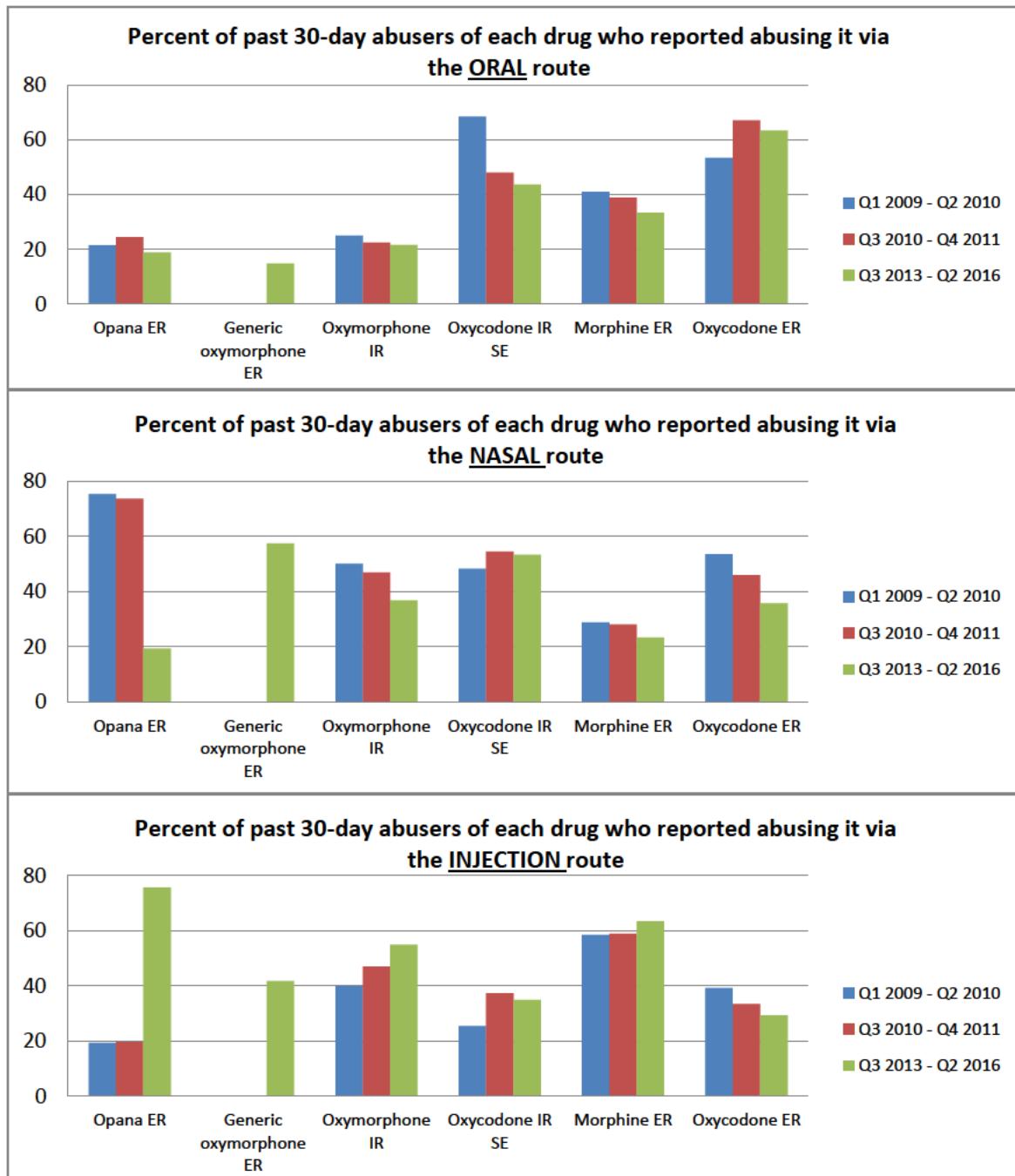
Key Epidemiology Study Findings:

NAVIPPRO® Study:

Among Opana ER abusers being assessed for treatment within the NAVIPPRO® ASI-MV® network, there was a marked shift in reported routes of abuse (ROAs) of this drug after its reformulation, from predominantly nasal to predominantly injection routes. As shown in **Figure E3**, among the fixed set of assessment sites, there was a large decrease in the proportion of Opana ER abusers who reported abusing it via the nasal route and a concurrent increase in the proportion who reported abuse via injection. The shift from Opana ER nasal to injection abuse was temporally associated with the introduction of OPR. Oral abuse of all oxymorphone formulations remained low throughout, with fewer than one fourth of abusers of these products reporting abusing them orally. In contrast, more than half of oxycodone ER abusers reported abusing it via oral routes, and this proportion increased slightly following OxyContin's reformulation.

Pre-post means analyses indicate that the changes in the proportion of Opana ER abusers snorting and injecting were statistically significant and significantly larger when comparing OP to OPR than when comparing OP to generic oxymorphone ER. The shift in Opana ER ROA was seen consistently in all sensitivity analyses. With the exception of oxycodone ER, there was a general pattern of increasing abuse via the injection route for comparator opioids; however, a shift of similar magnitude to that seen with Opana ER did not occur for any other opioid analyzed. Oxycodone ER did not show a shift from the nasal to the injection route following the reformulation of OxyContin in Q3 2010.

Figure E3. Route of abuse patterns among abusers of Opana ER* and each opioid comparator across three time periods, using the restricted set of fixed ASI-MV® sites, NAVIPPRO® study



*OP in the first two time periods and OPR in the third time period (post-period)

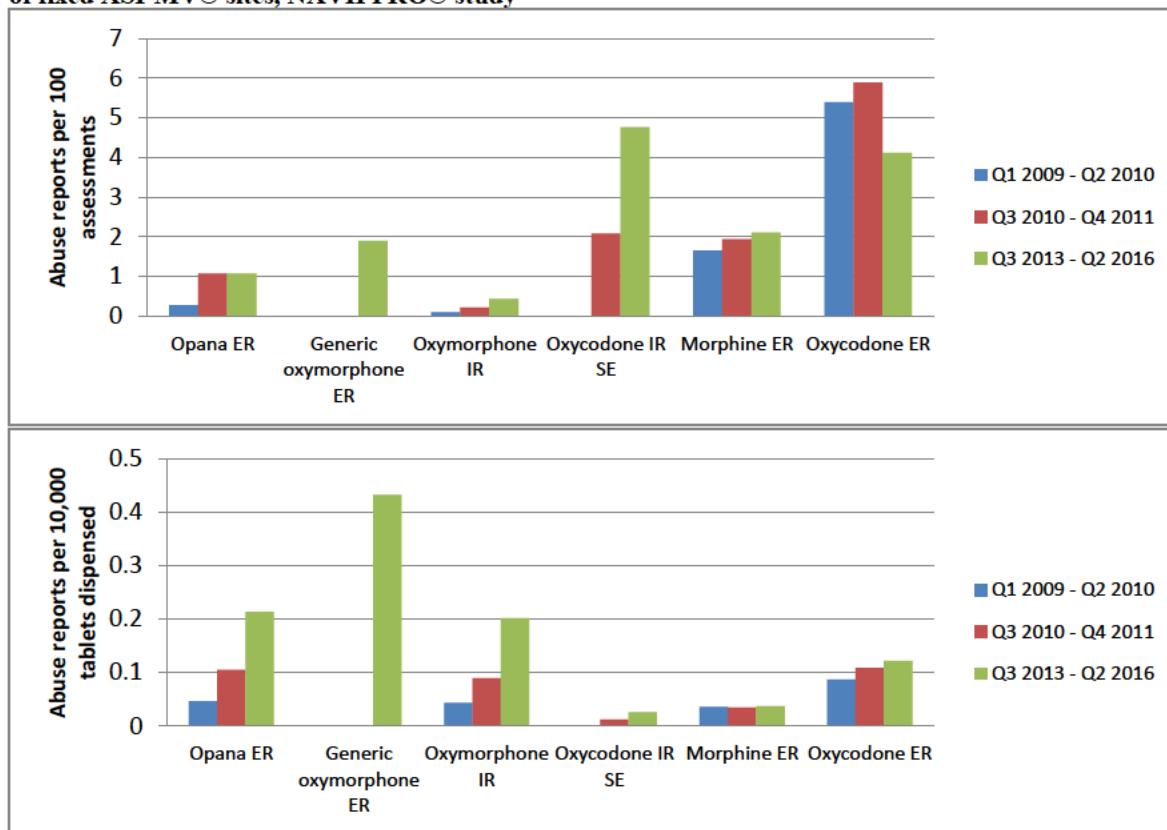
Source: Figure generated by DEPI reviewer using data from the NAVIPPRO® study report (December 2016)

Because the above analyses do not account for changes in the overall abuse rates for a product, it is also important to examine changes in abuse rates *in the overall study population*, not only among those who abuse each product. **Figure E4** depicts the changes in mean overall abuse prevalence per 100 assessments (top panel) and abuse rate

per 10,000 tablets dispensed (bottom panel) across the same three time periods as in the previous analysis, using the fixed set of sites. The prevalence of Opana ER abuse per 100 assessments increased from the first to the second pre-period but showed no change from the second pre-period to the post-period. Adjusting for the number of tablets dispensed, the abuse rate for Opana ER increased significantly from the sensitivity pre-period (Q3 2010 – Q4 2011) to the post-period. Both the prevalence per 100 assessments and the abuse rate per 10,000 tablets dispensed were significantly greater for generic oxymorphone ER than for OPR during the post-period.

In contrast, sensitivity analyses showed significant decreases in Opana ER abuse prevalence per 100 assessments in both Tennessee and non-Tennessee sites, comparing OP in the sensitivity pre-period to OPR in the post-period. In Tennessee, the tablet-adjusted abuse rate increased Tennessee, whereas in non-Tennessee sites, the tablet-adjusted abuse rate decreased significantly.

Figure E4. Mean past 30-day abuse reports via any route per 100 assessments (top panel) and per 10,000 tablets dispensed (bottom panel) for Opana ER* and comparators, using the restricted set of fixed ASI-MV® sites, NAVIPPRO® study**



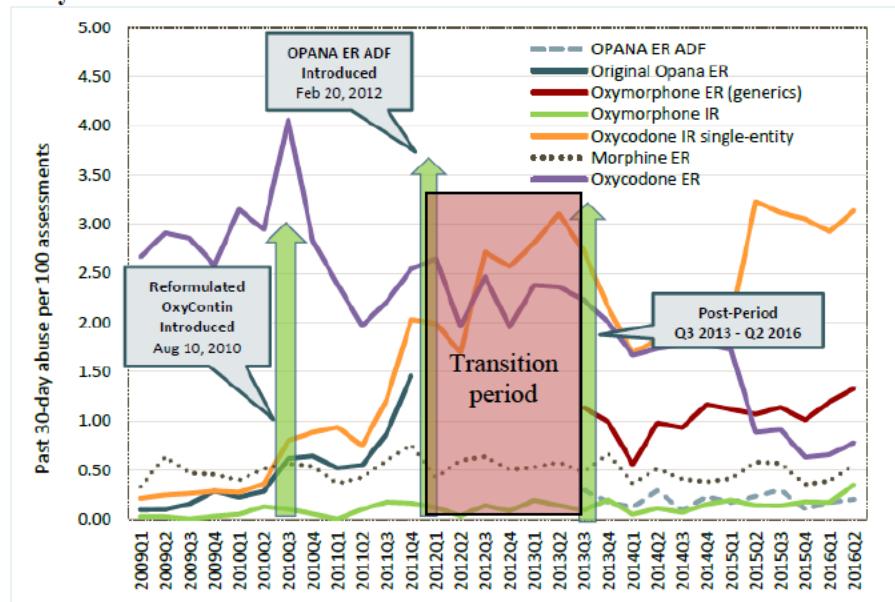
* OP in the first two time periods and OPR in the third time period (post-period)

** Oxycodone IR SE rates were not reliable until separate data collection for IR oxycodone SE products began in early 2010.

Source: Figure generated by DEPI reviewer based on data in NAVIPPRO® study report (December 2016),

Comparing mean abuse prevalence in the fixed sites across three study periods indicates that the mean Opana ER nasal abuse prevalence decreased significantly, from 0.78 to 0.21 per 100 assessments, comparing the sensitivity pre-period after OxyContin's reformulation to the post-period. Post-period OPR abuse prevalence returned to levels not significantly different from OP abuse prevalence in the earlier 6-quarter pre-period prior to OxyContin's introduction. **Figure E5** shows trends in quarterly nasal abuse prevalence for Opana ER and comparators per 100 assessments within the fixed site sample. The data show a rising prevalence of nasal OP abuse during the pre-period. During the post-period, the prevalence of OPR nasal abuse remained relatively stable at levels considerably lower than those just prior to Opana ER's reformulation and similar to those seen early in the pre-period. The prevalence of generic oxymorphone ER nasal abuse during the post-period was consistently higher than that of OPR. Of note, an abrupt decline in oxycodone ER nasal abuse prevalence and a sharp increase in oxycodone IR SE are seen following a change in the ASI-MV® screen order implemented in March 2015.

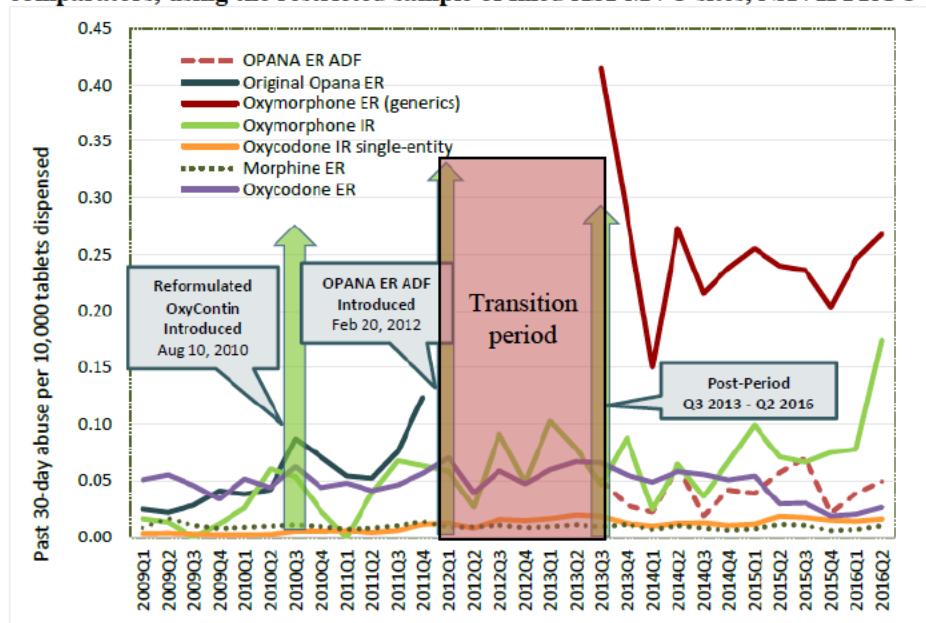
Figure E5. Quarterly prevalence of past 30-day nasal abuse per 100 ASI-MV® assessments for Opana ER and comparators, using the restricted sample of fixed ASI-MV® sites, NAVIPPRO® study



Source: NAVIPPRO® study report (December 2016), transition period added by DEPI reviewer

The pattern was similar after adjusting for the number of tablets dispensed. Using the tablets-dispensed denominator (**Figure E6**), a decline is again seen in nasal abuse rates for OPR relative to those for OP just prior to Opana ER's reformulation. Generic oxymorphone ER demonstrated the highest tablet-adjusted nasal abuse rates of all the opioids analyzed. During the post-period, tablet-adjusted nasal abuse rates for OPR were lower than for generic oxymorphone ER and more similar to IR oxymorphone and ER oxycodone. IR oxycodone SE and ER morphine had the lowest utilization-adjusted nasal abuse rates.

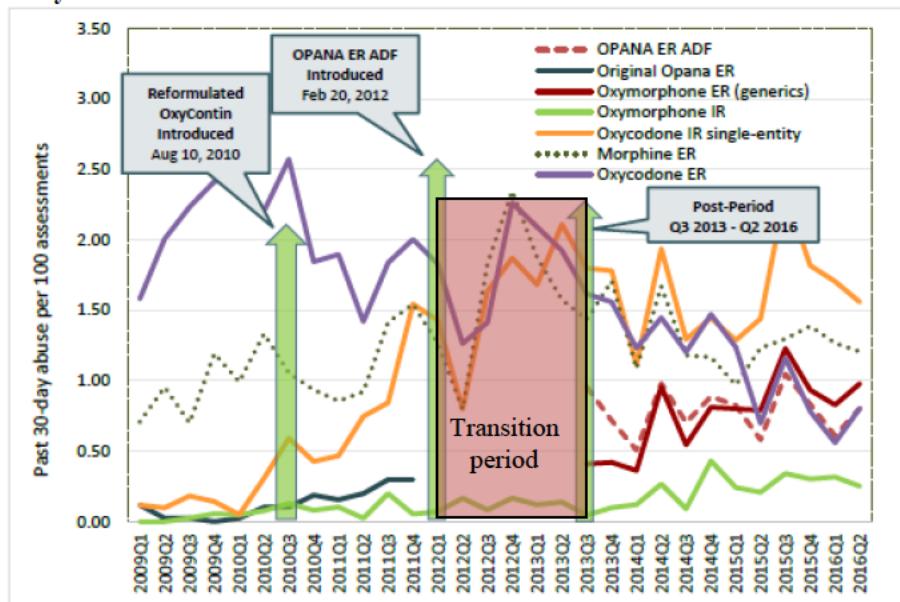
Figure E6. Quarterly rates of past 30-day nasal abuse per 10,000 tablets dispensed for Opana ER and comparators, using the restricted sample of fixed ASI-MV® sites, NAVIPPRO® study



Source: NAVIPPRO® study report (December 2016), transition period added by DEPI reviewer

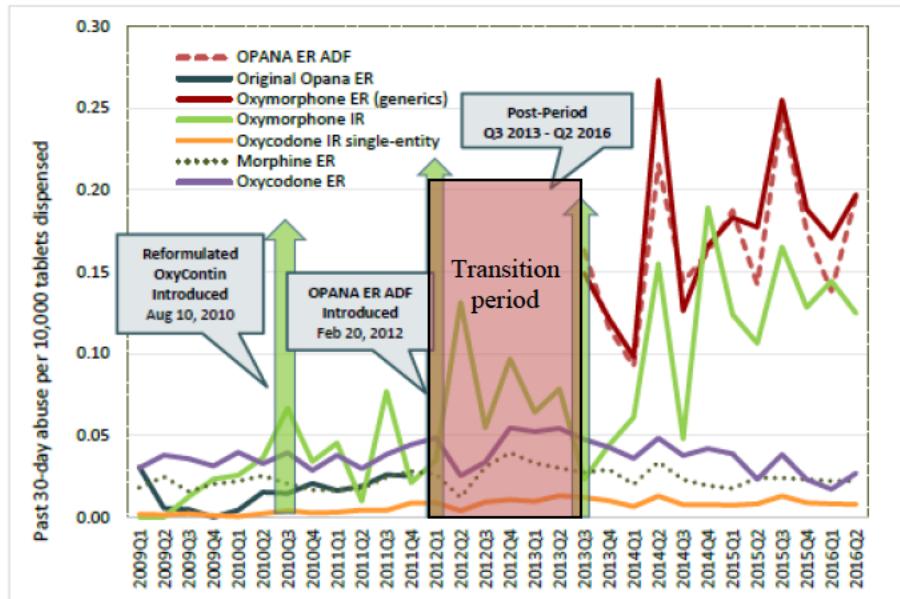
Within the fixed site sample, the mean Opana ER injection abuse prevalence increased markedly across the three study periods, from 0.05 to 0.21 abuse reports per 100 assessments in the first and second pre-periods, respectively, then to 0.81 per 100 assessments in the post-period. However, the mean injection abuse prevalence for generic oxymorphone ER was not significantly different from that for OPR in the post-period. **Figure E7** depicts trends in quarterly injection abuse prevalence for Opana ER and comparators as a proportion of assessments within the ASI-MV® network using the restricted set of fixed sites. **Figure E8** depicts quarterly tablet-adjusted injection abuse rates for Opana ER and comparators, using the fixed set of sites. Adjusting for the number of tablets dispensed, there was again a marked increase in the mean injection abuse rate for Opana ER across the three study periods. Again, injection abuse rates for OPR and generic oxymorphone ER were not significantly different from one another during the post-period. Tablet-adjusted injection abuse rates also increased for oxycodone IR SE and IR oxymorphone, whereas morphine ER and oxycodone ER rates did not change significantly across the study periods.

Figure E7. Quarterly prevalence of past 30-day injection abuse per 100 ASI-MV® assessments for Opana ER and comparators, using the restricted sample of fixed ASI-MV® sites, NAVIPPRO® study



Source: NAVIPPRO® study report (December 2016), transition period added by DEPI reviewer

Figure E8. Quarterly rates of past 30-day injection abuse per 10,000 tablets dispensed for Opana ER and comparators, using the restricted sample of fixed ASI-MV® sites, NAVIPPRO® study

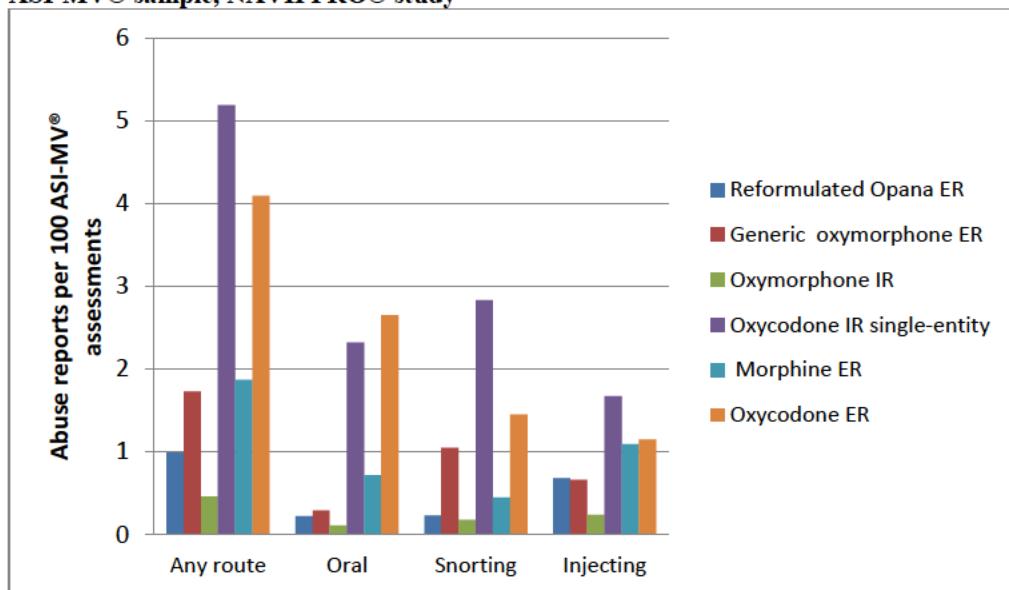


Source: NAVIPPRO® study report (December 2016), transition period added by DEPI reviewer

Comparing abuse rates across drugs during the most recent available time period can also be valuable in considering the current risk-benefit balance of opioid products. Because abuse patterns vary considerably across geographic regions, here we focused on the full

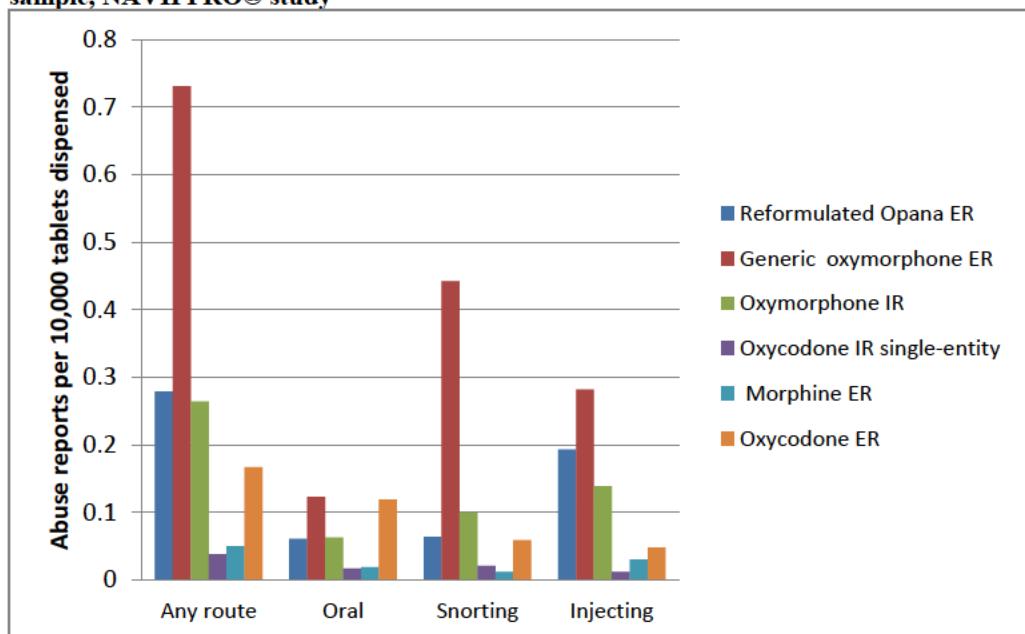
ASI-MV® sample to cover the largest geographic area. **Figure E9** compares the proportion of assessments reporting past 30-day abuse of OPR and comparators, overall and via specific routes, during the 3-year post-period. Among the opioids included in this analysis, the most common drugs abused overall and via the oral route were oxycodone IR SE and oxycodone ER. Via the nasal route, oxycodone IR SE was the most common drug mentioned, followed by oxycodone ER and generic oxymorphone ER. Via the injection route, abuse of oxycodone IR SE was the most common, followed by oxycodone ER and morphine ER. **Figure E10** depicts post-period abuse rates per 10,000 tablets dispensed. Here, generic oxymorphone ER had the highest overall and nasal abuse rates. Oral abuse rates were highest for generic oxymorphone ER and oxycodone ER. Generic oxymorphone ER and OPR had the highest injection abuse rates, followed by oxymorphone IR.

Figure E9. Prevalence of past 30-day abuse per 100 ASI-MV® assessments for Opana ER and comparators, overall and via specific routes, post-period only (7/1/2013 – 6/30/2016), using the full ASI-MV® sample, NAVIPPRO® study



Source: Figure generated by DEPI reviewer using data in the NAVIPPRO® study report (December 2016)

Figure E10. Past 30-day abuse rates per 10,000 tablets dispensed for Opana ER and comparators, overall and via specific routes, post-period only (7/1/2013 – 6/30/2016), using the full ASI-MV® sample, NAVIPPRO® study



Source: Figure generated by DEPI reviewer using data in the NAVIPPRO® study report (December 2016)

RADARS® Poison Center Study:

A shift in the ROA profile for Opana ER was also apparent in the RADARS® Poison Center study, examining intentional abuse exposure calls to U.S. poison centers. Prior to its reformulation (“pre-CRF” period), Opana ER cases involving the inhalation route far outnumbered those involving injection (**Table E2**). Following reformulation (“post-CRF” period), the number and proportion Opana ER abuse calls involving inhalation declined, while the number and proportion involving injection increased markedly. A similar shift in ROA was not observed for ER morphine across the study periods, or in ER oxycodone abuse cases after OxyContin was reformulated. Again, there were only six mentions of generic oxymorphone ER during the post-period, so a route-specific analysis was not feasible for these products.

Table E2. Number and percentage of Opana ER intentional abuse exposures involving inhalation and injection routes, RADARS® Poison Center Study, Q1 2010 – Q2 2016*

	INHALATION CASES	INJECTION CASES	TOTAL ABUSE CASES**	% OF ABUSE CASES VIA <u>INHALATION</u> ROUTE	% OF ABUSE CASES VIA <u>INJECTION</u> ROUTE
Pre-CRF (Q1 2010 - Q4 2011)	98	19	290	34%	7%
Post-CRF (Q3 2013 - Q2 2016)	39	53	190	21%	29%

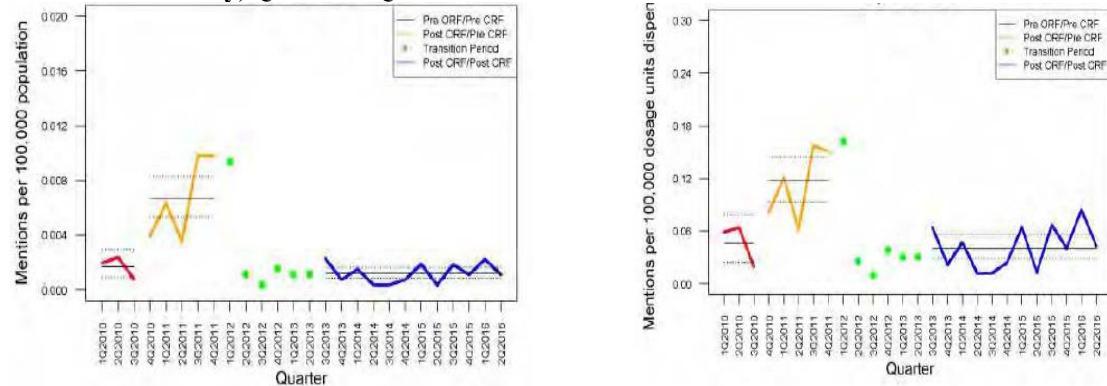
Source: Table generated by reviewer, using data provided in RADARS® PC study report (November 2016) and Sponsor's updated response to June 1, 2016 FDA Information Request (November 2016)

* RADARS® PC program began collecting information on route of administration in Q1 2010

**Not all cases have information on ROA. ROA is missing in >20% of Opana ER exposure cases.

Figure E11 depicts quarterly and mean population- and utilization-adjusted *rates* for Opana ER intentional abuse calls involving the inhalation route, across the study periods. Mean rates of Opana ER inhalation abuse calls decreased significantly, comparing the post-ORF/pre-CRF period to the 3-year post- period, returning to rates similar to those seen in the pre-ORF/pre-CRF period.

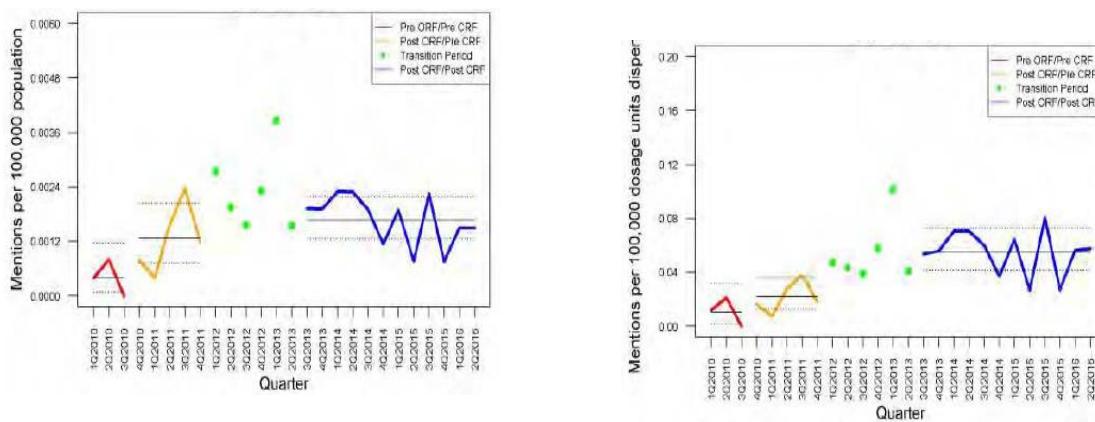
Figure E11. Mean rates of Opana ER intentional abuse exposure calls involving the inhalation route, per 100,000 population (left panel) and per 100,000 dosing units dispensed (right panel), RADARS® Poison Center study, Q1 2010 – Q2 2016



Source: Sponsor's updated response to June 1, 2016 FDA Information Request (November 2016)

As shown in **Figure E12**, the population-adjusted injection abuse call rate for Opana ER was significantly higher in the post-period, compared to the pre-ORF/pre-CRF period, but not compared to the post-ORF/pre-CRF. Adjusting for utilization, however, there was a significant increase in Opana ER injection abuse call rates from the post-ORF/pre-CRF period to the 3-year post-period.

Figure E12. Mean rates of Opana ER intentional abuse exposures involving the injection route, per 100,000 population (left panel) and per 100,000 dosing units dispensed (right panel), RADARS® Poison Center study, Q1 2010 – Q2 2016

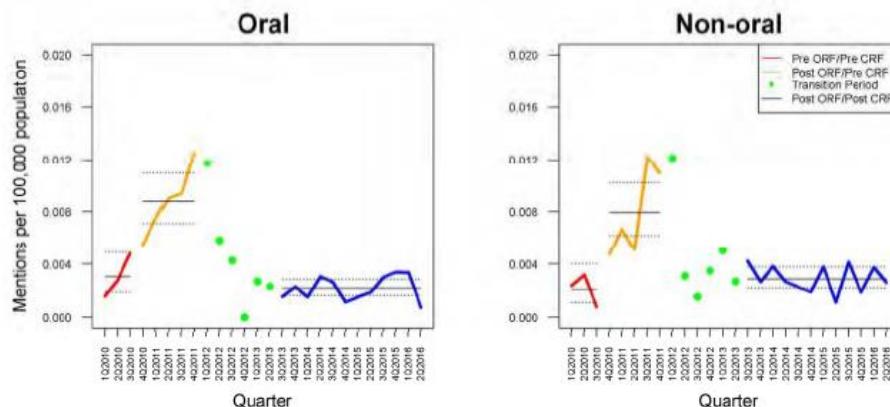


Source: Sponsor's updated response to June 1, 2016 FDA Information Request (November 2016)

Overall population- and utilization-adjusted Opana ER intentional abuse call rates (via any route) decreased significantly when comparing the post-ORF/pre-CRF period to the post-period. Adjusted for utilization, relative reductions for morphine ER and oxymorphone IR were both greater in magnitude than for Opana ER, although 95% confidence intervals overlapped with those for Opana ER.

Considering that OPR was designed to deter abuse via routes other than swallowing whole, it is also notable that reductions in Opana ER intentional abuse call rates were similar for cases involving oral (swallowing whole) and non-oral (e.g., chewing, inhalation, injection) routes of administration (**Figure E13**).

Figure E13. Mean Opana ER intentional abuse exposure call rates per 100,000 population, by oral and non-oral routes* of administration, RADARS® Poison Center Study, 1Q2009 – 2Q 2016

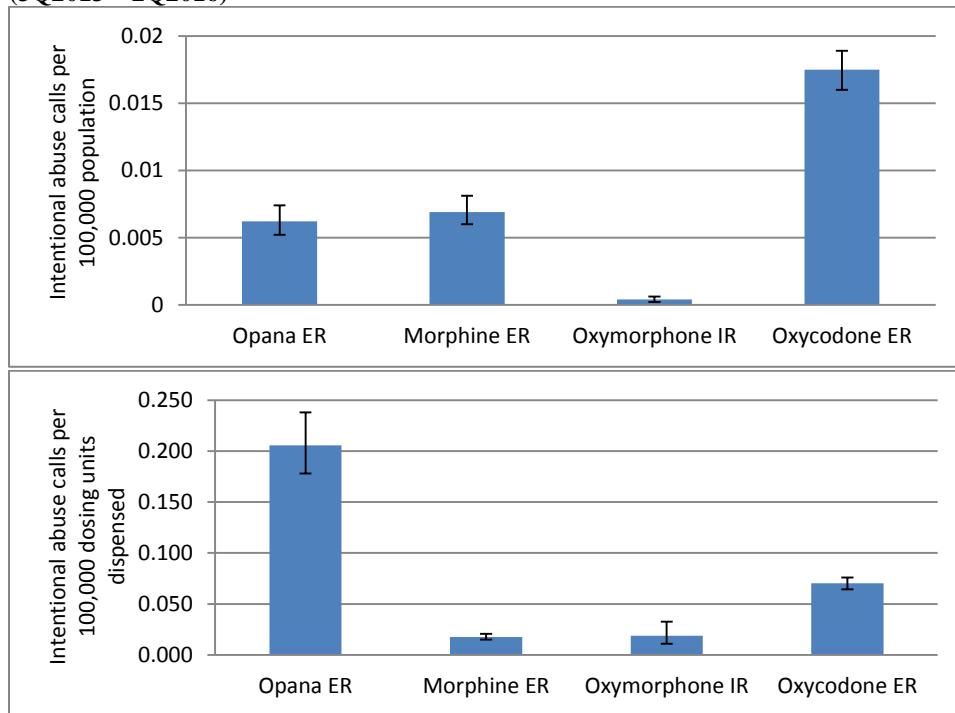


*Oral includes swallowing whole. Non-oral include all other routes, including chewing, snorting, injecting, and other routes.

Source: RADARS® PC study report (November 2016)

Again, an examination of post-period abuse rates for Opana ER and comparators is informative. **Figure E14** compares the post-period intentional abuse exposure call rates for Opana ER and comparators per 100,000 population (top panel) and per 100,000 dosing units dispensed (bottom panel). Of the analyzed opioids, oxycodone ER had the highest population-adjusted call rates, while Opana ER had the highest utilization-adjusted call rates. Reliable rates could not be calculated for generic oxymorphone ER.

Figure E14. Intentional abuse call rates (any route) per 100,000 population (top panel) and per 100,000 dosing units dispensed (bottom panel), RADARS® Poison Center Program, post-period only (3Q2013 – 2Q2016)



Source: Figure generated by reviewer based on data provided in RADARS® PC study report (November 2016) and Sponsor's updated response to June 1 information request (November 2016)

Discussion of the postmarketing data

The postmarketing data present a complex picture of the use and abuse of Opana ER and other oxymorphone products. Nonetheless, the totality of the evidence is compelling that, among those abusing Opana ER, the reformulation caused a shift in non-oral routes from predominantly nasal to predominantly injection. The NAVIPPRO® study data provide evidence that such a shift occurred among Opana ER abusers being assessed for substance abuse treatment. Although a modest shift toward injection was seen among abusers of several comparator opioids across time periods, a shift of this large magnitude was unique to Opana ER. Of particular note, ER oxycodone abusers did not show a shift from nasal to injection abuse following OxyContin's reformulation. The RADARS® PC data also suggest a shift from the inhalation to injection route among Opana ER abuse cases identified through poison center calls. And finally, although FAERS data cannot be used to determine the incidence of abuse, the pattern of spontaneous adverse event reports is qualitatively consistent with this shift in the routes by which Opana ER is

abused, with cases of nasal abuse of Opana ER reported primarily before the product's reformulation and intravenous abuse reports emerging after introduction of OPR. The shift from nasal to injection abuse of Opana ER seen in the postmarketing data is particularly concerning in light of the 59 TMA reports in FAERS associated with intravenous abuse of Opana ER after its reformulation, as well as the unprecedented outbreak of HIV attributed primarily to injection of this drug in a rural Indiana community. Oxymorphone's very low oral bioavailability may have contributed to the apparent shift from nasal to injection abuse among Opana ER abusers after the product's reformulation. If Opana ER is an abuser's drug of choice or is readily available, injection may become a more attractive option if reformulation makes nasal abuse more difficult and the oral route is not perceived as effective or economical.

Assessing the impact of Opana ER's reformulation on abuse levels in the population is more challenging than assessing the reformulation's effect on ROA patterns only among abusers of the drug. This challenge arises because comparisons of abuse rates over time and across products are more vulnerable to bias due to sampling and misclassification, and because trends in use and abuse of various products can be influenced by external factors that are exceedingly difficult to measure. Both the NAVIPPRO® and RADARS® PC study results suggest that Opana ER's reformulation may have resulted in a decline in nasal abuse rates relative to what they would have been without reformulation. The magnitude of effect is difficult to determine, however, because of potentially substantial product misclassification in both studies. Both studies also indicate a marked increase in rates of Opana ER abuse via injection, although increases appear to have begun prior to the reformulation. In the NAVIPPRO® study, high injection abuse rates were also seen for generic oxymorphone ER after it became available, and the increases in injection abuse rates across study periods were not significantly different when comparing OP to OPR and when comparing OP to generic oxymorphone ER. Increases in injection abuse rates were also observed for two comparator opioids. If generic oxymorphone ER is indeed a good proxy for what would have happened to Opana ER abuse rates and patterns without reformulation, the findings suggest that Opana ER injection abuse rates in this population may be similar to what they would have been without reformulation and that factors other than the reformulation may be contributing to the increase in injection abuse of oxymorphone ER in general. It is unclear, however, how well generic oxymorphone ER actually represents what would have happened to Opana ER abuse without reformulation. It is possible that changes in Opana ER abuse patterns could have carried over to generic oxymorphone ER products when they became widely available. And again, the persistence of OP abuse reports during the post-period raises concerns about product misclassification and the potential for bias, the direction of which is difficult to determine.

The high post-period abuse rates for generic oxymorphone ER could not be confirmed in the RADARS® PC data. It is possible that this marked discrepancy between the RADARS® and NAVIPPRO® reflects real differences in study populations and the outcomes being measured, but it also highlights ongoing uncertainties about data quality in these studies. In particular, it is possible that some poison center cases involving generic oxymorphone ER were reported and/or recorded as the well-recognized brand product Opana ER. Either product could also be classified as oxymorphone without

further specification, of which there were a non-trivial number of cases. Nonetheless, the data from the NAVIPPRO® study suggest that generic oxymorphone ER may also pose serious safety risks due to high rates of abuse in this population, via both nasal and injection routes, relative to prescription volume.

The data are also difficult to interpret with regard to the impact of Opana ER's reformulation on overall abuse of the drug. The NAVIPPRO® data suggest that although the reformulation of Opana ER did not significantly reduce abuse rates among those being assessed for substance abuse within the fixed site sample, it may have attenuated the rise in Opana ER abuse in this population, and sensitivity analyses stratifying by Tennessee and non-Tennessee sites suggested decreases in the prevalence of Opana ER abuse after reformulation. The RADARS® PC study showed significant declines in Opana ER abuse call rates after reformulation. However, these declines were similar to those seen for comparators without properties intended to deter abuse, and reductions in Opana ER abuse calls involving non-oral routes were similar to reductions in abuse calls where the drug was swallowed whole. Together, these findings suggest that factors other than the reformulation itself may have contributed to the observed decline in Opana ER abuse poison center call rates. The abrupt change in abuse rate trends was seen only for Opana ER, suggesting a direct effect of the reformulation.

Finally, utilization-adjusted post-period abuse rate comparisons in both studies suggest that OPR may have a greater risk of abuse than comparator opioid analgesics included in these analyses, with the notable exception of generic oxymorphone ER in the NAVIPPRO study. Direct comparisons of abuse rates in the NAVIPPRO® study must be interpreted cautiously, because (1) abuse patterns vary geographically and the ASI-MV® sample is not nationally representative, oversampling some areas and providing no information from other areas, (2) patterns in persons being assessed for substance abuse treatment may not reflect patterns in the broader population, and (3) differential misclassification could have resulted in biased estimates. Direct comparisons of poison center call rates across products must also be interpreted with caution, as it is unknown whether the proportion of abuse or overdose events resulting in a poison center call is the same across different opioids; and differential misclassification, particularly of ER vs. IR and brand vs. generic products, may have occurred. In particular, some cases involving generic oxymorphone could have been identified as the recognizable brand product Opana ER.

Conclusions

The postmarketing data have many limitations and their interpretation is not straightforward; however, the evidence is compelling that among those abusing Opana ER, the reformulation caused a marked shift in the route by which the drug is abused, from nasal to injection. This shift is particularly concerning, considering the more than 50 cases of TMA identified in FAERS and the large HIV outbreak associated with intravenous abuse of Opana ER. The postmarketing studies suggest that the reformulation likely reduced nasal abuse rates for Opana ER, but because of data limitations it is difficult to determine the magnitude of this apparent effect. The study results also indicate an increase in Opana ER injection abuse rates over the study period. It is not

entirely clear whether the increases in Opana ER injection abuse rates are greater than they would have been had the drug not been reformulated, as increases appear to have begun prior to Opana ER's reformulation and rates were similarly high for generic oxymorphone ER during the post-period among those being assessed for substance abuse treatment. Some data suggest that the reformulation resulted in post-period Opana ER abuse rates that were lower than they might have been without the reformulation; however, the evidence is difficult to interpret with regard to the overall impact of Opana ER's reformulation on abuse of the drug.

Although the diagnoses for which oxymorphone ER is prescribed are similar to those of oxycodone ER and morphine ER, ER oxymorphone comprises only 5% of the ER/LA opioid analgesic market and a tiny fraction of the total prescription opioid market. Not surprisingly, other opioids with larger prescription volume contribute a larger proportion of abuse cases identified in these studies. After adjusting for differences in prescription volume, however, OPR, generic oxymorphone ER, and oxymorphone IR had the highest post-period injection abuse rates and generic oxymorphone ER had the highest overall and nasal abuse rates of the opioids analyzed in the NAVIPPRO® study. In the RADARS® Poison Center study, Opana ER had post-period intentional abuse call rates that were considerably higher than morphine ER, oxymorphone IR, or oxycodone ER. The high abuse rates for generic oxymorphone ER seen in the NAVIPPRO® study could not be confirmed in the poison center data, possibly due to inaccurate reporting of generic products in this data source. All of these across-product comparisons must be interpreted with caution due to the limitations of these data.

1 BACKGROUND AND REGULATORY HISTORY

Opana ER (oxymorphone hydrochloride) is a schedule II, extended-release (ER), single entity (SE) opioid analgesic developed by Endo Pharmaceuticals Inc. and initially approved by the United States Food and Drug Administration (FDA) on June 22, 2006 for relief of moderate-to-severe pain in patients requiring continuous around-the-clock opioid analgesic treatment for an extended period of time (NDA 21-610). Opana ER was formulated with a proprietary TIMERx® delivery technology, which uses a hydrophilic polysaccharide matrix to control release of the active drug into the gastrointestinal tract by forming a gel when exposed to water. The approved labeling stated that Opana ER should be swallowed whole, and warned that crushing, chewing, snorting, or injecting the dissolved product will result in uncontrolled delivery and pose significant risk that could result in overdose and death. Opana ER was not formulated to deter abuse, and approved labeling did not include language on abuse-deterrent properties.

Endo's reformulated version of Opana ER, also called Opana ER (OPR), was initially approved by FDA on December 9, 2011 (NDA 201-655). OPR was designed using high-molecular-weight polyethylene oxides (PEO) within a proprietary INTAC® hydrophilic matrix to make the tablets more difficult to crush, thereby intending to deter abuse through the crush-and-snort route. Additionally, OPR contained gelling properties, making it difficult to dissolve the drug in solution and draw into a syringe ("poor syringeability"), thereby designed to deter abuse through the injection route as well. Endo's original NDA for OPR included data from studies designed to assess the potentially abuse-deterrent properties of the new formulation. Although FDA approved the application because OPR was determined to be safe and effective, approved labeling did not include language on abuse-deterrent properties. In publically available documents, FDA stated "While the new formulation has demonstrated a minimal improvement in resistance to tampering by crushing, thereby limiting the likelihood of abuse by crushing followed by ingestion, and by insufflation (snorting) to some degree, it can still be [redacted], cut, [redacted] rendering it readily abusable by ingestion and intravenous injection, and possibly still by insufflation; although whether [redacted] tablets can be snorted was not studied. Of more concern, when chewed [redacted] the new formulation essentially dose dumps like an immediate-release formulation."¹⁰

Endo gradually replaced original Opana ER (OP) with OPR in the first half of 2012, notifying FDA in May 2012 that it had voluntarily ceased marketing OP. Of note, in December 2011, the plant manufacturing OP under contract for Endo voluntarily stopped production of OP, based on consumer complaints of chipped and broken pills and inconsistent packaging practices possibly resulting in rare tablet mix ups (see **Appendix A** for full information provided by the Sponsor in response to FDA request). Following this production stoppage, Endo invoked strictly limited marketing of the product, indicating to physicians that they should not start new patients on Opana ER, but rather should ensure that existing supplies go to currently treated patients. Despite these actions, there were spot shortages of Opana ER availability throughout the country in the first half of 2012; however, OP did not officially go into drug shortage. Subsequent to the supply disruption, Endo accelerated production and shipping of OPR,

which began shipping in February 2012. However, Endo could not supply the full Opana ER market with OPR for several months following its introduction to the market.

FDA first approved ANDAs for generic versions of Opana ER in December 2010. The first generic oxymorphone ER products entered the market in July 2011, with additional products entering the market in 2013. All generic oxymorphone ER products reference OP. **Table 1** below summarizes dates of importance in the approval and marketing of ER oxymorphone products in the U.S.

Table 1. Marketing history for brand and generic oxymorphone ER products in the U.S.

Strength (mg)	Brand or Generic	Original or Reformulated	Initial Approval Date	Date First Distributed	Date of Discontinuation
5, 10, 20, 40	Brand	Original	22-Jun-2006	Jul-2006	May-2012
7.5, 15, 30	Brand	Original	29-Feb-2008	1-Apr-2008	7.5 and 15 mg – Mar-2011 30 mg – May-2012
5, 7.5, 10, 15, 20, 30, 40	Brand	Reformulated	9-Dec-2011	Feb-2012 Dec-2012 (7.5 and 15 mg)	N/A
7.5, 15	Generic – Actavis	Original	13-Dec-2010	15-Jul-2011	N/A
5, 10, 20, 30, 40	Generic – Actavis	Original	11-Jul-2013	12-Sep-2013	N/A
5, 10, 20, 40	Generic – Impax	Original	14-Jun-2010	2-Jan-2013	N/A
30	Generic – Impax	Original	22-Jul-2010	2-Jan-2013	N/A
7.5, 15	Generic – Impax	Original	21-Dec-2010	2-Jan-2013	N/A
5, 7.5, 10, 15, 20, 30, 40	Generic – Roxane	Original	15-Jul-2013	Unknown	N/A

Source: Endo response to FDA General Advice Letter, November 6, 2013

On August 13, 2012, Endo submitted a citizen petition (CP) to FDA requesting that FDA determine that OP was withdrawn for safety reasons. In addition, the Petition requested that FDA suspend or withdraw the approval of any abbreviated new drug applications (ANDAs) for generic products referencing OP (NDA 21-610). On May 10, 2013, FDA denied the Sponsor's petition based on a determination that OP was not withdrawn from sale for reasons of safety or effectiveness. In its response to Endo's CP, FDA cited among its reasons for denial data from the 2011 NDA submission indicating that OPR can be readily prepared for injection and certain data that suggest that OPR can more easily be prepared for injection than original Opana ER.¹¹ FDA's response letter also noted that the postmarketing data had multiple deficiencies and that it was not possible to draw meaningful conclusions from only 2-3 quarters of data; however the letter also noted that if one were to treat the available data as a reliable indicator of abuse rates despite the data limitations, "one of the postmarketing investigations suggested the troubling possibility that a higher (and rising) percentage of OPR abuse is occurring via injection than was the case with [original Opana ER]."

Several public health concerns have emerged in recent years related to the abuse of oxymorphone, particularly among those who inject the drug. Opana® (not specified whether ER or IR) was reported as the most frequently-injected prescription opioid

among a cluster of new hepatitis C cases in rural New York state in 2012.¹² Additionally, injection of OPR has been linked to a potentially fatal bleeding disorder resembling thrombotic thrombocytopenic purpura (TTP) in individuals who inject the drug. TTP is a rare coagulation disorder that causes microscopic clots to form in small blood vessels. The January 11, 2013 publication of the Center for Disease Control and Prevention's Morbidity and Mortality Weekly Report (MMWR) describes cases of unexplained microangiopathy hemolytic anemia and thrombocytopenia among 15 Tennessee residents, 14 of whom reported having injected OPR.¹³ Following an FDA analysis of FAERS reports, FDA issued a warning about the risk of TTP with intravenous abuse of Opana ER¹⁴ and the risk of thrombotic microangiopathy with intravenous abuse of Opana ER was added to the Abuse section (9.2) of product labeling.

In early 2015, a rural county in Indiana noted an alarming and unprecedented increase in the incidence of new HIV diagnoses among its citizens.¹⁵ Between November 2014 and November 2015, 181 new HIV cases were ultimately confirmed in Scott County, Indiana. Epidemiologic investigation revealed a high prevalence of ER oxymorphone injection and needle-sharing among the newly-infected individuals: 88% of the cases (92% of cases reporting injection drug use) reported injecting oxymorphone. FDA communications with officials involved in investigating this outbreak have clarified that cases consistently identified OPR as the primary oxymorphone product they injected.¹⁶

In January 2016, Endo submitted an application to FDA to update the OPR labeling to include a description of potential abuse-deterrent properties. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Office of Surveillance and Epidemiology (OSE), requesting a review of submitted postmarketing epidemiologic studies and spontaneous adverse event reports. While the submission was under FDA review, Endo withdrew the supplement, and plans for an FDA Advisory Committee meeting were cancelled. However, based on preliminary review, FDA was concerned that some of these data suggested that OPR may be less safe than OP, and that other oxymorphone products may also have significant abuse-related safety concerns. Endo agreed to participate in an FDA Advisory Committee meeting to publically discuss the abuse-related safety concerns surrounding Opana ER and other oxymorphone products, following submission and FDA review of an additional year of postmarketing data. Therefore, although postmarketing data were originally submitted to support a request for abuse-deterrence labeling, the current OSE review evaluates the these data from a safety perspective, with the goal of understanding the overall risk-benefit balance of OPR relative to that of OP and other oxymorphone products. The overarching purpose of this integrated OSE review is to critically evaluate the most current available postmarketing data to determine what the impact of Opana ER's reformulation has been on abuse of this product in post-approval settings, both overall and via specific routes of administration, and to interpret these findings within the context of abuse rates and patterns for comparator opioids, including OP, generic oxymorphone ER, and other selected comparators.

2 REVIEW OF POST MARKETING DATA

2.1 DRUG UTILIZATION ANALYSIS

2.1.1 Methods and Materials

Proprietary drug utilization databases available to the Agency were used to conduct this analysis to provide context for the review of the epidemiologic data on abuse patterns of oxymorphone products and selected comparators. See **Appendix B** for detailed descriptions and limitations of the databases.

2.1.1.1 Determining setting of care

The IMS Health, IMS National Sales Perspectives™ database was used to determine the settings of distribution for oxymorphone ER (brand and generic formulations) for 2015. Sales data for oxymorphone ER by bottles/packages from manufacturers to all U.S. channels of distribution revealed that approximately 92% of oxymorphone ER bottles/packages were distributed to outpatient retail pharmacies, 6% were to non-retail settings, and 2% were to mail-order/specialty pharmacies.^c As a result, only outpatient retail pharmacy utilization patterns were examined. Mail-order/specialty pharmacy and non-retail pharmacy settings data were not included in this review.

2.1.1.2 Data sources used

The IMS, National Prescription Audit™ database was used to obtain nationally estimated numbers of prescriptions dispensed for all ER/LA opioid analgesics from U.S. outpatient retail pharmacies from 2009 through 2015, annually. Additionally, this database was used to obtain nationally estimated numbers of prescriptions dispensed for OP, OPR, generic oxymorphone ER, oxymorphone IR, original OxyContin, reformulated OxyContin (ORF), original generic oxycodone ER and reformulated generic oxycodone ER from U.S. outpatient retail pharmacies from January 2009 through June 2016, quarterly.

The IMS, Total Patient Tracker™ database was used to obtain the nationally estimated number of patients who received dispensed prescriptions for OP, OPR, generic oxymorphone ER, oxymorphone IR, oxycodone ER and morphine ER, stratified by age and sex, from U.S. outpatient retail pharmacies, from 2009 through 2015, annually.

inVentiv Health Research & Insights, LLC., TreatmentAnswers™, a U.S. office-based physician survey database, was used to obtain the top four diagnosis categories associated with the drug use mentions^d for oxymorphone ER, oxymorphone IR, oxycodone ER and

^c IMS Health, IMS National Sales Perspective. Year 2015. Extracted October 2016. File: NSP 2016-323 oxymorph ER chann 10-18-16.xlsx.

^d The term "drug use mentions" to refer to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a

morphine ER for the 5-year time period from 2011 through 2015, aggregated. International Classification of Diseases (ICD-9-CM) codes were used to capture diagnosis data associated with drug use mentions. Diagnosis categories specified by the World Health Organization¹⁷ were used to group ICD-9-CM codes into the following relevant categories:

- 140-239 "Neoplasms"
- 320-389 "Diseases of the nervous system & sense organs"
- 710-739 "Diseases of the musculoskeletal system & connective tissue"
- 800-999 "Injury and poisoning"
- All other ICD-9 codes categorized as "All other categories"

2.1.2 Results of Drug Utilization Analysis

2.1.2.1 Number of ER/LA opioid prescriptions dispensed

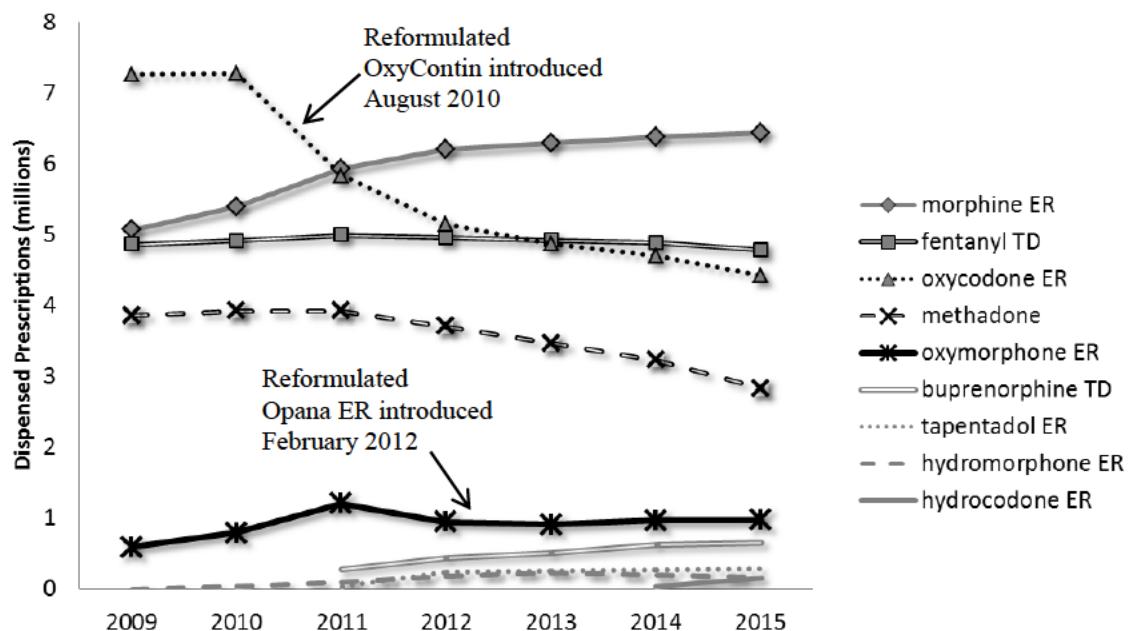
Figure 1 below and Table 1 in Appendix C show the nationally estimated number of ER/LA opioid analgesic prescriptions dispensed from U.S. outpatient retail pharmacies from 2009 through 2015, yearly. Approximately 21-22 million ER/LA opioid analgesic prescriptions were dispensed annually from 2009 through 2015. In 2015, morphine ER accounted for 31% (6.4 million prescriptions) of the total ER/LA prescriptions dispensed, a 27% increase from 2009 (5.1 million prescriptions). Fentanyl TD accounted for 23% (4.8 million prescriptions) of the total ER/LA prescriptions dispensed, with relatively consistent prescription counts during the time examined. Oxycodone ER accounted for 21% (4.4 million prescriptions), a 39% decrease from 2009 (7.3 million prescriptions).

Oxymorphone ER prescriptions—including OP, OPR, and generic oxymorphone ER—accounted for 5% (968,000 prescriptions) of the total ER/LA prescriptions dispensed in 2015, a 66% overall increase from 583,000 prescriptions dispensed in 2009. During the time examined, the number of oxymorphone ER prescriptions peaked in 2011 with approximately 1.2 million prescriptions dispensed. Morphine/naltrexone ER accounted for only 28,000 to 46,000 dispensed prescriptions annually in 2010, 2011, and 2015, and a negligible number of prescriptions dispensed annually during its withdrawal from the market between 2012 and 2014 (data not shown).^e

prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit

^e IMS Health, National Prescription Audit™. 2010-2015. Extracted October 2016. File: NPA TPT Embeda 2009-2015 10.18.2016.xlsx.

Figure 1. Nationally Estimated Number of Dispensed Prescriptions for Extended Release/Long Acting Opioid Analgesics from U.S. Outpatient Retail Pharmacies, 2009 through 2015, Annually.

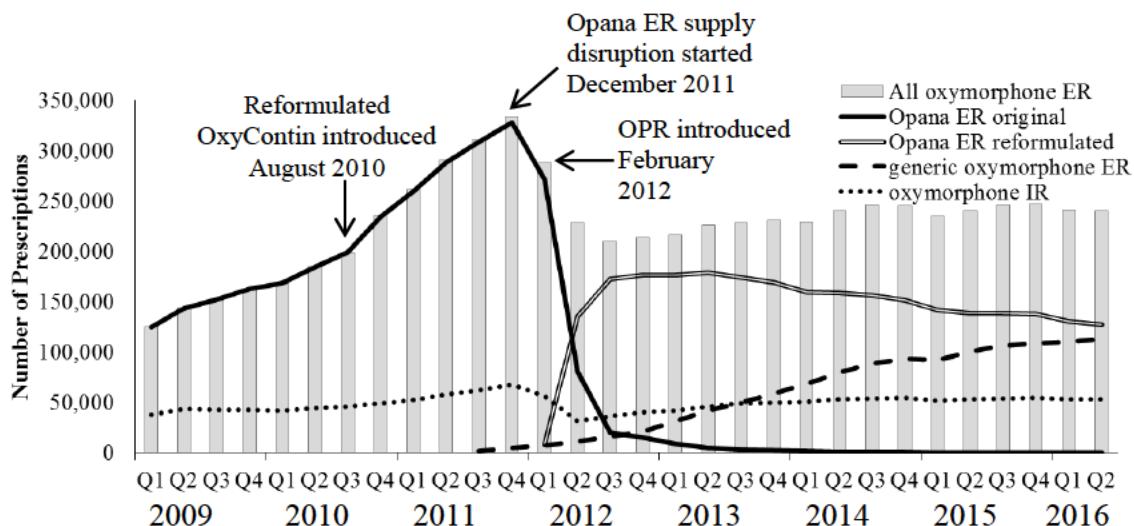


Source: IMS Health, National Prescription Audit™. 2009-2015. Extracted September 2016. File: NPA ER_LA opioids yearly 2009-2015.xlsx.

2.1.2.2 Number of OP, OPR, and generic oxymorphone ER prescriptions dispensed

Figure 2 below focuses in on the nationally estimated number of dispensed prescriptions for OP, OPR, generic oxymorphone ER, and oxymorphone IR dispensed from U.S. outpatient retail pharmacies from January 2009 through June 2016, quarterly, while **Table 2 in Appendix C** displays this data from 2009 through 2015, annually. The number of OP prescriptions dispensed more than doubled between the first quarter of 2009 (125,000 prescriptions) and the fourth quarter of 2011 (328,000 prescriptions). Around the time of the supply disruption and subsequent withdrawal from the market after OPR introduction, OP prescriptions declined sharply between the first and third quarters of 2012. This sharp decline was accompanied by a rapid increase in OPR prescriptions during this same time frame. The number of OPR prescriptions dispensed subsequently decreased steadily from approximately 179,000 prescriptions in the second quarter of 2013 to 127,000 prescriptions in the second quarter of 2016. Introduced in the third quarter of 2011, generic oxymorphone ER prescriptions steadily increased to 112,000 prescriptions dispensed in the second quarter of 2016. Oxymorphone IR prescriptions ranged between 31,000 and 67,000 prescriptions dispensed quarterly during the time examined, with a notable decrease in 2012.

Figure 2. Nationally Estimated Number of Dispensed Prescriptions for Opana ER Original, Opana ER Reformulated, Generic Oxymorphone ER, and Oxymorphone IR (Brand and Generic) from U.S. Outpatient Retail Pharmacies, January 2009 through June 2016, Quarterly.

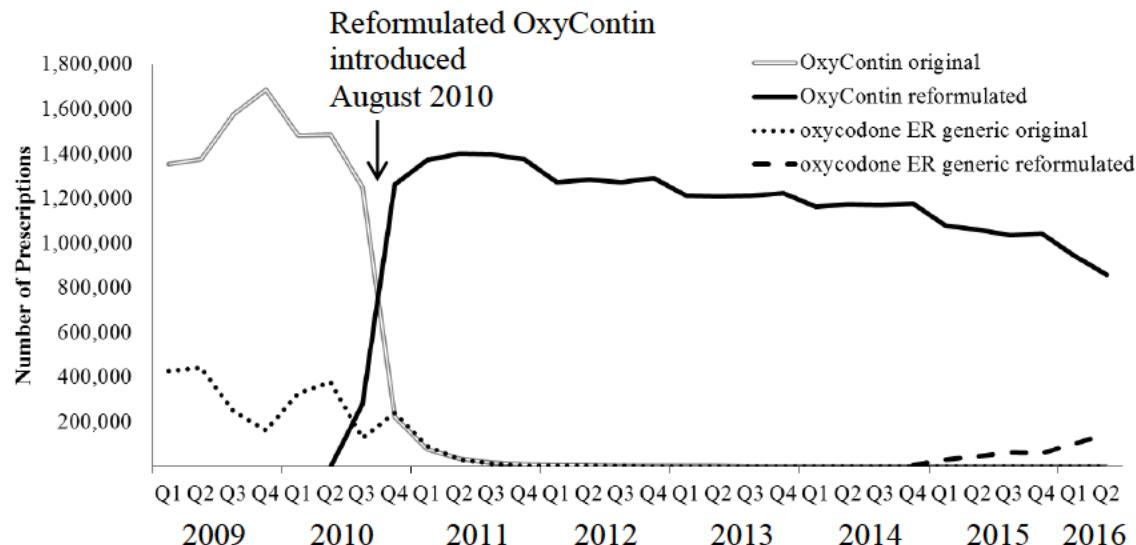


Source: IMS Health, National Prescription Audit™. January 2009 - June 2016. Extracted September 2016. File: NPA oxymorphER_IR quarterly 2009-2016.xlsx.

2.1.2.3 Number of OxyContin original, ORF, generic oxycodone ER original, and generic oxycodone ER reformulated prescriptions dispensed

In 2010, the year before OP was reformulated, OxyContin was reformulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse. **Figure 3** below displays the nationally estimated numbers of original OxyContin, ORF, generic oxycodone ER original, and generic oxycodone ER reformulated prescriptions dispensed from U.S. outpatient retail pharmacies from January 2009 through June 2016, quarterly, while **Table 3 in Appendix C** displays this data from 2009 through 2015, annually. In August 2010, distribution of the original formulation of OxyContin ceased and ORF became available in its place. As a result, the number of OxyContin original prescriptions dropped precipitously from 1.5 million prescriptions dispensed in the second quarter of 2010 to 257,000 prescriptions in the third quarter of 2010. By the end of 2011, quarterly prescriptions dispensed for OxyContin original and generic oxycodone ER original were each less than 10,000 and continued to decrease through the second quarter of 2016. Approximately 1.3 million prescriptions were dispensed for ORF in the fourth quarter of 2010 and steadily declined through the second quarter of 2016 (857,000 prescriptions). Generic oxycodone ER reformulated was introduced in the fourth quarter of 2014 and increased to 142,000 prescriptions dispensed in the second quarter of 2016.

Figure 3. Nationally Estimated Number of Dispensed Prescriptions for OxyContin Original, OxyContin Reformulated, Generic Oxycodone ER Original, and Generic Oxycodone ER Reformulated from U.S. Outpatient Retail Pharmacies, January 2009 through June 2016, Quarterly.



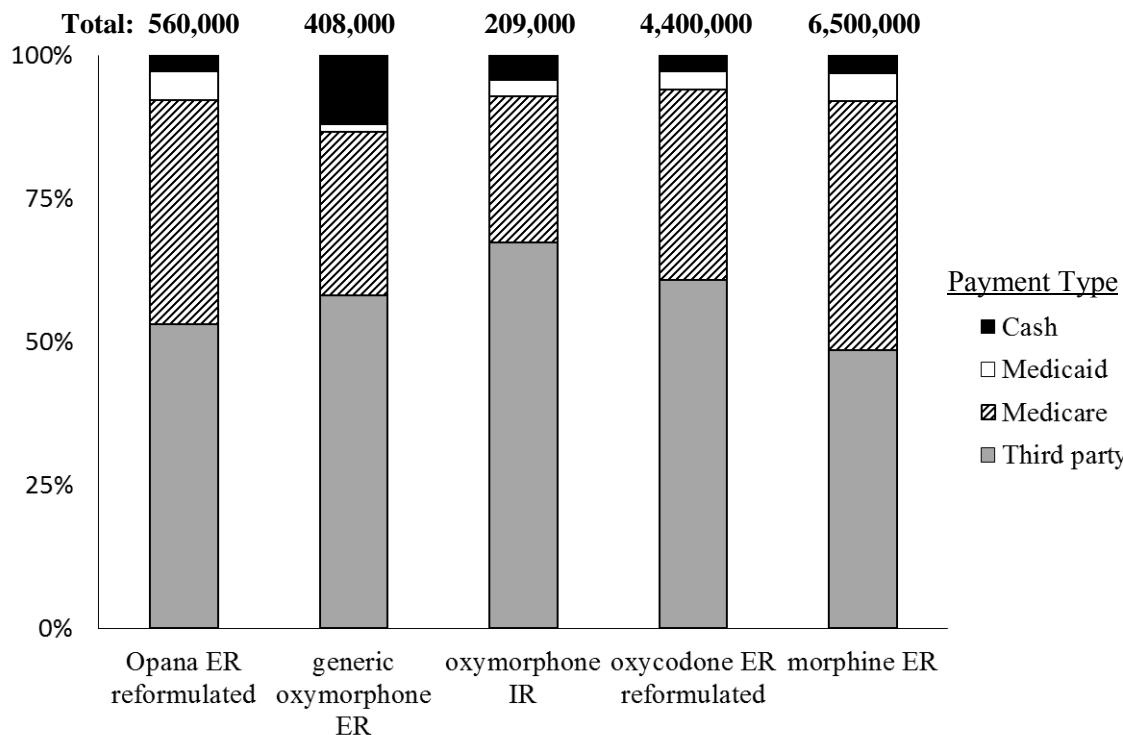
Source: IMS Health, National Prescription Audit™. 2009-2015. Extracted September 2016. File: NPA oxycodER quarterly 2009-2016.xlsx.

2.1.2.4 Number of OP, OPR, generic oxymorphone ER, oxymorphone IR, oxycodone ER, and morphine ER prescriptions dispensed, by method of payment

Figure 4 and Table 4 in Appendix C below provide the nationally estimated number of dispensed prescriptions for OPR, generic oxymorphone ER, oxymorphone IR, oxycodone ER reformulated, and morphine ER, stratified by method of payment (cash, Medicaid, Medicare, or third-party health insurance)^f, from outpatient retail pharmacies in 2015. Overall, the trends in methods of payment across products were similar during the time examined. For OPR, the majority of prescriptions (53%) were billed to third party insurance, followed by Medicare (39%). For generic oxymorphone ER, oxymorphone IR, oxycodone ER reformulated, and morphine ER, 48%-67% of prescriptions were billed to a third-party health insurance, and 26%-44% were billed to Medicare. Approximately 12% of generic oxymorphone ER prescriptions were paid in cash (the full prescription amount was billed to the patient; no amount was paid by another payer), compared to 3%-4% for the other products and formulations.

^f The method of payment indicates how the prescription was paid for by the consumer: cash, Medicaid, Medicare or third-party health insurance, such as HMO, PPO, PBM, other third-party, HMO/PBM or PPO/PBM.

Figure 4. Nationally Estimated Number of Dispensed Prescriptions for Opana ER Reformulated, Generic Oxymorphone ER, Oxymorphone IR, Oxycodone ER Reformulated, and Morphine ER,* Stratified by Method of Payment, from U.S. Outpatient Retail Pharmacies in 2015.



Source: IMS Health, National Prescription Audit™, Extended Insights. 2015. Ad-hoc analysis provided October 2016.

File: NPA adhoc oxymorphER_IR morphER oxycodER payer REVISED 10.28.16.xlsx.

*Opana ER original and oxycodone ER original were not included due to very low prescription counts in 2015.

2.1.2.5 Number of patients dispensed oxymorphone ER, oxymorphone IR, oxycodone ER, and morphine ER prescriptions, by patient age group and sex

Tables 5 and 6 in Appendix C provide the nationally estimated number of unique patients who received prescriptions for OP, OPR, generic oxymorphone ER, oxymorphone IR, oxycodone ER, and morphine ER, stratified by age group (0-39, 40-64, 65+ years) and sex, from outpatient retail pharmacies from 2009 through 2015, annually. For each of these product groups, the majority of patients dispensed the products were aged 40-64 years, and the annual age distributions did not change substantially during this time period. In general, slightly more women than men were dispensed the products. The annual number of patients dispensed OP peaked at approximately 235,000 patients in 2011, then declined sharply through 2015. The annual number of patients dispensed OPR remained approximately steady between 2012 and 2015, ranging from 117,000 to 153,000 patients. The annual number of patients dispensed oxycodone ER declined during the time examined, while the annual number of patients dispensed morphine ER increased during the same time frame.

2.1.2.6 Diagnoses associated with oxymorphone ER, oxymorphone IR, oxycodone ER and morphine ER

Table 2 below provides the top four diagnosis categories associated with drug use mentions^d of oxymorphone ER, oxymorphone IR, oxycodone ER, and morphine ER from U.S. office-based physician surveys between 2011 and 2015, aggregated. Across all products, diseases of the musculoskeletal system and connective tissue (ICD-9-CM 710 to 739) were associated with the majority (56%-77%) of drug use mentions. Examples of diagnosis codes in this category include rheumatoid arthritis (ICD-9-CM 714.1) and sciatica (724.3). Diseases of the nervous system and sense organs (ICD-9-CM 320 to 389) were associated with 11% to 16% of drug use mentions for each product. Examples of diagnosis codes in this category include pain not elsewhere classified (ICD-9-CM 338) and migraine headache (346). Injuries and poisonings (ICD-9-CM 800 to 999) comprised 3% to 11% of drug use mentions for each product, and neoplasms (ICD-9-CM 140 to 239) made up 1% to 8% of drug use mentions for each product. Compared to oxymorphone ER, oxycodone ER, and morphine ER; oxymorphone IR was associated with a higher proportion of drug use mentions associated with injury and poisoning and a lower proportion associated with diseases of the musculoskeletal system and connective tissue.

During the time examined, a nationally estimated 1.8 million oxymorphone ER drug use mentions were reported, of which 1.4 million (95% confidence interval [CI] 1.2-1.6 million) were associated with diseases of the musculoskeletal system & connective tissue.

Out of an estimated 107,000 oxymorphone IR drug use mentions, 60,000 (95% CI 19,000 – 101,000) were associated with diseases of the musculoskeletal system & connective tissue. An estimated 18,000 oxymorphone IR drug use mentions (95% CI <500 – 40,000) were associated with diseases of the nervous system & sense organs, while 12,000 (95% CI <500 – 29,000) and 6,000 (95% CI <500 – 18,000) were associated with injury & poisoning and neoplasms, respectively. Of note, the projected estimates of drug use mentions for oxymorphone IR were below the acceptable count (<100,000 drug use mentions) to provide a reliable estimate of national use.

Table 2. Diagnosis Categories Associated with Drug Use Mentions of Oxymorphone ER, Oxymorphone IR, Oxycodone ER and Morphine ER as Reported by U.S. Office-Based Physician Surveys, Stratified by Drug, from 2011 through 2015, Aggregated.

	2011 through 2015		
	Drug use mentions* (N)	Share	95% confidence interval
Oxymorphone ER	1,756,000	100%	1,537,000-1,976,000
Diseases of the musculoskeletal system & connective tissue	1,359,000	77%	1,166,000-1,552,000
Diseases of the nervous system & sense organs	187,000	11%	115,000-258,000
Injury & poisoning	57,000	3%	17,000-96,000
Neoplasms	11,000	1%	<500-28,000
All other categories	143,000	8%	80,000-205,000
Oxymorphone IR	107,000	100%	53,000-162,000
Diseases of the musculoskeletal system & connective tissue	60,000	56%	19,000-101,000
Diseases of the nervous system & sense organs	18,000	16%	<500-40,000
Injury & poisoning	12,000	11%	<500-29,000
Neoplasms	6,000	5%	<500-18,000
All other categories	13,000	12%	<500-32,000
Oxycodone ER	8,928,000	100%	8,433,000-9,423,000
Diseases of the musculoskeletal system & connective tissue	5,835,000	65%	5,434,000-6,235,000
Diseases of the nervous system & sense organs	1,328,000	15%	1,137,000-1,519,000
Injury & poisoning	418,000	5%	311,000-526,000
Neoplasms	416,000	5%	309,000-523,000
All other categories	931,000	10%	771,000-1,091,000
Morphine ER	8,449,000	100%	7,967,000-8,930,000
Diseases of the musculoskeletal system & connective tissue	5,756,000	68%	5,359,000-6,154,000
Diseases of the nervous system & sense organs	1,091,000	13%	918,000-1,264,000
Neoplasms	705,000	8%	566,000-844,000
Injury & poisoning	217,000	3%	139,000-294,000
All other categories	679,000	8%	543,000-816,000

Source: inVentiv Health Research & Insights, LLC., TreatmentAnswers™. 2011-2015. Extracted October 2016. File: PDDA oxymorpher_ER oxycodER morphER 2011-2015.xlsx.

* The term "drug use mentions" to refer to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

2.1.3 Discussion of Drug Utilization Data

Drug utilization data indicate that approximately 968,000 prescriptions for oxymorphone ER—brand and generic—were dispensed in 2015. With the launch of OPR in 2012, OPR utilization increased sharply and OP utilization correspondingly declined sharply.

However, despite the quick uptake of OPR after its introduction into the market, annual utilization of OPR in the outpatient setting did not increase to the level of utilization of OP in 2011. One possible contributing factor may have been the market introduction of generic oxymorphone ER in July 2011, which has steadily increased in market share through June 2016. An overall decrease in oxycodone ER utilization was also observed following the reformulation of OxyContin in 2010 and the exit of generic oxycodone ER from the market shortly thereafter. A limited supply of authorized generic versions of the reformulated, generic oxycodone ER was reintroduced in late 2014.¹⁸ Currently, only OxyContin generics specifically authorized by the Sponsor are available.¹⁹

Oxymorphone ER comprises a small share of the opioid analgesic market, accounting for approximately 5% of the overall ER/LA opioid analgesic market. Previously conducted FDA drug utilization reviews show that, altogether, ER/LA opioid products account for approximately 10% of the overall opioid analgesic market.¹ OP, OPR, and generic oxymorphone ER were most commonly dispensed to patients 40-64 years of age, similar to oxycodone ER or morphine ER utilization. Overall, slightly more female than male patients were dispensed oxymorphone ER.

Of note, 12% of generic oxymorphone ER prescriptions in 2015 were paid in cash directly and not paid by other methods, such as Medicare, Medicaid or a third-party health insurance. In comparison, 3-4% of OPR, oxymorphone IR, oxycodone ER reformulated, and morphine ER prescriptions were paid in cash directly by the patient. While the total number of cash prescriptions for morphine ER and oxycodone ER are greater than for generic oxymorphone ER, the proportion of generic oxymorphone ER cash prescriptions purchased without third party payer involvement is much larger. The meaning of this finding is not entirely clear; however, differences in payment source may indicate some underlying differences in the patient populations receiving these prescriptions. Some studies suggest that cash payment for controlled substances may be associated with an increased likelihood of abuse or diversion.^{20,21,22} However, factors such as insurance coverage, product pricing, and patient or prescriber preference may also play a role in product selection and payment method.

According to U.S. office-based physician surveys database, the diagnosis category "Diseases of the musculoskeletal system and connective tissue" (ICD-9-CM codes 710-739) was associated with 77% of oxymorphone ER use as well as the majority of oxymorphone IR, oxycodone ER, and morphine ER use. The diagnosis category "Diseases of the nervous system and sense organs" (ICD-9 codes 320-389) was associated with 11% of oxymorphone ER use, and categories "Injury and poisoning" (ICD-9 codes 800-999) as well as "Neoplasms" (ICD-9 codes 140-239) each were associated with less than 5% of oxymorphone ER use. Proportionally, diagnosis categories associated with oxymorphone ER use were similar to those associated with oxycodone ER and morphine ER use, with the exception of "neoplasms," which was indicated as a diagnosis less frequently for oxymorphone ER (1%) than for either oxycodone ER (5%) or morphine ER (8%).

Overall, no large differences were seen between the diagnoses associated with oxymorphone ER and those associated with morphine ER or oxycodone ER. However, the statistical accuracy of these data increases as the projected number of records increase. Data below 100,000 projected drug use mentions may not be representative of actual physician prescribing habits at a national level because results below this threshold represent insufficient raw physician responses prior to applied projection factors. The majority of the results for oxymorphone ER and oxymorphone IR fell below this threshold with wide confidence intervals. Therefore, these data should be interpreted with caution and may not represent reliable national estimates.

2.2 FAERS ANALYSIS –SPONTANEOUS ADVERSE EVENT REPORTS

The purpose of the FDA’s review of spontaneous reports was to assess and characterize reported non-oral abuse of Opana ER before and after a formulation change, to describe reported cases of thrombotic microangiopathy that have been associated with Opana ER use, and reported cases of HIV, and viral hepatitis (B and C) infections associated with Opana ER use.

2.2.1 Methods and Materials

2.2.1.1 FAERS Case Definitions

2.2.1.1.1 Non-oral abuse

For the purposes of this review, cases reporting Opana ER abuse or misuse, in terms of substance abuse, overdose, or a non-medically indicated non-oral route and reporting an event date or year were included.

2.2.1.1.2 Thrombotic microangiopathy (TMA)

A broad case definition was adopted to capture all potential cases of TTP-like illness described with injection of specific opioids, recognizing that individual cases may report signs and symptoms of TMA but not a specific diagnosis. Similar to DPV’s 2013 Opana ER and TMA review,²³ the following case definition was utilized to identify cases of TMA.

Inclusion Criteria: 1, 2, and 3

1. A) Patient known to have injected an opioid formulated with a PEO matrix [Opana ER, OxyContin, Hysingla ER, Zohydro ER, and Nucynta ER]
OR
B) Patient known to have injected a generic oxymorphone^g product
2. A) Diagnosis of TMA [which includes TTP or hemolytic uremic syndrome (HUS)]
OR
B) Thrombocytopenia AND anemia with evidence of hemolysis. [Evidence of hemolysis includes: red cell fragmentation on peripheral smear (e.g., schistocytes), elevated lactate dehydrogenase (LDH), elevated reticulocyte count (without evidence of blood loss) or elevated total bilirubin (without evidence of hepatitis)].
3. Absence of definitive evidence of an alternative etiology of TMA

^g The generic oxymorphone ER products are not known to be formulated with a PEO matrix, and were included for completeness.

2.2.1.1.3 Human Immunodeficiency Virus (HIV) and Viral Hepatitis Infections

For the purposes of these analyses, we included all HIV and hepatitis cases that met the following criteria:

Inclusion Criteria: 1 and 2 and 3

1. Injection of oxymorphone
2. Reported an event date or year
3. A) Reported diagnosis of 1) HIV or 2) hepatitis B or C
OR
B) Provided positive results of 1) HIV or 2) hepatitis B or C screening

2.2.1.2 FAERS Search Strategies

The FAERS database was searched using the strategies detailed in **Appendix D Tables 1 – 10.**

The FAERS searches were conducted using the marketing date of February 2012 to distinguish between OP and OPR in the FAERS reports. Since there was an unknown period of time after approval of OPR where both formulations were marketed, other descriptors (e.g., crush resistant, new formulation) in the case narratives were considered, in addition to event dates or years, to make a determination of which Opana ER formulation was likely used.

2.2.1.2.1 Non-oral abuse

To analyze non-oral abuse, FAERS was searched for all adverse events associated with Opana ER since approval. Reports providing an event date or year were searched for the terms *chew, inhal, insuffl, nasal, smoke, snort, inject, or intravenous* in the case narrative for further review. Chewing, which may be considered oral abuse, was included in our analysis because OPR, with properties to deter crushing, could have affected abuse by this route.

Additionally, a FAERS search for reports of non-oral abuse with all oxymorphone products (including generics) with event dates since July 2011 was conducted to identify non-oral abuse reports attributed to a generic oxymorphone product.

2.2.1.2.2 Thrombotic microangiopathy

A broad FAERS search, similar to DPV's previous review of Opana ER and TMA,²⁴ was conducted to identify additional reports of TMA received since the 2013 review. For completeness, we also searched broadly for FAERS reports of TMA prior to approval of OPR and with all other oxymorphone products (ER and IR).

A reformulated OxyContin (NDA 022272, Purdue Pharma LP) was FDA approved on April 5, 2010. Similar to OPR, the ORF tablets have a PEO matrix, which was added to deter abuse by making it more difficult to crush or dissolve the tablets. Because of the similarity in the abuse-deterrent mechanism and inactive ingredients and the possibility of intravenous abuse of ORF, we searched for reports of TMA with OxyContin.

Other approved opioids containing a PEO polymer matrix were searched similarly in FAERS for reports of TMA. These include Hysingla ER (hydrocodone bitartrate, NDA 206627, Purdue Pharma), Zohydro ER (hydrocodone bitartrate, NDA 202880, Zogenix), and Nucynta ER (tapentadol hydrochloride, NDA 200533, Janssen Pharmaceuticals).

2.2.1.2.1.1 Literature review

For completeness, and to ensure we were not missing reports of TMA with intravenous abuse of opioid products other than Opana ER, we also searched the medical literature for case reports of TMA associated with OxyContin, Hysingla ER, Zohydro ER, and Nucynta ER to supplement the FAERS searches. See **Appendix F** for the literature search strategy.

2.2.1.2.3 Human Immunodeficiency Virus (HIV) and Viral Hepatitis Infections

A broad search strategy was utilized to capture cases of HIV and hepatitis B and C infections associated with Opana ER abuse.

2.2.2 Results of FAERS Analysis

2.2.2.1 Non-Oral abuse reported with Opana ER

The search strategies retrieved 370 reports. As event date is not a required data element in FAERS, the 370 reports were filtered for reports with event dates or years, resulting in 248 reports. Of the 248 reports, 131 were excluded leaving 117 cases of non-oral abuse. Of the 131 excluded reports, 57 reports were duplicates, 58 reports were not abuse, misuse, or overdose reports, 7 reported oral abuse, 5 lacked sufficient information to assess, and 4 were not related to Opana ER. **Table 3** illustrates the 117 FAERS cases of non-oral abuse with Opana ER by ROA and event year.

Appendix G lists all the FAERS case numbers, FAERS version numbers, and manufacturer control numbers for the 117 cases in this case series.

Table 3. FAERS Cases of Non-Oral Abuse of Opana ER with Event Dates, that also Report the Terms, *chew, inhal, insuffl, nasal, smoke, snort, inject, or intravenous* in the Narrative from June 22, 2006 to June 1, 2016 (N=117)

Year of Event*	Route of Abuse			
	Chew†	Insufflate	Injecting	Total cases
2006		1		1
2007	1	7		8
2008	2	7		9
2009		7		7
2010	1	1		2
2011	1	8		9
2012‡	4	3	31	38
2013			30	30
2014			8	8
2015			3	3
2016			2	2
Total Cases	9	34	74	117

* Reports were included in this analysis only if they provided an event date or year in the FAERS report. The date or year of event is not a required data element for FDA to accept the report and place in FAERS; therefore, it can be assumed this list may not be inclusive of all reports of non-oral abuse associated with Opana ER in FAERS.

† Chewing, which may indicate oral abuse, was included in our analysis assuming OPR with properties to deter crushing, could have affected abuse by this route.

‡ Reformulated Opana ER was approved December 9, 2011 and was marketed beginning February 2012. It is expected that there would be a time period where both formulations were available to patients; however, the duration of overlap is uncertain.

OPR was approved December 9, 2011 and became available in February 2012. FAERS received 36 reports of non-oral abuse prior to approval of OPR and 81 reports of non-oral abuse after approval of OPR. Abuse via the nasal route was primarily reported during the time OP was marketed. In 2012, reports of injecting Opana ER emerged in FAERS. This coincides with the introduction of OPR, and also with the introduction of the lower dosage strengths of generic oxymorphone ER products.

Table 4 characterizes the 117 FAERS cases reporting non-oral abuse for this case series.

Table 4. Descriptive Characteristics of Opana ER Non-Oral Abuse FAERS Cases with Event Dates Between June 22, 2006 and June 1, 2016 (N=117)

Sex (n=103)	Male Female	57 46
Age in years (n=92)	Mean Median Range	31 28 14 – 59
Country/ Reporter's State (n=102)	United States AR (4); CA (1); CO (4); FL (2); GA (1); IN (2); KY (3); MD (1); MI (1); MN (1); NC (23); NY (3); OH (5); PA (3); SC (1); TN (41); VA (1); WA (1); WI (1); WV (2); WY (1)	117
Reporter (n= 102)	Consumer Health care provider	17 85
Report Type	Expedited (15-Day) Direct Non-Expedited	104 7 6
Serious Outcomes* (n=116)	Death Hospitalization Life-threatening Disability Other serious	22 59 7 1 93
Preferred Terms†	Drug abuse Incorrect route of drug administration Wrong technique in product usage process Thrombotic thrombocytopenic purpura Acute kidney injury Microangiopathic haemolytic anaemia Overdose Intentional product misuse Thrombotic microangiopathy Haemolytic uraemic syndrome Hepatitis C Thrombocytopenia Toxicity to various agents Endocarditis Anaemia Drug diversion Intentional product use issue Thrombocytopenic purpura	84 69 63 28 27 20 18 18 15 11 9 8 8 7 6 6 6 6

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events. A report may have one or more outcome.

† Most frequently reported MedDRA preferred terms with N ≥ 6. A report may include more than one preferred term.

FAERS received a similar number of cases of non-oral abuse of Opana ER for both males and females, with a median age of 28 years (range, 14 – 59 years). Of the 117 cases, 102 cases provided a reporter state, of which 21 states were represented. Cases of chewing and insufflation (31/102) were reported from 18 states across the country. The cases of intravenous abuse (71/102) were reported from 11 states including Minnesota and Arkansas and east, from New York to Florida. Reports from two states, Tennessee and North Carolina, jointly accounted for 63% (64/102) of the cases. Forty-one cases from

Tennessee were identified: six cases of nasal abuse from 2006 and 2009 in eastern Tennessee and 35 cases of intravenous abuse from 2012 and 2013 in central and eastern Tennessee. Approximately 96% (22/23) of the cases from North Carolina reported intravenous abuse from 2012 to 2016 in central and western North Carolina; the remaining case describes abuse of OP by crushing and snorting in 2012. In the case series, two cases reported event dates in 2016. Both were reported from North Carolina and describe intravenous abuse of Opana ER, with one case reporting concomitant intravenous abuse of MS Contin 60 mg.

Twenty-two cases reported an outcome of death; 12 individuals died from overdose from 2006 through 2011, and 10 died from 2012 through 2015 — 6 from overdose and 4 from acute infectious complications of intravenous abuse.

The most frequently reported MedDRA preferred terms ($n \geq 6$) for this case series of non-oral abuse are reported in Table 4 above. These preferred terms are consistent with the known adverse event profile of Opana ER or with known complications of intravenous drug abuse.

An additional search for non-oral abuse reported with all oxymorphone products, did not identify any non-oral abuse reports that could be attributed to a generic oxymorphone product. However, this additional search did identify five additional reports of injecting OPR in 2012-2014, one report of chewing the “new crush resistant” Opana ER in 2012, and one report of chewing Opana ER in 2015.

2.2.2.2 Thrombotic Microangiopathy

DPV’s 2013 review of Opana ER and TMA²⁵ evaluated 29 cases received from December 9, 2011 through March 26, 2013. Most of the patients were from a single rural county in northeast Tennessee, although a few cases were reported from counties in middle Tennessee, and one report was from North Carolina. In general, all of the patients had some or all of the findings of schistocytes, microangiopathic hemolytic anemia (MAHA), elevated lactate dehydrogenase (LDH), thrombocytopenia and varying degrees of renal insufficiency and neurologic findings after intravenous abuse of Opana ER. Treatment was reported for 23 patients; 17 were treated with plasmapheresis, one patient received dialysis, one required plasma exchange, one needed platelet transfusion, and three did not require treatment.

Following DPV’s review of Opana ER and TMA, the risk of TMA with intravenous abuse of Opana ER was added to the Abuse section (9.2) of product labeling.

FAERS was similarly searched to identify additional cases of TMA received from March 27, 2013 through June 1, 2016. The FAERS search retrieved 34 reports. After applying the case definition, four reports were excluded; one did not meet inclusion criteria and three were duplicates. Thus, 30 cases were included in the case series.

Table 5 summarizes characteristics of the 30 cases of TMA associated with intravenous abuse of Opana ER in this case series. **Appendix H** lists all the FAERS case numbers,

FAERS version numbers, and manufacturer control numbers for the 30 cases in this case series.

Table 5. Descriptive Characteristics of TMA Reported with Intravenous Abuse of Opana ER from March 27, 2013^{*} to June 1, 2016 (N=30)

Sex	Male (15)	Female (15)	
Age (n=30)	Mean: 32 years	Median: 28 years Range: 19 – 52 years	
Reporter's State	AR (3); FL (1); NC (17); PA (2); SC (3); TN (3); Unknown (1)		
Initial FDA Received Year	2013	8	
	2014	17	
	2015	4	
	2016	1	
Event Year	2013	8	
	2015	1	
	Unknown	21	
Report Type	Direct	5	
	Expedited (15-Day)	25	
Serious Outcomes (n=29) [†]	Death	1	
	Hospitalization	27	
	Life-threatening	4	
	Other serious	25	
Preferred Terms [‡]	Thrombotic thrombocytopenic purpura	19	
	Drug abuse	18	
	Microangiopathic haemolytic anaemia	15	
	Acute kidney injury	12	
	Incorrect route of drug administration	11	
	Thrombotic microangiopathy	11	
	Hepatitis C	7	
Platelet Count on Admission (n=21)	Median: 65 x 10 ³ /µL	Range: 5 – 135 x 10 ³ /µL	
Serum creatinine on Admission (n=16)	Mean: 3.75 mg/dL	Median: 1.94 mg/dL	Range: 0.4 – 14.4 mg/dL
Hemoglobin on admission (n=7) [§]	Median: 8.4 g/dL	Range: 5.8 – 11.2 g/dL	
Treatment (n=25)	Plasmapheresis (9)	Hemodialysis (4)	
	Platelet transfusion (1)	Supportive care (13)	Splenectomy (1)
ADAMSTS13 (n=13) [¶]	Median: 66%	Range: 23 – 105%	
LDH (n=15) ^{**}	Median: 554 U/L	Range: 294 – 4000 U/L	
Schistocytes	Present (10)	Not reported (20)	
Hepatitis C (n=13)	Positive (9)	Negative (1)	Previously diagnosed (3)
Infectious comorbid conditions (n=11)	Endocarditis (6)	Bacteremia (2)	Sepsis (3)
ADAMSTS13 = A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13; LDH = Lactate dehydrogenase			
[*] DPV's last review of Opana ER and TMA searched for reports received prior to this date. ³			
[†] One case may report more than one outcome.			
[‡] Most frequently reported MedDRA preferred terms with N ≥ 5, although none of the PTs were reported 5 or 6 times.			
[§] Four additional cases did not report hemoglobin values. Results were reported as reticulocytosis.			
One case may report more than one treatment.			
[¶] Additional 4 cases reported "normal" ADAMSTS13 results.			
^{**} One additional case reported "elevated" LDH.			

All cases reported intravenous abuse of Opana ER. Approximately equal cases were reported in males and females with a median age of 28 years. One patient was pregnant; she required a single plasma exchange treatment for the thrombotic events and antibiotic treatment for septic arthritis. The majority of the reports were submitted via literature reports in 2014. Of the 30 reports, 22 were literature reports.^{26,27,28,29,30,31} The largest number of cases came from Wake Forest School of Medicine, Winston-Salem, NC.^{11,12} The authors discussed the use of supportive care in Opana ER-induced TMA or MAHA in lieu of the standard of care, plasmapheresis.

Four FAERS cases were retrieved from 2015 and one from 2016. Of the four cases from 2015, two were spontaneous reports from North Carolina that identified OPR abuse – one occurred as recently as March 2015 and the other case noted the event occurred “sometime in the previous 12 months.” The two remaining reports from 2015 and the report from 2016 were sourced from medical literature and were reported from Florida, Pennsylvania, and South Carolina, respectively. The case report from South Carolina reported abuse of OPR.

There was one FAERS case (#9498513) with an outcome of death. This death, reported in 2013, was due to intractable sepsis and endocarditis; the case further detailed that TTP improved considerably after three plasmapheresis treatments with recovery of platelet counts prior to death. Another FAERS case (#9455798) of interest was also reported in 2013. It described injection of both morphine sulfate ER and Opana ER; however, the patient signed out of the hospital against medical advice prior to receiving plasmapheresis for her newly diagnosed TTP, and no follow-up was provided.

In the case series, the median platelet count on admission was $65 \times 10^3/\mu\text{L}$ (range, 5 – $135 \times 10^3/\mu\text{L}$). Sixteen cases reported a serum creatinine on admission. The mean was 3.75 mg/dL (range, 0.4 – 14.4 mg/dL). Neurologic sequelae were reported in two cases: one with neurologic impairment and one with cerebrovascular accident and persistent visual disturbances. Six cases reported admission blood pressures of 140/90 mmHg or greater or reported hypertensive emergency/urgency. None of the patients were reported as HIV-positive. In general, all patients had some or all of the findings of schistocytes, MAHA, elevated LDH, thrombocytopenia and varying degrees of renal insufficiency and neurologic findings.

The FAERS search for cases of TMA prior to the approval of OPR retrieved zero reports.

The FAERS search for cases of TMA with all oxymorphone products (ER and IR) retrieved 113 reports. Zero cases described intravenous abuse of a generic oxymorphone (ER or IR) product and TMA. This search did, however, identify three additional cases^h of TMA with intravenous abuse of Opana ER; all reported the reformulated version.

^h 1) FAERS case # 11048286, received April 2015. 2) FAERS case #9019472, received January 2013. 3) FAERS case #12510194, received June 2016.

The FAERS search for cases of TMA with OxyContin retrieved 148 reports. Three cases, all from Australia, met the case definition for TMA and are described in more detail below.

FAERS Case #10299601, Received July 2014, Australia, Literature³²

A 29-year-old female with a history of anxiety and depression had been purchasing reformulated OxyContin 20 mg tablets without a prescription to crush and inject the drug intravenously since April 2014. The patient had previously crushed and injected the original OxyContin after buying it on the streets without a prescription. On [REDACTED] and [REDACTED] (b) (6) she was hospitalized with TTP and kidney injury. Admission labs for her [REDACTED] (b) (6) hospitalization were platelet count of $30 \times 10^3/\text{mcL}$ (normal 150-400) and creatine [creatinine] clearance 95 $\mu\text{mol}/\text{L}$ (normal 46-90). She was diagnosed with MAHA and had renal failure and severe thrombocytopenia. Differential diagnosis was TTP. A renal biopsy was not performed. She also developed blurring vision due to retinal ischemia, probably related to TTP. Treatment included plasma exchange, fresh frozen plasma (FFP), platelet transfusions and supportive care. At the time of her [REDACTED] admission, her platelet count was $8 \times 10^3/\text{mcL}$ (normal 150-400), hemoglobin 81 g/L (normal 115-160), creatinine renal clearance 118 $\mu\text{mol}/\text{L}$ (normal 46-90) with a glomerular filtration rate of 54 ml/min, lactate dehydrogenase 1630 U/L, and blood bilirubin 51 $\mu\text{mol}/\text{L}$ (normal < 20). Treatment included plasma exchange and oral prednisolone. She recovered from the events on [REDACTED] (b) (6) (platelet count was $314 \times 10^3/\text{mcL}$ (normal 150-400); creatine [creatinine] clearance 77 $\mu\text{mol}/\text{L}$ (normal 46-90)) and was discharged from the hospital. Outcome of the blurry vision was not reported.

Reviewer's comments: There is temporal association of intravenous abuse of ORF and the diagnosis of TTP in this case. The clinical course and available laboratory data described in this case are consistent with those described in individuals known to have intravenously abused Opana ER.⁸ The patient was successfully treated with plasma exchange and steroids. The subjective history provided in the FAERS case, above, is different from the corresponding published case report; however, the objective details are identical. On April 1, 2014, the original formulation of OxyContin was withdrawn from the Australian market and replaced with a PEO-containing reformulated version.^{33,34}

FAERS Case #11906673, Received January 2016, Australia

A 28-year-old male reported dissolving three 80 mg OxyContin in water, then boiling and injecting it into his vein, half in the morning and half in the evening on October 1, 2015. He presented to the emergency department with abdominal pain and vomiting on [REDACTED] (b) (6). On admission his labs were creatinine 218, lactate dehydrogenase 1400, bilirubin 112, and platelets 59. [The units and normal ranges were not provided]. The patient left against medical advice and was readmitted with abdominal pain on [REDACTED] (b) (6). His labs on admission were creatinine 283, platelets 90, hemoglobin 93 [g/L], LD 586, haptoglobin 0.03, ADAMTS 13 > 68%. He was diagnosed with atypical HUS and received supportive care. He was discharged from the hospital on [REDACTED] (b) (6). He reported he injected OxyContin only one time on October 1, 2016.

Reviewer's comments: The past medical history and medication history were not reported and; therefore, it is unknown if there could be an alternative etiology or contributing factor. However, this case does demonstrate temporal association of intravenous abuse of ORF and diagnosis of atypical HUS. The clinical course and available laboratory data described in this case are consistent with those described in individuals known to have intravenously abused Opana ER.⁸

FAERS Case #11617284, Received October 2015, Australia, Literature³⁵

A 56-year-old male with an unknown past medical history presented with a 3-day history of periumbilical abdominal pain. Prior to admission, he was injecting the new tamper-resistant OxyContin (Mundipharma; Sponsor)ⁱ over the previous 5 weeks because the crushable formulation was no longer available. His labs show a hemoglobin level of 87 g/L (normal, 135-180 g/L), a total white cell count of 15.0 x10⁹/L, a neutrophil count of 10.84 x 10⁹/L (normal 2-8 x 10⁹/L), a monocyte count of 1.47 x 10⁹/L (normal, 0.1-1.0 x10⁹/L) and a platelet count of 53 x 10⁹/L (normal, 140-400 x 10⁹/L). Electrolyte levels were normal, and serum creatinine level was normal at 66 µmol/L. The patient's unconjugated bilirubin level was 34 µmol/L (normal, <20 µmol/L) and lactate dehydrogenase level was 7639 U/L (normal, 150-280 U/L); other liver function test results were normal. His reticulocyte count was 168 x10⁹/L (normal, 10-100 x 10⁹/L), haptoglobin level was 0.04 g/L (normal, 0.36-1.95 g/L) and Coombs test result was negative. Three percent of his red blood cells were fragmented and polychromasia was present, consistent with microangiopathic haemolytic anaemia. ADAMSTS13 activity was 70% (normal, 40%-130%). His serological tests were negative for hepatitis B, hepatitis C, and HIV. He was successfully treated with supportive care which was noted by his improving laboratory parameters.

Reviewer's comments: This case demonstrates temporal association between intravenous abuse of ORF and the diagnosis of MAHA. The clinical course and available laboratory data described in this case are consistent with those described in individuals known to have intravenously abused Opana ER.⁸

FAERS searches for reports of TMA and Hysingla ER (hydrocodone bitartrate, NDA 206627, Purdue Pharma) and Zohydro ER (hydrocodone bitartrate, NDA 202880, Zogenix) retrieved zero reports. A FAERS search for reports of TMA and tapentadol hydrochloride retrieved eight reports; however, upon further review they did not report intravenous abuse or TMA.

2.2.2.2.1 Literature Review

The medical literature searches in PubMed retrieved two cases of TMA with OxyContin. Both cases were also retrieved in FAERS (#10299601, 11617284) and have been summarized above. Zero cases of TMA were retrieved with the Hysingla ER, Zohydro ER, and Nucynta ER literature searches.

ⁱ OxyContin manufactured by Mundipharma is not available in the US.

2.2.2.3 Human Immunodeficiency Virus Infections

The FAERS search for OP and HIV retrieved 18 reports. Twelve reports did not describe intravenous drug abuse and were not HIV cases. The remaining six reports described injecting Opana ER; however, five reported negative HIV results and one likely involved OPR. The OPR case (FAERS # 11239565) occurred in April 2015 and is described below.

The FAERS search for OPR and HIV retrieved 10 reports. Of the 10 reports, 9 were excluded: 8 were not HIV reports and 1 reported HIV in the past medical history but was not an intravenous abuse case. One case reported a new diagnosis of HIV after intravenous abuse of Opana ER.

Thus, two cases are included in this case series of HIV associated with intravenous abuse of Opana ER. Both cases describe new HIV diagnoses and both likely involved OPR. Additionally, both were sourced from [REDACTED] (b)(6) (i.e., [REDACTED] (b)(6) and [REDACTED] (b)(6)) in 2015 and are described in more detail below.

FAERS Case # 11005182, Received April 2015

A 49-year-old male was interviewed by [REDACTED] (b)(6) on the [REDACTED] (b)(6) for injecting Opana and being diagnosed with HIV. He was no longer able to snort the medication to which he became addicted, and he found a way to remove the drug's hard coating and receive Opana's powerful dose all at once by injection. He had no plans to quit injecting Opana and had done it three times by two in the afternoon. Reportedly, he stated "I'd like to say that I'm going to quit, but I'd probably be lying to you."

Reviewer's comments: In this case, the drug intravenously abused was described as Opana. The Opana was likely OPR based on the patient's descriptions – hard coating and unable to be snorted. This [REDACTED] (b)(6) report lacks clinical details; however, intravenous drug abuse is a well-known risk factor for acquiring HIV.

FAERS Case # 11239565, Received July 2015

A 28-year-old male was interviewed by [REDACTED] (b)(6) in a piece titled [REDACTED] (b)(6) on June 19, 2015. His past medical history is positive for intravenous drug abuse, OxyContin since 2007 and Opana ER since 2012. He often reused needles more than 100 times and shared them with two to three people each round. He was tested positive for HIV early 2015 and has since initiated HIV medication and enrolled in a drug detoxification program.

Reviewer's comments: In this case, the drug intravenously abused is Opana ER. This report lacks sufficient information to make further assessments of Opana ER. This [REDACTED] (b)(6) report lacks clinical details; however, this is a case of intravenous drug abuse with multiple users which is a well-known risk factor for acquiring HIV.

2.2.2.4 Viral Hepatitis Infections

A FAERS search for OP and hepatitis B or C retrieved 16 reports. We did not identify any reports of hepatitis B or C associated with intravenous abuse of OP: 15 were coroner's reports noting hepatic changes, 1 report was a duplicate, and 1 reported a new diagnosis of hepatitis C subsequent to the intravenous abuse of OPR in July 2012.

A FAERS search for OPR and hepatitis B or C retrieved 12 reports. After applying the case definition, 2 reports were excluded: 1 was a duplicate, and 1 lacked temporal association to Opana ER exposure. The 10 remaining cases (along with the 1 case identified through the OP search) were included in the case series, of which 9 patients were newly diagnosed with hepatitis C and 1 patient screened positive for hepatitis C. The FAERS reports did not provide details on the laboratory tests utilized.

The screening and diagnosis of hepatitis is part of routine evaluation for infectious diseases in known intravenous drug abusers. Hepatitis was not the primary adverse event being reported in these FAERS cases; therefore, further assessment was limited by lack of information in the reports.

Appendix I lists all the FAERS case numbers, FAERS version numbers, and manufacturer control numbers for all 11 of the newly diagnosed hepatitis C cases identified from FAERS.

2.2.3 Discussion of FAERS Data

We identified 117 FAERS cases of non-oral abuse of Opana ER received from June 22, 2006 to June 1, 2016. Most of the cases received prior to approval of OPR in late 2011 described nasal abuse, and most cases received after approval of OPR described intravenous abuse. Although FAERS data cannot be used to inform how the rates of abuse may have changed, these findings are qualitatively consistent with a shift from nasal to intravenous abuse of Opana ER following its reformulation. Although we did not identify any cases of non-oral abuse of a generic oxymorphone product, this FAERS assessment has important limitations that must be considered when interpreting this finding. Spontaneous postmarket data often do not contain enough product-identifying information (e.g., generic product manufacture, NDC number) necessary for identifying specific products, particularly generic products. Further, misclassification of reports as brand or generic is common,³⁶ and brand names (e.g., Opana, Opana ER) may be more likely to be reported due to familiarity with the name. Therefore, even when the brand name "Opana ER" is mentioned in a report, we cannot be completely certain that the brand product was actually used. For this case series, it is possible that some of the 117 Opana ER non-oral abuse cases may have been misclassified (e.g., involved a generic oxymorphone product). Thus, the absence of non-oral abuse reports for generic oxymorphone products in FAERS does not provide evidence that generic oxymorphone products are not being abused via non-oral routes.

We provided an update on cases of TMA associated with intravenous abuse of Opana ER. FAERS continues to receive reports of TMA in individuals who abuse Opana ER

intravenously. Our analysis of these cases is consistent with the risk described in current OPR labeling. Overall, there have been 59 cases of TMA with Opana ER reported to FAERS from December 9, 2011 through June 1, 2016. These cases coincide with the emergence of intravenous abuse of Opana ER reported to FAERS. Zero cases of TMA were retrieved prior to the approval of OPR, when nasal abuse was predominantly reported to FAERS. We did not identify any cases of TMA associated with generic oxymorphone products. However, as previously stated given the limitations of data quality in FAERS, the lack of reports for the generic oxymorphone products should be interpreted with caution. FAERS searches for cases of TMA with other opioids containing a PEO polymer yielded three foreign cases with OxyContin and zero U.S. cases. There is plausibility (i.e., PEO polymer) by which OxyContin may be associated with TMA³⁷; however, our ability to assess these cases is limited because the formulation of the foreign OxyContin product may be different than the OxyContin product marketed in the U.S. We did not identify any reports of TMA associated with the opioids Hysingla ER, Zohydro ER, or Nucynta ER, which are also formulated with a PEO polymer.

Intravenous abuse of any drug product carries risk of infectious diseases (e.g., HIV and viral hepatitis) inherent to the ROA and not properties of the drug. Consistent with the emergence of FAERS reports of intravenous abuse of Opana ER, we identified FAERS cases of HIV and hepatitis C. This contrasts with zero reports of HIV or hepatitis C that were identified in patients prior to approval of OPR.

Spontaneous adverse event data, such as those derived from FAERS, have limitations, including under reporting. In particular, cases of drug abuse are likely under reported to FAERS because abusers themselves are unlikely to report. As previously noted, it is expected that there would be a time period of overlap when both Opana ER formulations were available and used. Only cases that reported an event date or year were included in these analyses to allow potential inference of which Opana ER formulation (OP or OPR) may have been used. However, event dates or years are not required data elements for the agency to accept FAERS reports; therefore, the event date field is not always populated, and those reports were not captured in our analyses.

FAERS reporting may also be stimulated due to news media coverage and interest in the medical community to publish. FDA and CDC previously communicated about intravenous abuse of Opana ER and the risk of TTP-like illness via a warning statement³⁸ and Morbidity and Mortality Weekly Report (MMWR),⁶ respectively. The 2015 HIV outbreak linked to the intravenous abuse of Opana ER in southern Indiana also drew national and international headlines. Given the spontaneous nature of adverse event reports and the limitations described, these data cannot be used to inform the rate of abuse or associated abuse-related events (e.g., TMA, HIV, viral hepatitis infections) with use of Opana ER.

2.2.4 FAERS Review Conclusions

DPV identified FAERS cases of non-oral abuse associated with Opana ER before and after reformulation. Nasal abuse was primarily reported before reformulation and

intravenous abuse was primarily reported after reformulation. These findings are qualitatively consistent with a shift from nasal to intravenous abuse of Opana ER following its reformulation. FAERS continues to receive reports of TMA associated with intravenous abuse of OPR, which is a known risk and consistent with current OPR labeling. DPV did not identify any FAERS cases of TMA associated with intravenous abuse of generic oxymorphone products or the PEO-containing opioids, Hysingla ER, Zohydro ER, or Nucynta ER. DPV identified three foreign cases of TMA associated with intravenous abuse of OxyContin, which also contains a PEO polymer; however, no U.S. cases were identified. Additionally, we note FAERS reports of HIV and viral hepatitis temporally associated with intravenous abuse of Opana ER. Based on the limitations of spontaneous postmarket data, the FAERS data should not be used to make conclusions about rates of abuse or abuse-related events, such as TMA or infectious etiologies.

2.3 POSTMARKETING EPIDEMIOLOGIC STUDIES

2.3.1 Methods and Materials

In this review, DEPI evaluates four postmarketing epidemiologic studies submitted by the Sponsor:

1. National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) Final Report – Post Market Epidemiology Study to Evaluate Abuse of OPANA ER Extended-Release Tablets (received December 23, 2016): **Hereafter referred to as the “NAVIPPRO® Study,”** and associated MS excel spreadsheet tables provided
2. Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System Report – Analysis of Reformulated Opana ER using the RADARS® System Poison Center Program (received November 30, 2016): **Hereafter referred to as the “RADARS® Poison Center (PC) Study”**
3. RADARS® System Report – Analysis of Reformulated Opana ER using the RADARS® Drug Diversion Program (received November 30, 2016): **Hereafter referred to as the “RADARS® Drug Diversion (DD) and Street Price Study”**
4. RADARS® System Report – Street Prices of Opana ER (received November 30, 2016): **Hereafter referred to as the “RADARS® StreetRx Study.”**

In addition, this review discusses selected data, analyses, and other information from interim reports for the above studies. These reports and IR responses were submitted to FDA in January 2016 under Supplement 009, subsequently withdrawn, and resubmitted as general correspondence, upon FDA request, on January 20, 2017. We also reference data, analyses, and clarifications submitted in response to FDA’s requests for information, sent June 1, 2016 and July 11, 2016, based on the January 2016 interim reports. Updated responses to FDA information requests regarding the RADARS® PC and DD studies were received November 30, 2016.

This review critically evaluates the above studies’ data sources, methods, and results from an epidemiologic perspective, using the 2015 FDA guidance on evaluation of abuse-deterrent opioids³⁹ as a point of reference, recognizing that Endo withdrew its supplemental application seeking abuse-deterrent labeling in August 2016. The FDA guidance categorizes postmarket studies as either formal studies or supportive information. Per the guidance, formal studies are hypothesis-driven, population-based, observational evaluations that follow good epidemiological practices and use outcomes that provide meaningful measures of abuse. Supportive information can provide additional context on societal, behavioral, and clinical aspects of abuse. Based on the FDA guidance, we considered the first two epidemiologic studies (NAVIPPRO® and RADARS® PC) to be formal studies, and the RADARS® DD and Street Price and StreetRx studies supportive information.

Please note: Names and abbreviations used for opioid products, particularly for original and reformulated Opana ER, varied in the study reports submitted. For brevity, this review refers to original Opana ER as OP and reformulated Opana ER as OPR. However, reformulated Opana ER is referred to in figures and tables excerpted from NAVIPPRO® study reports as Opana ADF (Abuse-Deterrent Formulation) and, from the RADARS® study reports, as Opana CRF (Crush-Resistant Formulation).

2.3.2 NAVIPPRO® Study

2.3.2.1 Study Methods

2.3.2.1.1 Data Source

The National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) is a cross-sectional surveillance system that measures patterns of abuse of opioid analgesics and other drugs. The Addiction Severity Index – Multimedia Version (ASI-MV®) is a proprietary data collection tool used by sites in the NAVIPPRO® system. The ASI-MV® is a self-administered, structured, computerized interview that collects information from adults being assessed for substance abuse disorders within a network of substance abuse treatment centers and other settings. 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.

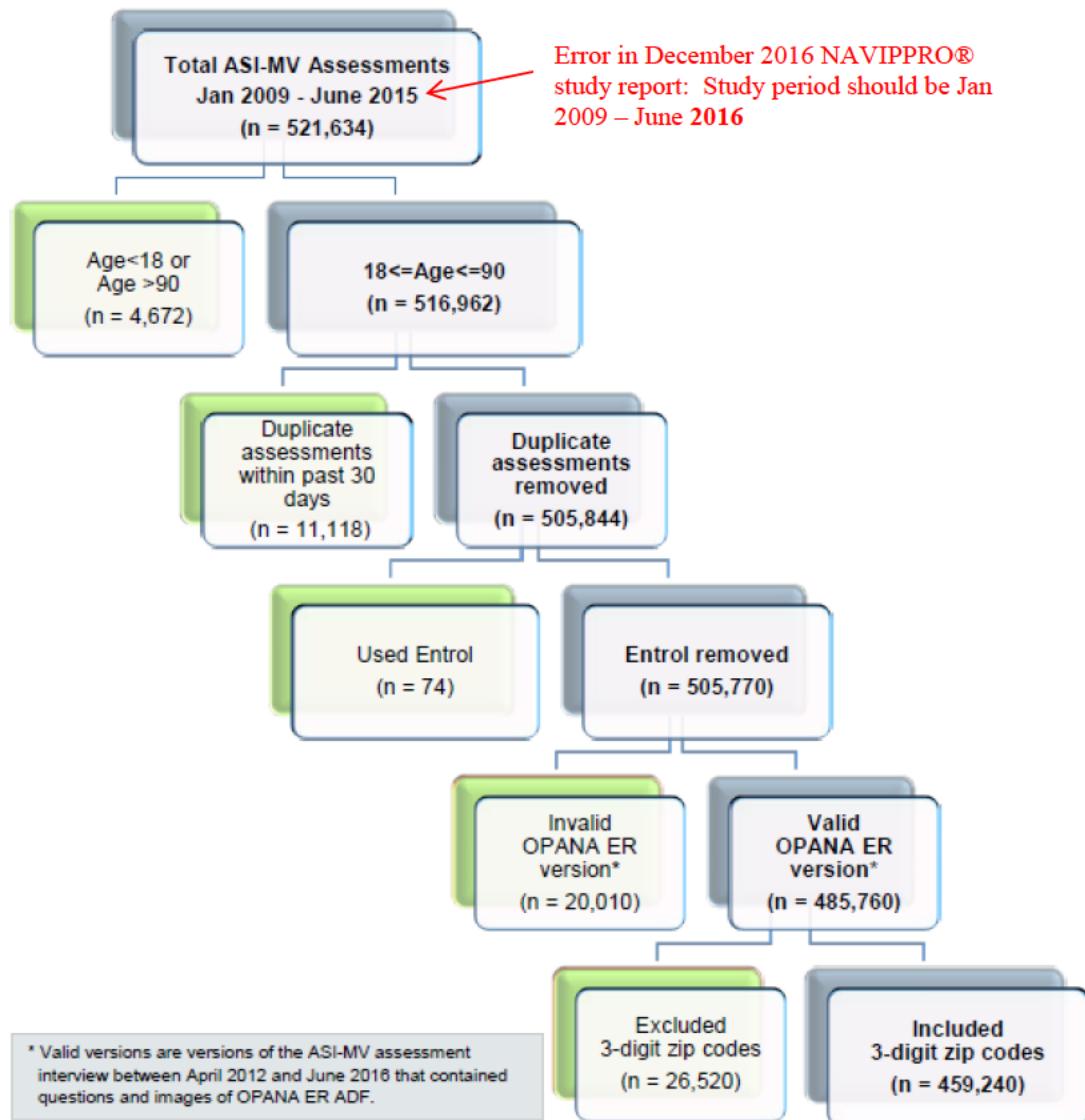
Prescription dispensing data for opioid products were obtained from IMS Health LifeLink® Longitudinal Prescription (LRx) Data (Danbury, CT, USA), and are based on projections from the National Prescription Audit™ (NPA). These data cover more than 70% of prescription activity in the U.S., including retail, mail service, and long-term care pharmacies and provide national level projected prescription tracking. The database produces projected total prescriptions and dosage units dispensed at various levels of aggregation, including state and 3-digit ZIP code for all opioid products and available dosage strengths.

2.3.2.1.2 Population

The study population includes adults (aged ≥18 years) who were assessed for substance abuse treatment using the ASI-MV® at a site participating in the NAVIPPRO® surveillance program during the study period. **Figure 5** shows how the final analytic sample was derived, resulting in a final sample of 459,240 assessments from 1,084 sites in 40 states, after inclusion and exclusion criteria were applied. To exclude sparse data on outliers, the analytic sample includes only patient 3-digit ZIP codes contributing at least five assessments during the study period and at least one assessment during each year of the study period. Duplicate cases were also removed, defined as individuals who had taken an ASI-MV® assessment more than once within a 30-day period. “Entrol” is a fake drug name included in the interview as a negative control to identify likely unreliable

responses. As the ASI-MV® assessment tool changes regularly to incorporate changes in the prescription opioid market, beginning in April 2012, only assessments using the ASI-MV® version containing questions and images for OPR were included in the analytic sample.

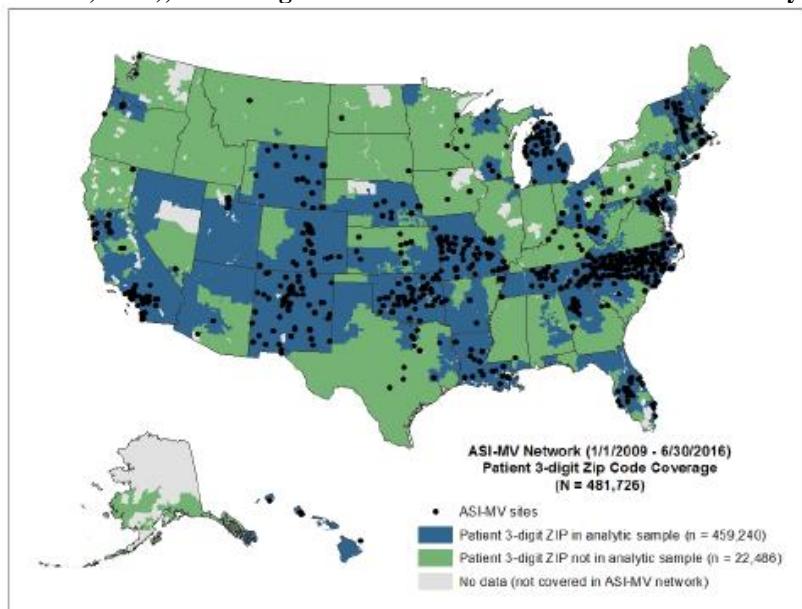
Figure 5. Study sample selection inclusions and exclusions



Source: NAVIPPRO® study report (December 2016)

Figure 6 shows the geographic distribution of sites participating in the ASI-MV® network and home 3-digit ZIP codes of adults assessed for substance abuse disorders within the network at any time during the study period, noting those ZIP codes included (blue) and not included (green) in the analytic sample.

Figure 6. Distribution of sites and home 3-digit ZIP codes of adults assessed for substance abuse disorders within the NAVIPPRO® ASI-MV® network during the study period (January 1, 2009 – June 30, 2016), indicating those included and not included in the analytic sample



Source: NAVIPPRO® study report (December 2016)

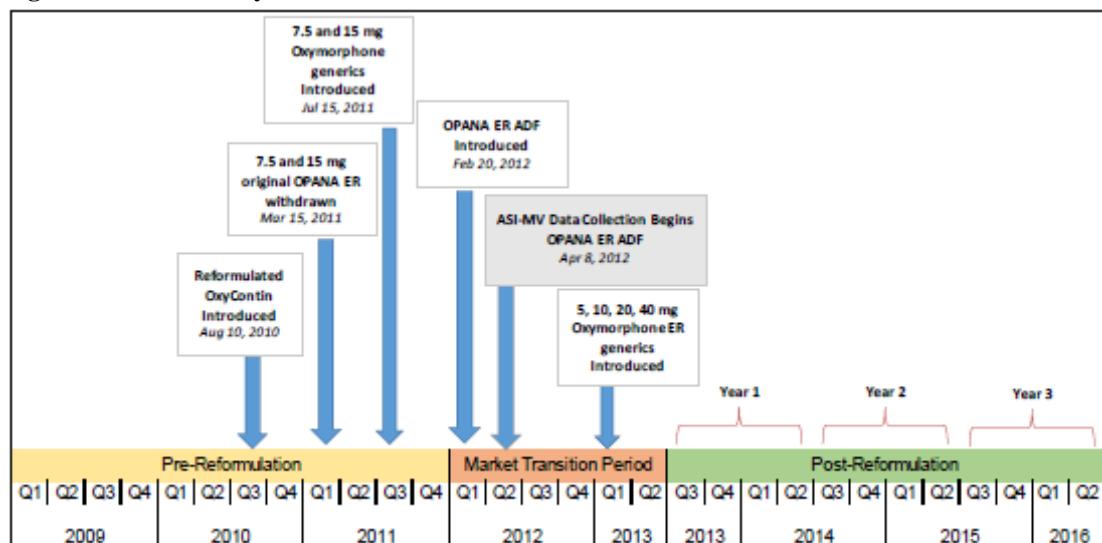
Treatment centers within the NAVIPPRO® system are not randomly selected to join the network. Therefore, results of the analyses conducted on the patient data collected from these treatment centers may not be generalizable to all patients assessed for substance abuse treatment in the U.S. The data set is not nationally representative and thus is not intended to be used for estimating national prevalence rates. This is also a dynamic system where new sites are regularly added to the network and attrition among participating sites occurs throughout the study period. As shown in **Appendix J, Table J1**, the number sites and assessments from some states changed notably across the study periods (e.g., Tennessee, West Virginia, New Mexico).

In addition to the primary analytic sample described above, a sensitivity analysis was conducted using a fixed set of sites that contributed data consecutively during each quarter of the total study period from January 2009 through June 2016. This restricted sample included a total of 120,081 assessments from 53 sites located in 15 states. Of these assessments, 46,851 were included during the pre-period and 50,285 during the post-period. Within this fixed sample of sites, 11,915 assessments were submitted from two sites located within Tennessee, representing approximately 10% of the total number of assessments and 4% of the sites.

2.3.2.1.3 Study Time Frame

Figure 7 depicts the overall study timeline, including times of market introduction of various oxymorphone ER products, as well as the reformulation of OxyContin.

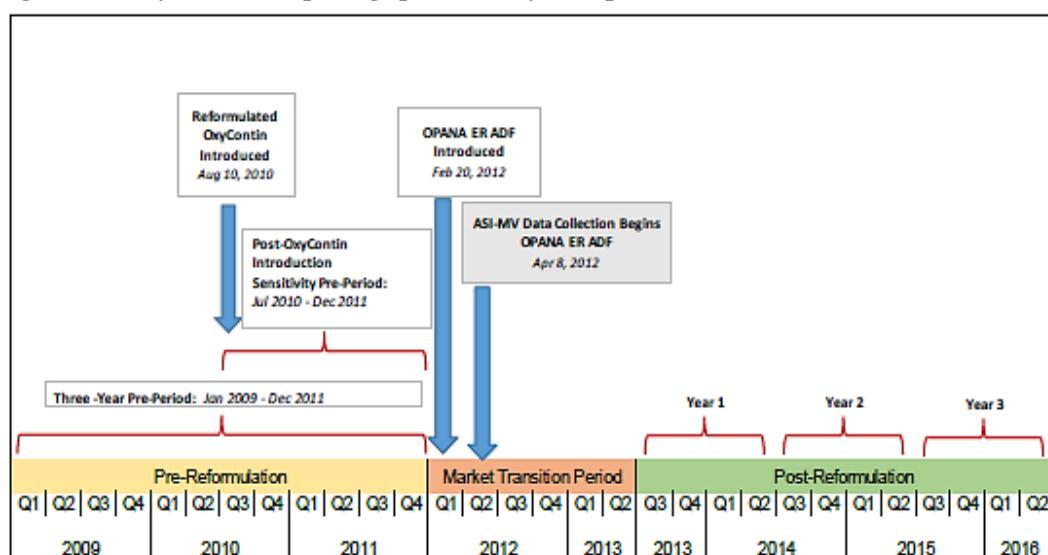
Figure 7. Overall study timeline



Source: NAVIPPRO® study report (December 2016)

Figure 8 describes the study periods used in this investigation to evaluate changes in abuse of Opana ER, including a “3-year pre-period” as well as a 6-quarter “sensitivity pre-period” beginning in Q3 2010, when a reformulated version of OxyContin was introduced to the market with properties expected to deter abuse. A 6-quarter “market transition” period is also included to account for major changes in the ER oxymorphone market, including the gradual market replacement of OP with OPR in the first half of 2012, as well as introduction of the full range of dosage forms for generic oxymorphone ER products. The use of a transition period also allows time for sites within the ASI-MV® network to upload software containing updated ASI-MV® versions that include pictures of these newly introduced products.

Figure 8. Study timeline depicting specific study time periods



Source: NAVIPPRO® study report (December 2016)

Selected additional analyses use the following mutually exclusive time periods:

- Pre-period: Q1 2009 – Q2 2010 (6-quarter period prior to introduction of reformulated OxyContin)
- Sensitivity pre-period: Q3 2010 – Q4 2011 (6-quarter period from introduction of reformulated OxyContin to introduction of OPR)
- Post-period: Q3 2013 – Q2 2016 (3-year post-reformulation period for Opana ER, following the market transition period)

2.3.2.1.4 Outcome definition and measurement

In the NAVIPPRO® study, abuse is defined as any non-medical use of a prescription opioid product within the past 30 days prior to assessment, as determined by individuals' responses to a series of follow-up questions, asking whether (1) they have a current pain problem and have taken the medication as prescribed, (2) they have obtained the medication only from their own physician, and (3) they have not used the drug via an alternate route of administration (ROA). Individuals are also asked if they have used a prescription opioid in the past 30 days "not in a way prescribed by [their] doctor, that is, for the way it makes [them] feel and not for pain relief." An algorithm based on answers to these questions identifies an individual as having engaged in abuse of the medication.

The ASI-MV® captures product-specific data about past 30-day use and abuse for over 60 prescription opioid products. Respondents are guided to questions using screens with names and pictures of various products. According to the study report, a pilot test (N=31 clients) showed good agreement between the electronic presentation of these questions and an interview (average ICC = 0.70 and average Kappa = 0.65).

Regarding ROA, if a respondent indicates past 30-day use of a drug, he/she is asked the follow-up question, "*How have you usually used [DRUG]? Please select all that apply,*" followed by the choices below:

- Swallowed it whole
- Dissolved it in my mouth like a cough drop
- Chewed it, and then swallowed it
- Drank it after it dissolved in liquid
- Snorted it
- Smoked it
- Injected it with a needle into my vein
- Injected it with a needle into my skin or muscle
- Other

During the study period, there were multiple updates to the ASI-MV® survey instrument screens that collect information on abuse of oxymorphone products:

- October 2011:** Generic oxymorphone ER added (7.5mg and 15mg), with product pictures

- **April 2012:** Reformulated Opana ER added, with product pictures
- **February 2013:** Additional generic oxymorphone ER products added (5mg, 10mg, 20mg, and 40mg), with product pictures
- **May 2014:** Image and location for original Opana ER removed and text button for original Opana ER added in a less prominent location on the screen (without product pictures)
- **March 2015:** Order of opioid product screens changed, based on prescription volume. Products with higher prescription volume [e.g., hydrocodone, oxycodone immediate-release (IR) combination products] moved to the top, while products with lower prescription volume moved to the bottom, as shown below in **Table 6**.

Table 6. Change in NAVIPPRO® ASI-MV® screen order

Previous opioid product screen order (before 03/14/2015)	Updated opioid product screen order (after 03/14/2015)
<ol style="list-style-type: none"> 1. Oxycodone ER 2. Oxycodone IR single-entity 3. Oxycodone IR combination 4. Hydrocodone 5. Methadone 6. Meperidine 7. Fentanyl 8. Hydromorphone 9. Morphine 10. Oxymorphone 11. Tramadol 12. Buprenorphine 13. Tapentadol 	<ol style="list-style-type: none"> 1. Hydrocodone 2. Oxycodone IR Combination 3. Oxycodone IR single-entity 4. Oxycodone ER 5. Tramadol 6. Buprenorphine 7. Morphine 8. Fentanyl 9. Methadone 10. Hydromorphone 11. Oxymorphone 12. Tapentadol 13. Meperidine

Source: NAVIPPRO® study report (December 2016)

2.3.2.1.5 Comparators

Primary comparators for OPR included the following products:

- original Opana ER (OP)
- generic oxymorphone ER.

Secondary comparators include the following products:

- oxymorphone IR products, brand and generic
- oxycodone IR SE products, brand and generic
- morphine ER products (excluding Embeda®), brand and generic
- oxycodone ER.

2.3.2.1.6 Statistical analyses

For additional discussion of the NAVIPPRO® study's statistical methods, please refer to separate review by the Division of Biometrics VII.

Briefly, for Opana ER and comparator opioids, abuse prevalence was estimated two ways: (1) prevalence of past 30-day abuse of the individual product or drug category as a proportion per 100 ASI-MV® assessments in the study sample and (2) prevalence of past 30-day abuse of the individual drug product or drug category relative to available total prescription volume of that drug product or category during the study period, measured using the number of dosage units (tablets) dispensed within the home 3-digit ZIP codes of individuals assessed during the analyzed time period. We use the following terminology in this review:

- Population-adjusted abuse prevalence = number of abuse reports per 100 assessments at the sites included in the ASI-MV® study sample during the analyzed time period
- Tablet-adjusted abuse rate = number of abuse reports per 10,000 tablets dispensed within the home 3-digit ZIP codes of individuals included in the ASI-MV® study sample during the analyzed time period

Analyses examining the changes in these rates over time were conducted using log-binomial and log-Poisson regression models to estimate and contrast pre-period and post-period product and route-specific prevalence of past 30-day abuse. Most analyses were conducted at the individual level; that is, for each individual assessment in the study sample, the outcome (i.e. abuse or abuse via a specific route) is binary indicating whether or not the individual abused a given drug. Relative risks and relative percent change were the effect sizes used. Additional analyses included adjustment for prescription volume, as described above.

Because the distribution of treatment sites contributing data varies geographically over time, the sampling frame is not stable across study periods. Sensitivity analyses were therefore performed to evaluate the potential impact of geographical variation in the ASI-MV® sample on abuse estimates. In stratified analyses, Tennessee was analyzed separately because of an unexpectedly high number of Opana ER abuse cases observed in this state, coupled with a marked increase in the number of assessments from Tennessee across the study period. Sensitivity analyses stratifying by location of assessment sites were performed, to include assessments from sites within Tennessee only and all sites excluding those from Tennessee. In addition, sensitivity analyses used a restricted sample of shared, or “fixed” sites that had contributed at least one ASI-MV® assessment *during each quarter* of the pre- and post-reformulation study periods. Finally, additional sensitivity analyses further stratified this fixed site sample into sites within Tennessee and excluding Tennessee.

2.3.2.2 Study Results

2.3.2.2.1 Description of the study population

Table 7 describes the ASI-MV® analytic sample and number of abuse events during the 3-year pre-period, the 6-quarter sensitivity pre-period, and the post-period (excluding the transition period). The table also describes the number of OP and OPR (“Opana ER

ADF") abuse cases reported within the sample. According to supplementary data tables provided, there were also 532 abuse reports for OP during the post-period in the ASI-MV® network in addition to the 1,675 abuse reports for OPR shown below.^j **These post-period OP abuse reports were not included in any of the study analyses.**

The table also presents a separate description of the study sample for sites within Tennessee only. Comparing the Tennessee sample to non-Tennessee sample, there are a number of notable findings:

- Within Tennessee, the number of sites increased by almost 50% and the number of assessments more than quadrupled from the 3-year pre-period to the 3-year post-period. This trend differs from the non-Tennessee sample, where both the number of sites and the number of assessments decreased.
- The proportion of ASI-MV® assessments in which past 30-day prescription opioid abuse was reported was much higher in Tennessee (49%) than in the non-Tennessee sample (20%). These percentages increased slightly in both the Tennessee and overall sample across the study periods.
- The proportion of prescription opioid abusers who reported past 30-day abuse of Opana ER was many times higher in Tennessee than in the non-Tennessee sample, both in the pre- and post-periods.
- One quarter of Opana ER abuse reports were from Tennessee during the 3-year pre-period, whereas three quarters of Opana ER abuse reports during the post-period came from sites within Tennessee.

^j Data provided in supplemental spreadsheet "Copy of overall-study-abuse-counts.xlsx," accompanying NAVIPPRO® Final Report – Post Market Epidemiology Study to Evaluate Abuse of Opana ER Extended-Release Tablets (received December 23, 2016)

Table 7. Description of ASI-MV® analytic sample and number of Opana ER abuse cases, overall and for sites within and excluding Tennessee, by study period

	Total Study Period (Jan 2009 – Jun 2016)	Pre-Period Three-Year Pre-period (Jan 2009 – Dec 2011)	Pre-Period 18-Month Sensitivity Pre-period* (July 2010 – Dec 2011)	Post-Period (Jul 2013 – Jun 2016)
Overall ASI-MV network				
No. of assessments	459,240	206,466	103,385	168,078
No. of ASI-MV sites	1,084	687	589	644
No. of states	40	36	34	37
Total prescription opioid abusers	99,484	39,808	21,410	41,317
Total Original OPANA ER past 30-day abuse cases	2,835	1,570	1,220	N/A
Total OPANA ER ADF past 30-day abuse cases	2,149**	N/A	N/A	1,675
ASI-MV sites within Tennessee				
No. of assessments	31,024	4,695	2,982	20,964
No. of ASI-MV sites	53	26	20	38
Total prescription opioid abusers	15,268	2,102	1,480	10,432
Total Original OPANA ER past 30-day abuse cases	1,112	400	353	N/A
Total OPANA ER ADF past 30-day abuse cases	1,545**	N/A	N/A	1,250
ASI-MV sites Excluding Tennessee				
No. of assessments	428,216	201,771	100,403	147,114
No. of ASI-MV sites	1,031	661	569	605
No. of states	39	35	33	36
Total prescription opioid abusers	84,216	37,706	19,930	30,885
Total Original OPANA ER past 30-day abuse cases	1,723	1,170	867	N/A
Total OPANA ER ADF past 30-day abuse cases	604	N/A	N/A	425

*The 6-quarter sensitivity pre-period from July 2010 through December 2011 was used for sensitivity analyses and represents a period of time after introduction of an ADF oxycodone ER (reformulated OxyContin) and prior to introduction of OPR (“Opana ER ADF”).

**The number of past 30-day abuse cases for OPR (“Opana ER ADF”) for the total study period includes the count of abuse cases from the post-period as well as the transition period (not displayed in this table).
Source: NAVIPPRO® study report (December 2016)

Table 8 describes selected characteristics of the total ASI-MV® analytic sample and of Opana ER abusers in the pre- and post-reformulation periods. Notably, the percent of assessments from residential/inpatient substance abuse treatment centers increased from 17.6% to 27.9%, while the proportions from other settings decreased. The percent of assessments with severity scores of 6 or higher on the ASI-MV® (indicating a “considerable” or “extreme” drug problem) increased from 30.5% to 38.6%. The proportion of individuals reporting a history of injecting either any drug or any prescription opioid also increased across the study periods. Together, these changes suggest a shift in the study population over time to include a higher proportion of individuals with more severe substance use disorders.

In addition, there were some notable characteristics of Opana ER abusers, as compared to the overall sample. Opana ER abusers were more likely to be younger, female, and assessed in residential/inpatient settings. Notably, the percent of Opana ER abusers being assessed in residential/inpatient treatment settings increased from 38.7% to 74.8% when comparing the pre- to post-periods. In the same timeframe, the percent of Opana ER abusers reporting a history of injecting prescription opioids increased from 46.2% to 74.8%. Similar proportions and increases were observed among abusers of comparator opioids (data not shown). A large majority of Opana ER abusers were found to have a “considerable” or “extreme” substance abuse problem as determined by ASI-MV® severity scores, and this remained relatively stable from the pre- to post-periods, at more than 85%. These proportions were much higher among Opana ER abusers than in the overall ASI-MV® sample but fairly similar to percentages seen for abusers of comparator opioids.

Table 8. Selected characteristics of the ASI-MV® analytic sample and Opana ER abusers within the ASI-MV® network, by study period

Demographic Characteristic		Total Analytic Sample (N=459,240)	Analytic Sample Pre-Period* (n=206,466)	Analytic Sample Post -Period** (n=168,078)	Original OPANA ER abusers Pre-Period* (n=1,570)	OPANA ER ADF abusers Post-Period** (n=1,675)
Age	Younger than 21	7.9	9.2	6.3	15.7	6.4
	21 to 34	50.4	48.9	51.9	71.4	69.4
	35 to 54	36.3	36.9	35.9	12.4	23.1
	55 and older	5.4	5.0	6.0	< 1.0	1.1
	Unknown	0.0	0.0	0.0	0.0	0.0
Gender	Male	63.8	64.5	62.5	50.7	45.6
	Female	36.2	35.5	37.5	49.3	54.3
Race	White	59.4	54.1	66.2	91.7	93.5
	Black	18.9	19.9	17.9	1.5	1.8
	Hispanic	15.2	19.6	9.0	5.0	2.0
	Other	6.5	6.3	6.9	1.8	2.7
Criminal justice-required substance abuse treatment	Yes	58.7	59.6	56.8	25.0	26.7
	No	41.1	40.2	3.0	74.8	73.2
	Unknown/Missing	< 1.0	< 1.0	< 1.0	< 1.0	< 1.0
Modality	Residential/Inpatient	22.1	17.6	27.9	38.7	76.3
	Outpatient/Non-methadone	31.6	33.9	29.4	37.4	10.7
	Methadone/LAAM	2.2	2.3	1.9	5.6	1.6
	Corrections	31.2	33.5	27.9	11.1	5.1
	Other	12.8	12.8	13.0	7.3	6.3
ASI-MV severity score* (%)	0-1	39.1	42.2	35.6	< 1.0	< 1.0
	2-3	10.7	11.3	9.9	1.2	< 1.0
	4-5	13.8	14.0	13.3	6.4	4.7
	6-7	24.1	22.1	26.1	31.7	33.6
	8-9	10.2	8.4	12.5	55.4	55.9
	Unknown/Missing	2.2	2.0	2.3	4.4	4.4
History of injection of any drugs (%)	At least one drug injected	20.9	18.0	24.4	52.1	81.2
History of injection of Rx opioids (%)	At least one prescription opioid injected	14.1	11.2	17.7	46.2	78.7

* Pre-period = January 1, 2009 - December 31, 2011

**Post period = July 1, 2013 – June 30, 2016

*ASI-MV® severity score interpretation: 0-1=no real problem, treatment not indicated; 2-3=slight problem, treatment probably not necessary; 4-5=moderate problem, some treatment indicated; 6-7=considerable problem, treatment necessary; 8-9=extreme problem, treatment absolutely necessary

Source: Table excerpted by DEPI reviewer from table included in NAVIPPRO® study report (December 2016)

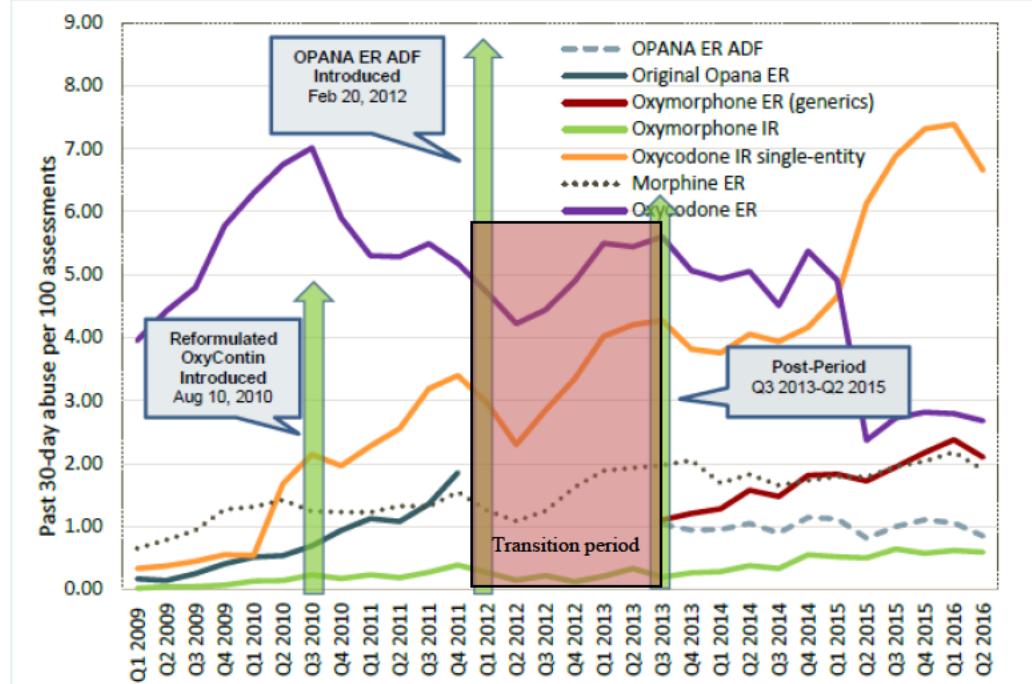
2.3.2.2.2 Change in overall abuse prevalence for Opana ER and comparators within the ASI-MV® network

2.3.2.2.2.1 Overview of abuse trends within the ASI-MV® network

Figure 9 gives an overview of trends in quarterly abuse prevalence for Opana ER and the selected comparators per 100 ASI-MV® assessments, based on the full analytic sample. The figure indicates that in this population, oxycodone ER and oxycodone IR single-entity (SE) were the most commonly reported opioids abused. OP abuse prevalence increased throughout the pre-reformulation period. Abuse prevalence for generic

oxymorphone ER was similar to that of OPR at the beginning of the post-period (Q3 2013) and continued to increase during the post-period, whereas rates for OPR remained relatively stable during the post-period. Note that the ASI-MV® instrument only began collecting abuse reports for oxycodone IR single-entity (SE) products separately from IR oxycodone combination products in early 2010. Also, the order of ASI-MV® product screens was changed in March 2015, corresponding to abrupt changes in ER oxycodone and IR oxycodone SE abuse prevalence.

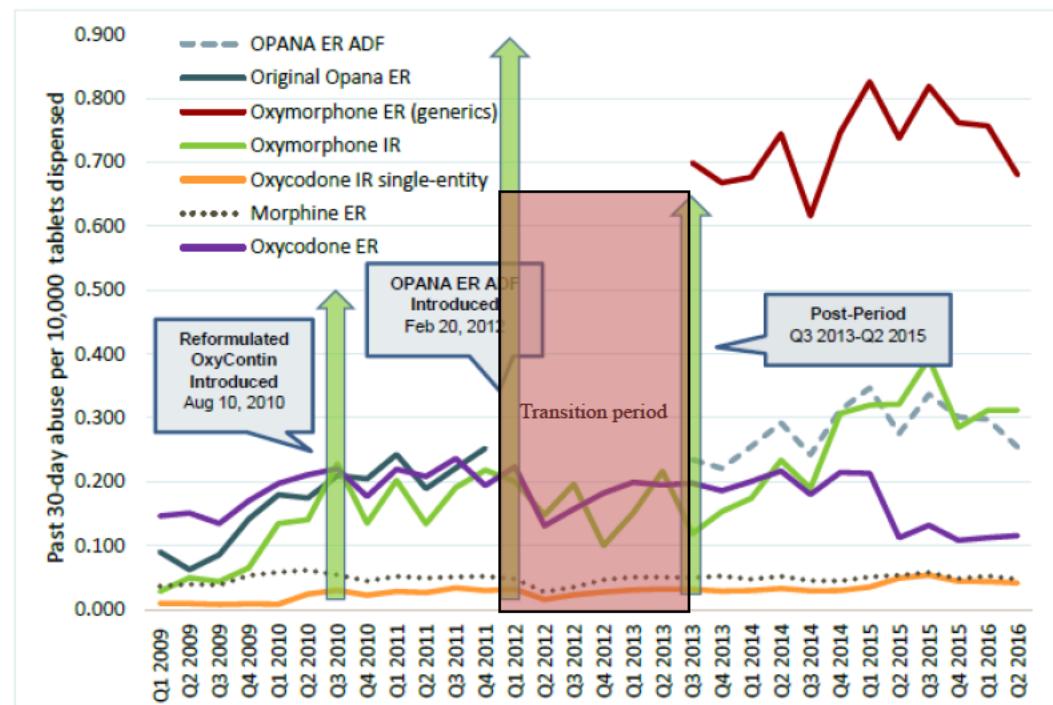
Figure 9. Quarterly prevalence rates of past 30-day abuse via any route of administration for Opana ER and comparators, per 100 ASI-MV® assessments, full analytic sample, Q1 2009 - Q2 2016



Source: NAVIPPRO® study report (December 2016), transition period added by DEPI reviewer

Figure 10 shows trends in quarterly abuse rates per 10,000 tablets dispensed, based on the full analytic sample. In this figure, the highest abuse rates were for generic oxymorphone ER during the post-period. The utilization-adjusted Opana ER (OP during the pre-period and OPR during the post-period) and oxymorphone IR abuse rates were fairly similar, and increasing during both the pre- and post-period. Rates for all oxymorphone products were substantially higher than rates for morphine ER or oxycodone IR SE.

Figure 10. Quarterly prevalence rates of past 30-day abuse via any route of administration for Opana ER and comparators, per 10,000 tablets dispensed, full analytic sample, Q1 2009 - Q2 2016



Source: NAVIPPRO® study report (December 2016), transition period added by DEPI reviewer

Additional analyses, submitted in response to FDA's June 1, 2016 request for information, indicate that abuse prevalence for Opana ER and opioid comparators varied widely by treatment setting (residential/inpatient, outpatient/non-methadone, methadone, corrections, other) with the highest prevalence occurring in residential/inpatient settings and the lowest in corrections and other settings (data not shown).

2.3.2.2.2 Change in mean overall (any route) abuse rates from pre- to post-reformulation periods

Tables J2-J5 in Appendix J contain the results of comparison of means analyses for the full ASI-MV® sample. However, as described in the previous section, there were considerable shifts in the ASI-MV® study sample across the time periods as sites dropped in and out of the surveillance network, including a marked increase in the proportion of individuals being assessed in residential/inpatient settings as well as in the number of sites and assessments from Tennessee – a sample with a considerably higher prevalence of prescription opioid abuse and Opana ER abuse specifically. Because these changes in distribution of geographic regions and type of assessment setting could introduce considerable bias when comparing abuse rates over time, the sensitivity analyses using the restricted set of fixed sites are valuable for assessing the change in abuse rates for Opana ER and comparators. **Therefore, for comparisons of abuse rates and trends across study periods, we will focus on results from the fixed site analyses.**

As shown in **Table 9**, the abuse prevalence for OP increased significantly, comparing the 6-quarter time period prior to introduction of reformulated OxyContin ("Pre-period") to

the 6-quarter period after OxyContin's reformulation but prior to Opana ER's reformulation ("Sensitivity pre-period"). The abuse prevalence of OPR during the post-period was not significantly different from that of OP during this 6-quarter sensitivity pre-period. However, the abuse prevalence of generic oxymorphone ER in the post-period was significantly higher than that for either OP during the sensitivity pre-period or that of OPR during the post-period.

Abuse prevalence for oxymorphone IR, oxycodone IR SE, and morphine ER increased across the time periods. Oxycodone ER abuse prevalence increased non-significantly following the introduction of reformulated OxyContin and then decreased significantly when comparing the 6-quarter sensitivity pre-period following OxyContin's reformulation to the post-period, following Opana ER's reformulation.

Table 9. Mean past 30-day abuse prevalence via any route per 100 ASI-MV® assessments for Opana ER and comparators in three time periods, with 95% confidence intervals, using the restricted sample of fixed ASI-MV® sites

	Pre-Period**	Sensitivity Pre-Period**	Post-Period**
Original Opana ER [†]	0.27 (0.21 – 0.34)	1.07 (0.94 – 1.21)	0.32 (0.27 – 0.37)
Opana ER ADF [*]	N/A	N/A	1.07 (0.98 – 1.16)
Oxymorphone ER (generics)	N/A	N/A	1.89 (1.77 – 2.02)
Oxymorphone IR	0.09 (0.06 – 0.13)	0.21 (0.16 – 0.28)	0.43 (0.37 – 0.49)
Oxycodone IR single-entity	0.60 (0.51 – 0.70)	2.08 (1.90 – 2.27)	4.76 (4.57 – 4.95)
Morphine ER [§]	1.65 (1.50 – 1.83)	1.93 (1.76 – 2.12)	2.10 (1.97 – 2.23)
Oxycodone ER [¶]	5.39 (5.11 – 5.69)	5.89 (5.59 – 6.21)	4.11 (3.93 – 4.29)

** Pre-Period = first 18-month period prior to introduction of Opana ER ADF (1/1/2009 - 6/30/2010)
Sensitivity Pre-period = 18 month time period after introduction of ADF oxycodone ER and prior to introduction of Opana ER ADF (Q3 2010 – Q4 2011; 7/1/2010 - 12/31/2011)

Post-period = three-year period after introduction of Opana ER ADF and market transition for oxymorphone products (Q3 2013 – Q2 2016; 7/1/2013 – 6/30/2016). Period 2 = last 18-month period prior to introduction of Opana ER ADF (7/31/2010 - 12/31/2011)

Note that the transition period of market change for oxymorphone products (1/1/2012 - 6/30/2013) is excluded from analyses.

† Original Opana ER category represents brand original formulation Opana ER in the pre-period only.

‡ Opana ER ADF category represents brand Opana ER ADF only in the post-period.

§ Morphine ER = all extended-release morphine products excluding EMBEDA.

¶ Oxycodone ER = includes all brand and generic products

Source: NAVIPPRO® study report (December 2016)

Within the fixed set of ASI-MV® sites, the mean tablet-adjusted abuse rate for Opana ER rose significantly across the three time periods, approximately doubling from the sensitivity pre-period to the post-period, comparing OP to OPR. (**Table 10**). Again, post-

period estimates for OP include the large number of abuse reports for this product long after it exited the market, and it is unclear which product(s) these cases might actually have been abusing. The tablet-adjusted abuse rate for generic oxymorphone ER in the post-period was higher than that of OP during either pre-period and also higher than OPR during the post-period. Tablet-adjusted abuse rates for oxymorphone IR, oxycodone IR SE, and oxycodone ER also increased significantly across the time periods, while mean morphine ER abuse rates remained relatively stable across the time periods.

Table 10. Mean past 30-day abuse rates via any route per 10,000 tablets dispensed for Opana ER and comparators in three time periods, with 95% confidence intervals, using the restricted sample of fixed ASI-MV® sites

	Pre-Period**	Sensitivity Pre-Period**	Post-Period**
Original Opana ER [†]	0.047 (0.036 – 0.060)	0.105 (0.093 – 0.119)	20.535 (17.552 – 24.024)
Opana ER ADF [‡]	N/A	N/A	0.214 (0.196 – 0.233)
Oxymorphone ER (generics)	N/A	N/A	0.432 (0.405 – 0.461)
Oxymorphone IR	0.043 (0.028 – 0.067)	0.089 (0.067 – 0.117)	0.202 (0.176 – 0.231)
Oxycodone IR single-entity	0.006 (0.005 – 0.007)	0.012 (0.011 – 0.013)	0.026 (0.025 – 0.027)
Morphine ER [§]	0.036 (0.032 – 0.039)	0.035 (0.032 – 0.039)	0.037 (0.035 – 0.040)
Oxycodone ER [¶]	0.087 (0.082 – 0.092)	0.109 (0.104 – 0.115)	0.122 (0.117 – 0.128)

** Pre-Period - first 18-month period prior to introduction of Opana ER ADF (1/1/2009 -6/30/2010)
 Sensitivity Pre-period - 18 month time period after introduction of ADF oxycodone ER and prior to introduction of Opana ER ADF (Q3 2010 –Q4 2011; 7/1/2010 -12/31/2011)

Post-period - three-year period after introduction of Opana ER ADF and market transition for oxymorphone products (Q3 2013 – Q2 2016; 7/1/2013 – 6/30/2016). Period 2 - last 18-month period prior to introduction of Opana ER ADF (7/1/2010 -12/31/2011)

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

† Original Opana ER category represents brand original formulation Opana ER in the pre-period only.

‡ Opana ER ADF category represents brand Opana ER ADF only in the post-period.

§ Morphine ER - all extended-release morphine products excluding EMBEDA.

¶ Oxycodone ER - Includes all brand and generic products

Source: NAVIPPRO® study report (December 2016)

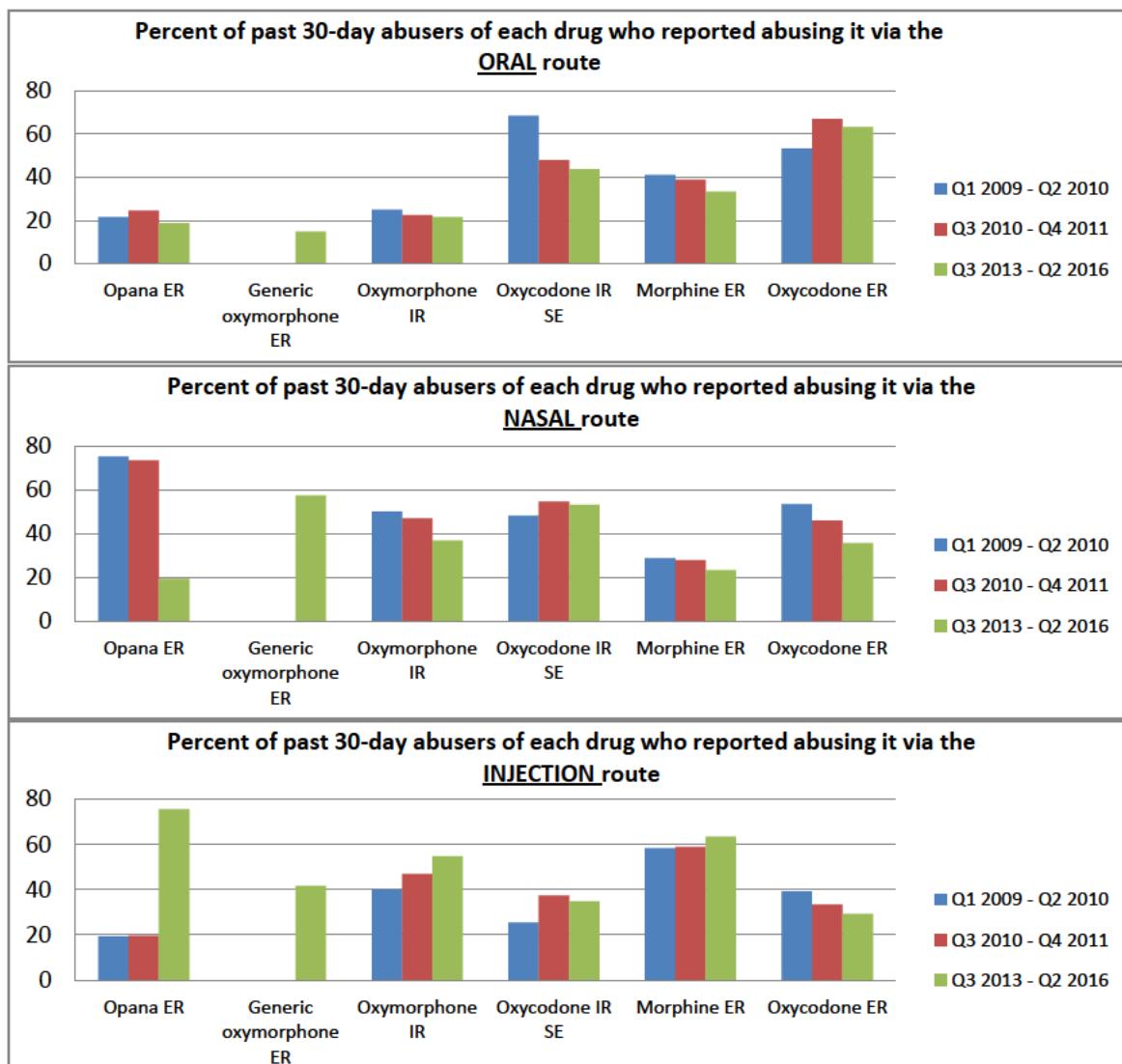
Because of the observed increase in the number of assessments from Tennessee as well as the higher prevalence of Opana ER abuse among individuals assessed in this state, the investigators conducted selected analyses separately for Tennessee and non-Tennessee sites. The results of these analyses, using the 6-quarter “sensitivity” pre-period following OxyContin’s reformulation, are shown in **Appendix J, Tables J6-J9**. Within Tennessee, the abuse prevalence of Opana ER per 100 assessments decreased significantly by 49%, comparing OP in the sensitivity pre-period to OPR in the post-period. The tablet-

adjusted abuse rate increased by 68% within Tennessee, again comparing OP to OPR. Among sites excluding Tennessee, both the abuse prevalence per 100 assessments and the rate per 10,000 tablets declined by more than 50%, comparing OP to OPR.

2.3.2.2.3 Changes in ROA among past 30-day abusers of Opana ER and selected opioid comparators

Figure 11 provides a visual display of the changes across the three time periods in the percent of past 30-day abusers of each opioid within the fixed sample of ASI-MV® sites who report abusing the products via the oral (top panel), nasal (middle panel) and injection (bottom panel) routes, from January 1, 2009 through June 30, 2016. A more detailed discussion of the changes by each ROA follows.

Figure 11. Route of abuse patterns among abusers of Opana ER and each opioid comparator across three time periods, using the restricted set of fixed ASI-MV® sites



*OP in the first two time periods and OPR in the third time period (post-period)Source: Figure generated by DEPI reviewer using data from the NAVIPPRO® study report (December 2016)

Table 11 examines the proportion of past 30-day abusers of Opana ER and each opioid comparator who reported abusing those drugs via the oral route. These proportions are presented for the same three time periods as in the previous section. Among past 30-day abusers of oxymorphone products, 25% or fewer reported abusing the drug via oral routes. These proportions were the lowest of the selected opioid groups. Following Opana ER's reformulation, the proportion of abusers who reported abusing it via the oral route decreased slightly, but this difference was not statistically significant. Oral abuse of generic oxymorphone ER during the post-period was also low (14.77%). Again, post-period estimates for OP include the large number of abuse reports for this product long after it exited the market, and it is unclear which product(s) these cases might actually have been abusing. Overall, the proportion of abusers who reported oral abuse of the analyzed opioids decreased over time, with the exception of oxycodone ER, for which the proportion who reported abusing it orally increased significantly following introduction of reformulated OxyContin.

Table 11. Mean percentage and 95% confidence intervals for past 30-day abuse via oral routes for Opana ER and comparators among abusers of those products across three time periods, using the restricted sample of fixed ASI-MV® sites

	Pre-Period**	Sensitivity Pre-Period**	Post-Period**
Original Opana ER [†]	21.47 (12.95 – 35.60)	24.54 (19.65 – 30.64)	17.11 (11.97 – 24.45)
Opana ER ADF [*]	N/A	N/A	18.88 (15.76 – 22.61)
Oxymorphone ER (generics)	N/A	N/A	14.77 (12.63 – 17.29)
Oxymorphone IR	25.00 (11.70 – 53.41)	22.45 (13.34 – 37.78)	21.58 (16.59 – 28.06)
Oxycodone IR single-entity	68.54 (61.10 – 78.88)	48.02 (43.71 – 52.75)	43.73 (41.76 – 45.79)
Morphine ER [§]	41.15 (36.57 – 46.31)	38.86 (34.58 – 43.66)	33.36 (30.58 – 36.39)
Oxycodone ER [¶]	53.43 (50.75 – 56.24)	67.12 (64.67 – 69.66)	63.41 (61.31 – 65.58)

** Pre-Period = first 18-month period prior to introduction of Opana ER ADF (1/1/2009 -6/30/2010)

Sensitivity Pre-period = 18 month time period after introduction of ADF oxycodone ER and prior to introduction of Opana ER ADF (Q3 2010 –Q4 2011; 7/1/2010 -12/31/2011)

Post-period = three-year period after introduction of Opana ER ADF and market transition for oxymorphone products (Q3 2013 – Q2 2016; 7/1/2013 – 6/30/2016). Period 2 = last 18-month period prior to introduction of Opana ER ADF (7/31/2010 -12/31/2011)

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

[†] Original Opana ER category represents brand original formulation Opana ER in the pre-period only.

^{*} Opana ER ADF category represents brand Opana ER ADF only in the post-period.

[§] Morphine ER = all extended-release morphine products excluding EMBEDA.

[¶] Oxycodone ER = includes all brand and generic products

Source: NAVIPPRO® study report (December 2016)

As shown in **Table 12**, the percent of past 30-day Opana ER abusers who reported abuse via the nasal route decreased markedly, from 75.2% and 73.5% in the pre-period and sensitivity pre-period, respectively, to 19.3% in the post-period. The percent of generic oxymorphone ER abusers who reported snorting this product during the post-period was significantly higher (57.4%) than the percent of OPR abusers who reported snorting it. Nasal abuse patterns among abusers of comparator opioids varied, but only among oxycodone ER abusers did it decrease significantly, from 53.5% in the pre-period to 35.7% in the post-period. However, the magnitude of change was far greater for Opana ER than for any other opioid studied.

Table 12. Mean percentage and 95% confidence intervals for past 30-day abuse via snorting for Opana ER and comparators among abusers of those products across three time periods, using the restricted sample of fixed ASI-MV® sites

	Pre-Period**	Sensitivity Pre-Period**	Post-Period**
Original Opana ER [†]	75.18 (64.79 – 87.23)	73.51 (68.15 – 79.28)	49.03 (41.56 – 57.83)
Opana ER ADF [‡]	N/A	N/A	19.27 (16.11 – 23.06)
Oxymorphone ER (generics)	N/A	N/A	57.42 (54.25 – 60.77)
Oxymorphone IR	50.0 (32.26 – 77.50)	46.94 (34.85 – 63.21)	36.81 (30.76 – 44.05)
Oxycodone IR single-entity	48.24 (40.45 – 57.53)	54.54 (50.21 – 59.26)	53.19 (51.20 – 55.26)
Morphine ER [§]	28.79 (24.61 – 33.68)	27.99 (24.08 – 32.54)	23.37 (20.90 – 26.13)
Oxycodone ER [¶]	53.52 (50.81 – 56.38)	45.95 (43.34 – 48.72)	35.67 (33.60 – 37.85)

** Pre-Period = first 18-month period prior to introduction of Opana ER ADF (1/1/2009 – 6/30/2010)

Sensitivity Pre-period = 18 month time period after introduction of ADF oxycodone ER and prior to introduction of Opana ER ADF (Q3 2010 – Q4 2011; 7/1/2010 – 12/31/2011)

Post-period = three-year period after introduction of Opana ER ADF and market transition for oxymorphone products (Q3 2013 – Q2 2016; 7/1/2013 – 6/30/2016). Period 2 = last 18-month period prior to introduction of Opana ER ADF (7/31/2010 – 12/31/2011)

Note that the transition period of market change for oxymorphone products (1/1/2012 – 6/30/2013) is excluded from analyses.

[†] Original Opana ER category represents brand original formulation Opana ER in the pre-period only.

[‡] Opana ER ADF category represents brand Opana ER ADF only in the post-period.

[§] Morphine ER = all extended-release morphine products excluding EMBEDA.

[¶] Oxycodone ER = includes all brand and generic products

Source: NAVIPPRO® study report (December 2016)

Additional analyses provided in response to FDA's request,^k also using the restricted set of fixed sites (**Table 13**), found that the relative reduction in the proportion of abusers

^k This analysis was not included in the NAVIPPRO® final study report (December 2016).

who reported abuse via snorting (-70.1%) was significantly larger when comparing OP abusers in the pre-period to OPR abusers in the 2-year post-period than when comparing OP abusers in the pre-period to generic oxymorphone ER abusers (-19.6) in the 2-year post-period.

Table 13. Change in proportion of past 30-day abuse via snorting among abusers of the products for reformulated Opana ER and generic oxymorphone ER relative to original Opana ER in the pre-period, using the restricted sample of fixed ASI-MV® sites; January 1, 2009 - June 30, 2015

	Pre-period* percent of past 30-day abuse	Post-period** percent of past 30-day abuse	Relative proportion comparing pre- to post period percent of past 30-day abuse (RR)	Pre-post period percent change (relative to original Opana ER In the pre-period)	P-value for pre-post period percent change (relative to original Opana ER In the pre-period)	Relative proportion comparing difference of pre-post period differences in percent of past 30-day abuse (RRR)	P-value for percent change comparing pre-post period differences in Oxymorphone ER (generics) versus Opana ER ADF
Original OPANA ER†	72.18 (67.86 – 76.76)	–	Ref	Ref	–	–	–
OPANA ER ADF‡	–	21.61 (17.86 – 26.16)	0.30 (0.25, 0.37)	-70.05 (-75.50, -63.40)	<.0001	Ref	Ref
Oxymorphone ER (generics)	–	58.05 (54.09 – 62.31)	0.80 (0.73, 0.88)	-19.57 (-26.77, -11.66)	<.0001	2.69 (2.19, 3.29)	<.0001

† Note: Models for this analysis utilize the REPEATED statement which invokes the GEE estimation method by accounting for within-subject correlation using a compound symmetric structure such that repeated measurements are permitted to be correlated within each unique subject. Each subject-by-drug combination was treated as a unique subject to ensure that the correlation among repeated measurements was not inflated due to the non-exclusive nature of the formation of the drug groups.

* Pre-period = three-year prior to introduction of OPANA ER ADF (1/1/2009 - 12/31/2011)

** Post-period = two-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2015).

Note that the transition period of market change for oxymorphone products (1/1/2012 – 6/30/2013) is excluded from analyses.

† Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

‡ OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

Ref = Reference category for comparison

Source: Sponsor's response to FDA's July 11, 2016 information request, based on NAVIPPRO® study interim report (January 2016)

As shown in **Table 14**, the proportion of past 30-day Opana ER abusers who reported injecting the product increased markedly, from 19.3% and 19.5% during the pre-period and sensitivity pre-period, respectively, to 75.6% during the 3-year post-period. The proportion of generic oxymorphone ER abusers during the post-period who reported injecting the product (41.7%) was higher than that of OP during either pre-period but lower than that of OPR during the post-period. Again, patterns varied across comparators, but with the exception of ER oxycodone, there was a general trend toward increasing injection abuse among abusers of these products. However, none of the selected comparators showed an increase in the percent injection of a magnitude comparable to that of Opana ER following its reformulation.

Table 14. Mean percentage and 95% confidence intervals for past 30-day abuse via injecting for Opana ER and comparators among abusers of those products across three time periods, using the restricted sample of fixed ASI-MV® sites

	Pre-Period**	Sensitivity Pre-Period**	Post-Period**
Original OPANA ER [†]	19.34 (11.53 – 32.45)	19.58 (15.17 – 25.26)	45.02 (37.60 – 53.90)
OPANA ER ADF [‡]	N/A	N/A	75.55 (71.89 – 79.41)
Oxymorphone ER (generics)	N/A	N/A	41.67 (38.54 – 45.04)
Oxymorphone IR	40.00 (23.39 – 68.42)	46.94 (34.85 – 63.21)	54.76 (48.37 – 61.98)
Oxycodone IR single-entity	25.84 (19.30 – 34.59)	37.30 (32.97 – 42.20)	34.89 (32.98 – 36.90)
Morphine ER [§]	58.36 (53.75 – 63.37)	58.94 (54.65 – 63.58)	63.42 (60.55 – 66.42)
Oxycodone ER [¶]	39.21 (36.57 – 42.03)	33.38 (30.89 – 36.07)	29.25 (27.29 – 31.34)

** Pre-Period = first 18-month period prior to introduction of OPANA ER ADF (1/1/2009 -6/30/2010)

Sensitivity Pre-period = 18 month time period after introduction of ADF oxycodone ER and prior to introduction of OPANA ER ADF (Q3 2010 –Q4 2011; 7/1/2010 -12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (Q3 2013 – Q2 2016; 7/1/2013 – 6/30/2016). Period 2 = last 18-month period prior to introduction of OPANA ER ADF (7/31/2010 -12/31/2011)

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

† Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

‡ OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

§ Morphine ER = all extended-release morphine products excluding EMBEDA.

¶ Oxycodone ER = includes all brand and generic products

Source: NAVIPPRO® study report (December 2016)

Additional interim report analyses,¹ also using the restricted set of fixed sites (**Table 15**), found that the relative increase in the proportion of abusers who reported abuse via injection (+313.1%) was significantly greater when comparing OP abusers in the pre-period to OPR abusers in the 2-year post-period than when comparing OP abusers in the pre-period to generic oxymorphone ER abusers (+121.4%) in the 2-year post-period.

¹ This analysis was not included in the NAVIPPRO® final study report (December 2016).

Table 15. Change in proportion of past 30-day abuse via injection among abusers of the products for reformulated Opana ER and generic oxymorphone ER relative to original Opana ER in the pre-period, among fixed sites only

	Pre-period* percent of past 30-day abuse	Post-period** percent of past 30-day abuse	Relative proportion comparing pre- to post period percent of past 30-day abuse (RR)	Pre-post period percent change (relative to original Opana ER in the pre-period)	P-value for pre-post period percent change (relative to original Opana ER in the pre-period)	Relative proportion comparing difference of pre-post period differences in percent of past 30-day abuse (RRR)	P-value for percent change comparing pre-post period differences in Oxymorphone ER (generics) versus Opana ER ADF
Original Opana ER†	17.11 (13.53, 21.63)	-	Ref	Ref	Ref	-	-
Opana ER ADF‡	-	70.66 (65.88, 75.79)	4.13 (3.21, 5.32)	313.08 (220.53, 432.35)	<.0001	Ref	Ref
Oxymorphone ER (generics)	-	37.88 (34.05, 42.14)	2.21 (1.71, 2.87)	121.41 (71.08, 186.55)	<.0001	0.54 (0.47, 0.61)	<.0001

* Note: Models for this analysis utilize the REPEATED statement which invokes the GEE estimation method by accounting for within-subject correlation using a compound symmetric structure such that repeated measurements are permitted to be correlated within each unique subject. Each subject-BY-drug combination was treated as a unique subject to ensure that the correlation among repeated measurements was not inflated due to the non-exclusive nature of the formation of the drug groups.

† Pre-period = three-year prior to introduction of Opana ER ADF (1/1/2009 -12/31/2011)

** Post-period = two-year period after introduction of Opana ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2015).

Note that the transition period of market change for oxymorphone products (1/1/2012 – 6/30/2013) is excluded from analyses.

† Original Opana ER category represents brand original formulation Opana ER in the pre-period only.

‡ Opana ER ADF category represents brand Opana ER ADF only in the post-period.

Ref = Reference category for comparison

Source: Sponsor's response to FDA's July 11, 2016 information request, based on NAVIPPRO® study interim report (January 2016)

Tables J10-J13 in Appendix J show changes in the proportion of past 30-day abusers of Opana ER and comparators who report snorting and injecting the products, analyzed separately for sites within Tennessee and sites outside Tennessee. Results of these analyses were generally consistent with those shown above.

Additional sensitivity analyses examined the fixed site sample separately for Tennessee sites (two) and non-Tennessee sites. The results of these analyses were also generally consistent with the above findings, except that the proportions of generic oxymorphone ER abusers who reported nasal abuse (29.1%) and injection abuse (32.0%) were somewhat lower in the non-Tennessee fixed site sample than in the other analyses (data not shown).

2.3.2.2.4 Changes in route-specific abuse (snorting and injecting), as a proportion of ASI-MV® assessments and per 10,000 tablets dispensed

Because overall abuse rates vary across drugs and study periods, examining reported routes of abuse among abusers of a particular drug does not fully characterize changes in abuse patterns across time periods. Therefore, it is valuable not only to examine changes in the proportion of abusers who abuse a drug via specific routes, but also to examine levels of abuse via specific routes, both as a proportion of ASI-MV® assessments and relative to prescription volume of each product. Again, changes in the sampling frame due to sites dropping in and out of the network have the potential to bias these trends, and therefore it is useful to examine the restricted sample of fixed sites that contributed data consistently over the study period.

Changes in nasal abuse prevalence and rates

Comparing mean abuse prevalence in the set of fixed sites across three study periods indicates that the mean Opana ER nasal abuse prevalence decreased significantly, from 0.78 (95% CI 0.68-0.91) to 0.21 (95% CI 0.12-0.18) per 100 assessments, comparing the sensitivity pre-period following reformulated OxyContin's introduction to the post-period (**Table 16**). Post-period OPR abuse prevalence was not significantly different from OP abuse prevalence in the earlier pre-period prior to OxyContin's introduction, however. The prevalence of nasal abuse for generic oxymorphone ER was significantly greater during that post-period than either that of OP during the sensitivity pre-period or OPR during the post-period. The mean prevalence of nasal abuse increased significantly for oxymorphone IR and oxycodone IR SE across the study periods, and remained stable for morphine ER. Nasal abuse prevalence of oxycodone ER did not change significantly from the pre-period to the sensitivity pre-period, following introduction of reformulated OxyContin, but then decreased significantly during the post-period.

Table 16. Mean prevalence of past 30-day abuse via snorting per 100 ASI-MV® assessments for Opana ER and comparators across three time periods, with 95% confidence intervals, using the restricted sample of fixed ASI-MV® sites

	Pre-Period**	Sensitivity Pre-Period**	Post-Period**
Original Opana ER [†]	0.19 (0.14 – 0.26)	0.78 (0.68 – 0.91)	0.15 (0.12 – 0.18)
Opana ER ADF [‡]	N/A	N/A	0.21 (0.17 – 0.25)
Oxymorphone ER (generics)	N/A	N/A	1.08 (0.99 – 1.18)
Oxymorphone IR	0.04 (0.02 – 0.08)	0.10 (0.07 – 0.15)	0.16 (0.12 – 0.19)
Oxycodone IR single-entity	0.28 (0.22 – 0.35)	1.11 (0.98 – 1.25)	2.52 (2.38 – 2.66)
Morphine ER [§]	0.47 (0.39 – 0.56)	0.54 (0.45 – 0.64)	0.48 (0.42 – 0.55)
Oxycodone ER [¶]	2.87 (2.66 – 3.09)	2.68 (2.48 – 2.90)	1.45 (1.34 – 1.56)

** Pre-Period = first 18-month period prior to introduction of Opana ER ADF (1/1/2009 - 6/30/2010)
Sensitivity Pre-period = 18 month time period after introduction of ADF oxycodone ER and prior to introduction of Opana ER ADF (Q3 2010 – Q4 2011; 7/1/2010 - 12/31/2011)

Post-period = three-year period after introduction of Opana ER ADF and market transition for oxymorphone products (Q3 2013 – Q2 2016; 7/1/2013 – 6/30/2016). Period 2 = last 18-month period prior to introduction of Opana ER ADF (7/31/2010 - 12/31/2011)

Note that the transition period of market change for oxymorphone products (1/1/2012 - 6/30/2013) is excluded from analyses.

† Original Opana ER category represents brand original formulation Opana ER in the pre-period only.

‡ Opana ER ADF category represents brand Opana ER ADF only in the post-period.

§ Morphine ER = all extended-release morphine products excluding EMBEDA.

¶ Oxycodone ER = includes all brand and generic products

Source: NAVIPPRO® study report (December 2016)

Adjusting for the number of tablets dispensed within the fixed ASI-MV® site coverage area (**Table 17**), the changes in nasal abuse rates were similar to that seen above for Opana ER and generic oxymorphone ER. Here, nasal abuse rates increased for oxycodone IR SE, decreased slightly for ER morphine, and remained fairly stable for oxycodone ER across the study periods.

Table 17. Mean rates of past 30-day abuse via snorting per 10,000 tablets dispensed for Opana ER and comparators across three time periods, with 95% confidence intervals, using the restricted sample of fixed ASI-MV® sites

	Pre-Period**	Sensitivity Pre-Period**	Post-Period**
Original Opana ER [†]	0.034 (0.025 – 0.045)	0.078 (0.067 – 0.090)	9.478 (7.523 – 11.940)
Opana ER ADF [*]	N/A	N/A	0.041 (0.034 – 0.050)
Oxymorphone ER (generics)	N/A	N/A	0.247 (0.227 – 0.269)
Oxymorphone IR	0.021 (0.012 – 0.040)	0.042 (0.028 – 0.063)	0.074 (0.059 – 0.092)
Oxycodone IR single-entity	0.003 (0.002 – 0.003)	0.006 (0.006 – 0.007)	0.014 (0.013 – 0.015)
Morphine ER [§]	0.010 (0.008 – 0.012)	0.010 (0.008 – 0.012)	0.009 (0.008 – 0.010)
Oxycodone ER [¶]	0.046 (0.043 – 0.050)	0.050 (0.046 – 0.054)	0.043 (0.040 – 0.046)

** Pre-Period = first 18-month period prior to introduction of Opana ER ADF (1/1/2009 -6/30/2010)
Sensitivity Pre-period = 18 month time period after introduction of ADF oxycodone ER and prior to introduction of Opana ER ADF (Q3 2010 –Q4 2011; 7/1/2010 -12/31/2011)

Post-period = three-year period after introduction of Opana ER ADF and market transition for oxymorphone products (Q3 2013 – Q2 2016; 7/1/2013 – 6/30/2016). Period 2 = last 18-month period prior to introduction of Opana ER ADF (7/31/2010 -12/31/2011)

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

† Original Opana ER category represents brand original formulation Opana ER in the pre-period only.

* Opana ER ADF category represents brand Opana ER ADF only in the post-period.

§ Morphine ER = all extended-release morphine products excluding EMBEDA.

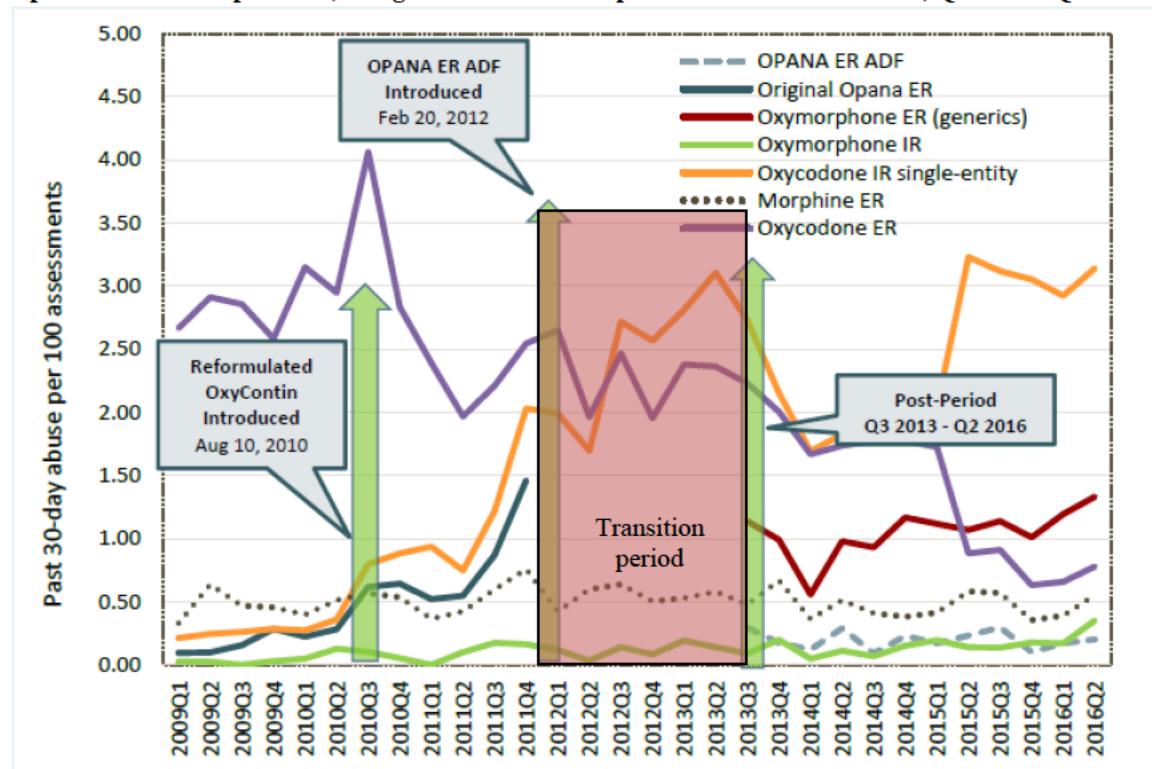
¶ Oxycodone ER = includes all brand and generic products

Source: NAVIPPRO® study report (December 2016)

Figure 12 shows trends in quarterly nasal abuse prevalence for Opana ER and comparators, as a proportion of assessments within the ASI-MV® network, using the fixed site sample. The data show a rising prevalence of both OPR and oxycodone IR SE via snorting during the pre-period, although IR oxycodone SE rates were not reliable until separate data collection for IR oxycodone SE products began in early 2010. During the post-period, the prevalence of OPR abuse via snorting remained relatively stable at levels lower than those just prior to Opana ER's reformulation but similar to those seen early in the pre-period, and the prevalence of generic oxymorphone ER snorting during the post-period was consistently higher than that for OPR. Nasal abuse prevalence for oxycodone

ER was substantially higher than any of the comparators during the pre-period. An abrupt increase in oxycodone IR SE and a sharp decline in oxycodone ER nasal abuse prevalence are seen following the ASI-MV® screen order change in March 2015.

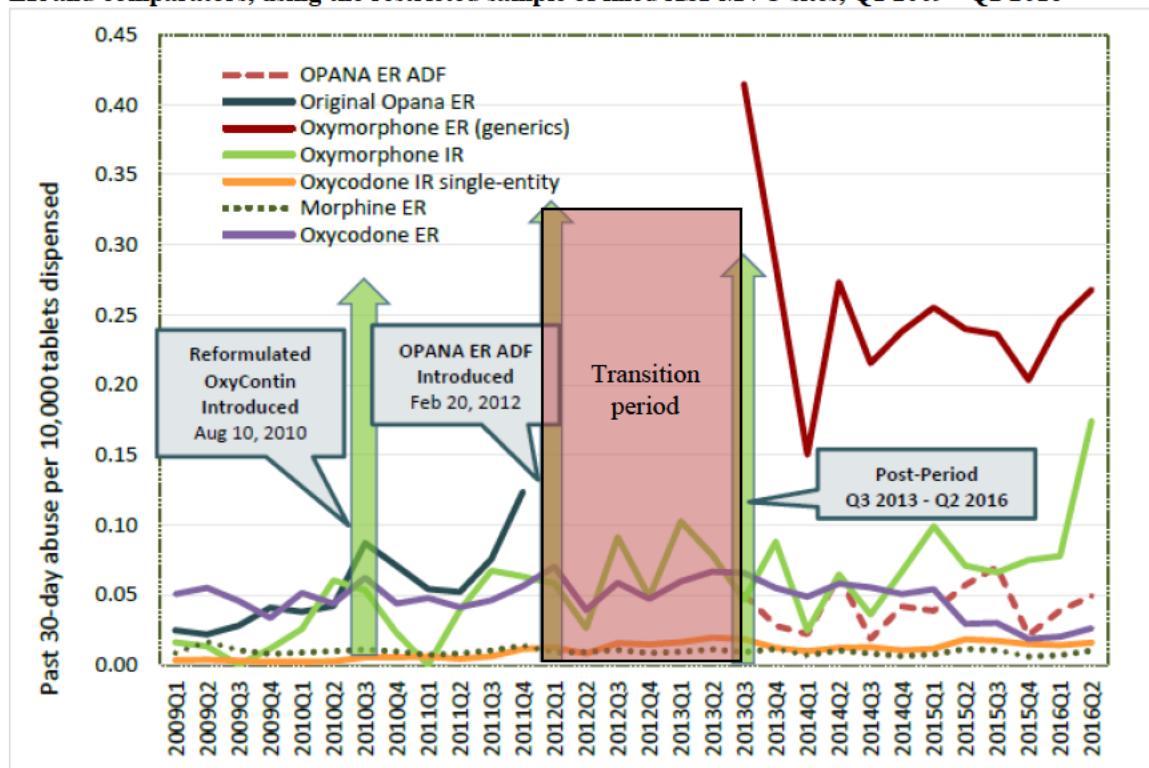
Figure 12. Quarterly prevalence of past 30-day abuse via snorting per 100 ASI-MV® assessments for Opana ER and comparators, using the restricted sample of fixed ASI-MV® sites, Q1 2009 - Q2 2016



Source: NAVIPPRO® study report (December 2016), transition period added by DEPI reviewer

Using the tablets-dispensed denominator (**Figure 13**), generic oxymorphone ER demonstrated the highest nasal abuse rates of all the studied opioids. During the post-period, tablet-adjusted nasal abuse rates for OPR were lower than for generic oxymorphone ER and more similar to oxymorphone IR and oxycodone ER. The lowest utilization-adjusted rates of nasal abuse were seen for oxycodone IR SE and morphine ER throughout the time period.

Figure 13. Quarterly rates of past 30-day abuse via snorting per 10,000 tablets dispensed for Opana ER and comparators, using the restricted sample of fixed ASI-MV® sites, Q1 2009 - Q2 2016



Source: NAVIPPRO® study report (December 2016), transition period added by DEPI reviewer

Results of formal trend analyses based on the full ASI-MV® analytic sample were provided in the December 2016 NAVIPPRO® study report. These showed a significant positive slope in OP nasal abuse prevalence during the pre-period (both the first 6-quarter pre-period and the second 6-quarter sensitivity pre-period), with a flat slope for OPR during the post-period. There was also a drop in level (intercept), comparing OPR nasal abuse prevalence trends during the post-period to the OP trend during the 6-quarter sensitivity pre-period just prior to Opana ER's reformulation. These patterns were similar for tablet-adjusted abuse rate analyses.

Changes in injection abuse prevalence and rates

As shown in **Table 18**, the mean Opana ER injection abuse prevalence increased markedly across the three study periods using the fixed site sample – more than 15-fold comparing OP in the pre-period to OPR in the post-period. However, the mean injection abuse prevalence for generic oxymorphone ER was not significantly different from that for OPR in the post-period. Oxymorphone IR, oxycodone IR SE, and morphine ER injection abuse prevalence also increased across the three study periods. Oxycodone ER showed a significant decrease in mean injection abuse prevalence from the sensitivity pre-period to the post-period but not from the pre-period to the sensitivity pre-period.

Table 18. Mean prevalence of past 30-day abuse via injection per 100 ASI-MV® assessments for Opana ER and comparators across three time periods, with 95% confidence intervals, using the restricted sample of fixed ASI-MV® sites

	Pre-Period**	Sensitivity Pre-Period**	Post-Period**
Original OPANA ER [†]	0.05 (0.03 – 0.09)	0.21 (0.16 – 0.28)	0.14 (0.11 – 0.18)
OPANA ER ADF [‡]	N/A	N/A	0.81 (0.73 – 0.89)
Oxymorphone ER (generics)	N/A	N/A	0.78 (0.70 – 0.86)
Oxymorphone IR	0.04 (0.02 – 0.07)	0.10 (0.07 – 0.15)	0.23 (0.19 – 0.28)
Oxycodone IR single-entity	0.15 (0.11 – 0.21)	0.78 (0.67 – 0.90)	1.64 (1.53 – 1.76)
Morphine ER [§]	0.98 (0.86 – 1.11)	1.14 (1.01 – 1.28)	1.33 (1.23 – 1.43)
Oxycodone ER [¶]	2.13 (1.95 – 2.32)	1.94 (1.77 – 2.13)	1.18 (1.08 – 1.28)

** Pre-Period = first 18-month period prior to introduction of OPANA ER ADF (1/1/2009 -6/30/2010)

Sensitivity Pre-period = 18 month time period after introduction of ADF oxycodone ER and prior to introduction of OPANA ER ADF (Q3 2010 –Q4 2011; 7/1/2010 -12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (Q3 2013 – Q2 2016; 7/1/2013 – 6/30/2016). Period 2 = last 18-month period prior to introduction of OPANA ER ADF (7/31/2010 -12/31/2011)

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

† Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

‡ OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

§ Morphine ER = all extended-release morphine products excluding EMBEDA.

¶ Oxycodone ER = includes all brand and generic products

Source: NAVIPPRO® study report (December 2016)

Adjusting for the number of tablets dispensed, there was a marked increase in the mean injection abuse rate for Opana ER across the three study periods (**Table 19**). The post-period OPR tablet-adjusted injection abuse rate was 18 times higher than OP rates during the pre-period (prior to reformulated OxyContin's introduction) and more than seven times higher than OP rates during the sensitivity pre-period. Again, injection abuse rates for OPR and generic oxymorphone ER were not significantly different from one another during the post-period. Tablet-adjusted injection abuse rates increased for oxycodone IR SE and oxymorphone, whereas morphine ER and oxycodone ER rates did not change significantly across the study periods.

Table 19. Mean rates of past 30-day abuse via injection per 10,000 tablets dispensed for Opana ER and comparators across three time periods, with 95% confidence intervals, using the restricted sample of fixed ASI-MV® sites

	Pre-Period**	Sensitivity Pre-Period**	Post-Period**
Original OPANA ER†	0.009 (0.005 – 0.016)	0.021 (0.016 – 0.028)	8.951 (7.058 – 11.353)
OPANA ER ADF‡	N/A	N/A	0.162 (0.147 – 0.179)
Oxymorphone ER (generics)	N/A	N/A	0.178 (0.161 – 0.197)
Oxymorphone IR	0.017 (0.009 – 0.034)	0.042 (0.028 – 0.063)	0.110 (0.091 – 0.132)
Oxycodone IR single-entity	0.001 (0.001 – 0.002)	0.004 (0.004 – 0.005)	0.009 (0.008 – 0.010)
Morphine ER§	0.021 (0.019 – 0.024)	0.021 (0.018 – 0.023)	0.024 (0.022 – 0.026)
Oxycodone ER¶	0.034 (0.032 – 0.038)	0.036 (0.033 – 0.040)	0.035 (0.033 – 0.038)

** Pre-Period = first 18-month period prior to introduction of OPANA ER ADF (1/1/2009 -6/30/2010)

Sensitivity Pre-period = 18 month time period after introduction of ADF oxycodone ER and prior to introduction of OPANA ER ADF (Q3 2010 –Q4 2011; 7/1/2010 -12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (Q3 2013 – Q2 2016; 7/1/2013 – 6/30/2016). Period 2 = last 18-month period prior to introduction of OPANA ER ADF (7/31/2010 -12/31/2011)

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

† Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

‡ OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

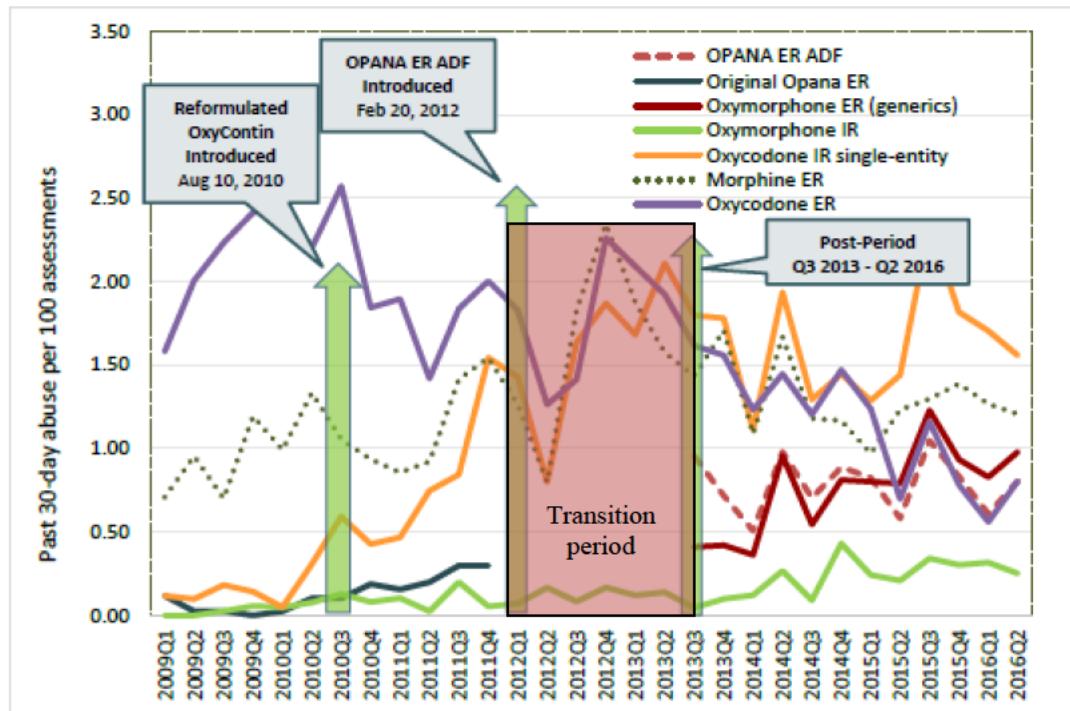
§ Morphine ER = all extended-release morphine products excluding EMBEDA.

¶ Oxycodone ER = includes all brand and generic products

Source: NAVIPPRO® study report (December 2016)

Figure 14 displays trends in quarterly injection abuse prevalence for Opana ER and comparators as a proportion of assessments within the ASI-MV® network using the restricted set of fixed sites. Although there is a moderate amount of quarter-to-quarter variability, some patterns can be seen. Increasing trends are observed for both OP and oxycodone IR SE during the pre-period. Also apparent is the higher prevalence of injection abuse of both OPR and generic oxymorphone ER in the post-period, compared to OP in the pre-period, with the prevalence of oxymorphone IR injection abuse remaining lower.

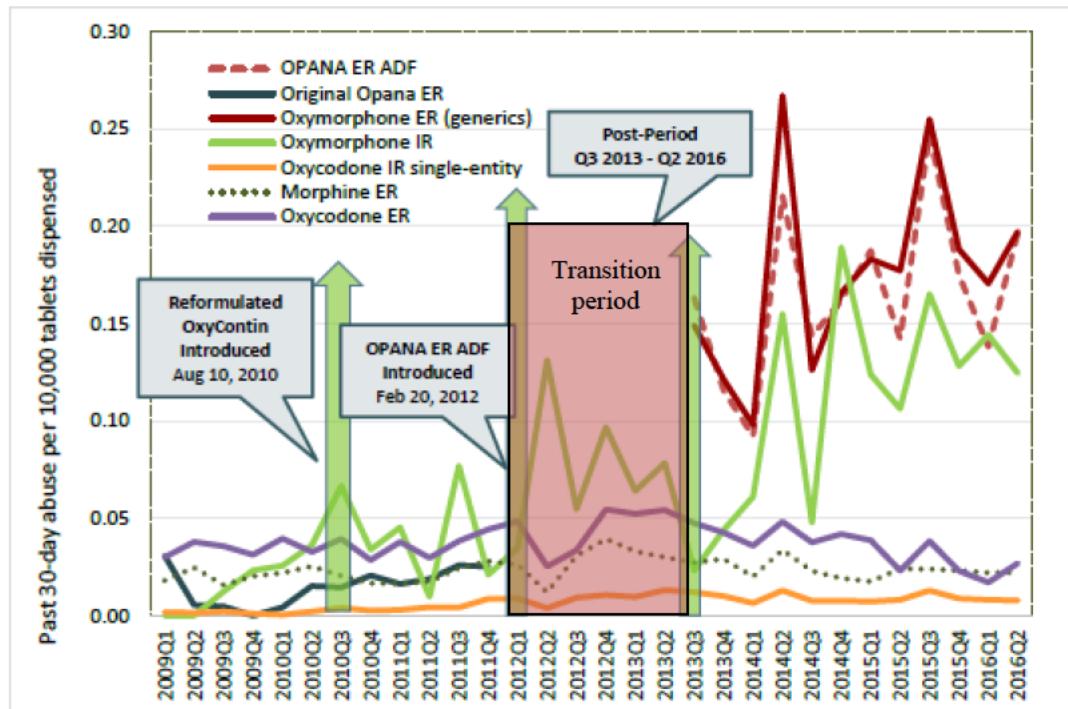
Figure 14. Quarterly prevalence of past 30-day abuse via injection per 100 ASI-MV® assessments for Opana ER and comparators, using the restricted sample of fixed ASI-MV® sites, Q1 2009 - Q2 2016



Source: NAVIPPRO® study report (December 2016), transition period added by DEPI reviewer

As shown in **Figure 15**, tablet-adjusted Opana ER injection abuse rates increased modestly during the pre-period and then markedly from the pre-period to the post-period, and rates for OPR and generic oxymorphone ER were similar during the post period. Oxymorphone IR rates also trended upward, nearing the levels of OPR and generic oxymorphone ER by the latter part of the post-period. Oxycodone ER injection abuse rates remained relatively stable across the study period and were higher than OP during the pre-period but lower than both OPR, generic oxymorphone ER, and oxymorphone IR during the post-period.

Figure 15. Quarterly rates of past 30-day abuse via injection per 10,000 tablets dispensed for Opana ER and comparators, using the restricted sample of fixed ASI-MV® sites, Q1 2009 - Q2 2016



Source: NAVIPPRO® study report (December 2016), transition period added by DEPI reviewer

Results of formal trend analyses based on the full ASI-MV® analytic sample were provided in the December 2016 NAVIPPRO® study report. These showed a significant positive slope in OP injection abuse prevalence during the pre-period (both the first and the second 6-quarter periods), with a flat slope for OPR during the post-period. There was an increase in level (intercept), comparing OPR during the post-period to OP during the 6-quarter sensitivity pre-period just prior to Opana ER's reformulation. These patterns were similar for tablet-adjusted abuse rate analyses.

Route-specific stratified analyses: Tennessee versus non-Tennessee sites

Route-specific means analyses for sites within Tennessee are included in **Appendix J, Figures J1 and J2 and Tables J14-J17**. In Tennessee, the prevalence of Opana ER nasal abuse per 100 assessments showed a relative decrease of 79.4%, comparing OP in the 3-year pre-period to OPR during the post-period. The prevalence of Opana ER injection abuse increased by 264.6%. Adjusting for the number of tablets dispensed, the relative decrease the Opana ER nasal abuse rate was more modest, at -37.6%, and an increase of almost 1000% was seen in tablet-adjusted injection abuse rates, comparing OP to OPR. Analyses using the 6-quarter sensitivity pre-period showed similar patterns. Results were also similar in sensitivity analyses including only the two Tennessee sites that contributed data in all study quarters (data not shown). Again, post-period nasal abuse rates for generic oxymorphone ER were much higher than for OPR, while injection

abuse rates were similar. Of additional note, increases in injection abuse for oxymorphone IR were of similar magnitude to those for Opana ER in Tennessee.

Route-specific analyses for sites excluding Tennessee are included in **Appendix J, Figures J3 and J4, and Tables J18-J21**. Again, there was a statistically significant 87.0% relative decrease in the prevalence of Opana ER abuse via the nasal route per 100 assessments, comparing OP in the 3-year pre-period to OPR in the post-period. Tablet-adjusted Opana ER nasal abuse rates decreased to a similar degree. Analyses using the 6-quarter sensitivity pre-period showed similar patterns. Increases in injection abuse were of smaller magnitude than in the Tennessee sample, but still statistically significant. Opana ER injection abuse prevalence increased by 56.1%, and tablet-adjusted Opana ER injection abuse rates increased by 74.8%, comparing OP in the 3-year pre-period to OPR in the post-period. Using the 6-quarter sensitivity pre-period, there was no significant change in the prevalence of Opana ER injection abuse per 100 assessments and a significant 35% increase in the rate per 10,000 tablets dispensed. In the fixed-site non-Tennessee sample, there was a marked reduction in nasal abuse per 100 assessments and per 10,000 tablets dispensed, comparing OP nasal abuse in the 6-quarter sensitivity pre-period to OPR, and the tablet-adjusted generic oxymorphone ER nasal abuse rate was four times the OPR nasal abuse rate in the post-period. Here, there was no significant increase in Opana ER injection abuse prevalence per 100 assessments, comparing OP in this 6-quarter pre-period to OPR in the post-period. However, the injection abuse rates comparing OP to generic ER oxymorphone also did not change significantly in the non-Tennessee fixed site analyses.

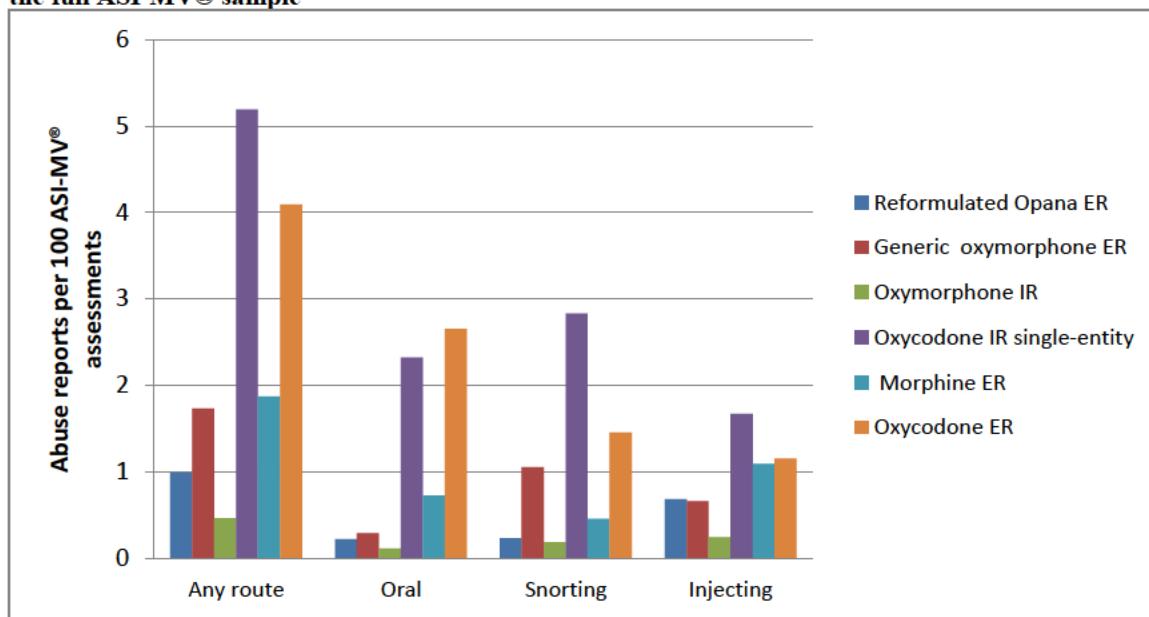
Post-period abuse rate comparisons: overall and route-specific

Comparing abuse rates across drugs within a single time period can help put abuse rates for a drug in context. Because abuse patterns can vary considerably across geographic regions, in these analyses it is more appropriate to use the full ASI-MV® sample to cover the largest geographic area.

Figure 16 compares the proportion of ASI-MV® assessments reporting past 30-day abuse of reformulated Opana ER and comparators, overall and via specific routes, during the post-period. Among the opioids included in this analysis, the most common drugs abused overall and via the oral route were oxycodone IR SE and oxycodone ER. Via the nasal route, oxycodone IR SE was the most common drug mentioned, followed by oxycodone ER and generic oxymorphone ER. Via the injection route, oxycodone IR SE was the most common, followed by oxycodone ER and morphine ER.

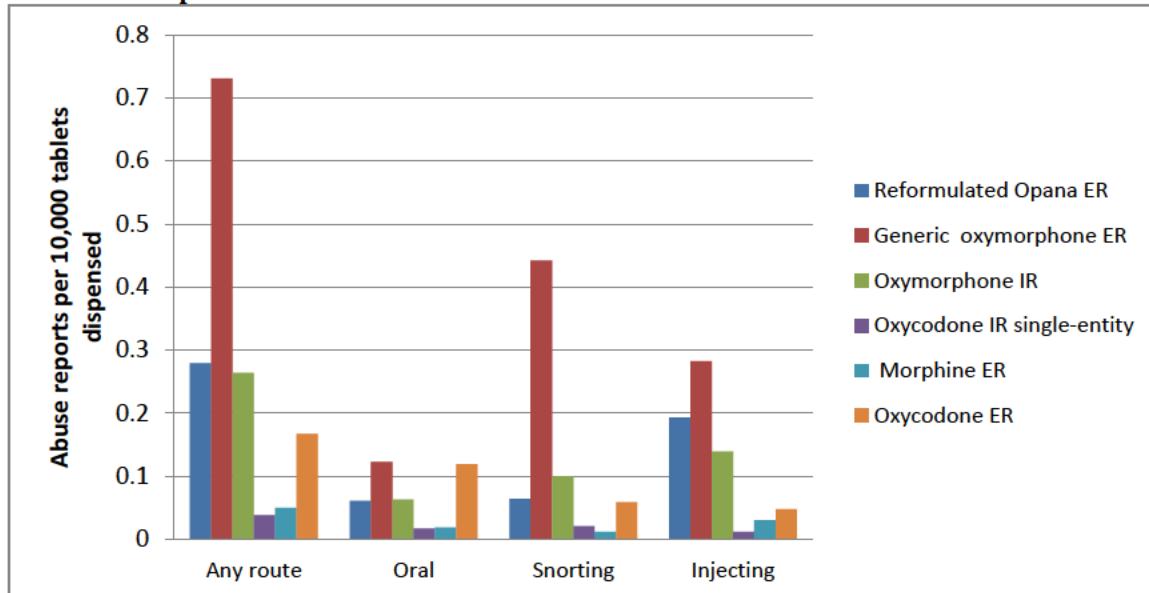
Figure 17 depicts post-period abuse rates per 10,000 tablets dispensed for reformulated Opana ER and comparators, overall and via specific routes. Here, generic oxymorphone ER had the highest overall and nasal abuse rates, by far. Oral abuse rates were highest for generic oxymorphone ER and oxycodone ER. Generic oxymorphone ER and OPR had the highest injection abuse rates, followed by oxymorphone IR. In this analysis, using the full ASI-MV® analytic sample, tablet-adjusted injection abuse rates for generic oxymorphone ER were significantly higher than for OPR ($p<0.001$).

Figure 16. Prevalence of past 30-day abuse per 100 ASI-MV® assessments for reformulated Opana ER and comparators, overall and via specific routes, post-period only (7/1/2013 – 6/30/2016), using the full ASI-MV® sample



Source: Figure generated by DEPI reviewer using data in the NAVIPPRO® study report (December 2016)

Figure 17. Past 30-day abuse rates per 10,000 tablets dispensed for reformulated Opana ER and comparators, overall and via specific routes, post-period only (7/1/2013 – 6/30/2016), using the full ASI-MV® sample



Source: Figure generated by DEPI reviewer using data in the NAVIPPRO® study report (December 2016)

As shown in **Tables J6–J9 and Figures J1–J4 in Appendix J**, the post-period abuse prevalence per 100 assessments and tablet-adjusted abuse rates for both OPR, generic oxymorphone ER, and other opioid comparators were generally far higher at sites within Tennessee than for sites outside Tennessee, particularly via non-oral routes. The

difference between Tennessee and non-Tennessee abuse levels was generally higher when examining abuse prevalence per 100 assessments than tablet-adjusted abuse rates. Comparing Tennessee to non-Tennessee samples, the rankings of the opioids analyzed were generally similar with respect to overall and route-specific, but there were some differences between the two groups in relative route-specific abuse rates (data not shown).

2.3.2.3 Reviewer comments on the NAVIPPRO® Study

2.3.2.3.1 Methodological Considerations

Sampling: The nature of NAVIPPRO®'s sampling strategy presents challenges in interpreting changes in prescription opioid abuse rates over time. First, this is a convenience sample, with some geographic areas over-represented and some regions under-represented. Second, the distribution of the ASI-MV® sites changes each quarter—both geographically and in terms of assessment setting (e.g., residential/inpatient, methadone clinic, corrections). Therefore, the study populations cannot be assumed to be comparable across study periods. The Tennessee/non-Tennessee analyses illustrate how the geographic distribution of ASI-MV® assessments can change dramatically over time and how different geographic regions may have very different population characteristics and abuse rates. Compared to the overall ASI-MV® sample, the Tennessee sample had a much higher proportion of individuals who reported abusing prescription opioids, entering residential/inpatient treatment, injecting drugs, and abusing Opana ER and other opioids. Therefore, the large increase in the number of assessments from Tennessee is likely to confound pre-post analyses of abuse rates when using the full ASI-MV® sample. In addition, even within Tennessee, these study population characteristics changed over time. Furthermore, the increases in the Tennessee study sample appear to be a result of both more participating sites, and more assessments per site. It is unclear to what degree the increase in assessments reflects greater access to treatment (e.g., due to expanded funding for opioid addiction treatment or other policy changes), increased demand (i.e. increasing numbers of individuals with opioid use disorders needing treatment), or both. This study report singled out Tennessee, presumably because it had a very high prevalence of Opana ER abuse and because the proportion of assessments from Tennessee increased over the study period, but the Tennessee scenario illustrates the broader complexities of the NAVIPPRO® study sampling.

Because of the potential biases created by the dynamic nature of this surveillance network due to sites dropping in and out of the network, the fixed site analyses are useful to stabilize the sampling frame and allow comparisons of abuse patterns over time. Since this restricted sample covers a smaller geographic area, results from these analyses may be less generalizable, but they likely have greater internal validity than analyses using the full analytic sample. Using a fixed set of sites controls for confounding due to shifts in both geographic distribution of the sites and in the distribution of site-level characteristics—for example, type or setting of treatment (e.g., inpatient vs. outpatient)—that are associated with abuse rates and patterns. Even in a fixed site analysis, however, changes in external factors—for example, availability of and reimbursement for

substance abuse treatment, criminal justice policies, and use of office-based opioid addiction treatment—may still affect access to treatment and the probability of an abuser being assessed at a given site. Changes in these factors could also result in changes in the proportion of individuals with more severe opioid use disorders being assessed. These external factors are extremely difficult to measure or control, and remain a challenge in interpreting these data. Analyses that use the number of assessments as the denominator control for the variation in the number of assessments each quarter, while the tablet-adjusted abuse rates allow the number of assessments to vary, controlling instead for the level of availability of each product within the communities in which the assessed individuals reside. Therefore, it is important to examine both types of analysis. Finally, it must be kept in mind that patterns observed among those being assessed for treatment do not necessarily reflect patterns in the broader population with substance use disorders but not seeking or being referred for treatment.

Looking at changes in the proportion of abusers of a particular drug who report abusing via a particular route may be less influenced by bias resulting from changes in the overall ASI-MV® study sample over time; however, this measure does not account for changes in the overall levels of abuse of the drug and must be interpreted in conjunction with other data.

Utilization adjustment: Utilization-adjusted analyses are critical to the assessment of abuse-deterrence, as (1) adjustment for varying levels of prescribed availability is important in comparing abuse levels across products, and (2) many factors other than reformulation can impact prescribing trends for a product. Some of these factors might include drug marketing practices, the availability of generic products, insurance reimbursement policies, use of prescription drug monitoring programs, and drug shortages. Reformulation itself may also affect utilization, although it is unknown how much of this change is the result of reduced demand by those abusing or diverting the drug versus reduced prescribing for other reasons, such as a perceived reduction in analgesic potency. Prescription- and tablet-adjusted analyses control for all of these changes in utilization, regardless of cause. Methodological uncertainties remain about the best way to measure community-level availability and to model the relationship between utilization and abuse rates at varying levels of market share, as this relationship may not always be linear. In general, FDA considers the number of tablets dispensed to be superior to the number of prescriptions dispensed, as every tablet presents an opportunity for diversion and abuse, and the average number of tablets per prescription may vary across opioids. Therefore, we focused on tablet-adjusted rates in our review when assessing utilization-adjusted abuse rates. Because diverted prescription drugs may be used in areas remote from where they are dispensed, the best catchment area for utilization data is also unclear. In this study, utilization-adjusted fixed site analysis results were similar using a catchment area for the utilization denominators defined as the area covering all home 3-digit ZIP codes of individuals assessed in a given time period and in sensitivity analyses using the area covered by states in which the fixed set of ASI-MV® sites were located.

Misclassification: In evaluating changes in Opana ER abuse rates across study periods, an important limitation of the data is the potential for misclassification of product-specific

abuse outcomes. A certain amount of misclassification is inevitable in any self-reported data; however, it is important to consider how false positive and negatives might affect study results. During the 3-year post-period, beginning more than 1 year after marketing of OP was discontinued, there were 532 assessments that reported past 30-day abuse of OP, in addition to the 1,675 reports of OPR abuse. It is unknown what proportion of these 532 OP abuse reports reflect true past 30-day abuse of OP – for example, abuse of residual supplies of OP after its market discontinuation – and what proportion were false positives. For example, if an individual actually abused OPR, generic oxymorphone ER, or oxymorphone IR but selected the OP screen button, then misclassification has occurred in the form of a false positive OP abuse event and a false negative abuse report for OPR, generic oxymorphone ER, or oxymorphone IR. If a respondent last abused OP two years prior to the assessment but mistakenly indicated past 30-day abuse of OP, then this also represents a false positive for OP abuse. Some misclassification is expected in this type of self-reported data, and it would be expected to occur in both the pre- and post-reformulation periods. If the number of false positives is similar to the number of false negatives throughout the study period and for all products analyzed, then the misclassification is non-differential and would be expected to attenuate differences seen across products and time periods, resulting in a bias toward the null. If these numbers differ across time periods or products, however, bias may occur in a direction that is difficult to predict. **Nonetheless, the high levels of persistent OP abuse reporting throughout the post-period despite trivial dispensing of this product during this time suggest the possibility of substantial misclassification and post-period rates for OPR, generic oxymorphone ER, and/or oxymorphone IR that may be substantially underestimated.**

Causal inference and the counterfactual. An overarching question that we attempted to answer in interpreting the postmarketing data was “What happened to Opana ER abuse rates and patterns *compared to what would have happened without the reformulation?*” This concept is sometimes referred to as the “counterfactual.” Because Opana ER was reformulated and the original version removed from the market, we cannot answer this question directly. However, the use of comparators can help to disentangle the effect of the reformulation itself from secular trends in opioid availability and abuse patterns, changes in the study populations, and the effects of other interventions to reduce opioid abuse and overdose. The ideal comparator is as similar to the index opioid as possible, with regard to pharmacologic properties, indication for use, marketing history, and baseline abuse patterns and rates. Because it is biologically equivalent to OP and contains no abuse-deterring technologies, generic oxymorphone ER—available during the post-reformulation period—may also provide a clue to what would have happened to Opana ER abuse patterns had it not been reformulated. Accordingly, differences in ROA patterns between OP in the pre-period and generic oxymorphone ER in the post-period might be viewed as an indicator of changes in abuse patterns due to factors unrelated to Opana ER’s reformulation. The assumption that post-period generic oxymorphone ER abuse patterns are behaving as Opana ER abuse patterns would have behaved without reformulation cannot be tested.

Inspecting patterns of abuse in other comparator opioids can also be helpful in assessing whether factors other than reformulation may have contributed to the observed changes in

Opana ER's ROA profile, as these may provide additional insight into secular trends in opioid abuse patterns. As there is no perfect comparator, multiple comparators were used in these studies to evaluate whether changes observed in Opana ER abuse were specific to this drug and therefore more likely attributable to the reformulation itself rather than other factors impacting multiple opioid products.

2.3.2.3.2 Interpretation of key findings, NAVIPPRO® study

Change in Opana ER overall abuse rates (via any route):

Within the restricted sample of sites that contributed data in every quarter, the prevalence of overall Opana ER abuse (via any route) did not change significantly from the 6-quarter pre-period to the post-period. However, the post-period abuse prevalence of generic oxymorphone ER was significantly higher than that of OPR. The tablet-adjusted abuse rate increased significantly comparing OP to OPR; however, comparing OP to generic oxymorphone ER, there was an even greater increase. The greater increases in mean abuse rates comparing OP to generic oxymorphone ER versus OPR suggest that although the reformulation of Opana ER may not have caused a decline in abuse in this population, Opana ER abuse rates might have risen even higher had it not been reformulated. In addition, while mean abuse rates for Opana ER did not decrease significantly, inspection of trends shows that the increasing trend in OP abuse seen during the pre-period did not continue during the post-period for OPR. If one assumes that pre-period trends would likely have continued unabated in the absence of reformulation, then deviation from this trajectory can be interpreted as a possible effect of the reformulation. The validity of this assumption cannot be tested, however. Finally, even in the fixed site analyses, the number and proportion of assessments from Tennessee sites—where Opana ER abuse rates are much higher than in the non-Tennessee sample—still increased across the study period, potentially creating bias. In the stratified analyses, both the Tennessee and non-Tennessee samples suggest a decrease in overall Opana ER abuse prevalence. However, in Tennessee, tablet-adjusted Opana ER abuse rates increased. Finally, the potential for underestimating post-period abuse rates due to misclassification of OP, OPR, and generic oxymorphone ER and IR further complicate the interpretation of these data. Overall, the data suggest that Opana ER's reformulation may have attenuated the rise in Opana ER abuse rates in this population, but the geographic variation and limitations of these data make it very difficult to evaluate the magnitude of this possible effect.

Change in proportion of Opana ER abusers who abuse it via specific routes:

The most notable and consistent finding from this study was the marked shift occurring in the reported ROAs for Opana ER among abusers of the product following reformulation, from predominantly snorting to predominantly injection, with persistently low levels of abuse via the oral route. This shift was seen in the overall ASI-MV® sample as well as in the fixed site sample, the Tennessee sample, the non-Tennessee sample, and the fixed site Tennessee and non-Tennessee samples. Although more modest shifts toward injection were observed for several comparators, the magnitude of Opana ER's change in ROA profile was unique. In particular, the increase in injection and decrease in snorting was significantly greater comparing OP to OPR than comparing OP to generic oxymorphone

ER. Such a shift from nasal to injection routes was not observed for oxycodone ER following OxyContin's reformulation, and a large proportion of oxycodone ER abusers reported oral abuse both before and after OxyContin's reformulation. Together, these findings indicate that the reformulation of Opana ER likely caused a meaningful shift in ROA from snorting to injecting among Opana ER abusers being assessed for substance abuse treatment.

Change in Opana ER nasal and injection abuse rates:

Another important question is whether the reformulation of Opana ER resulted in meaningful changes in abuse prevalence or tablet-adjusted nasal and injection abuse levels for this drug in the study population. In contrast to the analyses described above, this question is not limited to Opana ER abusers, but relates to changes in abuse rates in the overall sample, and more importantly, to what inferences can be made about changes in abuse rates in the underlying population from which the study sample was drawn.

The fixed site analyses indicate that Opana ER nasal abuse rates decreased significantly from the 6-quarter period immediately prior to reformulation to the post-period, both as a proportion of ASI-MV® assessments and per 10,000 tablets dispensed. The start of the decline was temporally associated with the market transition from OP to OPR. Post-period OPR nasal abuse rates were, however, similar to those seen in the early pre-period. Changes in utilization-adjusted nasal abuse rates varied across the selected opioid comparators, but rates were significantly higher for generic oxymorphone ER than for OPR during the post-period. Together, these findings suggest that Opana ER's reformulation likely reduced abuse via the nasal route in this population compared to what rates might have been without reformulation; however, the limitations of this data source around sampling and misclassification make it difficult to determine the magnitude of this apparent effect.

Fixed site analyses indicate that Opana ER injection abuse rates increased markedly from the 6-quarter period immediately prior to reformulation to the post-period, both as a proportion of ASI-MV® assessments and per 10,000 tablets dispensed. However, the increases in injection abuse rates for Opana ER began prior to market introduction of OPR, and the change in utilization-adjusted injection abuse rates was essentially identical comparing OP to OPR and comparing OP to generic oxymorphone ER in the post-period. Changes in utilization-adjusted injection rates for other opioid comparators were mixed, but none had increases of similar magnitude to that seen comparing OP to either OPR or generic oxymorphone ER. If generic oxymorphone ER is assumed to be an indicator of what Opana ER abuse rates might have been in the post-period without reformulation, these findings suggest that the increases in Opana ER injection abuse rates might be similar to what they would have been without reformulation. The validity of this assumption is unknown, however. Furthermore, the persistence of OP abuse reports during the post-period raise concerns about the potential for misclassification bias and underestimation of post-period OPR, generic oxymorphone ER and/or generic oxymorphone IR abuse rates. And again, the variation in abuse rates and trends between Tennessee and non-Tennessee samples further complicates interpretation of these findings. While similar results were seen using both the full and the fixed site Tennessee

sample, the non-Tennessee fixed site analysis did not show significant increases in injection abuse rates comparing OP in the 6-quarter sensitivity pre-period after OxyContin's reformulation to either OPR or generic ER oxymorphone in the post-period. Overall, the study findings suggest that Opana ER injection abuse rates increased across the study period, but the evidence is inconclusive as to whether Opana ER injection abuse rates are higher than they would have been in the absence of reformulation.

Post-period abuse rates for reformulated Opana ER and comparators

Finally, it is informative to examine post-period abuse rates for Opana ER and selected comparator opioids with similar pharmacologic properties and indications. Abuse prevalence rates calculated as a proportion of ASI-MV® assessments provide information on each product's relative contribution to overall prescription opioid abuse among those being assessed for substance abuse treatment within this site network, but they do not account for differences in availability of different opioids. As the amount dispensed for a given drug increases, so do opportunities for diversion and abuse. Therefore, it is also useful to examine tablet-adjusted abuse rates in order to better understand relative levels of abuse for different opioids in this population for a given prescription volume within areas in which assessed individuals reside.

During the post-period, abuse prevalence per 100 ASI-MV® assessments was highest for oxycodone ER and oxycodone IR SE. However, tablet-adjusted abuse rates were higher for oxymorphone products than for morphine ER, oxycodone IR SE, or oxycodone ER. Among the oxymorphone products, generic oxymorphone ER had the highest tablet-adjusted overall and nasal abuse rates. Tablet-adjusted injection abuse rates for OPR, generic oxymorphone ER, and oxymorphone IR were all substantially higher than those for oxycodone IR SE, morphine ER, or oxycodone ER.

Direct comparisons of abuse rates across drug products have limitations using these data and must be interpreted with caution. First, these are not geographically representative samples, and the Tennessee vs. non-Tennessee analyses illustrate how abuse rates can vary widely across geographic areas. Tennessee appears to represent a geographic "hot spot" with high abuse rates for Opana ER and other opioids; however, it is likely that other similar areas exist that are simply not captured well by the ASI-MV® surveillance network. Second, the patterns seen in this population cannot be assumed to reflect patterns among abusers who are not being assessed for substance abuse treatment. Third, it is unclear how well the number of tablets dispensed within home 3-digit ZIP codes of assessed individuals approximates the actual availability of these drugs within these communities, given diversion and long-distance trafficking of controlled substances. Fourth, differential misclassification of products could bias estimates in unpredictable ways; in particular, misclassification of OPR, generic oxymorphone ER, or oxymorphone IR as OP during the post-period could result in underestimates for these products. Finally, abuse rates for some opioids were observed to change abruptly when the ASI-MV® screen order was changed in 2015, suggesting that the order in which products are presented may have a considerable impact on relative abuse rate estimates.

2.3.3 RADARS® Poison Center Study

2.3.3.1 Study Methods

2.3.3.1.1 Data source

The RADARS® System provides postmarketing surveillance of prescription medication abuse, misuse, and diversion to pharmaceutical companies, regulatory agencies, and policy making organizations. RADARS® has multiple surveillance programs that gather data from various populations along the spectrum of drug abuse. This analysis uses surveillance data from the Poison Center Program (PCP). RADARS® PCP obtains data collected from individuals within the general population and from healthcare providers who call a poison control center seeking advice regarding potential toxic exposures, including exposures to prescription opioids and stimulants. Personnel at each participating poison center collect information using nationally standardized electronic data collection software. The objectives of the PCP are to detect product-specific prescription drug abuse and misuse in near real-time, and to identify geographic areas with disproportionately high rates of abuse and misuse.

2.3.3.1.2 Population

The PCP gathers data from 50 regional U.S. poison centers covering 48 states, including urban, suburban and rural regions (over 90% of the U.S. population).

2.3.3.1.3 Study time frame

Analyses were conducted using two different time period definitions. The first set of analyses used the following four categories, while the second set of analyses combines the first two time periods into a single period.

***Please note—the RADARS® PCP study report refers to reformulated OxyContin as ORF and reformulated Opana ER as CRF (also referred to in this review as OPR):**

Pre-ORF/Pre-CRF: 1Q2009 - 3Q2010; this is the pre-period prior to introduction of reformulated OxyContin (ORF), where 4Q2010 is the first full quarter following release ORF in August 2010.

Post-ORF/Pre-CRF: 4Q2010 - 4Q2011; this is the pre-period after ORF was introduced but prior to the introduction of reformulated Opana ER (CRF).

Transition: 1Q2012 - 2Q2013; there were several changes to the oxymorphone market in 2012 through mid-year 2013, including the introduction of reformulated Opana ER in February 2012, gradually replacing original Opana ER over the subsequent three months, and market introduction of generic versions of ER oxymorphone.

Post-ORF/Post-CRF: 3Q2013 - 2Q2016; the Post-ORF/Post-CRF period excludes the 6-quarter market transition period following reformulation of Opana ER.

2.3.3.1.3.1 Outcome definition and measurement

Intentional Abuse Exposures: In the RADARS® PCP, an intentional abuse exposure is 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.”

Route of administration for intentional abuse exposure cases: Since 2010, route of exposure in the RADARS® System has been determined by trained RADARS® System staff who review case notes to identify the route of administration for each opioid and/or stimulant mentioned in an exposure case.^m If it is reported that a case ‘took’ a drug, then the intended route of administration is assigned. Due to low mention counts for injection and inhalation use of Opana ER in the RADARS® PCP, route of administration was classified as “oral” (swallowing whole) or “non-oral” (injection, inhalation, chewed prior to swallowing) for this study. Upon FDA request, additional information was provided on cases in which inhalation and injection routes were reported.

Major Medical Outcomes and Deaths: Deaths from cases where an inquiry was initially placed at a regional poison center, regardless of reason for exposure, are summarized. As deaths are sparse in the RADARS® PCP, deaths and major medical outcomes are combined. Major medical outcomes are defined as “the patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement.”

Overdose: Overdose was defined as the total of intentional exposures, therapeutic errors and unintentional general exposures. Intentional exposures are defined as those resulting “from a purposeful action” and include suspected suicide, intentional misuse, intentional abuse, and intentional exposures where the specific motivation (suicide, misuse, or abuse) cannot be determined. Therapeutic errors are 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.” In the RADARS® PCP, accidental unsupervised ingestions among children are coded as unintentional general.

^m In recent discussions between FDA and RADARS® staff, we have learned that RADARS® investigators are no longer confident that, through review of case narratives, they can reliably identify route of exposure for each individual drug involved in multi-substance exposures. Therefore, they are revising their methodology for route-specific analyses to limit these cases to single-substance exposures only. This revised methodology does not yet apply to the analyses included in this review.

2.3.3.1.4 Comparators

Changes in reported trends of abuse and misuse of Opana ER between time periods are compared to two other opioid groups: ER morphine and SE IR oxymorphone. ER morphine includes branded (e.g., MS Contin®, Embeda®) and generic ER morphine tablets and capsules; other formulations (e.g., solutions) are not included. ER morphine was selected as a comparator because it displays similar proportions of unintended route use among treatment center samples as Opana ER. ER morphine is also an ER/LA opioid formulation with a relatively stable number of prescriptions during the analysis period. Secular changes in the abuse of ER opioids would be expected to be reflected in trends for this comparator.

SE IR oxymorphone includes branded (e.g., Opana IR) and generic IR oxymorphone products formulated as tablets, capsules, and/or solutions. This comparator is used because it contains the same active ingredient as Opana ER, but in an IR formulation. Note that because solutions are included in the numerator and denominator, rate per dosing units dispensed may show wide variability due to the inclusion of different formulations.

FDA requested additional analyses using ER oxycodone as a comparator. Therefore, some analyses include ER oxycodone as well as the above-mentioned comparators.

***Please note that terminology for opioid products differs slightly in the RADARS® PC study from the NAVIPPRO® study. This section of the review will use the terminology employed in the RADARS® PC study report.**

2.3.3.1.5 Statistical analyses

Please also see the Division of Biometrics VII review for further detail.

Population-Adjusted Rates: Population data are based on 2000 and 2010 United States Census Bureau information. Population growth/decline by region is accounted for by adjusting the population within each ZIP code by the change between the 2000 and 2010 Census data. The percentage change in the population within each 3-digit ZIP code tabulation area (ZCTA) is calculated by dividing the 2010 population by the 2000 population. This percentage change by 3-digit ZCTA is used to extrapolate the population for years beyond 2010. Population rates represent the sum of the product mentions by exposures of interest divided by the sum of the estimated population within 3-digit ZIP codes covered by the participating poison centers, scaled per 100,000 persons.

Prescriptions Dispensed-Adjusted Rates: Prescription data are obtained from IMS Government Solutions, Inc., a subsidiary of IMS Health Inc. (Atlanta, Georgia), and are an estimate of the number of prescriptions dispensed at retail pharmacies for a particular product within a given quarter in each 3-digit ZIP code in the U.S. Prescription rates represent the sum of the product mentions by exposures of interest divided by the sum of the estimated number of prescriptions dispensed within the 3-

digit ZIP codes covered by the participating poison centers, scaled per 1,000 prescriptions dispensed.

Dosing Units Dispensed-Adjusted Rates: Dosing units (e.g., tablets) dispensed data are obtained from IMS Health and are an estimate of the number of dosing units dispensed at retail pharmacies for a particular product within a given quarter in each 3-digit ZIP code in the U.S. Dosing units dispensed rates represent the sum of product mentions for the exposures of interest divided by the sum of the estimated number of dosing units dispensed across the 3-digit ZIP codes covered by the participating poison centers, scaled per 100,000 dosing units dispensed.

Comparison of Means Model: In these models, the mean rate of the outcome variable (unique product mentions by exposure cases defined above) was compared to the mean rate of the outcome variable in other time periods.

In models assessing the change in mean rates of Opana ER following introduction of OPR (CRF), the outcome was regressed on an indicator variable representing the three time periods. In models comparing mean Opana ER rates to other opioid groups, the outcome variable was regressed on an indicator variable representing the three time periods, the three drug groups, and a drug group by time period effect. Data are presented as the percentage change. The drug group by time period effect represents the difference in the change in rates from the reference period. In analyses of routes of administration, an indicator variable for route of administration substitutes for the drug group variable.

Interrupted Time Series Model: In these models, different linear trends were assumed for each of the three time periods. Tests for differences in the slopes and intercepts of these linear trends were conducted. In models assessing the change in Opana ER rates, the outcome was regressed on an indicator variable representing time period, a continuous variable for time, and a term for time period by time. In models comparing the change in Opana ER rates to other opioids, the outcome is regressed on an indicator variable representing time period, drug group, a continuous variable for time, a term for drug group by time period, a term for drug group by time, a term for time period by time, and a term for drug group by time period by time. Time is calculated to represent a one unit change from one quarter to the next, with the value centered at the first full quarter after the transition to CRF. Data are presented for the intercepts (the expected rate at the first full quarter after transition to CRF based on the slope from each of the three time periods) and slopes (the ratio of the average quarterly change in rates by time period). Results are presented as the percentage change in intercepts and in slopes. The percentage change in intercepts represents the rate ratio of the estimated rate in 3Q2013 based on the slope from the period of interest over the time trend of the estimated rate in 3Q2013 based on the Pre ORF/Pre CRF time trend. The percentage change in slopes represents the quarterly change rate ratio based on the time trend from the period of interest over the quarterly change rate ratio based on the reference time trend.

Models comparing rates use Poisson regression and assume independence between time points. Poisson regression models include a drug group specific dispersion

parameter to adjust for over- or under-dispersion and to allow variances to differ across drug groups. The denominators (population, prescriptions dispensed, and dosing units dispensed) enter the Poisson regression models as offset variables. Each contrast is presented as the later period vs. the reference period.

2.3.3.2 Study Results

2.3.3.2.1 Changes in intentional abuse exposure call rates, via any route

Table 20 shows the quarterly number of intentional abuse exposure calls for Opana ER in the RADARS® PC study for the four study periods. Intentional abuse exposure calls for Opana ER ranged from 8 to 72 events per quarter within the 43 poison centers that participated for every quarter of the study period.

Table 20. Opana ER intentional abuse exposure call counts and population rates, 1Q2009 - 2Q2016, RADARS® Poison Center Study

Period	Number of centers participating	Year-Quarter	Number of mentions	Population covered	Population rate per 100,000 (95% CI)
Pre ORF/Pre CRF	43	1Q2009	11	247,902,666.00	0.0044 (0.0022,0.0079)
	43	2Q2009	11	248,469,754.60	0.0044 (0.0022,0.0079)
	43	3Q2009	11	249,036,843.20	0.0044 (0.0022,0.0079)
	43	4Q2009	13	249,603,931.80	0.0052 (0.0028,0.0089)
	43	1Q2010	13	250,171,020.40	0.0052 (0.0028,0.0089)
	43	2Q2010	18	250,846,976.00	0.0072 (0.0043,0.0113)
	43	3Q2010	16	251,554,728.71	0.0064 (0.0036,0.0103)
Post ORF/Pre CRF	43	4Q2010	31	252,262,481.43	0.0123 (0.0083,0.0174)
	43	1Q2011	42	252,970,234.14	0.0166 (0.0120,0.0224)
	43	2Q2011	40	253,677,986.85	0.0158 (0.0113,0.0215)
	43	3Q2011	58	254,385,739.56	0.0228 (0.0173,0.0285)
	43	4Q2011	72	255,093,492.28	0.0282 (0.0221,0.0355)
Transition Period	43	1Q2012	72	255,801,244.99	0.0281 (0.0220,0.0354)
	43	2Q2012	31	256,508,997.70	0.0121 (0.0082,0.0172)
	43	3Q2012	18	257,216,750.41	0.0070 (0.0041,0.0111)
	43	4Q2012	11	257,924,503.13	0.0043 (0.0021,0.0076)
	43	1Q2013	22	258,632,255.84	0.0085 (0.0053,0.0129)
	43	2Q2013	16	259,340,008.55	0.0062 (0.0035,0.0100)
Post ORF/Post CRF	43	3Q2013	15	260,047,761.26	0.0058 (0.0032,0.0095)
	43	4Q2013	17	260,755,513.98	0.0065 (0.0038,0.0104)
	43	1Q2014	18	261,463,266.69	0.0069 (0.0041,0.0109)
	43	2Q2014	17	262,171,019.40	0.0065 (0.0038,0.0104)
	43	3Q2014	15	262,878,772.11	0.0057 (0.0032,0.0094)
	43	4Q2014	8	263,586,524.83	0.0030 (0.0013,0.0060)
	43	1Q2015	16	264,294,277.54	0.0061 (0.0035,0.0098)
	43	2Q2015	9	265,002,030.25	0.0034 (0.0016,0.0064)
	43	3Q2015	23	265,709,782.96	0.0087 (0.0055,0.0130)
	43	4Q2015	16	266,417,535.68	0.0060 (0.0034,0.0098)
	43	1Q2016	23	267,125,288.39	0.0086 (0.0055,0.0129)
	43	2Q2016	13	267,833,041.10	0.0049 (0.0026,0.0083)

Source: RADARS® PC study report (November 2016)

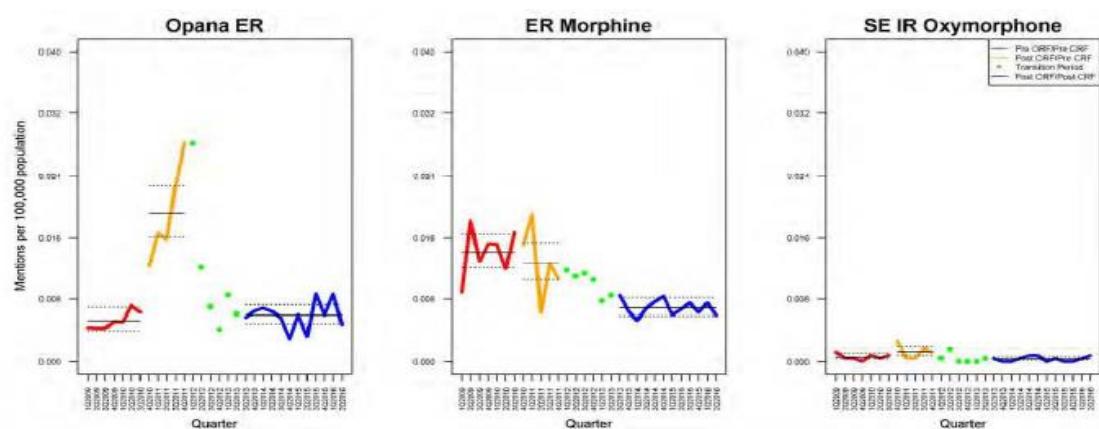
Additional data submitted in response to FDA's request showed that, from 3Q2013 through 2Q2015, there were only 5 abuse exposure calls mentioning generic oxymorphone ER, in addition to 2 calls mentioning ER oxymorphone that could not be otherwise specified and 34 calls mentioning oxymorphone where it could not be

determined if it was an IR or ER product. From 3Q2015 through 2Q2016, there was only one additional intentional abuse call mentioning generic oxymorphone ERⁿ, despite prescription volume for these products that, by the end of this time period, was only slightly lower than that for OPR.

Figure 18 and Table 21 depict mean intentional abuse exposure call population rates for the pre-period before OxyContin reformulation (pre-ORF/pre-CRF), after OxyContin reformulation but before Opana ER reformulation (post-ORF/pre-CRF), the transition period, and the post-Opana ER reformulation (post-ORF/post-CRF). The mean Opana ER intentional abuse exposure call rates in the pre-ORF/pre-CRF (red) and post-ORF/post-CRF (blue) were not significantly different, while from the pre-ORF/pre-CRF (red) to post-ORF/pre-CRF (yellow) periods, rates increased by 260%. Comparing the post-ORF/pre-CRF (yellow) to post-ORF/post-CRF (blue) periods, the mean intentional abuse rate for Opana ER decreased significantly by 68.7%.

Rates for ER morphine also decreased significantly, comparing the post-ORF/post-CRF (blue) to both the pre-ORF/pre-CRF (-50.9%) and post-ORF/pre-CRF periods (-45.3%). SE IR oxymorphone had very low population abuse call rates, but showed a significant 75% decrease, comparing the post-ORF/post-CRF (blue) to post-ORF/pre-CRF period (yellow). Additional data submitted by the Sponsor indicate that, comparing the pre-ORF/pre-CRF period to the post-ORF/post-CRF period, population abuse call rates for ER oxycodone also decreased significantly by 71%.^o

Figure 18. Mean intentional abuse exposure call rates per 100,000 population covered for Opana ER, ER morphine, and IR oxymorphone, RADARS® Poison Center Study, 1Q2009 – 2Q2016



Source: RADARS® PC study report (November 2016)

ⁿ Updated Sponsor response to June 1, 2016 FDA Information Request, received November 2016

^o Updated Sponsor response to June 1, 2016 FDA Information Request, received November 2016

Table 21. Intentional abuse exposure call population rates per 100,000 population covered for Opana ER, ER morphine, and IR oxymorphone —comparison of means model, RADARS® Poison Center Study, 1Q2009 – 2Q2016

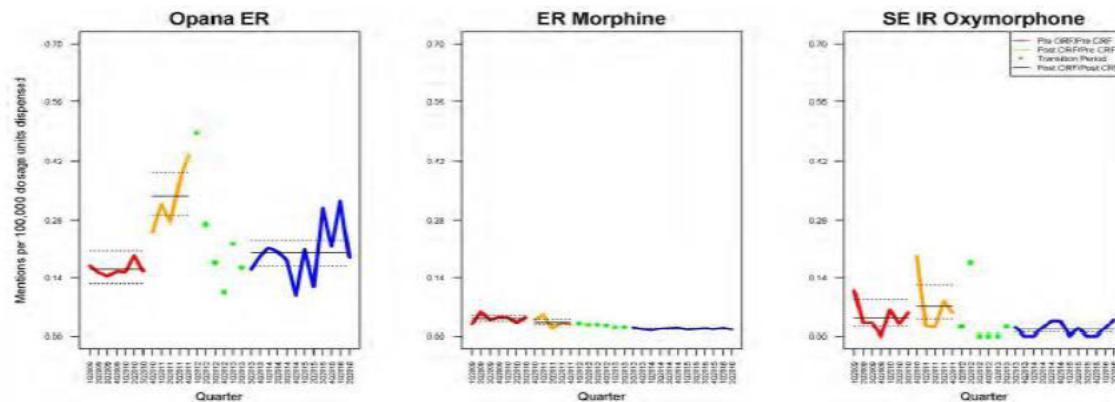
Drug Group	Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)	p-value for Percentage Change	Interaction p-value
Opana ER	Pre ORF/Pre CRF	0.0053 (0.0040,0.0070)	Post ORF/Post CRF over Pre ORF/Pre CRF	12.7% (-19.5%, 57.9%)	0.486	N/A
	Post ORF/Pre CRF	0.0192 (0.0161,0.0227)	Post ORF/Pre CRF over Pre ORF/Pre CRF	280.0% (160.2%, 398.2%)	<0.001	N/A
	Post ORF/Post CRF	0.0060 (0.0049,0.0073)	Post ORF/Post CRF over Post ORF/Pre CRF	-68.7% (-75.8%,-50.5%)	<0.001	N/A
ER Morphine	Pre ORF/Pre CRF	0.0141 (0.0121,0.0165)	Post ORF/Post CRF over Pre ORF/Pre CRF	-50.9% (-80.8%,-38.5%)	<0.001	<0.001
	Post ORF/Pre CRF	0.0127 (0.0105,0.0154)	Post ORF/Pre CRF over Pre ORF/Pre CRF	-10.2% (-29.8%, 14.8%)	0.391	<0.001
	Post ORF/Post CRF	0.0069 (0.0059,0.0082)	Post ORF/Post CRF over Post ORF/Pre CRF	-45.3% (-57.5%,-29.6%)	<0.001	0.002
SE IR Oxymorphone	Pre ORF/Pre CRF	0.0006 (0.0003,0.0011)	Post ORF/Post CRF over Pre ORF/Pre CRF	-44.8% (-77.0%, 32.5%)	0.184	0.136
	Post ORF/Pre CRF	0.0013 (0.0008,0.0021)	Post ORF/Pre CRF over Pre ORF/Pre CRF	120.4% (0.1%, 385.7%)	0.050*	0.260
	Post ORF/Post CRF	0.0003 (0.0002,0.0006)	Post ORF/Post CRF over Post ORF/Pre CRF	-75.0% (-88.6%,-44.9%)	<0.001	0.597

Source: RADARS® PC study report (November 2016)

Figure 19 and Table 22 show the mean intentional abuse call rates per 100,000 dosing units dispensed for Opana ER and comparators. Again, rates for Opana ER in the pre-ORF/pre-CRF (red) and post-ORF/post-CRF (blue) were not significantly different, but there was a significant decrease of 41.0% from the post-ORF/pre-CRF (yellow) to the post-ORF/post-CRF periods (blue). ER morphine showed a decrease of 51.5% from the post-ORF/pre-CRF (yellow) to post-ORF/post-CRF (blue) periods. SE IR oxymorphone also demonstrated a significant decrease of 77.4% from the post-ORF/pre-CRF (yellow) to post-ORF/post-CRF (blue) periods, although confidence intervals were quite wide. Additional data submitted by the Sponsor indicate a significant decrease of 42.6% in tablet-adjusted abuse exposure call rates for ER oxycodone, comparing the pre-ORF/pre-CRF period to the post-ORF/post-CRF period.^p

^p Updated Sponsor response to June 1, 2016 FDA Information Request, received November 2016

Figure 19. Mean intentional abuse exposure call rates per 100,000 dosing units dispensed for Opana ER, ER morphine, and SE IR oxymorphone, RADARS® Poison Center Study, 1Q2009 – 2Q2016



Source: RADARS® PC study report (November 2016)

Table 22. Intentional abuse exposure call rates per 100,000 dosing units dispensed for Opana ER, ER morphine, and IR oxymorphone —comparison of means model, RADARS® Poison Center Study, 1Q2009 – 2Q2016

Drug Group	Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)	p-value for Percentage Change	Interaction p-value
Opana ER	Pre ORF/Pre CRF	0.1604 (0.1268,0.2029)	Post ORF/Post CRF over Pre ORF/Pre CRF	23.4% (-7.3%, 64.4%)	0.150*	N/A
	Post ORF/Pre CRF	0.3356 (0.2902,0.3881)	Post ORF/Pre CRF over Pre ORF/Pre CRF	109.3% (58.7%, 175.9%)	<0.001	N/A
	Post ORF/Post CRF	0.1979 (0.1679,0.2333)	Post ORF/Post CRF over Post ORF/Pre CRF	-41.0% (-52.6%,-26.5%)	<0.001	N/A
ER Morphine	Pre ORF/Pre CRF	0.0442 (0.0380,0.0516)	Post ORF/Post CRF over Pre ORF/Pre CRF	-61.3% (-69.1%,-51.7%)	<0.001	<0.001
	Post ORF/Pre CRF	0.0353 (0.0292,0.0426)	Post ORF/Pre CRF over Pre ORF/Pre CRF	-20.3% (-37.6%, 1.7%)	0.068	<0.001
	Post ORF/Post CRF	0.0171 (0.0145,0.0201)	Post ORF/Post CRF over Post ORF/Pre CRF	-51.5% (-62.2%,-37.7%)	<0.001	0.250
SE IR Oxymorphone	Pre ORF/Pre CRF	0.0464 (0.0242,0.0890)	Post ORF/Post CRF over Pre ORF/Pre CRF	-64.0% (-85.7%,-9.5%)	0.030	0.012
	Post ORF/Pre CRF	0.0738 (0.0441,0.1235)	Post ORF/Pre CRF over Pre ORF/Pre CRF	50.1% (-30.7%, 265.2%)	0.274	0.539
	Post ORF/Post CRF	0.0167 (0.0087,0.0320)	Post ORF/Post CRF over Post ORF/Pre CRF	-77.4% (-90.1%,-48.1%)	<0.001	0.029**

Source: RADARS® PC study report (November 2016)

Comparison of means analyses were also conducted using the single 3-year pre-period. Here, there was a significant 50.0% reduction in the Opana ER intentional abuse population rate, and significant reductions of 48.0% for ER morphine and 57.7% for SE IR oxymorphone. Adjusting for dosing units dispensed, there was a non-significant

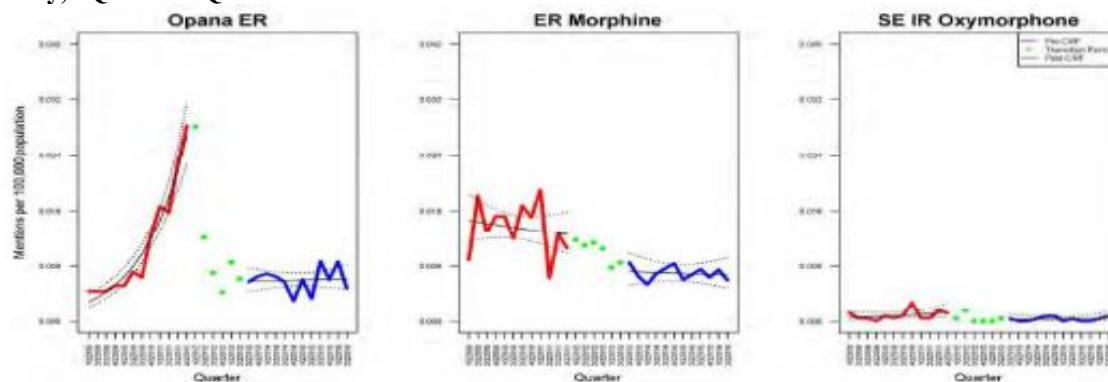
reduction of 25.7% for Opana ER, and significant reductions for ER morphine (55.7%) and SE IR oxymorphone (65.9%).

Additional analyses looking at Tennessee separately demonstrated a population-adjusted Opana ER abuse call rate approximately three times that non-Tennessee states during the pre-period and 10 times the rate non-Tennessee states during the post period. Dosage-unit adjusted Opana ER abuse rates were not significantly different within compared to outside Tennessee, however. In Tennessee, neither population- nor utilization-adjusted Opana ER abuse rates declined significantly after the reformulation, while results for non-Tennessee states were similar to those described above for the U.S. overall.⁹

Figure 20 and **Table 23** display the results of the interrupted time series, examining changes in population intentional abuse trends for Opana ER and comparators. The observed Opana ER intentional abuse exposure population rate in 3Q2013 (intercept) was significantly lower than the expected post-CRF intercept based on the pre-CRF period quarterly trend. The Opana ER intentional abuse exposure population rate slope in the post-CRF period was also significantly different from the pre-CRF slope. ER morphine did not demonstrate significant changes in either slope or intercept. SE IR oxymorphone demonstrated a significant change in intercept but the estimates were imprecise for this comparator and this change was not significantly different from that for Opana ER.

The pattern was similar after adjusting for the number of tablets dispensed (data not shown), with a significant decrease in the observed intercept for Opana ER in the post-period compared to the pre-CRF predicted value, as well as a significant decrease in slope. Significant changes in slope and intercept were not observed for ER morphine or SE IR oxymorphone tablet-adjusted intentional abuse exposure call rates.

Figure 20. Intentional abuse exposure call rates per 100,000 population covered for Opana ER, ER morphine, and SE IR oxymorphone —interrupted time series model, RADARS® Poison Center Study, 1Q2009 – 2Q2016



Source: RADARS® PC study report (November 2016)

⁹ Updated Sponsor response to June 1, 2016 FDA Information Request, received November 2016

Table 23. Intentional abuse exposure call rates per 100,000 population covered for Opana ER, ER morphine, and IR oxymorphone – interrupted time series model, RADARS® Poison Center Program, 1Q2009 – 2Q2016

Drug Group	Period	Parameter	Estimate (95% CI)	Percentage change (95% CI)	p-value for Percentage Change	Interaction p-value
Opana ER	Pre CRF	Intercept	0.1097 (0.0735,0.1638)	Reference	N/A	N/A
		Slope	1.2239 (1.1789,1.2705)	Reference	N/A	N/A
	Post CRF	Intercept	0.0058 (0.0044,0.0077)	-94.7% (-96.8%, -91.3%)	<0.001	N/A
		Slope	1.0057 (0.9631,1.0502)	-17.8% (-22.4%, -13.0%)	<0.001	N/A
ER Morphine	Pre CRF	Intercept	0.0113 (0.0071,0.0160)	Reference	N/A	N/A
		Slope	0.9860 (0.9516,1.0215)	Reference	N/A	N/A
	Post CRF	Intercept	0.0072 (0.0053,0.0098)	-36.5% (-63.7%, 11.1%)	0.112	<0.001
		Slope	0.9935 (0.9467,1.0426)	0.8% (-5.1%, 7.0%)	0.802	<0.001
SE IR Oxymorphone	Pre CRF	Intercept	0.0021 (0.0005,0.0100)	Reference	N/A	N/A
		Slope	1.0789 (0.9495,1.2260)	Reference	N/A	N/A
	Post CRF	Intercept	0.0003 (0.0001,0.0010)	-88.3% (-98.5%, -6.0%)	0.044	0.468
		Slope	1.0402 (0.8492,1.2742)	-3.6% (-24.1%, 22.5%)	0.765	0.204*

Source: RADARS® PC study report (November 2016)

2.3.3.3 Change in intentional abuse exposure call rates for Opana ER, via intended (oral) and unintended (non-oral) routes of administration

Table 24 displays the routes reported in intentional abuse exposure cases involving Opana ER, beginning in 2010 when RADARS® PCP began collecting information on route of exposure. During the pre-period (Pre ORF/Pre-CRF and Post ORF/Pre-CRF combined), 54% of abuse calls indicated that the exposure was via the oral route (swallowed whole), while 46% indicated that the exposure was via a non-oral (chewing, inhalation, injection, other) route. During the post-period (Post-ORF/Post-CRF), 43% of calls indicated exposure via the oral route, while 57% indicated exposure via a non-oral route.

Table 24. Opana ER intentional abuse exposure call counts by route of administration category, RADARS® Poison Center Study, 1Q2010 – 2Q2016

	Year/Quarter	Oral Route*	Non-oral Route**
Pre ORF/Pre CRF	1Q2010	4	6
	2Q2010	7	8
	3Q2010	12	2
Post ORF/Pre CRF	4Q2010	14	12
	1Q2011	19	17
	2Q2011	23	13
	3Q2011	24	31
	4Q2011	32	28
Transition	1Q2012	30	31
	2Q2012	15	8
	3Q2012	11	4
	4Q2012	0	9
	1Q2013	7	13
	2Q2013	6	7
Post ORF/Post CRF	3Q2013	4	11
	4Q2013	6	7
	1Q2014	4	10
	2Q2014	8	7
	3Q2014	7	6
	4Q2014	3	5
	1Q2015	4	10
	2Q2015	5	3
	3Q2015	8	11
	4Q2015	9	5
	1Q2016	9	10
	2Q2016	2	7

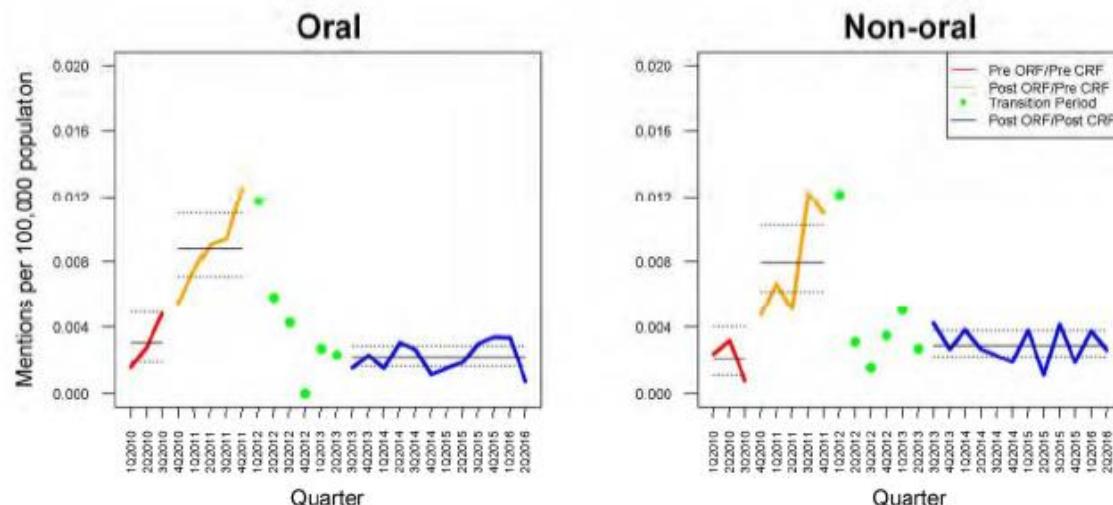
*Oral route = swallowed whole

**Non-oral route = chewing, inhalation, injection, other

Source: RADARS® PC study report (November 2016)

Figure 21 and Table 25 show mean Opana ER intentional abuse call rates per 100,000 population, stratified by route (oral and non-oral). For both route of administration categories, there were significant increases in abuse call rates from the pre-ORF/pre-CRF (red) to the post-ORF/pre-CRF (yellow) periods and then significant decreases from the post-ORF/pre-CRF (yellow) to the post-ORF/post-CRF (blue) time periods. The magnitude of change was not significantly different for the oral and non-oral routes. ER morphine and ER oxycodone also demonstrated significant reductions in abuse exposure call rates by both the oral and non-oral routes (**Appendix K, Tables K1-K4**).

Figure 21. Mean Opana ER intentional abuse exposure call rates per population covered, by oral* and non-oral routes of administration, RADARS® Poison Center Study, 1Q2010 – 2Q2016**



*Oral route = swallowed whole

**Non-oral route = chewing, inhalation, injection, other

Source: RADARS® PC study report (November 2016)

Table 25. Opana ER intentional abuse exposure rates per 100,000 population covered, by oral* and non-oral routes of administration—comparison of means, RADARS® Poison Center Study, 1Q2010 – 2Q2016**

Route of administration	Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)	p-value for Percentage Change	Interaction p-value
Non-oral	Pre ORF/Pre CRF	0.0021 (0.0011, 0.0040)	Post ORF/Post CRF over Pre ORF/Pre CRF	36.6% (-31.5%, 172.7%)	0.376	N/A
	Post ORF/Pre CRF	0.0080 (0.0062, 0.0103)	Post ORF/Pre CRF over Pre ORF/Pre CRF	274.5% (68.5%, 644.0%)	<0.001	N/A
	Post ORF/Post CRF	0.0029 (0.0022, 0.0038)	Post ORF/Post CRF over Post ORF/Pre CRF	-63.5% (-74.7%, -47.3%)	<0.001	N/A
Oral	Pre ORF/Pre CRF	0.0031 (0.0019, 0.0049)	Post ORF/Post CRF over Pre ORF/Pre CRF	-28.7% (-58.8%, 23.3%)	0.226	0.148
	Post ORF/Pre CRF	0.0068 (0.0071, 0.0109)	Post ORF/Pre CRF over Pre ORF/Pre CRF	188.9% (71.6%, 386.5%)	<0.001	0.555
	Post ORF/Post CRF	0.0022 (0.0017, 0.0029)	Post ORF/Post CRF over Post ORF/Pre CRF	-75.3% (-82.6%, -65.0%)	<0.001	0.130

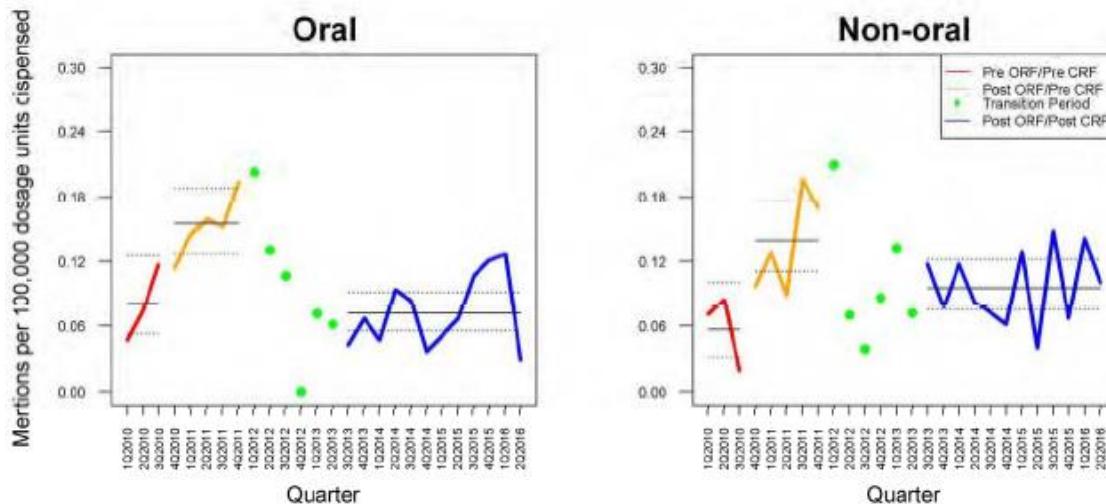
*Oral route = swallowed whole

**Non-oral route = chewing, inhalation, injection, other

Source: RADARS® PC study report (November 2016)

As shown in **Figure 22** and **Table 26**, the dosing unit-dispensed comparison of means analyses yielded similar results, with significant reductions in mean abuse call rates by both oral and non-oral routes, comparing the post-ORF/post-CRF (blue) to the post-ORF/pre-CRF (yellow) mean rates but not comparing post-ORF/post-CRF (blue) to pre-ORF/pre-CRF (red). The reduction in abuse call rates via non-oral routes was not significantly different from the reduction in abuse call rates via the oral route.

Figure 22. Mean Opana ER intentional abuse exposure rates per 100,000 dosing units dispensed, by oral* and non-oral routes of administration, RADARS® Poison Center Study, 1Q2010 – 2Q 2016**



*Oral route = swallowed whole

**Non-oral route = chewing, inhalation, injection, other

Source: RADARS® PC study report (November 2016)

Table 26. Opana ER intentional abuse exposure rates per 100,000 dosing units dispensed, by oral* and non-oral routes of administration—comparison of means, RADARS® Poison Center Study, 1Q2010 – 2Q 2016**

Route of administration	Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)	p-value for Percentage Change	Interaction p-value
Non-oral	Pre ORF/Pre CRF	0.0568 (0.0320, 0.1009)	Post ORF/Post CRF over Pre ORF/Pre CRF	68.8% (-9.4%, 214.5%)	0.099	N/A
	Post ORF/Pre CRF	0.1395 (0.1110, 0.1753)	Post ORF/Pre CRF over Pre ORF/Pre CRF	145.6% (32.3%, 355.9%)	0.004	N/A
	Post ORF/Post CRF	0.0958 (0.0754, 0.1218)	Post ORF/Post CRF over Post ORF/Pre CRF	-31.3% (-50.7%, -4.3%)	0.026	N/A
Oral	Pre ORF/Pre CRF	0.0816 (0.0530, 0.1257)	Post ORF/Post CRF over Pre ORF/Pre CRF	-12.0% (-46.5%, 44.9%)	0.617	0.110
	Post ORF/Pre CRF	0.1547 (0.1272, 0.1861)	Post ORF/Pre CRF over Pre ORF/Pre CRF	89.5% (18.0%, 204.3%)	0.008	0.514
	Post ORF/Post CRF	0.0719 (0.0560, 0.0922)	Post ORF/Post CRF over Post ORF/Pre CRF	-53.5% (-66.1%, -36.2%)	<0.001	0.094

*Oral route = swallowed whole

**Non-oral route = chewing, inhalation, injection, other

Source: RADARS® PC study report (November 2016)

As shown in **Table 27** below, there was a shift in the non-oral routes of abuse mentioned in Opana ER abuse calls, with a decrease in the proportion of abuse exposure calls specifically mentioning inhalation and a marked increase in the proportion specifically involving injection. The pattern was similar if the post-ORF/pre-CRF pre-period was used. Such a shift from inhalation to injection was not observed for ER oxycodone abuse cases following the reformulation of OxyContin. The proportions of ER oxycodone

abuse calls involving the inhalation and injection routes were roughly equal in both the pre-ORF/pre-CRF period and the post-ORF/post-CRF period (data not shown).

Table 27. Percent of Opana ER abuse exposures via inhalation and injection routes, RADARS® Poison Center study, 1Q2010 –2Q2016*

	INHALATION CASES	INJECTION CASES	TOTAL ABUSE CASES**	% OF ABUSE CASES VIA INHALATION ROUTE	% OF ABUSE CASES VIA INJECTION ROUTE
Pre-CRF (1Q2010 - 4 Q2011)	98	19	290	34%	7%
Post-CRF (3Q2013 - 2Q2016)	39	53	190	21%	29%

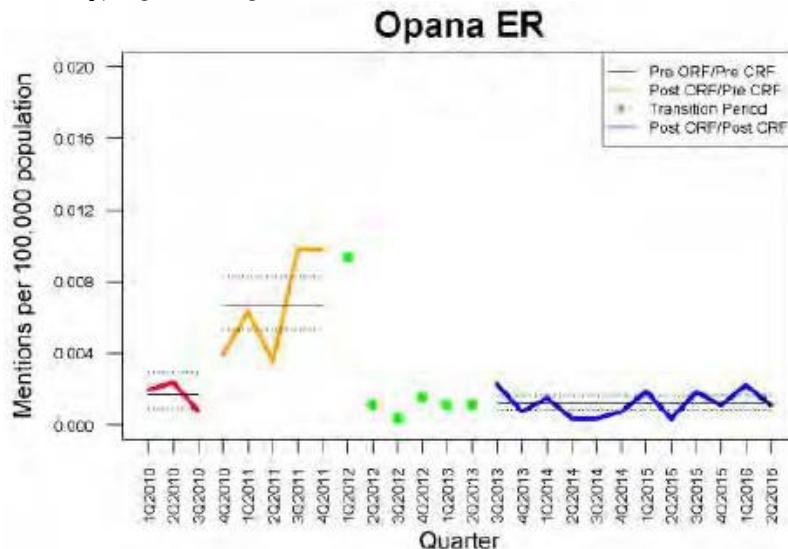
Source: Figure generated by reviewer, using data provided in RADARS® PC study report (November 2016) and Sponsor's updated response to June 1, 2016 FDA Information Request (November 2016)

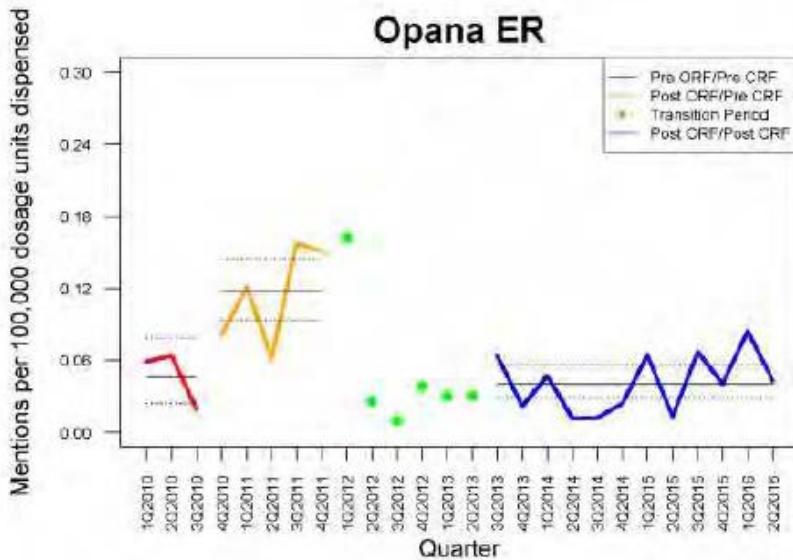
* RADARS® PC program began collecting information on route of administration in Q1 2010

**Not all cases have information on ROA.

Figure 23 depicts Opana ER mean rates of intentional abuse cases involving the inhalation route, per 100,000 population (upper panel) and per 100,000 dosing units dispensed (lower panel) across the three time periods. There were significant decreases in Opana ER abuse rates involving the inhalation route when comparing the post-ORF/pre-CRF to the post-ORF/post-CRF periods, but not when comparing the pre-ORF/pre-CRF to the post-ORF/post-CRF periods.

Figure 23. Mean rates of Opana ER intentional abuse exposures involving the inhalation route, per 100,000 population (upper panel) and per 100,000 dosing units (lower panel), RADARS® Poison Center study, 1Q2010 –2Q2016

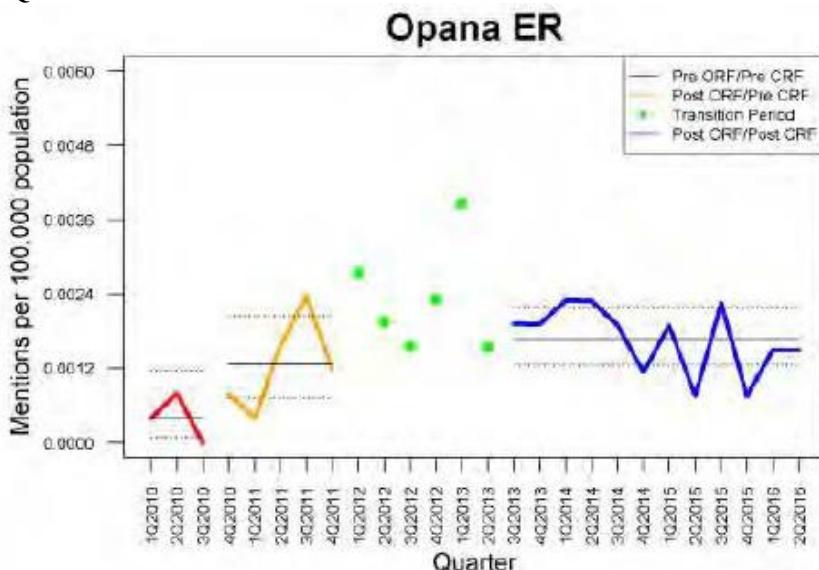


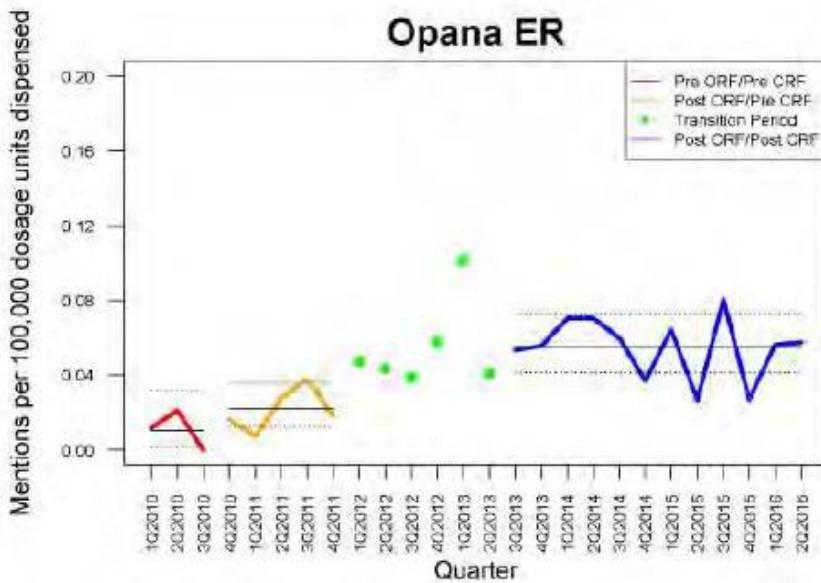


Source: Sponsor's updated response to June 1, 2016 FDA Information Request (November 2016)

Figure 24 depicts mean rates of Opana ER intentional abuse cases with route of abuse identified as injection, per 100,000 population (upper panel) and per 100,000 dosing using dispensed (lower panel) across the three time periods. The population injection abuse call rate for Opana ER was significantly higher in the post-ORF/post-CRF period (blue), compared to the pre-ORF/pre-CRF period (ref), but not compared to the post-ORF/pre-CRF period (yellow). Adjusting for dosage units dispensed, however, there was a significant increase in Opana ER injection abuse call rates from the post-ORF/pre-CRF (yellow) to the post-ORF/post-CRF period.

Figure 24. Mean rates of Opana ER intentional abuse exposures involving the injection route, per 100,000 population (upper panel) and per 100,000 dosing units (lower panel), RADARS® Poison Center study, 1Q2010 –2Q2016





Source: Sponsor's updated response to June 1, 2016 FDA Information Request (November 2016)

In contrast, both inhalation and injection abuse call rates decreased significantly for ER oxycodone, comparing the pre-ORF/pre-CRF to the post-ORF/post-CRF periods (**Appendix K, Figures K1 and K2**).

2.3.3.3.1 Changes in rates of other poison center study outcomes for Opana ER and comparators

Exposure cases resulting in major medical outcome or death:

Population rates for exposure cases resulting in a major medical outcome or death (not limited to intentional abuse calls) decreased significantly for Opana ER (-68.3%), ER morphine (-22.6%), and SE IR oxymorphone (-76.0%) from the post-ORF/pre-CRF to post-ORF/post-CRF periods. The magnitude of decrease was significantly greater for Opana ER than for ER morphine (**Appendix K, Figure K3 and Table K5**). Adjusting for total dosing units dispensed, Opana ER, ER morphine, and SE IR oxymorphone all showed significant rate reductions (-40.2%, -31.4%, and -78.3%, respectively), and the decreases for ER morphine and SE IR oxymorphone were not significantly different from those for Opana ER (**Appendix K, Figure K4 and Table K5**). Similar to the findings for the intentional abuse exposure cases, there were significant changes in the slope and intercept for Opana ER rates not observed for ER morphine or SE IR oxymorphone, comparing the pre-CRF to post-CRF periods (**Appendix K, Tables K6 and K7**).

Overdose:

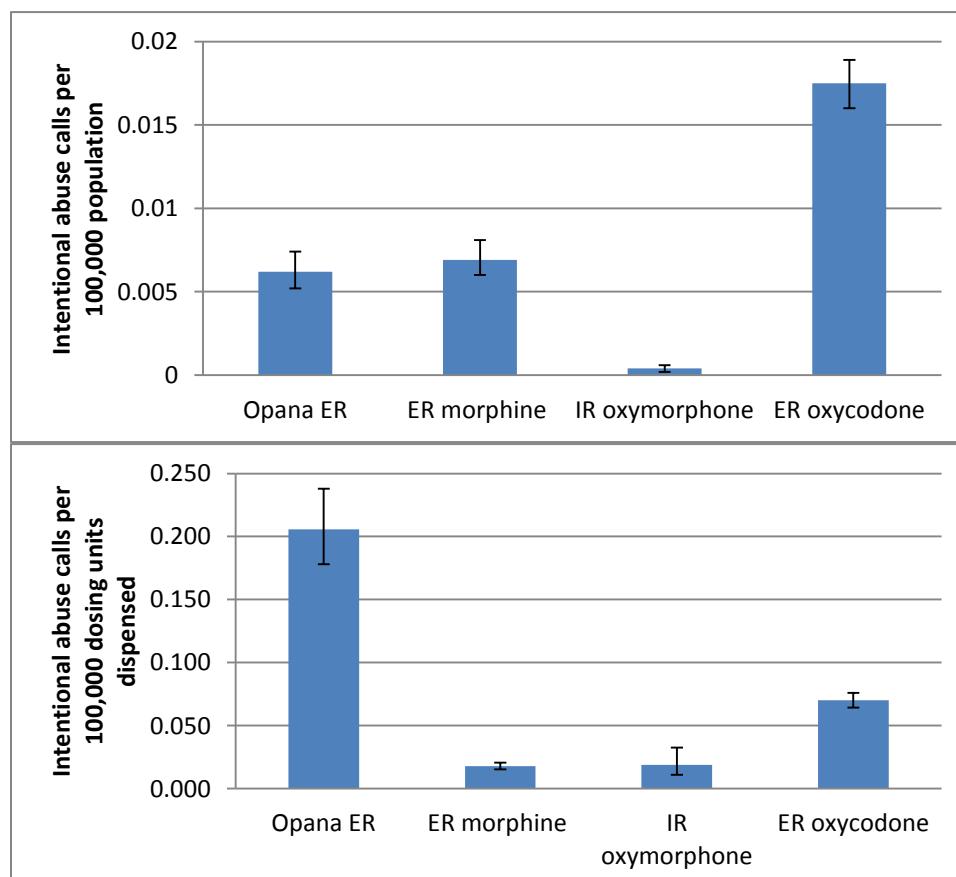
Patterns for the composite outcome defined in the RADARS® PCP as “overdose” were similar to those for the other outcomes described above. Significant reductions in population rates were seen for Opana ER, morphine ER, and SE IR oxymorphone when comparing the post-ORF/pre-CRF pre-period to the post-period. The magnitude of the reduction in population overdose rates

was significantly greater for Opana ER (-59.6%) than for ER morphine (-24.2%), but not greater than that for SE IR oxymorphone (-53.7%). Adjusting for the number of tablets dispensed, rate reductions for Opana ER, ER morphine, and SE IR oxymorphone were all significant (-24.0%, -32.8%, and -58.2%, respectively) and the decreases for ER morphine and SE IR oxymorphone were not significantly different from those for Opana ER (**Appendix K, Figures K5 and K6 and Tables K8 and K9**).

2.3.3.3.2 Comparison of post-period intentional abuse call rates for Opana ER and comparators

Figure 25 compares the post-period intentional abuse exposure call rates for Opana ER and included comparators, per 100,000 population (top panel) and per 100,000 dosing units dispensed (bottom panel). Of the opioids included in this analysis, ER oxycodone had the highest population-adjusted abuse call rates, while Opana ER had the highest utilization-adjusted call rates. Adjusting for the number of dosing units dispensed, intentional abuse call rates for Opana ER were approximately 10 times greater than for IR oxymorphone or for ER morphine and three times greater than for ER oxycodone. Reliable rates could not be calculated for generic oxymorphone ER.

Figure 25. Intentional abuse call rates (any route) per 100,000 population (top panel) and per 100,000 dosing units dispensed (bottom panel), RADARS® Poison Center Program, post-period only (3Q2013 –2Q2016)



Source: Figure generated by reviewer based on data provided in RADARS® PC study report (November 2016) and Sponsor's updated response to June 1 information request (November 2016)

2.3.3.4 Reviewer comments on the RADARS® Poison Center study

2.3.3.4.1 Methodological considerations

Strengths of the poison center data include its meaningful and clinically relevant abuse-related outcome measures, its product specificity, and its nearly national coverage. Poison center data also provide a window into abuse-related events in a broader population not limited to those entering or being assessed for substance abuse treatment. However, these data have limitations that must be taken into consideration when interpreting the results of this study. First, it is unclear what factors might influence whether an opioid abuse-related event generates a call to a poison center or how these might vary over time (for example, due to expanded access to naloxone, increasing experience with opioid overdoses, changing community norms, or use of alternative sources of information) or across drugs (for example, due to varying marketing history, level of familiarity, or pharmacology). Although there is some evidence that 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,^{40,41} there is also evidence suggesting that patterns of poison control call center use have been changing in recent years,⁴² further complicating the interpretation of poison center call data trends. In addition, overdoses resulting in rapid, unattended death are unlikely to generate a call to a poison control center. Therefore, poison center data may disproportionately fail to capture cases involving drugs with the highest risk of these fatal overdoses. For this reason, we do not consider poison control data to be a good source of information on the incidence of opioid overdose death in assessments of abuse deterrence.

Although the ability to measure adverse events involving specific opioid products is a strength of poison center data, it is unknown how accurately specific formulations are captured, particularly in cases involving opioids, including oxymorphone, that have both ER and IR formulations available, as well as both brand and generic products. If this type of outcome misclassification occurs equally across products and time periods, then any bias in comparisons between products or time periods is expected to be toward the null, with any true differences being attenuated. However, as new products are introduced and familiarity with different products changes over time, rates of misclassification may vary, creating bias of unpredictable direction.

2.3.3.4.2 Summary and interpretation of key findings

The RADARS® PC study also presents a complex picture of abuse of Opana ER and other opioids, albeit one that differs from the NAVIPPRO® results in some respects. The poison center data show a significant decrease in overall intentional abuse call rates for Opana ER when comparing the post-ORF/pre-CRF period to the post-ORF/post-CRF period (post- period). These reductions were seen in both population- and utilization-adjusted rates.

Several observations complicate the interpretation of the poison center data, particularly with respect to assessing the impact of Opana ER's reformulation on overall abuse rates:

1. Significant reductions were also seen for ER morphine and IR oxymorphone, opioids not formulated with properties intended to deter abuse.^r The relative reduction in population-adjusted intentional abuse call rates was significantly greater for Opana ER than for ER morphine, but not significantly different from IR oxymorphone. Adjusting for changes in utilization, the relative decrease in the Opana ER intentional abuse call rate was not significantly different from those for ER morphine or IR oxymorphone. ER oxycodone also demonstrated significant decreases in intentional abuse calls comparing the period prior to OxyContin's reformulation to the post-ORF/post-CRF period. The observation that products both with and without reformulation demonstrated large decreases in intentional abuse raises the question of what part of the decrease observed for Opana ER (and other products with properties intended to deter abuse) can be directly attributed to the reformulation itself.
2. Unlike in the NAVIPPRO® study, the poison centers recorded only a handful of generic oxymorphone ER abuse calls during the post-period, so this product is likely not useful in this study as a counterfactual, or a predictor of what might have happened to Opana ER abuse call rates had it not been reformulated. The near absence of generic oxymorphone ER abuse calls also raises concerns regarding misclassification. It is possible that both Opana ER and generic oxymorphone ER mentions were been recorded as “oxymorphone not otherwise specified,” for which there were 34 intentional abuse mentions in the post-period, and generic oxymorphone ER mentions may have been reported and/or recorded as Opana ER, potentially inflating post-period call rates.
3. Post-period Opana ER abuse rates were not significantly different from those observed during the early (pre-ORF/pre-CRF) pre-period. Rather, the observed decrease in Opana ER abuse rates from the later (post-ORF/post-CRF) pre-period to the post-period are the result of sharp rate increases during the 3-year pre-period. As in the NAVIPPRO® study, the interrupted time series analyses show significant downward changes in the trajectory of Opana ER intentional abuse call rates, comparing the pre- to post-reformulation periods. These changes in trend were not observed for the comparator products ER morphine or IR oxymorphone. This finding suggests that some of the observed change in abuse call rates may be attributable to Opana ER's reformulation itself, although it is difficult to determine the magnitude of effect. These findings also raise the questions of (1) why there was such a dramatic increase in Opana ER abuse call rates in the 18 months prior to reformulation, when similar increases were not seen for ER morphine, and (2) what is the most appropriate baseline period for assessing the impact of the reformulation. It has been hypothesized that the increase in Opana ER abuse calls was the result of OxyContin abusers switching to Opana ER following OxyContin's reformulation. While this is certainly possible, it does not easily explain the sharp increase in intentional abuse exposure calls for Opana ER involving the *oral* route, which would not offer an obvious advantage for abusers over reformulated OxyContin, which was also formulated to deter abuse by non-oral routes. It is possible that some exposures via non-oral routes could have been misclassified as the oral route, particularly if the caller did not recognize or report a non-oral route, or if multiple routes were involved in a multi-substance exposure. It is also possible that other factors—for

^r Embeda, an abuse-deterrent

example changes in advertising practices, increased street availability, or growing general interest in this product as a drug of abuse—could have been driving the rise in both Opana ER prescribing and abuse rates during the pre-period.

4. Following the reformulation of Opana ER, the reductions in intentional abuse rates were not significantly different for oral versus non-oral routes. Again, it is unclear why the reformulation of Opana ER would cause a decrease in oral abuse calls of a similar magnitude to that seen for non-oral abuse exposure calls. It is possible that reformulation could indirectly affect abuse via the oral route, perhaps through decreased diversion and availability on the illicit market. Again, misclassification of route could certainly be a factor, and it may not always be possible to identify the route used for each drug involved in a multi-substance exposure case. Nonetheless, the large reductions in abuse via the oral route, like the large reductions observed in both ER morphine and IR oxymorphone abuse calls, complicate the interpretation of these data and suggest that factors other than Opana ER's reformulation may have contributed to the observed reduction in Opana ER abuse call rates.

Similar to the NAVIPPRO® study, the poison center study data suggest that after Opana ER was reformulated, a shift occurred in the routes used to abuse this product. Prior to reformulation, inhalation abuse exposure cases involving Opana ER far outnumbered injection abuse exposures, while after reformulation there were more injection cases than inhalation cases. Such a shift from inhalation to injection was not observed for ER oxycodone after OxyContin was reformulated. In addition, both population- and utilization-adjusted rates of Opana ER inhalation abuse exposure calls decreased significantly, comparing the period after OxyContin reformulation but before Opana ER reformulation to the period after Opana ER reformulation, while utilization-adjusted but not population-adjusted injection abuse call rates increased significantly comparing these two time periods.

The RADARS® study results are also consistent with the NAVIPPRO® study in suggesting intentional abuse call rates for Opana ER during the post-reformulation period that were many times higher than for comparator opioids, including ER morphine, IR oxymorphone, and ER oxycodone, after adjusting for differences in utilization volume (tablets dispensed). These results suggest that, despite reformulation, Opana ER may remain a highly sought after drug of abuse in postmarket settings compared to other opioid products with similar indications and active pharmaceutical ingredients. The very low rates of calls mentioning generic oxymorphone ER, and to some degree IR oxymorphone, differ markedly from the NAVIPPRO® findings, which suggest high post-period abuse rates for these products as well. Utilization-adjusted rates for the more broadly defined “overdose” cases and cases resulting in a major medical outcome or death were also higher for Opana ER than for either ER morphine or IR oxymorphone (data were not available for ER oxycodone for these outcomes). In interpreting these comparisons, one must consider the possibility of misclassification of oxymorphone products as well as the possibility of variation across products in the likelihood of an abuse or overdose event generating a poison center call.

In summary, the RADARS® PC study are consistent with the NAVIPPRO® study findings in suggesting that following reformulation, there was a shift in the route of exposure reported in Opana ER intentional abuse cases, from inhalation to injection. The data also suggest that following Opana ER reformulation, there were significant decreases in both population- and

utilization-adjusted rates of Opana ER abuse calls involving inhalation. Utilization-adjusted but not population-adjusted Opana ER injection abuse call rates increased significantly following reformulation. Also consistent with the NAVIPPRO® study findings, the poison center data suggest that adjusting for differences in utilization, Opana ER abuse rates after reformulation remained substantially higher than those for ER morphine, IR oxymorphone, or ER oxycodone, and that some geographic regions, notably Tennessee, may have markedly higher levels of Opana ER abuse than the national average. Other states were not analyzed individually, so these data do not indicate whether the high Opana ER abuse rates in Tennessee are unique. Possibly due to limitations of the information collected from callers or methods of recording and classifying ER oxymorphone mentions, the number of generic oxymorphone ER cases during the post-period was likely an undercount and not reliable. Unlike the NAVIPPRO® study, the poison center data suggest that, overall, intentional abuse calls involving Opana ER decreased significantly following reformulation. However, given the similar reductions in oral and non-oral routes and in other products without properties intended to deter abuse, it is unclear how much of this decrease can be attributed to the reformulation itself.

2.3.4 RADARS® Drug Diversion Study and Street Price Study

2.3.4.1 Study Methods

2.3.4.1.1 Data source and population

The RADARS® Drug Diversion Program (DDP) gathers surveillance data on prescription drug diversion. Approximately 300 drug diversion investigators across 49 states and Puerto Rico submit data quarterly on the number of documented drug diversion cases within their jurisdiction for specific prescription drugs of interest. Drug diversion investigators represent municipal police departments, multi-jurisdictional drug task forces, county sheriffs' departments, regulatory agencies such as state medical and pharmacy boards, state police agencies, prosecutors' offices, and departments of health. In addition to the number of diversion cases, the DDP provides information on the cost of diverted products on the street, based on reports by diversion investigators.

The diversion report analyses for this study are restricted to 3-digit ZIP codes that were covered (at least partially) by a participating drug diversion agency every quarter between 1Q2011 and 2Q2016. A sensitivity analysis was conducted using all ZIP codes where data were collected during any quarter to determine if the interpretation of the results changed.

2.3.4.1.2 Outcome definition

A case is one which results in a written complaint or report containing information about specific drugs found outside of controlled distribution channels. The following are events that would constitute a diversion case:

- Undercover buys or “stings” which can involve more than one suspect. These can also go on for a few weeks. The undercover agent poses as person selling drugs to drug users.

- Pharmacy thefts which can include thefts by pharmacy employees or theft by an unknown person.
- Doctor shoppers who visit various physicians complaining of pain/ailment in order to obtain prescriptions for medications (mostly narcotics) from more than one doctor.
- Forged or altered prescriptions where the suspect forges a prescription or alters the information on the prescription such as the dosage size or quantity.
- Diversion of prescription medication by healthcare workers (primarily nurses) in hospitals, skilled nursing facilities, and assisted living facilities.
- Diversion by healthcare workers in an office setting (doctor's office) where medical assistants/technicians call in false prescriptions.
- Overdose cases where the person used prescription products without a legitimate prescription.
- Traffic stops where, upon searching the suspect or their vehicle, prescription products are found without a legitimate prescription.
- Home invasion/robberies where a person's medications are stolen from their home.
- "Pill mills" where prescription medications are not being prescribed for legitimate purposes.
- Supply chain diversion (any diversion from point of manufacturer to end user/retail) which includes thefts at wholesale distribution companies, cargo theft, and in transit loss/ thefts during product delivery.

Diversion cases are not collected by type of case. Therefore, the proportion of cases matching the events listed above cannot be calculated. Street price outcomes reflect the average price of the most common milligram strength reported by diversion investigators.

Note: Tables and figures excerpted from this study report refer to reformulated Opana ER as "CRF" (Crush-Resistant Formula).

2.3.4.1.3 Time period

For this study, data were divided into the following three time periods:

- **Pre-CRF period:** 1Q2011 through 4Q2011. (Data collection on Opana ER in the DDP began in January 2011.)
- **Transition period:** 1Q2012 through 2Q2013.
- **Post-CRF period:** 3Q2013 through 2Q2015.

2.3.4.1.4 Comparators

The Opana ER drug category includes reports of both the original and the reformulated ER oxymorphone tablets manufactured by Endo Pharmaceuticals under the brand name "Opana ER." Changes in Opana ER are compared to two other opioid groups: ER morphine and SE IR oxymorphone. ER morphine includes branded (e.g., MS Contin®, Embeda®) and generic ER morphine tablets and capsules. Other formulations (e.g., solutions) are not included. SE IR oxymorphone includes branded (Opana IR®) and generic IR oxymorphone products.

2.3.4.1.5 Statistical Analyses

Analyses examined changes in Opana ER diversion rates per population, prescriptions dispensed, and dosage units dispensed. Changes in the price per milligram according to drug diversion investigators are also examined.

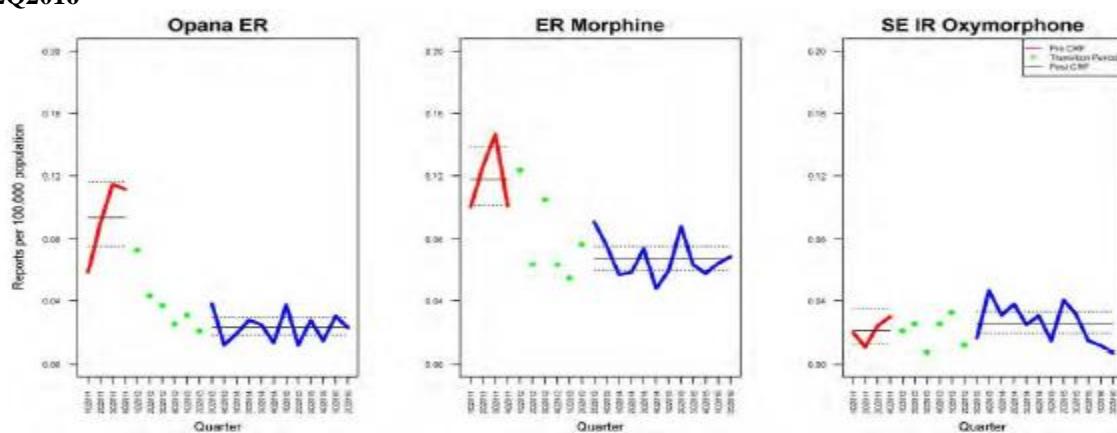
This study compared differences in rates and street price per milligram before and after reformulation of Opana ER. Analytic methods were similar to those used in the RADARS® PC study. To model street prices, the natural log of the price per milligram was regressed on an indicator variable representing time period, drug group, and a drug group by time period effect. The drug group by effect period term represents the difference in the change in geometric mean street price per milligram from the pre- to post-OPR across drug groups.

2.3.4.2 Study Results

2.3.4.2.1 Drug diversion rates

Within the 110 3-digit ZIP codes included in the study sample, the number of Opana ER diversion cases ranged from 8 to 77 per quarter. **Figure 26** and **Table 28** describe the change in the mean quarterly diversion rates per 100,000 covered population for Opana ER and comparators over time. Both Opana ER and ER morphine demonstrated significant reductions in diversion rates, although the decline for Opana ER was of significantly greater magnitude than for ER morphine. The change for IR oxymorphone was not significant.

Figure 26. Drug diversion rates per 100,000 population covered, RADARS® Drug Diversion Study, 1Q2011 – 2Q2016



Source: RADARS® Drug Diversion study report (November 2016)

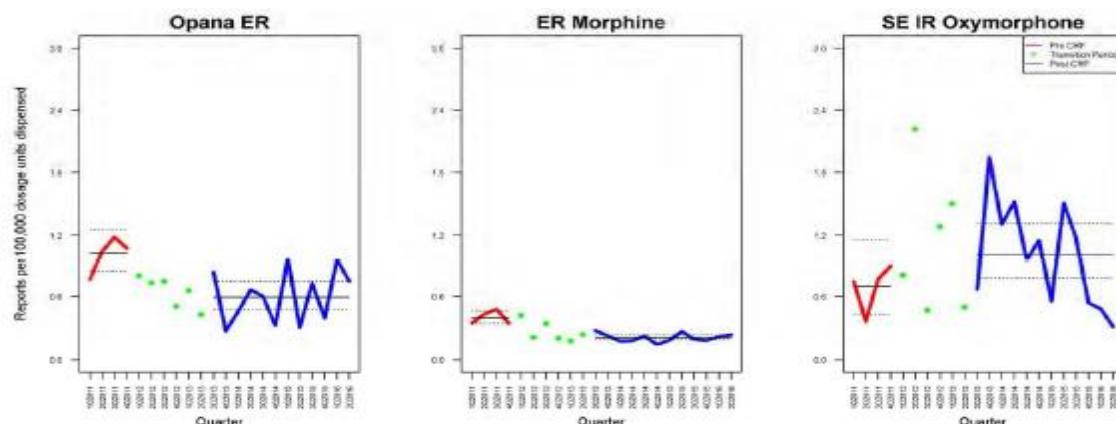
Table 28. Drug diversion rates per 100,000 population covered—comparison of means, RADARS® Drug Diversion Study, 1Q2011 – 2Q2016

Drug Group	Period	Estimate (95% CI)	Percentage change (95% CI)	p-value for Percentage Change	Interaction p-value
Opana ER	Pre CRF	0.0939 (0.0754, 0.1168)	Reference	N/A	N/A
	Post CRF	0.0232 (0.0180, 0.0297)	-75.3% (-82.3%, -55.6%)	<0.001	N/A
ER Morphine	Pre CRF	0.1186 (0.1017, 0.1383)	Reference	N/A	N/A
	Post CRF	0.0571 (0.0597, 0.0753)	-43.4% (-53.3%, -31.4%)	<0.001	<0.001
SE IR Oxymorphone	Pre CRF	0.0209 (0.0125, 0.0352)	Reference	N/A	N/A
	Post CRF	0.0255 (0.0195, 0.0332)	21.5% (-32.2%, 117.7%)	0.512	<0.001

Source: RADARS® Drug Diversion study report (November 2016)

Figure 27 and Table 29 describe the diversion rates per 100,000 dosage units dispensed for Opana® ER and comparators. Here, after adjusting for changes in drug utilization, significant diversion rate reductions of 42% and 49% were observed for Opana ER and ER morphine, respectively. The change for IR oxymorphone was not significant. Additional data submitted by the Sponsor in response to FDA's request indicates that diversion rates for generic oxymorphone ER ranged from 0.2 to 0.7 reports per 100,000 dosage units dispensed. This is similar to the range observed for Opana ER during the post-period.

Figure 27. Drug diversion rates per 100,000 dosage units dispensed, RADARS® Drug Diversion Study, 1Q2011 – 2Q2016



Source: RADARS® Drug Diversion study report (November 2016)

Table 29. Drug diversion rates per 100,000 dosage units dispensed—comparison of means, RADARS® Drug Diversion Study, 1Q2011 – 2Q2016

Drug Group	Period	Estimate (95% CI)	Percentage change (95% CI)	p-value for Percentage Change	Interaction p-value
Opana ER	Pre CRF	1.0295 (0.8438, 1.2560)	Reference	N/A	N/A
	Post CRF	0.5958 (0.4746, 0.7479)	~42.1% (-57.2%, -21.7%)	<0.001	N/A
ER Morphine	Pre CRF	0.3977 (0.3416, 0.4531)	Reference	N/A	N/A
	Post CRF	0.2038 (0.1817, 0.2286)	~48.8% (-57.6%, -38.0%)	<0.001	0.505
SE IR Oxymorphone	Pre CRF	0.6988 (0.4223, 1.1564)	Reference	N/A	N/A
	Post CRF	1.0125 (0.7811, 1.3125)	44.9% (-17.8%, 155.4%)	0.200	0.005*

Source: RADARS® Drug Diversion study report (November 2016)

2.3.4.2.2 Drug diversion investigator street price survey data

The number of street price surveys received from drug diversion investigators during each quarter of the study period ranged from 79 to 113. Of these, between 4 and 14 survey responses were specific to Opana ER each quarter.

As shown in **Table 30**, there was no significant change in mean price per milligram for Opana ER or ER morphine, while the mean price of IR oxymorphone decreased significantly. Mean prices for ER morphine were significantly lower than those for either Opana ER or IR oxymorphone in both time periods.

Table 30. Comparison of Geometric Mean Prices for Opana ER and comparators, Drug Diversion Program Street Price Survey, 1Q2011 – 2Q2015

Drug group	Period	Average price mg (adjusted for inflation)	Percentage change from Pre CRF (95% CI)	p-value for percentage change	p-value for interaction
Opana ER	Pre CRF	\$1.18(\$0.97, \$1.43)			
	Post CRF	\$1.45(\$1.22, \$1.71)	22.6%(-5.2%, 58.7%)	0.121	
ER morphine	Pre CRF	\$0.61(\$0.53, \$0.71)			
	Post CRF	\$0.59(\$0.51, \$0.69)	-3.2%(-21.3%, 19.1%)	0.760	0.161
SE IR oxymorphone	Pre CRF	\$2.75(\$2.06, \$3.66)			
	Post CRF	\$1.81(\$1.46, \$2.26)	-34.0%(-53.9%, -5.3%)	0.024	0.006

Source: RADARS® Drug Diversion study report (January 2016)

2.3.4.3 Reviewer comments on RADARS® Drug Diversion and Street Price Study

FDA considers drug diversion and street price data to be supportive, or supplemental, as these studies do not meet the criteria for a formal investigation outlined in FDA's 2015 guidance document.¹³ In particular, the outcomes of law enforcement diversion cases and street price are

not considered to be meaningful measures of misuse, abuse, addiction, overdose, or death, but rather provide context for the formal studies examining these outcomes.

The mean population-adjusted diversion rates declined significantly for both Opana ER and ER morphine following introduction of OPR, although the magnitude of decrease was greater for Opana ER. After adjusting for changes in utilization, however, the reductions diversion rates for Opana ER and ER morphine were essentially the same. In addition, the utilization-adjusted diversion rate for Opana ER was not significantly different from that for generic oxymorphone ER during the post-period. The extent to which the changes in Opana ER utilization were a result of the reformulation versus other factors is unknown. It is also unknown to what extent any reformulation-related changes in utilization were the result of decreased desirability and demand for abuse and diversion, as opposed to decreased prescribing for other reasons. Nonetheless, the study findings suggest that, while diversion of Opana ER may have declined following reformulation, factors other than the reformulation itself may have contributed substantially to the reduction seen in diversion rates for both Opana ER and other opioids.

As noted above, drug diversion rates are not considered a direct measure of abuse, but rather a measure of law enforcement activity. A case may represent an action against a large “pill mill,” a sting operation, or a traffic stop involving a possession of a small number of pills without a prescription. It is unclear how funding or local law enforcement priorities may influence the number of drug diversion cases and the drugs on which investigators focus efforts, and this may vary over time even within a consistent sample of jurisdictions. Using a fixed sample of ZIP codes throughout the study period improves the internal validity of the results when comparing drug diversion rates over time; however, the sample is not representative and therefore findings cannot be assumed to reflect national patterns.

There are presumably many factors that determine the price of a street drug, only one of which might be a drug’s having potentially abuse-deterring properties. The sponsor suggests that diversion investigators who report prices may be less likely to bargain a price because it is not needed to make an arrest, and therefore they may report higher values than regular users who purchase the drug from a dealer. Availability of alternative drugs – both licit and illicit – also may play a role in street price. An analysis of the determinants of prescription opioid street price is beyond the scope of this review, and the various unknown and unmeasurable factors make street price a particularly difficult metric to interpret and of limited utility in assessing the impact of drug reformulation on abuse patterns in the community.

2.3.5 RADARS® StreetRx Study

2.3.5.1 Methods

This is an observational study in which users of an internet site spontaneously and anonymously submit the street prices they paid, or heard were paid, for diverted prescription drugs and illicit drugs. Data from the RADARS® System StreetRx Program with sales dates from November 2010 (time of site inception) through June 2015 are presented. Data collection occurs via the website Streetrx.com. Users select the product involved from an extensive list provided on the website, which is regularly updated to reflect new drugs of interest. Anyone with internet access may visit the website and enter

his/her location (city, state, province, country), name of the drug purchased, price paid, dosage, and date of transaction. Visitors to the site can also view others' reports of street price paid for a range of both illicit and licit drugs. When possible, pictures of the drug appear on the website to help the user correctly identify the drug involved.

Geometric mean and median price per milligram by drug are presented. The price per milligram calculation is limited to solid dosage forms (e.g., tablet, capsule, film, patch). Data were log transformed for analysis. Means on the log scale are compared across drug groups.

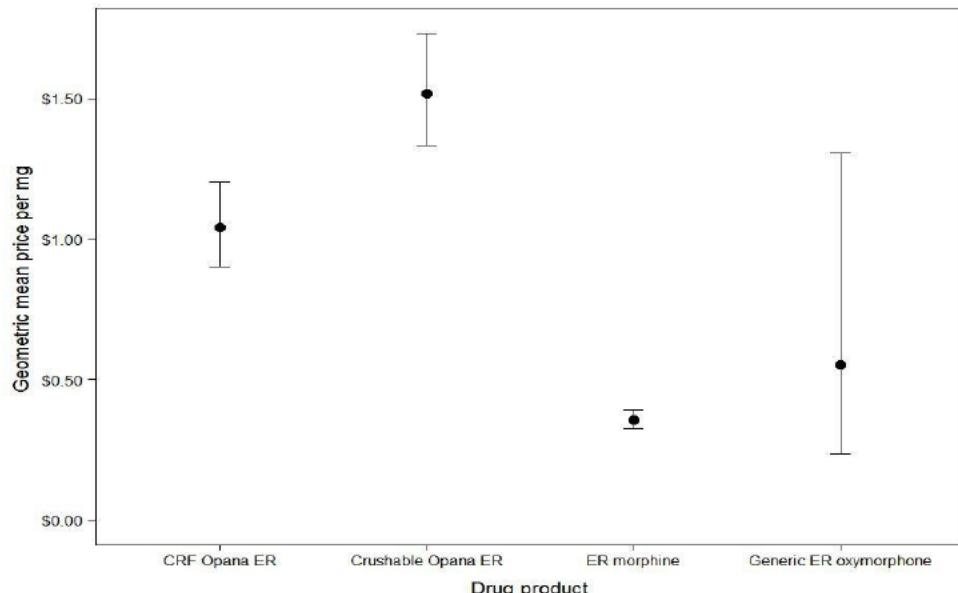
This analysis examined the differences between the drug groups listed below:

- **CRF Opana ER:** This group includes the reformulated Opana ER.
- **Crushable ER oxymorphone:** This group includes the original formulation of Opana ER and “generic oxymorphone ER tablets”.
- **ER morphine:** This group includes “Embeda®”, “MS Contin®”, “Kadian®”, “Activis”, and “generic ER morphine tablets”.
- **Generic oxymorphone ER:** This group includes only “generic ER oxymorphone tablets”.
- **Crushable Opana ER:** This group includes the original formulation of Opana ER.

2.3.5.2 Results

Figure 28 shows that the mean price of ER morphine was significantly lower than for either original (“crushable”) Opana ER or reformulated (“CRF”) Opana ER, and the mean price of reformulated Opana ER was significantly lower than that for original Opana ER. The 95% confidence interval for generic oxymorphone ER was extremely wide; however, the mean price was significantly lower than that of original Opana ER in this analysis and not significantly different from that of reformulated Opana ER.

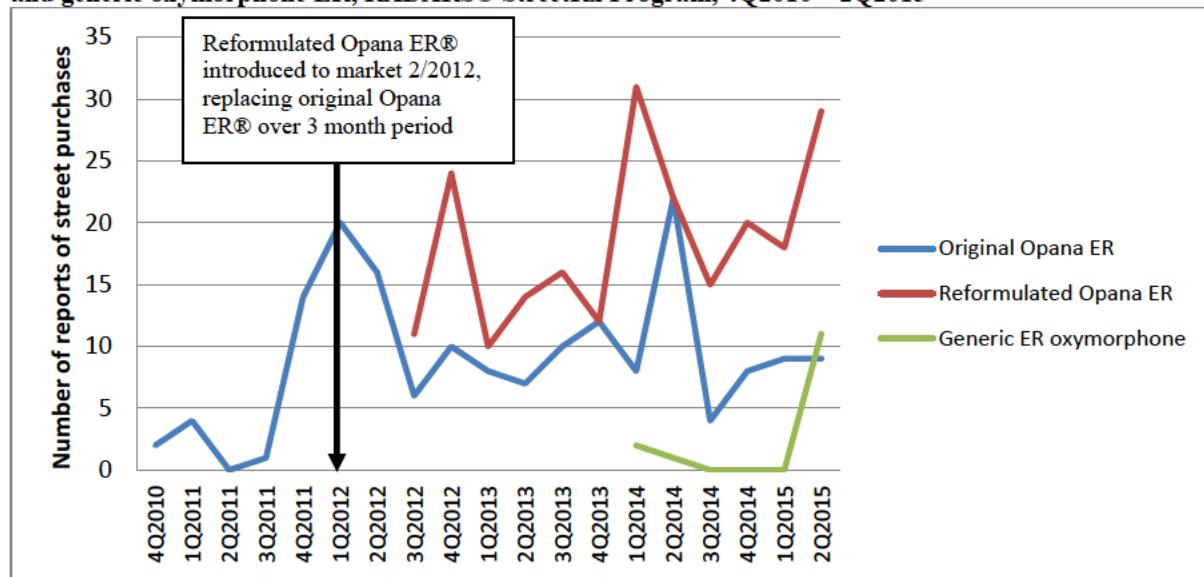
Figure 28. Geometric mean price per milligram and 95% confidence intervals for reformulated (“CRF”) Opana ER, original (“crushable”) Opana ER, ER morphine, and generic oxymorphone ER.



Source: StreetRx study report (January 2016)

As shown in **Figure 29**, long after reformulated Opana ER replaced original “crushable” Opana ER, reports of street purchases for original “crushable” Opana ER were still common, while very few reports for generic oxymorphone ER appeared after these products entered the market.

Figure 29. Quarterly number of street purchase reports for original Opana ER, reformulated Opana ER, and generic oxymorphone ER, RADARS® StreetRx Program, 4Q2010 – 2Q2015



Source: Figure generated by reviewer used data provided in StreetRx study report (January 2016)

2.3.5.3 Reviewer comments

As with the drug diversion and street price survey data in the previous section, the internet street price data from StreetRx.com are considered supportive, or supplementary. Similar concerns

apply here as well, regarding the difficulty interpreting the findings, given the many unknown and unmeasurable factors that likely influence the street price of a drug. In the StreetRx study, the persistent reporting of original “crushable” Opana ER years after marketing of this product was discontinued suggests that substantial misclassification of drug products might be occurring. Furthermore, there is no way to verify whether these purchases even took place. Individuals can enter prices paid based on hearsay, and it is theoretically possible for those with a financial interest in the street price of a drug (e.g., dealers) could enter fraudulent purchase prices in an attempt to influence local markets. For these reasons, we do not find these data to be particularly useful in evaluating the impact of Opana ER’s reformulation on abuse patterns.

2.4 OVERALL DISCUSSION AND INTERPRETATION OF THE POSTMARKETING DATA

The epidemiologic data indicate that there was a shift in the pattern of Opana ER abuse from the nasal to the injection route after the product was reformulated, and the totality of the evidence supports this shift being attributable to the reformulation itself. The possibility of this shift was noted in FDA's May 2013 response to Endo's 2012 citizens petition, but the postmarketing data were determined to be inconclusive at that time. The three full years of postmarketing data provide stronger evidence that the reformulation did cause such a shift in Opana ER ROA patterns in the community. Such a shift is particularly concerning in light of ongoing reports of TMA and the notable HIV outbreak associated with intravenous abuse of this drug.

Nonetheless, the overall interpretation of the data is not entirely straightforward, particularly with regard to the impact of the reformulation on Opana ER abuse overall and injection abuse rates in the community. Data from both the RADARS® and NAVIPPRO® studies suggest sharp increases in OP nasal abuse rates during the pre-period, followed by significant decreases after Opana ER's reformulation. Both studies also found increases in Opana ER injection abuse rates across the study period. The NAVIPPRO® data also suggest high rates of both nasal and injection abuse of generic oxymorphone ER and, to a lesser degree, oxymorphone IR products during the post-period. All of the limitations of the postmarketing data discussed in the previous sections must be considered in interpreting these results. First, both the NAVIPPRO® and RADARS® studies have limitations related to the accurate capture of specific opioid products and formulations, and the potential for bias due to differential misclassification. The relative absence of poison center abuse calls mentioning generic oxymorphone ER during the post-period and the persistently high number of OP post-period abuse reports in the NAVIPPRO study raise concerns about possible product misclassification. Second, both studies suffer from limitations related to sampling and the potential for bias as well as limited generalizability, particularly the NAVIPPRO® study.

Because of the evolving landscape of opioid abuse, as well as the limitations of the available data, determining the impact of reformulation on a product's community abuse is challenging. To evaluate the effect of the reformulation, we need to ask what happened to abuse patterns *compared to what would have happened* without the reformulation? This concept is sometimes referred to as the "counterfactual." Because Opana ER *was* reformulated and the original version removed from the market, we cannot directly answer this question. However, the use of comparators and examination of temporal relationships can be useful in trying to isolate the effect of the reformulation itself from the continuation of pre-existing trends, changes in overall opioid abuse patterns, or changes in the risk profile of the study populations. Because it is bioequivalent to OP (although with possible differences in inactive ingredients, cost, insurance coverage, etc.), generic oxymorphone ER may provide a clue to what might have happened to Opana ER abuse patterns had it not been reformulated. Other opioid comparators with characteristics similar to Opana ER can also help elucidate broader secular trends in opioid abuse within the study populations examined.

1. Evidence that the reformulation caused a shift in ROA from nasal to injection among those abusing Opana ER

The NAVIPPRO® fixed site analyses indicate that, among Opana ER abusers assessed for substance abuse treatment in these sites, there was a shift from predominantly nasal to predominantly injection abuse after the reformulation, with no increase in the relatively small proportion abusing the product orally. Stratified analyses examining Tennessee and non-Tennessee sites separately showed similar results. The much smaller shifts from snorting to injecting seen among abusers of several comparator opioids—including generic oxymorphone ER abusers in the post-period compared to OP abusers in the pre-period—suggest that secular trends or changes in the study sample population might explain a small part of the shift toward injection observed among Opana ER abusers. However, the large magnitude of this observed shift was unique to Opana ER, and the changes in ROA were significantly and meaningfully greater than for any comparator. The shift was temporally associated with Opana ER’s reformulation. Of note, a shift from snorting to injecting was not seen among oxycodone ER abusers following the reformulation of OxyContin in 2010. The RADARS® poison center data were qualitatively consistent with the NAVIPPRO® findings in that the proportion of Opana ER abuse exposure calls involving the injection route increased sharply—while the proportion of cases involving inhalation decreased—following Opana ER’s reformulation. A similar shift was not seen for either morphine ER or oxycodone ER. The FDA analysis of FAERS spontaneous adverse event reports was also qualitatively consistent with a change in the dominant route of Opana ER abuse from nasal to injection following reformulation.

In questions of causal inference, it is also useful to consider plausible biological mechanisms for an observed association. A plausible mechanism strengthens the argument for a causal relationship, in this case between Opana ER’s reformulation and the observed shift from snorting to injection of this drug. A full review of the experimental pre-marketing data evaluating the abuse deterrence of the formulation is beyond the scope of this review, but FDA’s response to Endo’s citizens’ petition stated that OPR can be readily prepared for injection and that certain data suggest that OPR can more easily be prepared for injection than original Opana ER.⁴³ An additional factor may be oxymorphone’s low oral bioavailability—approximately 10% compared to parenteral administration.⁴⁴ In contrast, approximately 60-70% of an oral dose of oxycodone is absorbed from the GI tract and becomes bioavailable, compared to a parenteral dose.⁴⁵ These differences in oral bioavailability may explain some of the differences in seen in ROA patterns for Opana ER and oxycodone ER after product reformulation. Based on interviews with individuals entering opioid addiction treatment programs who reported OxyContin abuse both before and after its reformulation, Cicero et al. found that 43% of these individuals indicated that they switched from primarily injecting/inhaling the drug to primarily swallowing it whole. In Cicero’s sample, 81% of OxyContin abusers reported oral abuse after reformulation, compared to 55.4% before reformulation.⁴⁶ In contrast, the NAVIPPRO® study data suggest that the proportion of Opana ER abusers who abuse the drug orally remained very low after the reformulation. If Opana ER is an abuser’s drug of choice or is readily available, injection may become a more attractive option if reformulation makes nasal abuse more difficult and the oral route is not perceived as effective or economical.

2. Impact of Opana ER’s reformulation on Opana ER abuse rates—nasal, injection, and overall

While it is important to understand how ROA patterns have changed among abusers of a drug product following reformulation, these analyses do not consider changes in the overall

prevalence of abuse of that drug in the population. Hypothetically, even if a much higher proportion of abusers of a drug are injecting it after reformulation, if the overall abuse prevalence for that drug declines dramatically after reformulation, the injection abuse rates for that drug could remain stable or even decline. Given the many difficult-to-measure factors affecting use and abuse trends in communities, determining the impact of a product's reformulation's on its abuse rates in the population is a more difficult task than assessing its impact on ROA patterns among abusers of the product. Nonetheless, this is an important component of evaluating the risk-benefit balance of a reformulated opioid product.

Again, we must consider the observed changes relative to what might have happened to abuse rates without the reformulation. We must also consider changing levels of prescribed availability for each product, as many factors—both related and unrelated to reformulation and abuse—may drive changes in prescription volume. As above, generic oxymorphone ER may provide a useful—if imperfect—indicator of what might have happened with Opana ER abuse rates had it not been reformulated. Morphine ER is another useful comparator in that, like Opana ER, it is a single-ingredient, extended-release opioid with a high proportion of its baseline abuse being non-oral. Neither is morphine ER an ideal comparator, however, in that relative to its large market share, its baseline abuse rates are much lower than for Opana ER in both of these studies, and it did not demonstrate similar sharp pre-period increases in abuse rates. Oxycodone IR SE is useful as a single-ingredient opioid that, like Opana ER, it showed a growing market share and increasing abuse levels during the pre-period. Because of the availability of both single-ingredient and combination IR oxycodone products, however, there are issues with accurate product classification in both of these studies. Oxymorphone IR is a useful comparator in that it has the same active pharmaceutical ingredient as Opana ER but without extended-release or abuse-deterring properties. However, IR oxymorphone has a much lower market share, which in these studies resulted in relatively imprecise abuse rate estimates. Finally, oxycodone ER is a useful comparator in that its trade product, OxyContin, was also replaced in the market with a reformulated version with properties to make it more difficult to crush and gelling properties to make injection more difficult. While its reformulation may make oxycodone ER less representative of broader trends in prescription opioid utilization and abuse, it allows comparison to an ER opioid product with widespread use that was reformulated to deter abuse.

Examining changes in mean abuse rates across study periods provides a simple and intuitive comparison; however, it is complicated by the observation that both utilization and abuse rates for Opana ER were increasing rapidly during the pre-period. Therefore, the definition of the pre-reformulation time period has a major effect on the comparison of means analyses, and examining changes in trends becomes an important part of the assessment. The trend analyses, however, rely on the assumptions that (1) pre-reformulation trends would have continued unchanged had Opana ER not been reformulated, or (2) any change in trends unrelated to reformulation would be similar for Opana ER and comparator opioids. The validity of these assumptions cannot be tested. Neither are the reasons fully understood for the sharp pre-period increases in Opana ER utilization and abuse, although the reformulation of OxyContin has been proposed as a contributing factor.

Impact on nasal abuse rates:

Within the fixed set of ASI-MV® sites, Opana ER mean nasal abuse rates decreased significantly, both as a proportion of ASI-MV® assessments and adjusted for changes in utilization, comparing the post-period to the 6-quarter period preceding reformulation. A change in trend also occurred, with a sharp downward inflection in Opana ER nasal abuse trends following reformulation. This post-period decline resulted in levels in the post-period that were similar to those observed for OP during the early pre-period. Adjusting for utilization volume, OPR nasal abuse rates were significantly lower than those for generic oxymorphone ER during the post-period. In the NAVIPPRO® study, the decreases in Opana ER nasal abuse rates were significantly greater than for any of the comparator opioids, and a similar magnitude of reduction or change in trend was not seen for any comparators. Poison center data were consistent with the decrease in Opana ER nasal abuse rates seen in the NAVIPPRO® study, indicating a sharp rise in calls involving Opana ER abuse via the inhalation route during the pre-period, followed by a significant decline in these call rates after the product's reformulation. Again, post-period Opana ER inhalation abuse rates returned to rates not significantly different from those in the early pre-period. Together, these findings suggest that post-period OPR nasal abuse rates were likely lower than they would have been had the product not been reformulated. The magnitude of this apparent effect is difficult to determine, however, due to the potential for substantial product misclassification and other limitations in both studies.

Impact on injection abuse rates:

Both studies also indicate increases in rates of Opana ER abuse via injection across the study period. High post-period injection abuse rates were also seen for generic oxymorphone ER in the NAVIPPRO® study, however, and the increases in injection abuse rates were not significantly different when comparing OP to OPR and when comparing OP to generic oxymorphone ER rates. Increases in injection abuse rates began prior to Opana ER's reformulation, and if generic oxymorphone ER is considered a good proxy for what would have happened to Opana ER abuse trends without reformulation, the findings suggest that the increases in Opana ER injection abuse rates in this population may be similar to what they would have been without reformulation and that other factors may be contributing to the increase. It is unclear, however, how well generic oxymorphone ER represents what would have happened to Opana ER abuse without reformulation. It is possible that changes in Opana ER abuse patterns carried over to the generic products when they became widely available. Again, persistent reports of OP abuse during the post-period—and not included in these analyses—raise concerns about possible misclassification and the potential for bias, the direction of which is difficult to predict. In addition, the high post-period abuse rates for generic oxymorphone ER could not be confirmed in the RADARS® PC data. It is possible that this discrepancy between the RADARS® and NAVIPPRO® data may reflect real differences in study populations and outcome measures, but it also highlights ongoing uncertainties about the ability of these data to reliably distinguish between different oxymorphone products, for example ER vs. IR and brand vs. generic. Thus, it is not entirely clear whether, overall, the increases in injection abuse rates for Opana ER are greater than they would have been without the reformulation.

Impact on overall abuse rates and other outcomes:

The data are difficult to interpret with regard to the impact of Opana ER's reformulation on overall abuse of the drug (via any route). The NAVIPPRO® data suggest that Opana ER's reformulation may have attenuated the rise, or possibly caused a downward turn in overall Opana ER abuse rates among individuals being assessed for abuse, but the geographic variation and limitations of these data make it very difficult draw conclusions from these data. Because of the many factors that may affect the likelihood of an abuser being assessed for substance abuse treatment, it is also unknown to what degree trends within the NAVIPPRO® study sample reflect those in the general population.

The RADARS® PC study, on the other hand, showed significant declines in Opana ER abuse call rates after reformulation; however, these declines were similar to those seen for opioid comparators without properties intended to deter abuse, and reductions in Opana ER abuse calls involving alternate routes of administration were not significantly different from reductions in abuse calls where the drug was swallowed whole. Together, these findings suggest that factors other than the reformulation may have caused, in whole or part, the reductions in Opana ER abuse exposure call rates. The abrupt change in trend for Opana ER abuse call rates, on the other hand, was not observed in comparator opioids, suggesting that at least some of the decrease may have been caused by the reformulation. Generic oxymorphone ER was not a useful comparator in the RADARS® PC study due to very low event counts, a finding that was inconsistent with the NAVIPPRO® data. It is unknown to what extent the low number of generic oxymorphone ER calls reflects a true absence of poison center versus the data source's inability to accurately capture or document events related to abuse of these products.

The drug diversion data are similar to the poison center data in suggesting that, while Opana ER diversion rates did appear to decline after reformulation, so did rates for comparator opioids not formulated with properties to deter abuse. Furthermore, post-period diversion rates were not significantly different for Opana ER and generic oxymorphone ER. Together, these data suggest that factors other than reformulation may explain some of the observed decline in Opana ER diversion rates following reformulation.

With regard to overdose and death, the RADARS® PC study uses a composite measure of several types of exposure calls to try to approximate overdose; however this outcome measure has not been validated and it is unclear what proportion of these calls represent unintentional overdoses as opposed to other types of exposures, such as accidental pediatric exposures, medical errors, and suicide attempts. Furthermore, poison center calls do not provide a reliable measure of overdose death, in that unattended out-of-hospital deaths due to opioids will generally not result in a call to a poison control center, and therefore would not be captured in these data. Because products causing the most severe overdoses may result in rapid death without a call to a poison control center, these products may be disproportionately underrepresented in poison control data. No other data were provided regarding relative rates of overdose or death associated with use or abuse of OP, OPR, or comparator opioids.

No studies addressed the question of the impact of Opana ER's reformulation on the risk of addiction or presented information on the risk of addiction associated with Opana ER or comparator opioids.

3. Abuse rates for reformulated Opana ER compared to selected comparator opioids

Another factor to consider in evaluating the risk-benefit balance for an opioid product is how abuse rates compare to those for similar currently marketed opioids. Prescription volume for brand and generic oxymorphone ER is low relative to other ER/LA opioid analgesics. Adjusting for these differing levels of prescribed availability, the NAVIPPRO® study suggests abuse rates for OPR that are many times higher than ER morphine or IR oxycodone SE, both overall and via each individual route. However, the study also suggests that abuse rates for generic oxymorphone ER are significantly higher than those for OPR for both overall abuse and nasal abuse, with injection rates that are similar to those for OPR. OPR, generic oxymorphone ER, and oxymorphone IR all had tablet-adjusted injection abuse rates that were considerably higher than any of the included comparators. Comparisons across opioid abuse rates within a single time period in the NAVIPPRO® study must be interpreted with caution, as the NAVIPPRO® sample is not nationally representative, and, as was discussed previously, abuse rates may vary considerably across geographic regions. The Tennessee data suggest that there are specific regions where both prescribing levels and abuse rates for Opana ER and other prescription opioids are particularly high. It is difficult to say how many more of these geographic “hot spots” of Opana ER abuse might exist, as they may or may not fall within the NAVIPPRO® sampling frame. Particularly if substance abuse treatment options are limited in an area, it is unlikely to contribute data to the NAVIPPRO® surveillance network. For example, the high levels of Opana ER abuse described in reports of the HIV outbreak in Scott County, Indiana⁶ may not be captured in the NAVIPPRO® sample at all, as there were no Indiana assessment sites included in the network. Again, possible misclassification bias must also be considered in making comparisons across individual products, particularly the possibility of OPR, generic oxymorphone ER, and oxymorphone IR abuse being underestimated due to misclassification of these products as OP.

The poison center data represent a near census of exposure calls in the U.S. and are consistent with the findings showing abuse call rates for Opana ER that are considerably higher than those for morphine ER, oxymorphone IR, or oxycodone ER after adjusting for differences in prescription volume. The poison center data could not, however, confirm high abuse rates for generic oxymorphone ER seen in the NAVIPPRO® study, and it is possible that some cases actually involving generic oxymorphone ER and possibly IR could be misclassified as the recognizable brand name Opana ER. Again, these comparisons must be interpreted cautiously, as the proportion of abuse events that result in a poison center call may vary across opioid products.

3 CONCLUSIONS

The postmarketing data have many limitations and their interpretation is not straightforward; however, the evidence is compelling that among those abusing Opana ER, the reformulation caused a marked shift in the route by which the drug is abused, from nasal to injection. This shift is particularly concerning, considering the more than 50 cases of TMA identified in FAERS and the large HIV outbreak associated with intravenous abuse of Opana ER. The postmarketing studies suggest that the reformulation likely reduced nasal abuse rates for Opana ER, but because of data limitations it is difficult to determine the magnitude of this apparent effect. The study results also indicate an increase in Opana ER injection abuse rates over the study period. It is not

entirely clear whether the increases in Opana ER injection abuse rates are greater than they would have been had the drug not been reformulated, as increases appear to have begun prior to Opana ER's reformulation and rates were similarly high for generic oxymorphone ER during the post-period among those being assessed for substance abuse treatment. Some data suggest that the reformulation resulted in post-period Opana ER abuse rates that were lower than they might have been without the reformulation; however, the evidence is difficult to interpret with regard to the overall impact of Opana ER's reformulation on abuse of the drug.

Although the diagnoses for which oxymorphone ER is prescribed are similar to those of oxycodone ER and morphine ER, ER oxymorphone comprises only 5% of the ER/LA opioid analgesic market and a tiny fraction of the total prescription opioid market. Not surprisingly, other opioids with larger prescription volume contribute a larger proportion of abuse cases identified in these studies. After adjusting for differences in prescription volume, however, OPR, generic oxymorphone ER, and oxymorphone IR had the highest post-period injection abuse rates and generic oxymorphone ER had the highest overall and nasal abuse rates of the opioids analyzed in the NAVIPPRO® study. In the RADARS® Poison Center study, Opana ER had post-period intentional abuse call rates that were considerably higher than morphine ER, oxymorphone IR, or oxycodone ER. The high abuse rates for generic oxymorphone ER seen in the NAVIPPRO® study could not be confirmed in the poison center data, possibly due to inaccurate reporting of generic products in this data source. All of these across-product comparisons must be interpreted with caution due to the limitations of these data.

4 APPENDICES

4.1 APPENDIX A. DETAILS OF OPANA ER MANUFACTURING STOPPAGE AND SUPPLY DISRUPTION

From Endo's response to FDA's request for information, received June 30, 2016:

In December, 2011, Novartis Consumer Health (NCH) voluntarily stopped manufacturing at their Lincoln, Nebraska (NE) plant, the only site where original Opana ER was manufactured under contract for Endo Pharmaceuticals Inc. All finished product in the plant was quarantined and not allowed to be shipped. In addition, NCH was contemplating a recall of all solid-dosage products manufactured prior to September 1, 2011 in its Lincoln, NE plant including original OPANA ER. The production stoppage, quarantine and possible recall of products manufactured by NCH in Lincoln, NE was based on consumer complaints of chipped and broken pills and inconsistent bottle packaging line clearance practices possibly resulting in rare tablet mix ups. Following discussion with U.S. Food and Drug Administration (including the Division of Anesthesia, Analgesia, and Addiction Products, Drug Shortages Program, Office of Surveillance and Epidemiology, and the Kansas City District Office) in early 2012, a joint decision was reached not to recall the original OPANA ER that was on the market due to the reasons noted above. With the stoppage of production at the NCH Lincoln, NE plant, Endo invoked strictly limited marketing of the product, indicating to physicians that they should not start new patients on OPANA ER, but rather should ensure that existing supplies go to currently treated patients. The goal of this was to make sure product was available to maintain current patients on OPANA ER and prevent the serious consequences of opioid withdrawal without having supply diverted to new patient starts.

Even with these plans in place to limit the impact to patients, there were spot shortages of OPANA ER availability throughout the country in the first half of 2012; however, it is important to note that original OPANA ER did not officially go into drug shortage.

Subsequent to the OPANA ER supply disruption precipitated by events at NCH in Lincoln, NE, Endo quickly moved to begin production of reformulated OPANA ER at its contract manufacturing facility (Pharmaceutical Manufacturing Research Services, Inc., Horsham, PA) to cover the shortages in the OPANA ER market. With an accelerated plan to begin production, because of the lack of availability of original OPANA ER, this product began shipping in February 2012. Due to the sooner than expected launch of reformulated OPANA ER with the need to ramp up production, Endo could not supply the full OPANA ER market with the reformulated OPANA ER for several months following its introduction to the market. A component of the joint decision (referenced above) between Endo and the FDA included the allowance for additional limited production of original OPANA ER at NCH in Lincoln, NE in order to not cause a drug shortage for OPANA ER. Therefore, the last batch of original OPANA ER produced from the Lincoln, NE facility was February 2012, which was released to the market in March 2012.

Up until October 2012 there was a rapid decline in the amount of original OPANA ER being dispensed at the retail pharmacy level. However, in October 2012 the levels of original

OPANA ER dispensed began to show a slower decline which was confirmed in the following months. As a result of this slowed decline, in January 2013 Endo initiated a Voluntary Return Program with the goal of further reducing the OPANA ER original formulation in the market.

The issues at NCH did not cause any drug shortages for OPANA (immediate-release oxymorphone tablets) as Endo was not a single source supplier at that time. At the time of this event, OPANA ER was the only extended-release oxymorphone on the market for the 5 mg, 10 mg, 20 mg, 30 mg, and 40 mg dosage strengths. The 7.5 mg and 15 mg dosage strengths were

available generically. Endo cannot comment on any drug shortages for the 7.5 mg and 15 mg generic oxymorphone ER product during this time as the product was not manufactured by Endo.

4.2 APPENDIX B. DRUG UTILIZATION DATABASE DESCRIPTIONS AND LIMITATIONS

Findings from this review should be interpreted in the context of the known limitations of the databases used. The drug utilization analysis focused only on the outpatient retail setting. Therefore, dispensed prescriptions and patient count estimates reported in this review may not apply to other settings of care in which these products may be used. All of the estimates provided in this review are projected national estimates, but no statistical tests were performed to determine statistical significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

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 3.5 billion prescription claims per year, captured from a sample of the universe of approximately 59,400 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 88% 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 45-75% (varies by class and geography) of mail service pharmacies and approximately 70-85% of long-term care pharmacies.

IMS Health, Total Patient Tracker™ (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may

arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

inVentiv Health Research & Insights LLC., TreatmentAnswers™

inVentiv Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

4.3 APPENDIX C. DRUG UTILIZATION TABLES

Table 1. Nationally Estimated Number of Dispensed Prescriptions for ER/LA Opioid Analgesics from U.S. Outpatient Retail Pharmacies 2009 through 2015, Annually.

	2009		2010		2011		2012		2013		2014		2015	
	Rx Count	Share												
Total	21,636,013	100%	22,321,194	100%	22,282,032	100%	21,800,992	100%	21,428,462	100%	21,241,544	100%	20,698,793	100%
Morphine ER	5,067,499	23%	5,386,291	24%	5,931,628	27%	6,198,303	28%	6,288,088	29%	6,375,570	30%	6,441,121	31%
Fentanyl TD	4,866,117	22%	4,912,480	22%	4,997,384	22%	4,961,133	23%	4,923,139	23%	4,881,447	23%	4,791,686	23%
Oxycodone ER	7,263,667	34%	7,281,009	33%	5,831,523	26%	5,148,631	24%	4,865,489	23%	4,699,154	22%	4,423,455	21%
Methadone	3,856,018	18%	3,927,576	18%	3,924,858	18%	3,708,511	17%	3,466,996	16%	3,227,178	15%	2,830,820	14%
Oxymorphone ER	582,710	3%	786,827	4%	1,196,953	5%	939,908	4%	901,307	4%	960,933	5%	968,029	5%
Buprenorphine TD	—	—	—	—	266,332	1%	431,793	2%	497,697	2%	613,086	3%	643,634	3%
Tapentadol ER	—	—	—	—	37,531	<1%	242,059	1%	259,294	1%	264,048	1%	289,459	1%
Hydromorphone ER	2	<1%	27,011	<1%	95,823	<1%	170,654	1%	226,452	1%	185,035	1%	160,632	1%
Hydrocodone ER	—	—	—	—	—	—	—	—	—	—	35,093	<1%	149,957	1%

Source: IMS Health National Prescription Audit™. 2009-2015. Extracted September 2016. File: NPA ER_LA opioids yearly 2009-2015 xlsx.

Table 2. Nationally Estimated Number of Dispensed Prescriptions for Opana ER Original, Opana ER Reformulated, Generic Oxymorphone ER, and Oxymorphone IR (Brand and Generic) from U.S. Outpatient Retail Pharmacies, 2009 through 2015, Annually.

	2009		2010		2011		2012		2013		2014		2015	
	Rx count	Share	Rx count	Share	Rx count	Share	Rx count	Share	Rx count	Share	Rx count	Share	Rx count	Share
All oxymorphone	747,804	100%	965,630	100%	1,427,296	100%	1,092,231	100%	1,075,036	100%	1,157,487	100%	1,165,166	100%
All oxymorphone ER	582,710	78%	786,827	81%	1,196,953	84%	939,908	86%	901,307	84%	960,933	83%	968,029	83%
Opana ER original	582,710	100%	785,362	100%	1,184,941	99%	386,660	41%	16,893	2%	1,789	<1%	187	<1%
Opana ER reformulated	—	—	—	—	—	—	491,704	52%	698,170	77%	624,494	65%	556,134	57%
oxymorphone ER generic	—	—	—	—	6,101	1%	53,823	6%	180,237	20%	329,451	34%	407,588	42%
oxymorphone IR	165,094	22%	180,894	19%	239,560	17%	163,380	15%	186,550	17%	212,113	18%	212,759	18%

Source: IMS Health, National Prescription Audit™. 2009-2015. Extracted September 2016. File: NPA oxymorphER_IR quarterly 2009-2015 xlsx.

Table 3. Nationally Estimated Number of Dispensed Prescriptions for OxyContin Original, OxyContin Reformulated, and Generic Oxycodone ER Original, and Generic Oxycodone ER Reformulated from U.S. Outpatient Retail Pharmacies 2009 through 2015, Annually.

	2009		2010		2011		2012		2013		2014		2015	
	Rx count	Share												
TOTAL oxycodone ER	7,263,667	100%	5,761,227	100%	5,811,684	100%	5,131,465	<1%	4,851,762	<1%	4,686,915	<1%	4,406,612	<1%
OxyContin original	5,990,029	82%	3,444,815	60%	135,709	2%	14,002	<1%	1,327	<1%	293	<1%	227	<1%
OxyContin reformulated	—	—	1,261,977	22%	5,537,806	95%	5,112,356	100%	4,850,153	100%	4,679,869	100%	4,214,781	96%
oxycodone ER generic original	1,273,638	18%	1,054,435	18%	138,169	2%	5,107	<1%	282	<1%	138	<1%	103	<1%
oxycodone ER generic reformulated	—	—	—	—	—	—	—	—	—	—	6,615	0%	191,501	4%

Source: IMS Health, National Prescription Audit™. 2009-2015. Extracted September 2016. File: NPA oxycodER quarterly 2009-2016.xlsx.

Table 4. Nationally Estimated Number of Dispensed Prescriptions for Opana ER Original, Opana ER Reformulated, Generic Oxymorphone ER, Oxymorphone IR, Morphine ER, Oxycodone ER Original, and Oxycodone ER Reformulated, Stratified by Method of Payment, from U.S. Outpatient Retail Pharmacies 2009 through 2015, Annually.

	2009		2010		2011		2012		2013		2014		2015	
	Rx count	Share												
Opana ER original	582,597	5%	786,692	6%	1,190,649	9%	390,158	3%	17,541	0%	1,862	0%	198	0%
Cash	21,185	4%	23,016	3%	38,511	3%	16,424	4%	1,144	7%	228	12%	63	32%
Medicaid	39,102	7%	67,480	9%	109,025	9%	25,430	7%	771	4%	128	7%	0	0%
Medicare	97,966	17%	155,835	20%	294,104	25%	105,309	27%	4,880	28%	383	21%	17	9%
Third party	424,344	73%	540,361	69%	749,010	63%	242,995	62%	10,746	61%	1,123	60%	118	60%
Opana ER reformulated							495,893	4%	703,509	6%	629,611	5%	560,238	5%
Cash							10,335	2%	15,384	2%	15,026	2%	15,995	3%
Medicaid							33,004	7%	41,664	6%	43,426	7%	28,278	5%
Medicare							142,511	29%	234,476	33%	220,834	35%	218,578	39%
Third party							310,043	63%	411,985	59%	350,325	56%	297,388	53%
generic oxymorphone ER					6,099	0%	53,821	0%	180,237	1%	329,443	3%	407,577	3%
Cash					524	9%	6,036	11%	19,034	11%	36,812	11%	49,368	12%
Medicaid					312	5%	3,128	6%	8,210	5%	7,188	2%	5,319	1%
Medicare					1,164	19%	11,715	22%	49,584	28%	101,752	31%	116,415	29%
Third party					4,099	67%	32,942	61%	103,408	57%	183,691	56%	236,476	58%
oxymorphone IR			15,114	0%	178,976	1%	142,275	1%	184,211	2%	208,711	2%	209,091	2%
Cash			1,059	7%	6,386	4%	5,834	4%	6,080	3%	7,676	4%	8,983	4%
Medicaid			1,243	8%	12,021	7%	5,486	4%	6,078	3%	7,098	3%	5,931	3%
Medicare			1,624	11%	25,787	14%	26,700	19%	44,155	24%	54,103	26%	53,413	26%
Third party			11,189	74%	134,783	75%	104,255	73%	127,898	69%	139,835	67%	140,764	67%
oxycodone ER original	7,262,909	56%	5,734,792	42%	279,893	2%	20,261	0%	1,698	0%	464	0%	354	0%
Cash	562,119	8%	364,342	6%	24,249	9%	2,737	14%	425	25%	238	51%	138	39%
Medicaid	401,077	6%	349,691	6%	12,600	5%	475	2%	53	3%	17	4%	5	1%
Medicare	1,515,503	21%	1,331,577	23%	64,540	23%	3,795	19%	270	16%	20	4%	34	10%
Third party	4,784,210	66%	3,689,182	64%	178,504	64%	13,253	65%	949	56%	188	41%	177	50%
oxycodone ER			1,545,883	11%	5,551,011	42%	5,128,217	41%	4,863,620	40%	4,698,539	38%	4,422,962	37%
Cash			57,435	4%	174,434	3%	146,827	3%	136,187	3%	127,773	3%	128,328	3%
Medicaid			101,706	7%	299,023	5%	194,047	4%	166,850	3%	155,229	3%	140,246	3%
Medicare			372,654	24%	1,409,508	25%	1,462,690	29%	1,511,263	31%	1,498,729	32%	1,470,788	33%
Third party			1,014,088	66%	3,668,047	66%	3,324,653	65%	3,049,320	63%	2,916,808	62%	2,683,600	61%
morphine ER	5,080,717	39%	5,531,583	41%	5,966,297	45%	6,198,094	50%	6,287,903	51%	6,375,387	52%	6,468,719	54%
Cash	257,346	5%	242,565	4%	244,051	4%	267,556	4%	291,337	5%	219,130	3%	201,201	3%
Medicaid	449,080	9%	522,818	9%	534,907	9%	457,998	7%	396,804	6%	375,169	6%	318,929	5%
Medicare	1,534,205	30%	1,827,011	33%	2,069,912	35%	2,302,076	37%	2,569,359	41%	2,717,910	43%	2,815,226	44%
Third party	2,840,085	56%	2,939,189	53%	3,117,427	52%	3,170,463	51%	3,030,403	48%	3,063,178	48%	3,133,363	48%

Source: IMS Health, National Prescription Audit™, Extended Insights. 2015. Ad-hoc analysis provided October 2016. File: NPA adhoc oxymorphER_IR morphER oxycodER payer REVISED 10.28.16.xlsx.

Table 5. Nationally Estimated Number of Patients* Who Received a Dispensed Prescription for Opana ER Original, Opana ER Reformulated, Generic Oxymorphone ER, Oxycodone ER, and/or Morphine ER, Stratified by Age, from U.S. Outpatient Retail Pharmacies 2009 through 2015, Annually.

	2009		2010		2011		2012		2013		2014		2015	
	Patients	Share												
Opana ER original	130,497	100%	179,277	100%	235,448	100%	160,002	100%	11,185	100%	1,302	100%	142	100%
0-39 years	29,724	23%	43,797	24%	60,375	26%	38,115	24%	2,181	20%	222	17%	21	15%
40-64 years	84,275	65%	115,401	64%	151,393	64%	105,250	66%	7,290	65%	900	69%	91	64%
65+ years	17,606	13%	21,554	12%	26,433	11%	17,361	11%	1,723	15%	170	13%	28	20%
Unspecified age	—	—	207	<1%	75	<1%	5	<1%	10	<1%	11	1%	2	1%
Opana ER reformulated	—	—	—	—	—	—	133,513	100%	153,093	100%	132,342	100%	117,472	100%
0-39 years	—	—	—	—	—	—	27,973	21%	27,951	18%	21,228	16%	16,105	14%
40-64 years	—	—	—	—	—	—	90,695	68%	104,482	68%	91,339	69%	80,425	68%
65+ years	—	—	—	—	—	—	15,857	12%	22,232	15%	20,697	16%	20,203	17%
Unspecified age	—	—	—	—	—	—	—	—	82	<1%	1,995	2%	2,735	2%
oxymorphone ER generic	—	—	—	—	3,262	100%	17,674	100%	53,948	100%	79,270	100%	93,779	100%
0-39 years	—	—	—	—	778	24%	5,536	31%	13,831	26%	18,179	23%	20,219	22%
40-64 years	—	—	—	—	2,044	63%	10,411	59%	34,153	63%	51,416	65%	61,327	65%
65+ years	—	—	—	—	449	14%	1,858	11%	6,487	12%	10,279	13%	11,599	12%
Unspecified age	—	—	—	—	—	—	2	<1%	26	<1%	1,372	2%	2,682	3%
oxymorphone IR	44,730	100%	48,857	100%	61,764	100%	54,154	100%	51,977	100%	53,882	100%	52,511	100%
0-39 years	9,870	22%	11,962	24%	15,853	26%	13,307	25%	11,734	23%	11,295	21%	10,476	20%
40-64 years	29,783	67%	31,804	65%	39,404	64%	34,862	64%	33,550	65%	35,038	65%	33,814	64%
65+ years	5,356	12%	5,495	11%	7,087	11%	6,363	12%	7,236	14%	7,819	15%	7,818	15%
Unspecified age	2	<1%	3	<1%	1	<1%	—	—	37	<1%	913	2%	1,323	3%
oxycodone ER	1,525,054	100%	1,481,740	100%	1,172,513	100%	1,077,965	100%	1,018,434	100%	975,021	100%	934,080	100%
0-39 years	287,867	19%	291,571	20%	196,831	17%	169,654	16%	151,359	15%	138,304	14%	126,801	14%
40-64 years	924,777	61%	903,434	61%	725,390	62%	665,863	62%	629,752	62%	602,338	62%	570,984	61%
65+ years	328,320	22%	300,966	20%	262,229	22%	254,335	24%	248,084	24%	243,028	25%	237,057	25%
Unspecified age	174	<1%	654	<1%	189	<1%	14	<1%	465	<1%	10,168	1%	15,369	2%
morphine ER	986,255	100%	1,084,717	100%	1,121,313	100%	1,224,934	100%	1,288,415	100%	1,320,255	100%	1,333,103	100%
0-39 years	147,472	15%	174,997	16%	178,846	16%	193,225	16%	187,844	15%	175,140	13%	168,377	13%
40-64 years	623,727	63%	688,072	63%	713,535	64%	777,967	64%	818,843	64%	837,179	63%	834,390	63%
65+ years	225,465	23%	233,701	22%	242,621	22%	268,935	22%	298,394	23%	322,224	24%	333,890	25%
Unspecified age	109	<1%	551	<1%	209	<1%	34	<1%	666	<1%	13,603	1%	21,663	2%

Source: IMS Health, Total Patient Tracker™. 2009-2015. Extracted September 2016. File: TPT oxymorphaER_IR oxycodER morphER yearly 2009-2015.xlsx.

* Patient count subtotals may not sum exactly due to rounding. Because of patients aging during the study period, patients may be counted more than once in the individual age categories. For this reason, summing across age groups or years is not advisable and will result in overestimates of patient counts.

Table 6. Nationally Estimated Number of Patients* Who Received Dispensed Prescriptions for Opana ER Original, Opana ER Reformulated, Generic Oxymorphone ER, Oxycodone ER, and/or Morphine ER, Stratified by Sex, from U.S. Outpatient Retail Pharmacies from 2009 through 2015, Annually.

	2009		2010		2011		2012		2013		2014		2015	
	Patients	Share												
Opana ER original	130,497	100%	179,277	100%	235,448	100%	160,002	100%	11,185	100%	1,302	100%	142	100%
Female	71,479	55%	95,838	53%	120,791	51%	81,577	51%	6,103	55%	701	54%	61	43%
Male	58,819	45%	83,165	46%	114,147	48%	78,191	49%	5,072	45%	594	46%	79	56%
Unspecified sex	220	<1%	275	<1%	521	<1%	222	<1%	9	<1%	6	<1%	2	1%
Opana ER reformulated	—	—	—	—	—	—	133,513	100%	153,093	100%	132,342	100%	117,472	100%
Female	—	—	—	—	—	—	69,993	52%	83,494	55%	72,731	55%	65,282	56%
Male	—	—	—	—	—	—	63,375	47%	69,420	45%	59,341	45%	52,043	44%
Unspecified sex	—	—	—	—	—	—	148	<1%	175	<1%	288	<1%	147	<1%
oxymorphone ER generic	—	—	—	—	3,262	100%	17,674	100%	53,948	100%	79,270	100%	93,779	100%
Female	—	—	—	—	1,845	57%	8,912	50%	26,821	50%	39,311	50%	47,079	50%
Male	—	—	—	—	1,406	43%	8,718	49%	27,012	50%	39,584	50%	46,427	50%
Unspecified sex	—	—	—	—	11	<1%	43	<1%	92	<1%	348	<1%	247	<1%
oxymorphone IR	44,730	100%	48,857	100%	61,764	100%	54,154	100%	51,977	100%	53,882	100%	52,511	100%
Female	25,087	56%	27,239	56%	33,808	55%	29,013	54%	28,696	55%	29,862	55%	29,330	56%
Male	19,596	44%	21,566	44%	27,846	45%	25,028	46%	23,221	45%	23,874	44%	23,068	44%
Unspecified sex	60	<1%	52	<1%	109	<1%	93	<1%	48	<1%	141	<1%	102	<1%
oxycodone ER	1,525,054	100%	1,481,740	100%	1,172,513	100%	1,077,965	100%	1,018,434	100%	975,021	100%	934,080	100%
Female	759,904	50%	732,493	49%	596,722	51%	550,508	51%	522,163	51%	501,362	51%	483,065	52%
Male	762,254	50%	746,117	50%	574,104	49%	525,786	49%	494,477	49%	471,478	48%	449,243	48%
Unspecified sex	2,699	<1%	3,050	<1%	1,743	<1%	1,774	<1%	1,955	<1%	2,333	<1%	1,879	<1%
morphine ER	986,255	100%	1,084,717	100%	1,121,313	100%	1,224,934	100%	1,288,415	100%	1,320,255	100%	1,333,103	100%
Female	544,114	55%	597,353	55%	610,904	54%	657,543	54%	691,881	54%	710,213	54%	719,733	54%
Male	440,421	45%	485,615	45%	508,629	45%	565,346	46%	594,183	46%	606,632	46%	611,216	46%
Unspecified sex	1,561	<1%	1,886	<1%	2,004	<1%	2,373	<1%	2,669	<1%	3,796	<1%	2,338	<1%

Source: IMS Health, Total Patient Tracker™. 2009-2015. Extracted September 2016. File: TPT oxymorphaER_IR oxycodER morphER yearly 2009-2015.xlsx.

* Patient count subtotals may not sum exactly due to rounding. Because of patients aging during the study period, patients may be counted more than once in the individual age categories. For this reason, summing across age groups or years is not advisable and will result in overestimates of patient counts.

4.4 APPENDIX D. FAERS SEARCH STRATEGIES

Table 1. FAERS Search Strategy for Non-Oral Abuse Associated with Opana ER*

	Search # 1	Search # 2
Date of search	June 1, 2016	June 1, 2016
Time period of search	June 22, 2006 [†] - December 08, 2011 [‡]	December 9, 2011 [§] – June 1, 2016
Search type	FBIS Quick Query	FBIS Quick Query
Product terms	Product Name: Opana ER NDA: 021610	Product Name: Opana ER NDA: 201655
Additional filters	Event Date Narrative Text Search : <i>chew, inhal, insuffl, inject, intravenous, nasal, smoke, snort</i>	

* See Appendix E for a description of the FAERS database.
[†] Approval date for OP.
[‡] Up to the date of approval for OPR. It is expected that there would be a time period where both formulations were available to patients.
[§] Approval date for OPR.
^{||} To assess modalities of non-oral abuse and misuse, DPV used a narrative text search to identify cases of interest.

Table 2. FAERS Search Strategy for Non-Oral Abuse Associated with All Oxymorphone Products*

Date of search	September 20, 2016
Time period of search	June 22, 2006 [†] - September 20, 2016
Search type	FBIS Quick Query
Product terms	Product Active Ingredient: oxymorphone, oxymorphone hydrochloride
MedDRA search terms (Version 19.0)	<i>Drug abuse and dependence (SMQ) Broad search</i>
Additional filters	Event Date after July 1, 2011 [‡] Narrative Text Search : <i>chew, inhal, insuffl, inject, intravenous, nasal, smoke, snort</i>

* See Appendix E for a description of the FAERS database.
[†] Approval date for OP.
[‡] Approximate date generic extended-release oxymorphone products were introduced to the U.S. market.
[§] Approval date for OPR.
^{||} To assess modalities of non-oral abuse and misuse, DPV used a narrative text search to identify cases of interest.

Table 3. FAERS Search Strategy for TMA Associated with Opana ER*

	Search # 1	Search # 2
Date of search	July 25, 2016	August 1, 2016
Time period of search	March 27, 2013 [†] - June 1, 2016	June 22, 2006 – December 8, 2011 [‡]
Search type	FBIS Quick Query	FBIS Quick Query
Product terms	Product Name: Opana ER NDA: 201655	Product Name: Opana ER NDA: 021610
MedDRA search terms (Version 19.0)	HGLT: 1. <i>Coagulopathies and bleeding diatheses (exclude thrombocytopenic)</i> 2. <i>Haemolyses and related conditions</i> 3. <i>Haematological disorders NEC</i> 4. <i>Platelet disorders</i>	

* See Appendix E for a description of the FAERS database.

	Search # 1	Search # 2
[†] Date since DPV's last focused review of Opana ER and TMA. ³		
[‡] Date of approval of OP up to the date of approval of OPR.		

Table 4. FAERS Search Strategy for TMA with All Oxymorphone Products*

Date of search	September 12, 2016
Time period of search	January 1, 1969 – September 12, 2016
Search type	FBIS Quick Query
Product terms	Product Active Ingredient: oxymorphone, oxymorphone hydrochloride
MedDRA search terms (Version 19.0)	HGLT: 1. <i>Coagulopathies and bleeding diatheses (exclude thrombocytopenic)</i> 2. <i>Haemolyses and related conditions</i> 3. <i>Haematological disorders NEC</i> 4. <i>Platelet disorders</i>

* See Appendix E for a description of the FAERS database.

Table 5. FAERS Search Strategy for TMA with OxyContin*

Date of search	August 16, 2016
Time period of search	January 1, 1969 – August 16, 2016
Search type	FBIS Quick Query
Product terms	Product Name: OxyContin NDA: 022272
MedDRA search terms (Version 19.0)	HGLT: 1. <i>Coagulopathies and bleeding diatheses (exclude thrombocytopenic)</i> 2. <i>Haemolyses and related conditions</i> 3. <i>Haematological disorders NEC</i> 4. <i>Platelet disorders</i>

* See Appendix E for a description of the FAERS database.

Table 6. FAERS Search Strategy for TMA with Hysingla ER*

Date of search	August 16, 2016
Time period of search	November 20, 2014 [†] – October 13, 2016
Search type	FBIS Quick Query
Product terms	Product Name: Hysingla ER NDA: 206627
MedDRA search terms (Version 19.0)	HGLT: 1. <i>Coagulopathies and bleeding diatheses (exclude thrombocytopenic)</i> 2. <i>Haemolyses and related conditions</i> 3. <i>Haematological disorders NEC</i> 4. <i>Platelet disorders</i>

* See Appendix E for a description of the FAERS database.

[†] Date of US approval

Table 7. FAERS Search Strategy for TMA with Zohydro ER*

Date of search	August 16, 2016
Time period of search	October 25, 2013 [†] – October 13, 2016
Search type	FBIS Quick Query
Product terms	Product Name: Zohydro NDA: 202880

MedDRA search terms (Version 19.0)	HGLT: 1. <i>Coagulopathies and bleeding diatheses (exclude thrombocytopenic)</i> 2. <i>Haemolyses and related conditions</i> 3. <i>Haematological disorders NEC</i> 4. <i>Platelet disorders</i>
* See Appendix E for a description of the FAERS database. † Date of US approval	

Table 8. FAERS Search Strategy for TMA with Nucynta ER*

Date of search	August 26, 2016
Time period of search	January 1, 1969 – August 26, 2016
Search type	FBIS Quick Query
Product terms	Product Active Ingredient: tapentadol, tapentadol hydrochloride
MedDRA search terms (Version 19.0)	HGLT: 1. <i>Coagulopathies and bleeding diatheses (exclude thrombocytopenic)</i> 2. <i>Haemolyses and related conditions</i> 3. <i>Haematological disorders NEC</i> 4. <i>Platelet disorders</i>

* See Appendix E for a description of the FAERS database.

Table 9. FAERS Search Strategy for HIV Infections Associated with Opana ER*

	Search # 1	Search # 2
Date of search	November 29, 2016	November 29, 2016
Time period of search	Event date: June 22, 2006 – February 29, 2012	Event date: December 9, 2011 – March 1, 2012
Search type	FBIS Quick Query	FBIS Quick Query
Product terms	Product active ingredient: oxymorphone, oxymorphone hydrochloride	Product active ingredient: oxymorphone, oxymorphone hydrochloride
MedDRA search terms (Version 19.0)	SOC: 1. <i>Immune system disorders</i> 2. <i>Infections and infestations</i> 3. <i>Investigations</i>	
Additional filter	Narrative text search: HIV	

* See Appendix E for a description of the FAERS database.

Table 10. FAERS Search Strategy for Viral Hepatitis Infections Associated with Opana ER*

	Search # 1	Search # 2
Date of search	November 30, 2016	November 30, 2016
Time period of search	Event date: June 22, 2006 – February 29, 2012	Event date: March 1, 2012 – June 1, 2016
Search type	FBIS Quick Query	FBIS Quick Query
Product terms	Product active ingredient: oxymorphone, oxymorphone hydrochloride	Product active ingredient: oxymorphone, oxymorphone hydrochloride
MedDRA search terms (Version 19.0)	HLT: 1. <i>Hepatitis viral infections</i> 2. <i>Hepatocellular damage and hepatitis NEC</i> 3. <i>Virus identification and serology</i>	

* See Appendix E for a description of the FAERS database.

4.5 APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

4.6 APPENDIX F. LITERATURE SEARCH STRATEGY FOR CASE REPORTS OF TMA WITH OXYCONTIN, HYSINGLA ER, ZOHYDRO ER, AND NUCYNTA ER

Date of search	October 26, 2016
Database	PubMed@FDA
Search terms	Hysingla AND Thrombotic Hysingla AND Microangiopathy Hysingla AND TTP Hysingla AND Platelet Zohydro AND Thrombotic Zohydro AND Microangiopathy Zohydro AND TTP Zohydro AND Platelet Hydrocodone AND Thrombotic Hydrocodone AND Microangiopathy Hydrocodone AND TTP Hydrocodone AND platelet OxyContin AND Thrombotic OxyContin AND Microangiopathy OxyContin AND TTP OxyContin AND Platelet Nucynta ER AND Thrombotic Nucynta ER AND Microangiopathy Nucynta ER AND TTP Nucynta ER AND Platelet
Years included in search	All years

4.7 APPENDIX G. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS FOR THE NON-ORAL ABUSE CASE SERIES

Count	FAERS Case Number	Version Number	Manufacturer Control Number
1	10007262	1	OPCR20140079
2	10007273	1	OPCR20140078
3	10067732	1	OPCR20130175
4	10070291	1	OPCR20140109
5	10070301	1	OPCR20140110
6	10070315	1	OPCR20140111
7	10070527	1	OPCR20140112
8	10082047	1	OPCR20140042
9	10283425 9518811	1 1	US-ENDO PHARMACEUTICALS INC.- OPER20130014 2013080209
10	10533537	2	US-ENDO PHARMACEUTICALS INC.- OPCR20140178
11	11005182	3	US-ENDO PHARMACEUTICALS INC.-2015- 000371
12	11045348	2	US-ENDO PHARMACEUTICALS INC.-2015- 000421
13	11239565	2	US-ENDO PHARMACEUTICALS INC.-2015- 001507
14	11934814	1	US-ENDO PHARMACEUTICALS INC.- OPCR20150003
15	12306003	2	US-ENDO PHARMACEUTICALS INC.-2016- 002790
16	12317049	1	Direct report
17	12406463	1	Direct report
18	6116047	2	OPER20060001
19	6439231	1	2007EN000233
20	6522986	1	2007EN000297
21	6524012	1	2007EN000296
22	6549059	2	OPER20080010

Count	FAERS Case Number	Version Number	Manufacturer Control Number
23	6587784	1	OPER20080037
24	6615731	1	OPER20080052
25	6615735	1	OPER20080059
26	6697234	1	OPER20080123
27	6727796	1	OPER20080145
28	6974332	3	OPER20090060
29	6974382	2	OPER20090059
30	6974504 6654047	2 1	OPER20090065 OPER20080096
31	6974642	1	OPER20090067
32	6974690	1	OPER20080228
33	6974715	1	OPER20090020
34	7007551	1	OPER20090100
35	7017509 6974724	1 4	OPER20090107 OPER20090066
36	7283077	1	OPER20100017
37	7536484	1	US-ENDO PHARMACEUTICALS INC.- OPER20100135
38	7774619	1	US-ENDO PHARMACEUTICALS INC.- OPER20110011
39	7971842	1	2007EN000298
40	7971844	1	2007EN000299
41	7985654	1	US-ENDO PHARMACEUTICALS INC.- OPER20110121
42	7987346	2	US-ENDO PHARMACEUTICALS INC.- OPER20110122
43	8046752	1	OPER20110146
44	8067322	1	US-ENDO PHARMACEUTICALS INC.- OPER20110172
45	8123180 7860161	2 2	OPER20110053 US-ENDO PHARMACEUTICALS INC.- OPER20110053
46	8181845	1	ENDO PHARMACEUTICALS INC.- OPER20110251

Count	FAERS Case Number	Version Number	Manufacturer Control Number
47	8318509	1	US-ENDO PHARMACEUTICALS INC.- OPER20110348
48	8502041	2	US-ENDO PHARMACEUTICALS INC.- OPIR20120035
49	8540558	1	US-ENDO PHARMACEUTICALS INC.- OPCR20120361
50	8543743	2	US-ENDO PHARMACEUTICALS INC.- OPER20120545
51	8552536	1	US-ENDO PHARMACEUTICALS INC.- OPCR20120432
52	8556553	1	US-ENDO PHARMACEUTICALS INC.- OPCR20120561
53	8684255	1	US-ENDO PHARMACEUTICALS INC.- OPER20120707
54	8725380	4	US-ENDO PHARMACEUTICALS INC.- OPCR20121730
55	8736847	6	US-ENDO PHARMACEUTICALS INC.- OPCR20121756
56	8736848	5	US-ENDO PHARMACEUTICALS INC.- OPCR20121770
57	8736849	6	US-ENDO PHARMACEUTICALS INC.- OPCR20121771
58	8736850	3	US-ENDO PHARMACEUTICALS INC.- OPCR20121772
59	8736851	6	US-ENDO PHARMACEUTICALS INC.- OPCR20121769
60	8763739	1	Direct report
61	8763748	1	Direct report
62	8801590	5	US-ENDO PHARMACEUTICALS INC.- OPCR20121888
63	8828029	4	US-ENDO PHARMACEUTICALS INC.- OPCR20121911
64	8828032	4	US-ENDO PHARMACEUTICALS INC.- OPCR20121912
65	8828033	1	US-ENDO PHARMACEUTICALS INC.- OPCR20121919
66	8828037	3	US-ENDO PHARMACEUTICALS INC.- OPCR20121918
67	8873918	4	US-ENDO PHARMACEUTICALS INC.- OPCR20121981
68	8910395	1	US-ENDO PHARMACEUTICALS INC.-

Count	FAERS Case Number	Version Number	Manufacturer Control Number
			OPCR20121999
69	8915016	3	US-ENDO PHARMACEUTICALS INC.- OPCR20122014
70	8915019	3	US-ENDO PHARMACEUTICALS INC.- OPCR20122016
71	8915027	3	US-ENDO PHARMACEUTICALS INC.- OPCR20122015
72	8915040	3	US-ENDO PHARMACEUTICALS INC.- OPCR20122022
73	8915656	3	US-ENDO PHARMACEUTICALS INC.- OPCR20122018
74	8915774	3	US-ENDO PHARMACEUTICALS INC.- OPCR20122020
75	8951199	1	US-ENDO PHARMACEUTICALS INC.- OPCR20122091
76	8978846	2	US-ENDO PHARMACEUTICALS INC.- OPCR20122110
77	9016020	1	US-ENDO PHARMACEUTICALS INC.- OPCR20130008
78	9016028	1	US-ENDO PHARMACEUTICALS INC.- OPCR20130009
79	9017564	1	US-ENDO PHARMACEUTICALS INC.- OPCR20130010
80	9019472	1	US-ENDO PHARMACEUTICALS INC.- OPCR20130018
81	9019665	1	US-ENDO PHARMACEUTICALS INC.- OPCR20130022
	9022001	1	US-ENDO PHARMACEUTICALS INC.- OPCR20130023
82	9019687	1	US-ENDO PHARMACEUTICALS INC.- OPCR20130015
83	9059242	2	US-ENDO PHARMACEUTICALS INC.- OPCR20130068
84	9059249	2	US-ENDO PHARMACEUTICALS INC.- OPCR20130067
85	9096147	1	US-ENDO PHARMACEUTICALS INC.- OPCR20130056
86	9113208	2	US-ENDO PHARMACEUTICALS INC.- OPCR20130069
87	9142856	1	US-ENDO PHARMACEUTICALS INC.- OPER20100017

Count	FAERS Case Number	Version Number	Manufacturer Control Number
88	9143002 8556356	1 1	US-ENDO PHARMACEUTICALS INC.- OPER20120551 OPER20120551
89	9147548	1	US-ENDO PHARMACEUTICALS INC.- OPCR20130108
90	9148635	1	US-ENDO PHARMACEUTICALS INC.- OPCR20122093
91	9149178	1	US-ENDO PHARMACEUTICALS INC.- OPCR20121775
92	9149193	1	US-ENDO PHARMACEUTICALS INC.- OPCR20121808
93	9152379	1	US-ENDO PHARMACEUTICALS INC.- OPCR20130114
94	9157242	1	US-ENDO PHARMACEUTICALS INC.- OPCR20130112
95	9253884	2	US-ENDO PHARMACEUTICALS INC.- OPCR20130175
96	9330919	1	OPER20130010
97	9420014	1	Direct report
98	9437017	1	US-ENDO PHARMACEUTICALS INC.- OPCR20130307
99	9455798	1	US-ENDO PHARMACEUTICALS INC.- OPCR20130316
100	9456114 10283414	1 1	US-ENDO PHARMACEUTICALS INC.- OPER20130015 US-ENDO PHARMACEUTICALS INC.- OPER20130017
101	9456130 10283424	1 1	US-ENDO PHARMACEUTICALS INC.- OPER20130020 US-ENDO PHARMACEUTICALS INC.- OPER20130016
102	9456203 10283421	1 1	US-ENDO PHARMACEUTICALS INC.- OPER20130022 US-ENDO PHARMACEUTICALS INC.- OPER20130018
103	9498513	2	US-ENDO PHARMACEUTICALS INC.- OPCR20130336
104	9674952	1	Direct report
105	9674954	1	Direct report
106	9725666	1	OPCR20130425

Count	FAERS Case Number	Version Number	Manufacturer Control Number
107	9861684	3	OPCR20140030
108	9881621	2	OPCR20140036
109	9881633	2	OPCR20140040
110	9882039	2	OPCR20140048
111	9882047	2	OPCR20140047
112	9882064	2	OPCR20140046
113	9882084	2	OPCR20140045
114	9882090	2	OPCR20140044
115	9882990	2	OPCR20140041
116	9882991	1	QPCR20140042
117	9882992	2	OPCR20140043

4.8 APPENDIX H. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS FOR THROMBOTIC MICROANGIOPATHY CASE SERIES

Count	FAERS Case Number	Version Number	Manufacturer Control Number
1	10007262	1	OPCR20140079
2	10007273	1	OPCR20140078
3	10067732 9253884	1 2	OPCR20130175 US-ENDO PHARMACEUTICALS INC.- OPCR20130175
4	10070301	1	OPCR20140110
5	10070315	1	OPCR20140111
6	10070527	1	OPCR20140112
7	10082047 10070291 9882991	1 1 1	OPCR20140042 OPCR20140109 QPCR20140042
8	11045348	2	US-ENDO PHARMACEUTICALS INC.-2015-000421
9	11048977	1	US-ENDO PHARMACEUTICALS INC.-2015-000429

Count	FAERS Case Number	Version Number	Manufacturer Control Number
10	11123045	1	US-ENDO PHARMACEUTICALS INC.-2015-000860
11	11701998	1	US-ENDO PHARMACEUTICALS INC-2015-003691
12	12207992	1	US-ENDO PHARMACEUTICALS INC-2016-001930
13	9410541	1	Direct report
14	9420003	1	Direct report
15	9420014	1	Direct report
16	9455798	1	US-ENDO PHARMACEUTICALS INC.-OPCR20130316
17	9498513	2	US-ENDO PHARMACEUTICALS INC.-OPCR20130336
18	9674952	1	Direct report
19	9674954	1	Direct report
20	9725666	1	OPCR20130425
21	9861684	3	OPCR20140030
22	9881621	2	OPCR20140036
23	9881633	2	OPCR20140040
24	9882039	2	OPCR20140048
25	9882047	2	OPCR20140047
26	9882064	2	OPCR20140046
27	9882084	2	OPCR20140045
28	9882090	2	OPCR20140044
29	9882990	2	OPCR20140041
30	9882992	2	OPCR20140043

4.9 APPENDIX I. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS FOR VIRAL HEPATITIS CASE SERIES

Count	FAERS Case Numbers	Version Number	Manufacturer Control Number
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Count	FAERS Case Numbers	Version Number	Manufacturer Control Number
1	10067732	1	OPCR20130175
2	10082047 9882991	1 1	OPCR20140042 QPCR20140042
3	9151993	1	Direct
4	9152019	1	Direct
5	9861684	3	OPCR20140030
6	9881633	2	OPCR20140040
7	9882064	2	OPCR20140046
8	9882090	2	OPCR20140044
9	9882990	2	OPCR20140041
10	9882992	2	OPCR20140043
11	8736847	6	US-ENDO PHARMACEUTICALS INC.- OPCR20121756

4.10 APPENDIX J. ADDITIONAL TABLES AND FIGURES FROM NAVIPPRO® STUDY

Table J1. Geographic distribution of total sites and total assessment within the ASI-MV® network, by state, 3-year pre-period (January 1, 2009 – December 31, 2011) and 3-year post-period (July 1, 2013 – June 30, 2016)

Pre-Period				Post-period			
State	Total ASI-MV sites	Total ASI-MV assessments	Total prescription opioid abusers	State	Total ASI-MV sites	Total ASI-MV assessments	Total prescription opioid abusers
AL	1	481	81	AL	1	163	37
AR	1	488	133	AR	3	1,094	307
CA	34	9,043	1,731	AZ	2	995	56
CO	27	6,866	976	CA	39	8,016	1,988
CT	1	1	0	CO	25	6,195	875
DC	4	1,299	79	DC	2	38	0
FL	16	7,239	2,133	FL	39	12,164	3,314
GA	7	409	65	GA	15	433	63
HI	3	220	31	HI	1	79	3
KS	9	417	70	KS	2	16	3
LA	18	5,596	954	KY	2	10	9
MA	13	809	291	LA	14	4,095	1,705
MD	28	11,265	2,613	MA	8	712	230
MI	39	15,157	3,622	MD	22	7,914	2,633
MN	1	2	1	ME	2	186	42
MO	43	11,862	3,440	MI	50	13,025	3,518
NC	131	33,711	4,958	MO	70	24,800	6,049
NE	11	1,371	157	NC	125	20,284	2,542
NH	4	74	18	NE	7	4,088	405
NM	131	56,791	8,650	NH	3	332	193
NV	1	226	147	NM	17	5,056	438
NY	7	1,810	369	NY	3	146	46
OH	7	655	131	OH	8	2,208	286
OK	57	19,019	1,984	OK	67	22,360	2,845
OR	3	2,296	436	OR	2	537	43
PA	5	655	281	PA	6	398	161
RI	1	6	1	RI	1	2	0
SC	7	636	182	SC	1	23	7
TN	26	4,895	2,102	TN	38	20,964	10,432
TX	3	173	33	TX	5	343	30
UT	3	406	240	UT	4	333	104
VA	5	91	18	VA	3	39	8
VT	19	6,144	1,823	VT	17	3,527	2,169
WI	1	7	1	WA	1	3	1
WV	5	2,411	1,571	WI	3	292	110
WY	15	4,355	486	WV	7	247	122
TOTAL	687	206,466	39,808	WY	30	6,961	743
				TOTAL	643	168,078	41,317

Table J2. Prevalence of past 30-day abuse via any route of administration for Opana ER and comparators, per 100 ASI-MV® assessments, pre-period vs. post-period, NAVIPPRO® study

	Pre-Period**	Post-Period**	Percent Change [†] from pre-period/post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent Change p-value
Original OPANA ER [‡]	0.79	N/A	N/A	N/A	N/A
OPANA ER ADF*	N/A	0.99 [§]	25.0 [§]	(16.6, 34.0) [§]	<.0001 [§]
Oxymorphone IR	0.17	0.46	172.2	(139.5, 209.4)	<.0001
Oxycodone IR single-entity	1.69	5.19	206.8	(195.0, 219.1)	<.0001
Morphine ER [¶]	1.22	1.87	53.6	(45.6, 62.1)	<.0001
Oxycodone ER	5.59	4.09	-26.9	(-29.0, -24.7)	<.0001

** Pre-period = three-year period prior to introduction of OPANA ER ADF (1/1/2009 -12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2016).

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

[†] Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

[‡] Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

^{*} OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

[§] Percent change estimates for OPANA ER ADF represent comparison of abuse prevalence for OPANA ER ADF in the post-period to original OPANA ER in the pre-period.

[¶] Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

Table J3. Prevalence of past 30-day abuse via any route of administration for Opana ER and comparators, per 100 ASI-MV® assessments, sensitivity pre-period vs. post-period, NAVIPPRO® study

	Sensitivity Pre-Period**	Post-Period**	Percent Change [†] from pre-period/ post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent Change p-value
Original OPANA ER [‡]	1.22	N/A	N/A	N/A	N/A
OPANA ER ADF*	N/A	0.99	-19.0	(-24.8, -12.8) [§]	<.0001 [§]
Oxymorphone IR	0.26	0.46	80.4	(56.7, 107.7)	<.0001
Oxycodone IR single-entity	2.69	5.19	93.2	(85.2, 101.5)	<.0001
Morphine ER	1.35	1.87	38.4	(29.8, 47.5)	<.0001
Oxycodone ER	5.80	4.09	-29.4	(-31.8, -27.0)	<.0001

** Sensitivity pre-period = (7/1/2010 -12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2016).

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

† Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

‡ Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

* OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

† Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

§ Percent change estimates for OPANA ER ADF represent comparison of abuse prevalence for OPANA ER ADF in the post-period to original OPANA ER in the pre-period.

|| Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

Table J4. Rates of past 30-day abuse via any route of administration for Opana ER and comparators, per 10,000 tablets dispensed, full pre-period vs. post-period, NAVIPPRO® study

	Pre-Period**	Post-Period**	Percent Change [†] from pre-period/ post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent change p-value
Original OPANA ER ^{††}	0.191	N/A	N/A	N/A	N/A
OPANA ER ADF [*]	N/A	0.279 [§]	46.1 [§]	(36.4, 56.5) [§]	<.0001 [§]
Oxymorphone IR	0.141	0.264	87.4	(65.0, 112.8)	<.0001
Oxycodone IR single-entity	0.023	0.038	67.0	(60.5, 73.8)	<.0001
Morphine ER ^{##}	0.050	0.050	1.1	(-4.1, 6.6)	0.6766
Oxycodone ER	0.188	0.167	-11.0	(-13.6, -8.3)	<.0001

** Pre-period = three-year period prior to introduction of OPANA ER ADF (1/1/2009 -12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2016).

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

† Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

†† Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

* OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

§ Percent change estimates for OPANA ER ADF represent comparison of abuse prevalence for OPANA ER ADF in the post-period to original OPANA ER in the pre-period.

Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

Table J5. Rates of past 30-day abuse via any route of administration for Opana ER and comparators, per 10,000 tablets dispensed, sensitivity pre-period vs. post-period, NAVIPPRO® study

	Sensitivity Pre-Period**	Post-Period**	Percent Change [†] from pre-period/post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent change p-value
Original OPANA ER ^{††}	0.223	N/A	N/A	N/A	N/A
OPANA ER ADF [‡]	N/A	0.279 [§]	25.3 [§]	(16.4, 34.9) [§]	<.0001 [§]
Oxymorphone IR	0.186	0.264	41.8	(23.2, 63.2)	<.0001
Oxycodone IR single-entity	0.029	0.038	31.9	(26.3, 37.7)	<.0001
Morphine ER	0.051	0.050	-0.7	(-6.8, 5.8)	0.8326
Oxycodone ER	0.209	0.167	-19.9	(-22.7, -17.1)	<.0001

** Sensitivity pre-period = (7/1/2010 - 12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2016).

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

† Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

†† Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

‡ OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

§ Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

|| Percent change estimates for OPANA ER ADF represent comparison of abuse prevalence for OPANA ER ADF in the post-period to original OPANA ER in the pre-period.

||| Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

Table J6. Prevalence of past 30-day abuse via any route for Opana ER and comparators, per 100 ASI-MV® assessments, Tennessee only, sensitivity pre-period vs. post-period, NAVIPPRO® study

	Sensitivity Pre-Period**	Post-Period**	Percent Change [†] From pre-period/post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent change p-value
Original OPANA ER [‡]	11.97	N/A	N/A	N/A	N/A
OPANA ER ADF*	N/A	6.11 [§]	-49.0 [§]	(-54.4, -42.9) [§]	<.0001 [§]
Oxymorphone IR	1.38	2.14	54.8	(12.6, 112.8)	0.0071
Oxycodone IR single-entity	18.57	19.57	5.4	(-2.8, 14.2)	0.2007
Morphine ER [#]	8.64	7.44	-13.9	(-24.3, -2.0)	0.0233
Oxycodone ER	20.53	11.39	-44.5	(-48.9, -39.8)	<.0001

** Sensitivity pre-period = 18 month time period after introduction of ADF oxycodone ER and prior to introduction of OPANA ER ADF (Q3 2010 –Q4 2011; 1/2010 –12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (Q3 2013 – Q2 2016; 7/1/2013 – 6/30/2015).

Note that the transition period of market change for oxymorphone products (1/1/2012 –6/30/2013) is excluded from analyses.

† Pre-post relative change reflects the percent change in the percent abuse from the pre-period to post-period.

‡ Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

* OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

§ Percent change estimates for OPANA ER ADF represent comparison of abuse prevalence for OPANA ER ADF in the post-period to original OPANA ER in the pre-period.

Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

Table J7. Rates of past 30-day abuse via any route for Opana ER and comparators, per 10,000 tablets dispensed, Tennessee only, sensitivity pre-period vs. post-period, NAVIPPRO® study

	Sensitivity Pre-Period**	Post-Period**	Percent Change [†] From pre-period/post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent change p-value
Original OPANA ER ^{‡†}	0.386	N/A	N/A	N/A	N/A
OPANA ER ADF [§]	N/A	0.648 [§]	68.1 [§]	(49.3, 89.1) [§]	<.0001 [§]
Oxymorphone IR	0.571	0.640	12.1	(-18.9, 55.0)	0.4900
Oxycodone IR single-entity	0.072	0.068	-5.3	(-13.4, 3.5)	0.2295
Morphine ER ^{#§}	0.084	0.091	8.2	(-5.2, 23.5)	0.2444
Oxycodone ER	0.270	0.246	-9.0	(-16.8, -0.5)	0.0382

** Sensitivity pre-period = 18 month time period after introduction of ADF oxycodone ER and prior to introduction of OPANA ER ADF (Q3 2010 –Q4 2011; 1/1/2010 –12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (Q3 2013 – Q2 2016; 7/1/2013 – 6/30/2015).

Note that the transition period of market change for oxymorphone products (1/1/2012 –6/30/2013) is excluded from analyses.

† Pre-post relative change reflects the percent change in the percent abuse from the pre-period to post-period.

‡ Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

§ OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

Percent change estimates for OPANA ER ADF represent comparison of abuse prevalence for OPANA ER ADF in the post-period to original OPANA ER in the pre-period.

Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

Table J8. Prevalence of past 30-day abuse via any route for Opana ER and comparators, per 100 ASI-MV® assessments, excluding Tennessee, sensitivity pre-period vs. post-period, NAVIPPRO® study

	Sensitivity Pre-Period**	Post-Period**	Percent Change [†] From pre-period/post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent change p-value
Original OPANA ER ^{††}	0.88	N/A	N/A	N/A	N/A
OPANA ER ADF*	N/A	0.29§	-66.6§	(-70.3, -62.5)§	<.0001§
Oxymorphone IR	0.22	0.24	7.0	(-9.8, 27.1)	0.4368
Oxycodone IR single-entity	2.17	3.21	48.2	(40.9, 55.9)	<.0001
Morphine ER ^{##}	1.12	1.13	1.4	(-6.1, 9.4)	0.7296
Oxycodone ER	5.32	3.12	-41.2	(-43.5, -38.9)	<.0001

** Sensitivity pre-period = 18 month time period after introduction of ADF oxycodone ER and prior to introduction of OPANA ER ADF (Q3 2010 –Q4 2011; 1/1/2010 –12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (Q3 2013 – Q2 2016; 7/1/2013 – 6/30/2015).

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

† Pre-post relative change reflects the percent change in the percent abuse from the pre-period to post-period.

†† Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

* OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

§ Percent change estimates for OPANA ER ADF represent comparison of abuse prevalence for OPANA ER ADF in the post-period to original OPANA ER in the pre-period.

Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

Table J9. Rates of past 30-day abuse via any route for Opana ER and comparators, per 10,000 tablets dispensed, excluding Tennessee, sensitivity pre-period vs. post-period, NAVIPPRO® study

	Sensitivity Pre-period**	Post-Period**	Percent Change [†] From pre-period/post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent change p-value
Original Opana ER ^{††}	0.176	N/A	N/A	N/A	N/A
Opana ER ADF [*]	N/A	0.082 [§]	-53.2 [§]	(-58.3, -47.5) [§]	<.0001 [§]
Oxymorphone IR	0.162	0.126	-22.3	(-34.4, -8.0)	0.0034
Oxycodone IR single-entity	0.024	0.023	-6.8	(-11.4, -1.9)	0.0072
Morphine ER ^{¶¶}	0.044	0.030	-33.4	(-38.3, -28.2)	<.0001
Oxycodone ER	0.197	0.122	-38.3	(-40.7, -35.8)	<.0001

^{**} Sensitivity pre-period = 18 month time period after introduction of ADF oxycodone ER and prior to introduction of Opana ER ADF (Q3 2010 – Q4 2011; 7/1/2010 -12/31/2011)

Post-period = three-year period after introduction of Opana ER ADF and market transition for oxymorphone products (Q3 2013 – Q2 2016; 7/1/2013 – 6/30/2016).

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

[†] Pre-post relative change reflects the percent change in the percent abuse from the pre-period to post-period.

^{††} Original Opana ER category represents brand original formulation Opana ER in the pre-period only.

^{*} Opana ER ADF category represents brand Opana ER ADF only in the post-period.

[§] Percent change estimates for Opana ER ADF represent comparison of abuse prevalence for Opana ER ADF in the post-period to original Opana ER in the pre-period.

^{¶¶} Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

Table J10. Percent of past 30-day abuse via snorting for Opana ER and comparators among abusers of the products, Tennessee only, pre-period vs. post-period, NAVIPPRO® study

	Pre-Period**	Post-Period**	Percent Change [†] from pre-period/post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent Change p-value
Original OPANA ER [‡]	82.40	N/A	N/A	N/A	N/A
OPANA ER ADF [*]	N/A	24.16 [§]	-70.7 [§]	(-73.8, -67.3) [§]	<.0001 [§]
Oxymorphone IR	67.39	45.39	-32.7	(-46.3, -15.5)	0.0006
Oxycodone IR single-entity	66.11	64.42	-2.6	(-8.5, 3.8)	0.4213
Morphine ER [¶]	26.31	22.63	-14.0	(-29.4, 4.8)	0.1342
Oxycodone ER	61.97	45.46	-26.7	(-31.6, -21.4)	<.0001

** Pre-period = three-year period prior to introduction of OPANA ER ADF (1/1/2009 -12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2016).

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

[†] Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

[‡] Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

^{*} OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

[§] Percent change estimates for OPANA ER ADF represent comparison of abuse prevalence for OPANA ER ADF in the post-period to original OPANA ER in the pre-period.

[¶] Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

Table J11. Percent of past 30-day abuse via injecting for Opana ER and comparators among abusers of the products, Tennessee only, pre-period vs. post-period, NAVIPPRO® study

	Pre-Period**	Post-Period**	Percent Change [†] from pre-period/post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent Change p-value
Original OPANA ER [‡]	14.23	N/A	N/A	N/A	N/A
OPANA ER ADF [*]	N/A	73.80 [§]	418.6 [§]	(304.0, 565.9) [§]	<.0001 [§]
Oxymorphone IR	26.09	50.40	93.2	(17.7, 217.2)	0.0092
Oxycodone IR single-entity	38.35	35.13	-8.4	(-18.0, 2.3)	0.1180
Morphine ER [¶]	70.36	68.52	-2.6	(-9.6, 4.9)	0.4873
Oxycodone ER	34.45	34.97	1.5	(-9.0, 13.2)	0.7878

** Pre-period = three-year period prior to introduction of OPANA ER ADF (1/1/2009 -12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2016).

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

[†] Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

[‡] Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

^{*} OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

[§] Percent change estimates for OPANA ER ADF represent comparison of abuse prevalence for OPANA ER ADF in the post-period to original OPANA ER in the pre-period.

[¶] Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

Table J12. Percent of past 30-day abuse via snorting for Opana ER and comparators among abusers of the products, excluding Tennessee, pre-period vs. post-period, NAVIPPRO® study

	Pre-Period**	Post-Period**	Percent Change [†] from pre-period/post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent Change p-value
Original OPANA ER [‡]	76.08	N/A	N/A	N/A	N/A
OPANA ER ADF*	N/A	20.01 [§]	-73.7 [§]	(-78.4, -68.0) [§]	<.0001 [§]
Oxymorphone IR	52.93	28.62	-45.9	(-55.8, -33.9)	<.0001
Oxycodone IR single-entity	57.21	45.98	-19.6	(-23.2, -15.9)	<.0001
Morphine ER [¶]	31.61	25.98	-17.8	(-25.9, -8.9)	0.0002
Oxycodone ER	48.14	30.79	-36.1	(-39.1, -32.9)	<.0001

** Pre-period = three-year period prior to introduction of OPANA ER ADF (1/1/2009 -12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2016).

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

[†] Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

[‡] Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

* OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

[§] Percent change estimates for OPANA ER ADF represent comparison of abuse prevalence for OPANA ER ADF in the post-period to original OPANA ER in the pre-period.

[¶] Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

Table J13. Percent of past 30-day abuse via injecting for Opana ER and comparators among abusers of the products, excluding Tennessee, pre-period vs. post-period, NAVIPPRO® study

	Pre-Period**	Post-Period**	Percent Change [†] from pre-period/post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent Change p-value
Original OPANA ER [‡]	16.76	N/A	N/A	N/A	N/A
OPANA ER ADF [*]	N/A	54.13 [§]	223.0 [§]	(174.0, 280.7) [§]	<.0001 [§]
Oxymorphone IR	35.87	56.34	57.1	(30.3, 89.4)	<.0001
Oxycodone IR single-entity	31.50	30.73	-2.5	(-9.9, 5.6)	0.5412
Morphine ER [¶]	45.16	49.40	9.4	(2.4, 16.8)	0.0075
Oxycodone ER	27.04	26.02	-3.8	(-9.8, 2.7)	0.2451

** Pre-period = three-year period prior to introduction of OPANA ER ADF (1/1/2009 -12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2016).

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

[†] Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

[‡] Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

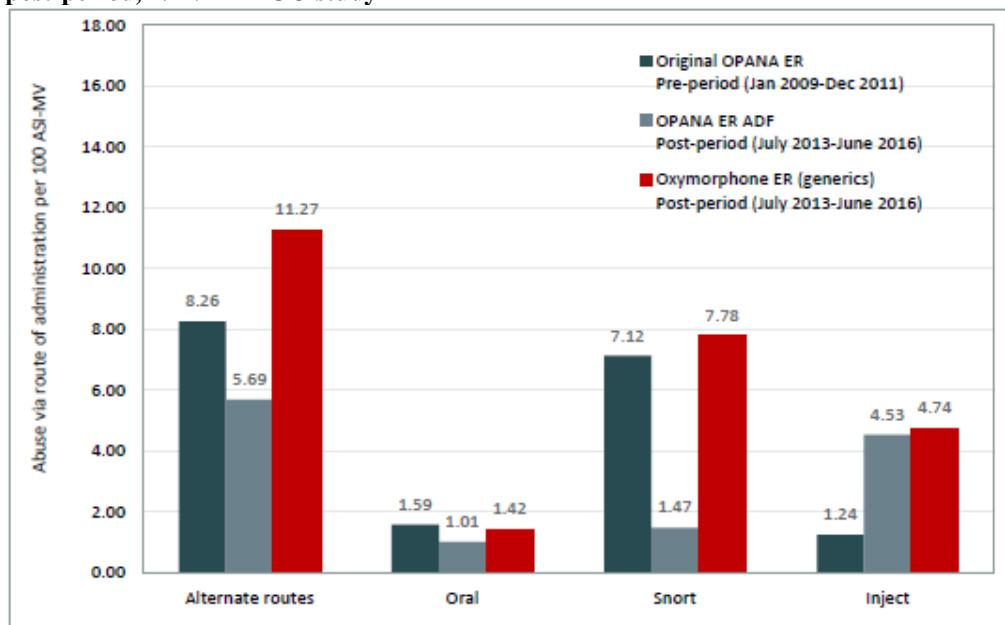
^{*} OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

[§] Percent change estimates for OPANA ER ADF represent comparison of abuse prevalence for OPANA ER ADF in the post-period to original OPANA ER in the pre-period.

[¶] Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

Figure J1. Prevalence of past 30-day abuse via specific routes of administration reported for OP, OPR, and generic oxymorphone ER per 100 ASI-MV® assessments, Tennessee only, pre-period vs. post-period, NAVIPPRO® study

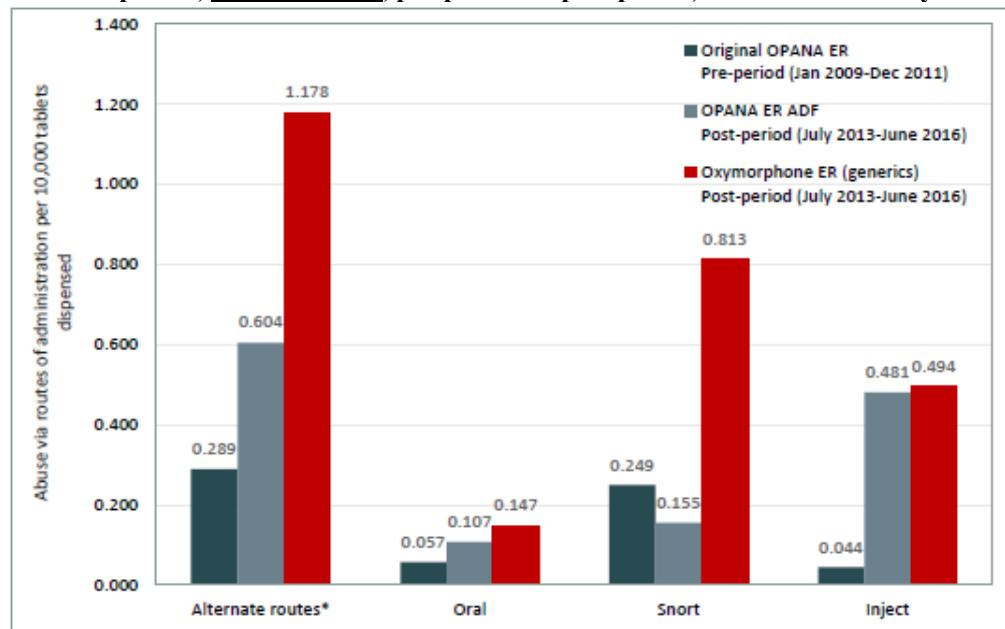


* alternate routes = composite category for all routes of administration excluding swallowed whole

** Results for OPANA ER are as presented original OPANA ER in pre-period and OPANA ER ADF in the post-period

Source: NAVIPPRO® study report (December 2016)

Figure J2. Rates of abuse via specific routes for OP, OPR, and generic oxymorphone ER per 10,000 tablets dispensed, Tennessee only, pre-period vs. post-period, NAVIPPRO® study



* alternate routes = all routes of administration excluding swallowed whole

**Results for OPANA ER are as presented original OPANA ER in pre-period and OPANA ER ADF in the post-period

Source: NAVIPPRO® study report (December 2016)

Table J14. Prevalence of past 30-day abuse via snorting for Opana ER and comparators per 100 ASI-MV® assessments, Tennessee only, NAVIPPRO® study

	Pre-Period**	Post-Period**	Percent Change [†] from pre-period/ post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent Change p-value
Original OPANA ER [‡]	7.12	N/A	N/A	N/A	N/A
OPANA ER ADF [*]	N/A	1.47	-79.4 [§]	(-82.4, -75.9) [§]	<.0001 [§]
Oxymorphone IR	0.67	0.97	43.6	(-1.1, 108.3)	0.0569
Oxycodone IR single-entity	8.02	12.61	57.2	(41.7, 74.4)	<.0001
Morphine ER	2.01	1.66	-17.6	(-34.4, 3.6)	0.0974
Oxycodone ER	11.50	5.15	-55.2	(-59.5, -50.5)	<.0001

** Pre-period = three-year period prior to introduction of OPANA ER ADF (1/1/2009 -12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2016).

Note that the transition period of market change for oxymorphone products (1/1/2012–6/30/2013) is excluded from analyses.

† Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

‡ Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

* OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

§ Percent change estimates for OPANA ER ADF represent comparison of abuse prevalence for OPANA ER ADF in the post-period to original OPANA ER in the pre-period.

|| Morphine ER = all extended-release morphine products excluding EMBEDA

Source: NAVIPPRO® study report (December 2016)

Table J15. Prevalence of past 30-day abuse via injecting for Opana ER and comparators per 100 ASI-MV® assessments, Tennessee only, NAVIPPRO® study

	Pre-Period**	Post-Period**	Percent Change [†] from pre-period/ post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent Change p-value
Original OPANA ER [‡]	1.24	N/A	N/A	N/A	N/A
OPANA ER ADF [*]	N/A	4.53	264.6 [§]	(177.4, 379.1) [§]	<.0001 [§]
Oxymorphone IR	0.27	1.07	299.8	(127.0, 604.3)	<.0001
Oxycodone IR single-entity	4.66	6.85	46.8	(27.6, 68.8)	<.0001
Morphine ER	5.37	5.09	-5.2	(-17.2, 8.5)	0.4377
Oxycodone ER	6.30	3.96	-37.2	(-45.0, -28.3)	<.0001

** Pre-period = three-year period prior to introduction of OPANA ER ADF (1/1/2009 -12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2016).

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

† Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

‡ Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

* OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

§ Percent change estimates for OPANA ER ADF represent comparison of abuse prevalence for OPANA ER ADF in the post-period to original OPANA ER in the pre-period.

|| Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

Table J16. Rates of past 30-day abuse via snorting for Opana ER and comparators per 10,000 tablets dispensed, Tennessee only, NAVIPPRO® study

	Pre-Period**	Post-Period**	Percent Change [†] from pre-period/ post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent change p-value
Original OPANA ER ^{††}	0.249	N/A	N/A	N/A	N/A
OPANA ER ADF [*]	N/A	0.155 [§]	-37.6 [§]	(-46.7, -27.0) [§]	<.0001 [§]
Oxymorphone IR	0.268	0.292	8.9	(-25.4, 59.1)	0.8581
Oxycodone IR single-entity	0.033	0.044	31.8	(18.3, 46.9)	<.0001
Morphine ER ^{§§}	0.017	0.020	16.1	(-7.8, 46.0)	0.2044
Oxycodone ER	0.114	0.111	-2.3	(-12.0, 8.5)	0.6635

** Pre-period = three-year period prior to introduction of OPANA ER ADF (1/1/2009 -12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2016).

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

† Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

†† Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

* OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

§ Percent change estimates for OPANA ER ADF represent comparison of abuse prevalence for OPANA ER ADF in the post-period to original OPANA ER in the pre-period.

§§ Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

Table J17. Rates of past 30-day abuse via injecting for Opana ER and comparators per 10,000 tablets dispensed, Tennessee only, NAVIPPRO® study

	Pre-Period**	Post-Period**	Percent Change [†] from pre-period/post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent change p-value
Original OPANA ER ^{††}	0.044	N/A	N/A	N/A	
OPANA ER ADF [*]	N/A	0.481 [§]	995.2 [§]	(740.0, 1,327.9) [§]	<.0001 [§]
Oxymorphone IR	0.104	0.317	205.8	(71.0, 447.0)	0.0002
Oxycodone IR single-entity	0.020	0.024	21.8	(5.7, 40.4)	0.0084
Morphine ER ^{##}	0.047	0.062	32.9	(15.7, 52.5)	<.0001
Oxycodone ER	0.063	0.085	35.2	(18.3, 54.7)	<.0001

** Pre-period = three-year period prior to introduction of OPANA ER ADF (1/1/2009 -12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2016).

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

† Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

†† Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

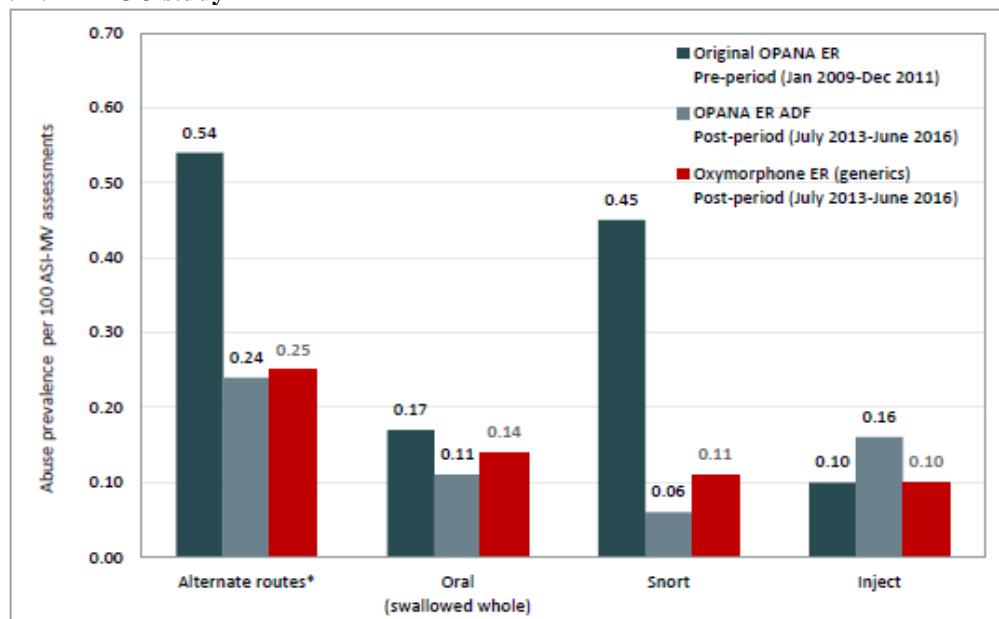
* OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

§ Percent change estimates for OPANA ER ADF represent comparison of abuse prevalence for OPANA ER ADF in the post-period to original OPANA ER in the pre-period.

Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

Figure J3. Prevalence of past 30-day abuse via specific routes for OP, OPR, and generic oxymorphone ER per 100 ASI-MV® assessments, excluding Tennessee, pre-period vs. post-period, NAVIPPRO® study

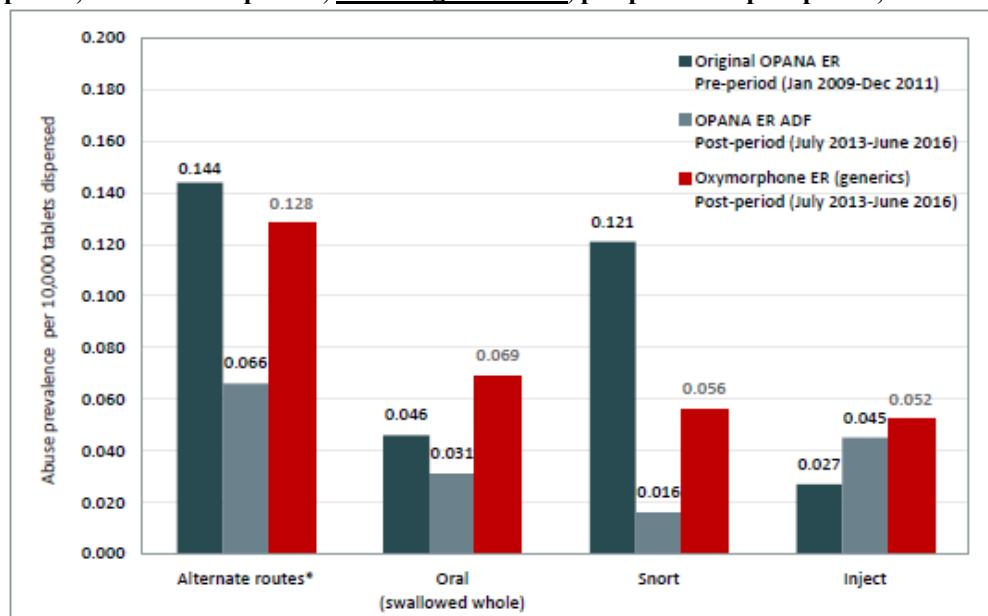


* Alternate routes = composite category for all routes of administration excluding swallowed whole

**Results for OPANA ER are as presented original OPANA ER in pre-period and OPANA ER ADF in the post-period

Source: NAVIPPRO® study report (December 2016)

Figure J4. Rates of past 30-day abuse via specific routes for OP, OPR, and generic oxymorphone ER per 10,000 tablets dispensed, excluding Tennessee, pre-period vs. post-period, NAVIPPRO® study



* Alternate routes = composite category for all routes of administration excluding swallowed whole

**Results for OPANA ER are as presented original OPANA ER in pre-period and OPANA ER ADF in the post-period

Source: NAVIPPRO® study report (December 2016)

Table J18. Prevalence of past 30-day abuse via snorting for Opana ER and comparators per 100 ASI-MV® assessments, excluding Tennessee, NAVIPPRO® study

	Pre-Period**	Post-Period**	Percent Change [†] from pre-period/post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent Change p-value
Original Opana ER [‡]	0.45	N/A	N/A	N/A	N/A
Opana ER ADF [*]	N/A	0.06 [§]	-87.0 [§]	(-89.6, -83.8) [§]	<.0001 [§]
Oxymorphone IR	0.08	0.07	-14.4	(-33.6, 10.4)	0.2321
Oxycodone IR single-entity	0.80	1.47	84.0	(72.4, 96.4)	<.0001
Morphine ER ^{##}	0.33	0.29	-10.6	(-21.0, 1.3)	0.0790
Oxycodone ER	2.51	0.95	-62.1	(-84.4, -59.8)	<.0001

** Pre-period = three-year period prior to introduction of Opana ER ADF (1/1/2009 -12/31/2011)

Post-period = three-year period after introduction of Opana ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2016).

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

† Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

‡ Original Opana ER category represents brand original formulation Opana ER in the pre-period only.

* Opana ER ADF category represents brand Opana ER ADF only in the post-period.

§ Percent change estimates for Opana ER ADF represent comparison of abuse prevalence for Opana ER ADF in the post-period to original Opana ER in the pre-period.

Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

Table J19. Prevalence of past 30-day abuse via injecting for Opana ER and comparators per 100 ASI-MV® assessments, excluding Tennessee, NAVIPPRO® study

	Pre-Period**	Post-Period**	Percent Change [†] from pre-period/post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent Change p-value
Original Opana ER [‡]	0.10	N/A	N/A	N/A	N/A
Opana ER ADF [*]	N/A	0.16 [§]	56.1 [§]	(28.7, 89.4) [§]	<.0001 [§]
Oxymorphone IR	0.06	0.13	136.0	(85.4, 200.5)	<.0001
Oxycodone IR single-entity	0.46	0.96	108.3	(91.4, 126.6)	<.0001
Morphine ER	0.47	0.56	17.8	(8.9, 29.8)	0.0010
Oxycodone ER	1.45	0.78	-45.8	(-49.5, -41.8)	<.0001

** Pre-period = three-year period prior to introduction of Opana ER ADF (1/1/2009 -12/31/2011)

Post-period = three-year period after introduction of Opana ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2016).

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

† Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

‡ Original Opana ER category represents brand original formulation Opana ER in the pre-period only.

* Opana ER ADF category represents brand Opana ER ADF only in the post-period.

§ Percent change estimates for Opana ER ADF represent comparison of abuse prevalence for Opana ER ADF in the post-period to original Opana ER in the pre-period.

|| Morphine ER = all extended-release morphine products excluding EMBEDA

Source: NAVIPPRO® study report

Table J20. Rates of past 30-day abuse via snorting for Opana ER and comparators per 10,000 tablets dispensed, excluding Tennessee, NAVIPPRO® study

	Pre-Period**	Post-Period**	Percent Change [†] from pre-period/post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent change p-value
Original OPANA ER ^{‡‡}	0.121	N/A	N/A	N/A	N/A
OPANA ER ADF [§]	N/A	0.016 [§]	-86.7 [§]	(-89.4, -83.3) [§]	<.0001 [§]
Oxymorphone IR	0.067	0.035	-46.9	(-58.8, -31.5)	<.0001
Oxycodone IR single-entity	0.011	0.010	-8.9	(-14.6, -2.7)	0.0051
Morphine ER ^{¶¶}	0.014	0.008	-47.1	(-53.2, -40.2)	<.0001
Oxycodone ER	0.088	0.037	-57.8	(-60.3, -55.3)	<.0001

** Pre-period = three-year period prior to introduction of OPANA ER ADF (1/1/2009 -12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2016).

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

† Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

‡‡ Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

§ OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

¶ Percent change estimates for OPANA ER ADF represent comparison of abuse prevalence for OPANA ER ADF in the post-period to original OPANA ER in the pre-period.

¶¶ Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

Table J21. Rates of past 30-day abuse via injecting for Opana ER and comparators per 10,000 tablets dispensed, excluding Tennessee, NAVIPPRO® study

	Pre-Period**	Post-Period**	Percent Change [†] from pre-period/post-period (%)	Percent Change 95% Confidence Interval (lower CI, upper CI)	Percent change p-value
Original OPANA ER ^{††}	0.027	N/A	N/A	N/A	N/A
OPANA ER ADF [‡]	N/A	0.045 [§]	65.6 [§]	(37.0, 100.3) [§]	<.0001 [§]
Oxymorphone IR	0.047	0.071	52.5	(20.7, 92.8)	0.0004
Oxycodone IR single-entity	0.007	0.007	4.4	(-4.0, 13.4)	0.3147
Morphine ER ^{¶¶}	0.021	0.015	-28.3	(-34.7, -21.4)	<.0001
Oxycodone ER	0.051	0.031	-38.2	(-42.3, -33.9)	<.0001

** Pre-period = three-year period prior to introduction of OPANA ER ADF (1/1/2009 -12/31/2011)

Post-period = three-year period after introduction of OPANA ER ADF and market transition for oxymorphone products (7/1/2013 – 6/30/2016).

Note that the transition period of market change for oxymorphone products (1/1/2012 -6/30/2013) is excluded from analyses.

† Pre-post percent change reflects the percent change in the percent abuse from the pre-period to post-period.

†† Original OPANA ER category represents brand original formulation OPANA ER in the pre-period only.

‡ OPANA ER ADF category represents brand OPANA ER ADF only in the post-period.

§ Percent change estimates for OPANA ER ADF represent comparison of abuse prevalence for OPANA ER ADF in the post-period to original OPANA ER in the pre-period.

¶ Morphine ER = all extended-release morphine products excluding EMBEDA.

Source: NAVIPPRO® study report (December 2016)

4.11 APPENDIX K. ADDITIONAL TABLES FROM RADARS® POISON CENTER STUDY

Table K1. Intentional abuse exposure population rate per 100,000 via oral routes of administration—comparison of means, RADARS® Poison Center Study, Q1 2010 – Q2 2016

Drug Group	Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)	p-value for Percentage Change	Interaction p-value
Opana ER	Pre ORF/Pre CRF	0.0029 (0.0019,0.0045)	Post ORF/Post CRF over Pre ORF/Pre CRF	-35.2% (-60.9%,7.4%)	0.092	.
	Post ORF/Pre CRF	0.0079 (0.0064,0.0097)	Post ORF/Pre CRF over Pre ORF/Pre CRF	169.7% (67.3%,334.8%)	<0.001	.
	Post ORF/Post CRF	0.0019 (0.0015,0.0025)	Post ORF/Post CRF over Post ORF/Pre CRF	-76.0% (-82.7%,-66.5%)	<0.001	.
ER Morphine	Pre ORF/Pre CRF	0.0085 (0.0063,0.0115)	Post ORF/Post CRF over Pre ORF/Pre CRF	-49.5% (-65.0%,-27.1%)	<0.001	0.434
	Post ORF/Pre CRF	0.0085 (0.0067,0.0108)	Post ORF/Pre CRF over Pre ORF/Pre CRF	0.1% (-31.7%,46.8%)	0.995	0.001
	Post ORF/Post CRF	0.0043 (0.0035,0.0053)	Post ORF/Post CRF over Post ORF/Pre CRF	-49.6% (-63.1%,-31.1%)	<0.001	0.001
ER Oxycodone	Pre ORF/Pre CRF	0.0288 (0.0247,0.0337)	Post ORF/Post CRF over Pre ORF/Pre CRF	-66.5% (-72.7%,-58.9%)	<0.001	0.018
	Post ORF/Pre CRF	0.0211 (0.0183,0.0242)	Post ORF/Pre CRF over Pre ORF/Pre CRF	-27.0% (-40.8%,-10.0%)	0.003	<0.001
	Post ORF/Post CRF	0.0097 (0.0085,0.0110)	Post ORF/Post CRF over Post ORF/Pre CRF	-54.1% (-62.1%,-44.4%)	<0.001	<0.001

Source: Sponsor's updated response to July 11, 2016 Information Request (November 2016)

Table K2. Intentional abuse exposure population rate per 100,000 via non-oral routes of administration—comparison of means, RADARS® Poison Center Study, Q1 2010 – Q2 2016

Drug Group	Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)	p-value for Percentage Change	Interaction p-value
Opana ER	Pre ORF/Pre CRF	0.0023 (0.0013,0.0040)	Post ORF/Post CRF over Pre ORF/Pre CRF	44.0% (-22.0%,165.6%)	0.244	-
	Post ORF/Pre CRF	0.0091 (0.0073,0.0113)	Post ORF/Pre CRF over Pre ORF/Pre CRF	301.4% (118.5%,637.2%)	<0.001	-
	Post ORF/Post CRF	0.0033 (0.0026,0.0041)	Post ORF/Post CRF over Post ORF/Pre CRF	-64.1% (-73.9%,-50.7%)	<0.001	-
ER Morphine	Pre ORF/Pre CRF	0.0031 (0.0019,0.0048)	Post ORF/Post CRF over Pre ORF/Pre CRF	-57.6% (-76.0%,-25.3%)	0.003	0.004
	Post ORF/Pre CRF	0.0023 (0.0015,0.0034)	Post ORF/Pre CRF over Pre ORF/Pre CRF	-25.2% (-59.3%,37.4%)	0.349	<0.001
	Post ORF/Post CRF	0.0013 (0.0009,0.0018)	Post ORF/Post CRF over Post ORF/Pre CRF	-43.4% (-66.6%,-4.0%)	0.035	0.147
ER Oxycodone	Pre ORF/Pre CRF	0.0213 (0.0177,0.0256)	Post ORF/Post CRF over Pre ORF/Pre CRF	-81.4% (-86.0%,-75.5%)	<0.001	<0.001
	Post ORF/Pre CRF	0.0107 (0.0088,0.0131)	Post ORF/Pre CRF over Pre ORF/Pre CRF	-49.6% (-61.6%,-33.8%)	<0.001	<0.001
	Post ORF/Post CRF	0.0039 (0.0032,0.0049)	Post ORF/Post CRF over Post ORF/Pre CRF	-63.2% (-72.4%,-50.8%)	<0.001	0.908

Source: Sponsor's updated response to July 11, 2016 Information Request (November 2016)

Table K3. Intentional abuse exposure dosing units dispensed rate per 100,000 via oral routes of administration—comparison of means, RADARS® Poison Center Study, Q1 2010 – Q2 2016

Drug Group	Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)	p-value for Percentage Change	Interaction p-value
Opana ER	Pre ORF/Pre CRF	0.0781 (0.0535,0.1140)	Post ORF/Post CRF over Pre ORF/Pre CRF	-20.0% (-48.6%,24.6%)	0.324	-
	Post ORF/Pre CRF	0.1381 (0.1157,0.1649)	Post ORF/Pre CRF over Pre ORF/Pre CRF	76.9% (16.5%,168.6%)	0.007	-
	Post ORF/Post CRF	0.0625 (0.0497,0.0786)	Post ORF/Post CRF over Post ORF/Pre CRF	-54.7% (-66.1%,-39.5%)	<0.001	-
ER Morphine	Pre ORF/Pre CRF	0.0252 (0.0188,0.0341)	Post ORF/Post CRF over Pre ORF/Pre CRF	-58.0% (-70.9%,-39.4%)	<0.001	0.028
	Post ORF/Pre CRF	0.0237 (0.0187,0.0298)	Post ORF/Pre CRF over Pre ORF/Pre CRF	-6.1% (-35.8%,37.5%)	0.746	0.028
	Post ORF/Post CRF	0.0108 (0.0086,0.0130)	Post ORF/Post CRF over Post ORF/Pre CRF	-55.3% (-67.2%,-39.0%)	<0.001	0.956
ER Oxycodone	Pre ORF/Pre CRF	0.0614 (0.0524,0.0720)	Post ORF/Post CRF over Pre ORF/Pre CRF	-36.9% (-48.7%,-22.2%)	<0.001	0.342
	Post ORF/Pre CRF	0.0607 (0.0526,0.0700)	Post ORF/Pre CRF over Pre ORF/Pre CRF	-1.2% (-20.3%,22.4%)	0.912	0.015
	Post ORF/Post CRF	0.0388 (0.0339,0.0444)	Post ORF/Post CRF over Post ORF/Pre CRF	-36.1% (-47.5%,-22.2%)	<0.001	0.053

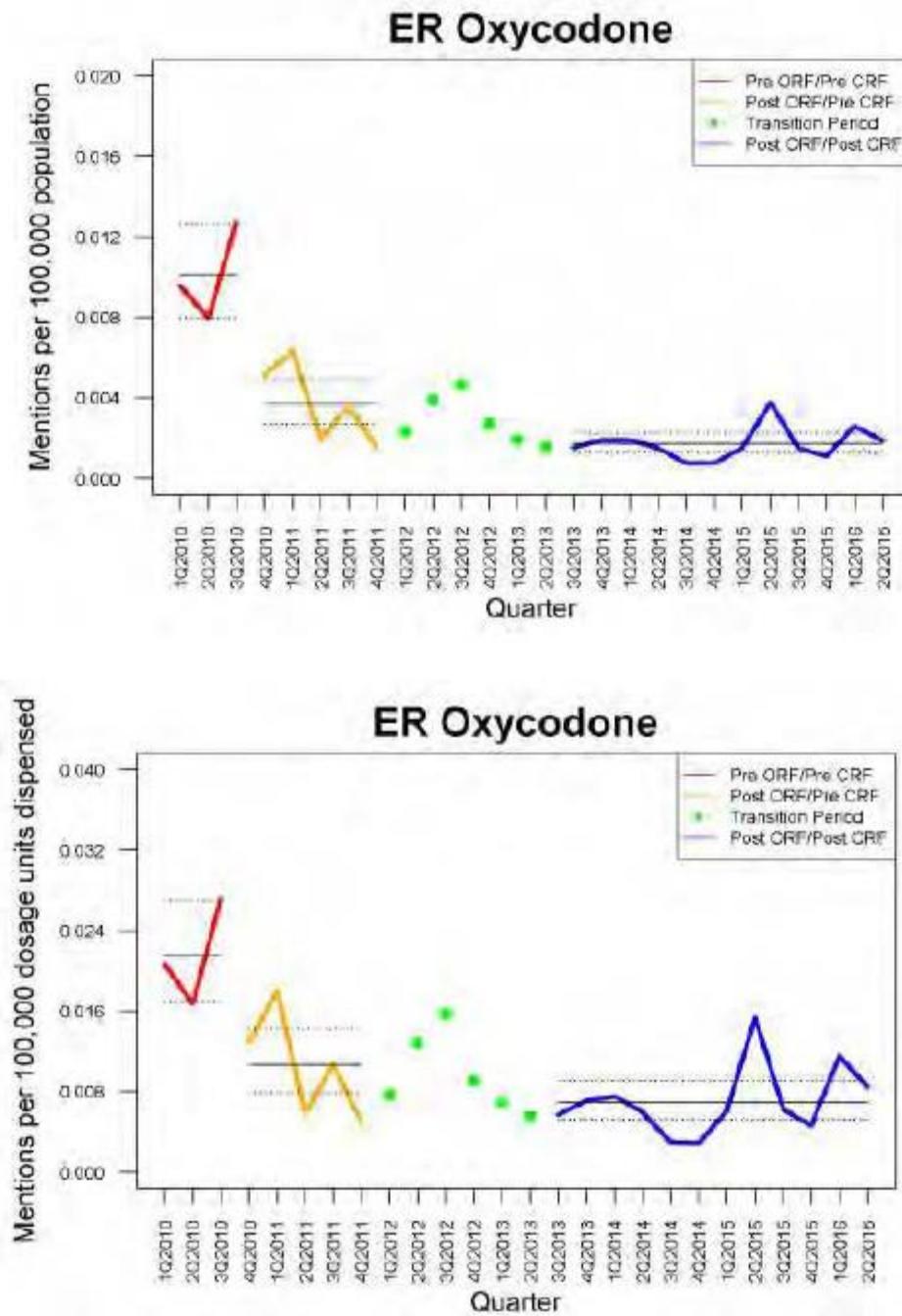
Source: Sponsor's updated response to July 11, 2016 Information Request (November 2016)

Table K4. Intentional abuse exposure dosing units dispensed rate per 100,000 via non-oral routes of administration—comparison of means, RADARS® Poison Center Study, Q1 2010 – Q2 2016

Drug Group	Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)	p-value for Percentage Change	Interaction p-value
Opana ER	Pre ORF/Pre CRF	0.0603 (0.0364,0.1000)	Post ORF/Post CRF over Pre ORF/Pre CRF	77.8% (3.1%,206.9%)	0.039	-
	Post ORF/Pre CRF	0.1588 (0.1308,0.1929)	Post ORF/Pre CRF over Pre ORF/Pre CRF	163.2% (53.2%,352.4%)	<0.001	-
	Post ORF/Post CRF	0.1073 (0.0874,0.1318)	Post ORF/Post CRF over Post ORF/Pre CRF	-32.4% (-49.1%,-10.4%)	0.007	-
ER Morphine	Pre ORF/Pre CRF	0.0091 (0.0057,0.0143)	Post ORF/Post CRF over Pre ORF/Pre CRF	-64.8% (-80.2%,-37.4%)	<0.001	<0.001
	Post ORF/Pre CRF	0.0064 (0.0042,0.0096)	Post ORF/Pre CRF over Pre ORF/Pre CRF	-29.8% (-62.1%,29.9%)	0.260	0.002
	Post ORF/Post CRF	0.0032 (0.0023,0.0045)	Post ORF/Post CRF over Post ORF/Pre CRF	-49.8% (-70.6%,-14.3%)	0.012	0.338
ER Oxycodone	Pre ORF/Pre CRF	0.0453 (0.0383,0.0535)	Post ORF/Post CRF over Pre ORF/Pre CRF	-65.0% (-72.8%,-55.0%)	<0.001	<0.001
	Post ORF/Pre CRF	0.0309 (0.0258,0.0370)	Post ORF/Pre CRF over Pre ORF/Pre CRF	-31.7% (-46.6%,-12.7%)	0.002	<0.001
	Post ORF/Post CRF	0.0158 (0.0131,0.0191)	Post ORF/Post CRF over Post ORF/Pre CRF	-48.7% (-60.5%,-33.4%)	<0.001	0.160

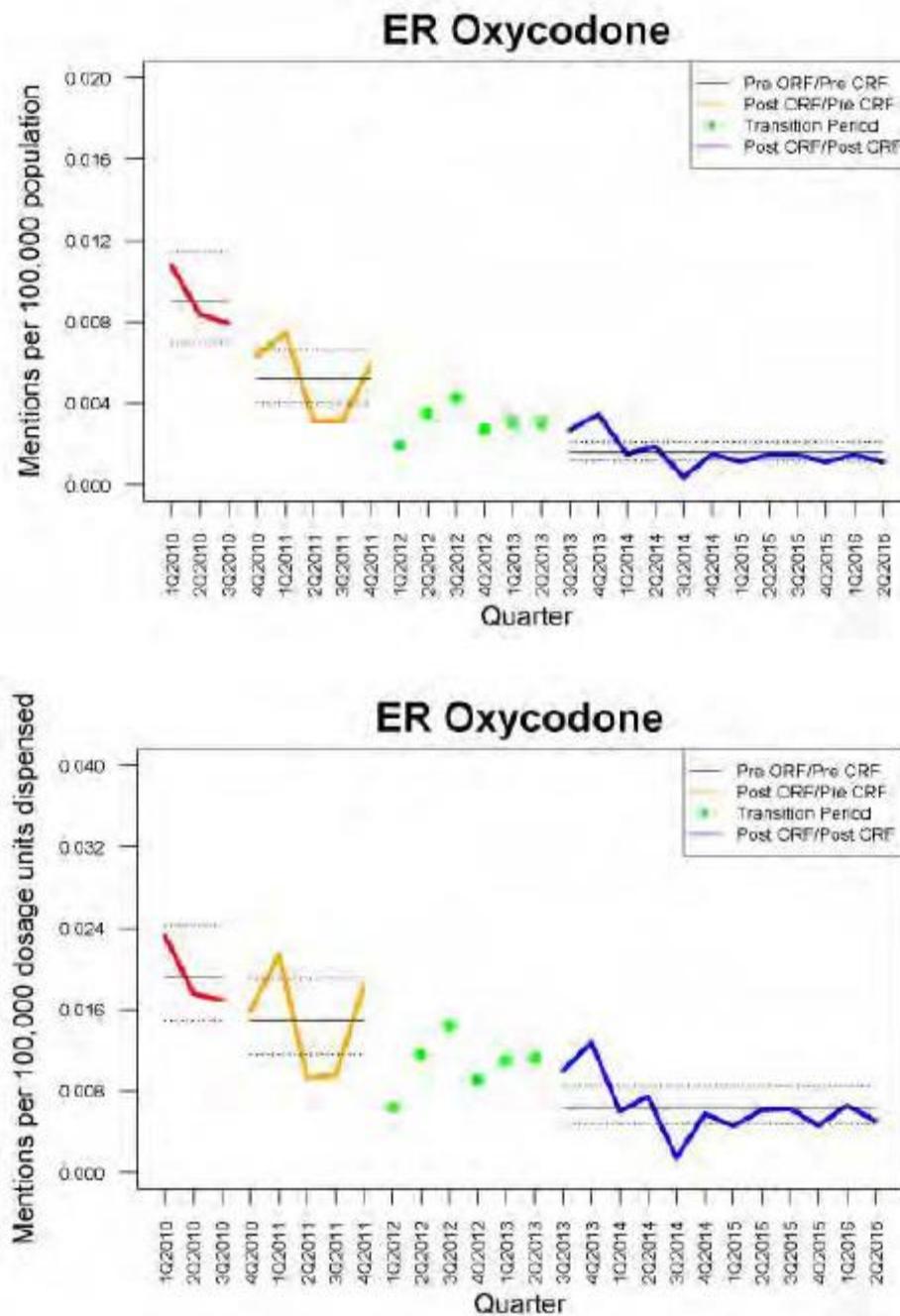
Source: Sponsor's updated response to July 11, 2016 Information Request (November 2016)

Figure K1. Oxycodone ER intentional abuse exposures via the inhalation route, per 100,000 population (upper panel) and per 100,000 dosing units (lower panel), RADARS® Poison Center study, Q1 2010 – Q2 2016



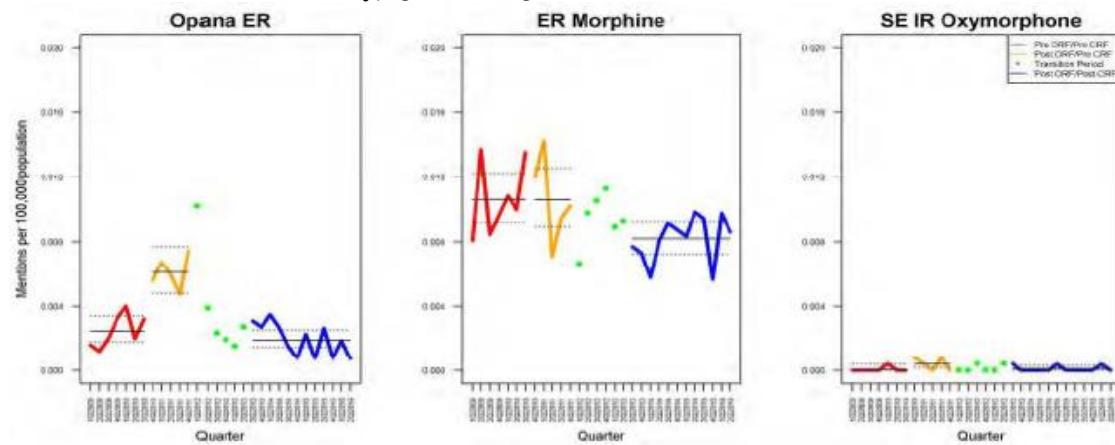
Source: Sponsor's updated response to June 1, 2016 FDA Information Request (November 2016)

Figure K2. Oxycodone ER intentional abuse exposures via the injection route, per 100,000 population (upper panel) and per 100,000 dosing units (lower panel), RADARS® Poison Center study, Q1 2010 – Q2 2016



Source: Sponsor's updated response to June 1, 2016 FDA Information Request (November 2016)

Figure K3. Major medical outcomes and death mean rates per 100,000 population covered, RADARS® Poison Center study, Q1 2010 – Q2 2016



Source: RADARS® PC study report (November 2016)

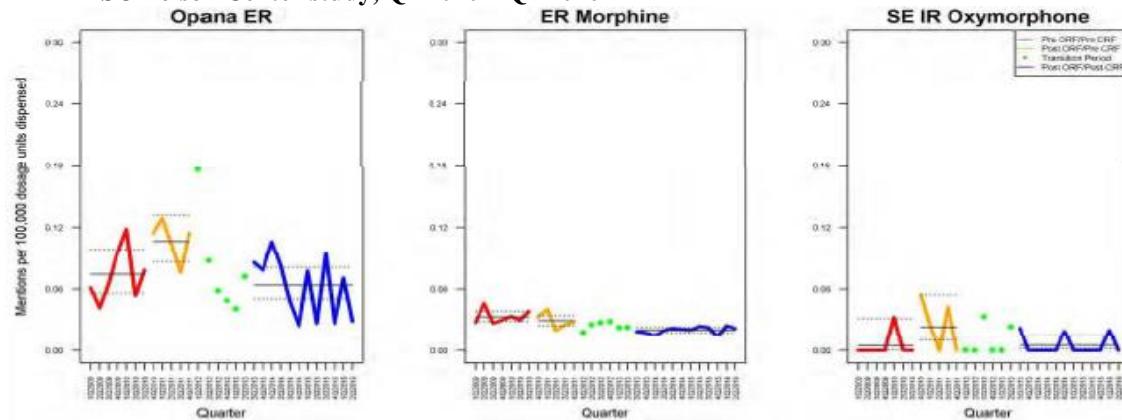
Table K5. Major medical outcomes and death rates per 100,000 population covered—comparison of means model, RADARS® Poison Center study, Q1 2010 – Q2 2016

Drug Group	Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)	p-value for Percentage Change	Interaction p-value
Opana ER	Pre ORF/Pre CRF	0.0025 (0.0018, 0.0034)	Post ORF/Post CRF over Pre ORF/Pre CRF	-21.7% (-48.1%, 18.0%)	0.242	N/A
	Post ORF/Pre CRF	0.0061 (0.0048, 0.0077)	Post ORF/Pre CRF over Pre ORF/Pre CRF	146.7% (66.7%, 265.2%)	<0.001	N/A
	Post ORF/Post CRF	0.0019 (0.0015, 0.0025)	Post ORF/Post CRF over Post ORF/Pre CRF	-66.3% (-77.7%, -54.8%)	<0.001	N/A
ER Morphine	Pre ORF/Pre CRF	0.0106 (0.0092, 0.0122)	Post ORF/Post CRF over Pre ORF/Pre CRF	-22.8% (-36.0%, -6.7%)	0.007	0.954
	Post ORF/Pre CRF	0.0106 (0.0089, 0.0125)	Post ORF/Pre CRF over Pre ORF/Pre CRF	-0.2% (-20.1%, 24.7%)	0.986	<0.001
	Post ORF/Post CRF	0.0082 (0.0072, 0.0092)	Post ORF/Post CRF over Post ORF/Pre CRF	-22.6% (-37.2%, -4.6%)	0.016	<0.001
SE IR Oxymorphone	Pre ORF/Pre CRF	0.0001 (0.0000, 0.0004)	Post ORF/Post CRF over Pre ORF/Pre CRF	65.5% (-80.8%, 1326%)	0.646	0.503
	Post ORF/Pre CRF	0.0004 (0.0002, 0.0009)	Post ORF/Pre CRF over Pre ORF/Pre CRF	588.9% (-10.7%, 5215%)	0.064	0.333
	Post ORF/Post CRF	0.0001 (0.0000, 0.0003)	Post ORF/Post CRF over Post ORF/Pre CRF	-76.0% (-93.8%, -6.2%)	0.040	0.699

Source:

Source: RADARS® PC study report (November 2016)

Figure K4. Major medical outcomes and death mean rates per 100,000 dosing units dispensed, RADARS® Poison Center study, Q1 2010 – Q2 2016



Source: RADARS® PC study report (November 2016)

Table K6. Major medical outcomes and death rates per 100,000 dosing units dispensed—comparison of means model, RADARS® Poison Center study, Q1 2010 – Q2 2016

Drug Group	Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)	p-value for Percentage Change	Interaction p-value
Opana ER	Pre ORF/Pre CRF	0.0742 (0.0559,0.0963)	Post ORF/Post CRF over Pre ORF/Pre CRF	-14.3% (-40.7%, 23.9%)	0.412	N/A
	Post ORF/Pre CRF	0.1063 (0.0861,0.1313)	Post ORF/Pre CRF over Pre ORF/Pre CRF	43.4% (0.8%, 104.0%)	0.045	N/A
	Post ORF/Post CRF	0.0636 (0.0501,0.0805)	Post ORF/Post CRF over Post ORF/Pre CRF	-40.2% (-56.5%, -17.9%)	0.001	N/A
ER Morphine	Pre ORF/Pre CRF	0.0331 (0.0287,0.0382)	Post ORF/Post CRF over Pre ORF/Pre CRF	-39.2% (-49.6%, -26.8%)	<0.001	0.103*
	Post ORF/Pre CRF	0.0293 (0.0248,0.0347)	Post ORF/Pre CRF over Pre ORF/Pre CRF	-11.4% (-28.9%, 10.3%)	0.279	0.023
	Post ORF/Post CRF	0.0201 (0.0179,0.0227)	Post ORF/Post CRF over Post ORF/Pre CRF	-31.4% (-44.2%, -15.7%)	<0.001	0.473
SE IR Oxymorphone	Pre ORF/Pre CRF	0.0046 (0.0007,0.0310)	Post ORF/Post CRF over Pre ORF/Pre CRF	8.0% (-88.0%, 869.5%)	0.945	0.839
	Post ORF/Pre CRF	0.0231 (0.0099,0.0540)	Post ORF/Pre CRF over Pre ORF/Pre CRF	397.1% (-38.0%, 3689%)	0.131	0.249
	Post ORF/Post CRF	0.0050 (0.0017,0.0150)	Post ORF/Post CRF over Post ORF/Pre CRF	-78.3% (-94.6%, -13.0%)	0.031	0.164

Source: RADARS® PC study report (November 2016)

Table K7. Major medical outcomes and death rates per 100,000 population covered—interrupted time series model, RADARS® Poison Center study, Q1 2010 – Q2 2016

Drug Group	Period	Parameter	Estimate (95% CI)	Percentage change (95% CI)	p-value for Percentage Change	Interaction p-value
Opana ER	Pre CRF	Intercept	0.0192 (0.0108,0.0343)	Reference	N/A	N/A
		Slope	1.1442 (1.0875,1.2038)	Reference	N/A	N/A
	Post CRF	Intercept	0.0031 (0.0021,0.0046)	-83.7% (-91.9%, -67.4%)	<0.001	N/A
		Slope	0.9071 (0.8466,0.9718)	-20.7% (-27.2%, -13.6%)	<0.001	N/A
ER Morphine	Pre CRF	Intercept	0.0108 (0.0072,0.0163)	Reference	N/A	N/A
		Slope	1.0017 (0.9704,1.0341)	Reference	N/A	N/A
	Post CRF	Intercept	0.0074 (0.0059,0.0094)	-31.2% (-57.2%, 10.5%)	0.122	<0.001
		Slope	1.0171 (0.9818,1.0537)	1.5% (-3.2%, 6.5%)	0.530	<0.001
SE IR Oxymorphone	Pre CRF	Intercept	0.0018 (0.0001,0.0305)	Reference	N/A	N/A
		Slope	1.2153 (0.9368,1.5790)	Reference	N/A	N/A
	Post CRF	Intercept	0.0001 (0.0000,0.0009)	-93.5% (-99.8%, 102.5%)	0.119	0.609
		Slope	0.9562 (0.6904,1.3242)	-21.4% (-48.2%, 19.3%)	0.258	0.969

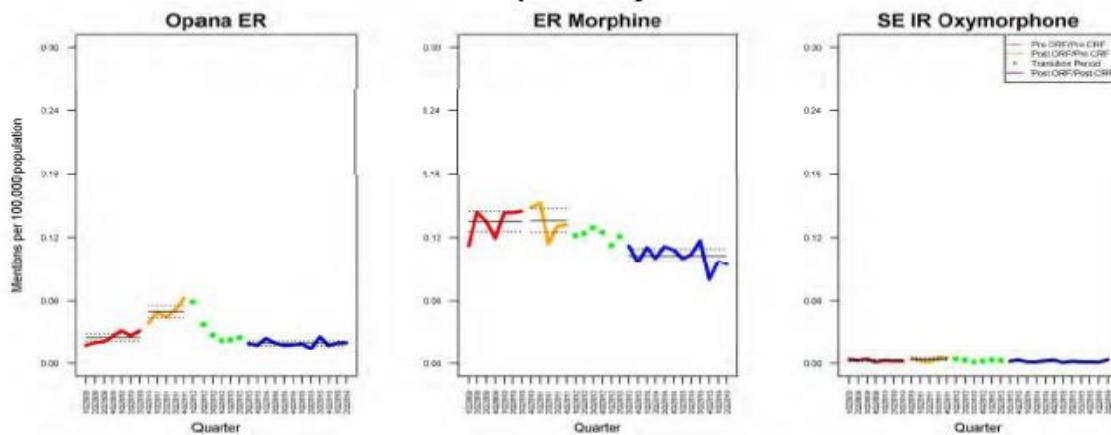
Source: RADARS® PC study report (November 2016)

Table K8. Major medical outcomes and death rates per 100,000 dosing units dispensed—interrupted time series model, RADARS® Poison Center study, Q1 2010 – Q2 2016

Drug Group	Period	Parameter	Estimate (95% CI)	Percentage change (95% CI)	p-value for Percentage Change	Interaction p-value
Opana ER	Pre CRF	Intercept	0.1571 (0.0879,0.2807)	Reference	N/A	N/A
		Slope	1.0489 (0.9968,1.1037)	Reference	N/A	N/A
	Post CRF	Intercept	0.0882 (0.0602,0.1292)	-43.8% (-72.0%, 12.5%)	0.104*	N/A
		Slope	0.9338 (0.8715,1.0006)	-11.0% (-18.3%, -3.0%)	0.008	N/A
ER Morphine	Pre CRF	Intercept	0.0248 (0.0166,0.0370)	Reference	N/A	N/A
		Slope	0.9808 (0.9508,1.0118)	Reference	N/A	N/A
	Post CRF	Intercept	0.0181 (0.0144,0.0227)	-27.0% (-54.0%, 16.0%)	0.183	0.538
		Slope	1.0194 (0.9849,1.0551)	3.9% (-0.8%, 8.9%)	0.103	0.002
SE IR Oxymorphone	Pre CRF	Intercept	0.0642 (0.0039,1.0595)	Reference	N/A	N/A
		Slope	1.1485 (0.8855,1.4896)	Reference	N/A	N/A
	Post CRF	Intercept	0.0066 (0.0009,0.0496)	-89.8% (-99.7%, 224.4%)	0.196	0.343
		Slope	0.9505 (0.6797,1.3293)	-17.2% (-45.9%, 26.5%)	0.382	0.741

Source: RADARS® PC study report (November 2016)

Figure K5. Overdose rates per 100,000 population covered—comparison of means model, RADARS® Poison Center study, Q1 2010 – Q2 2016



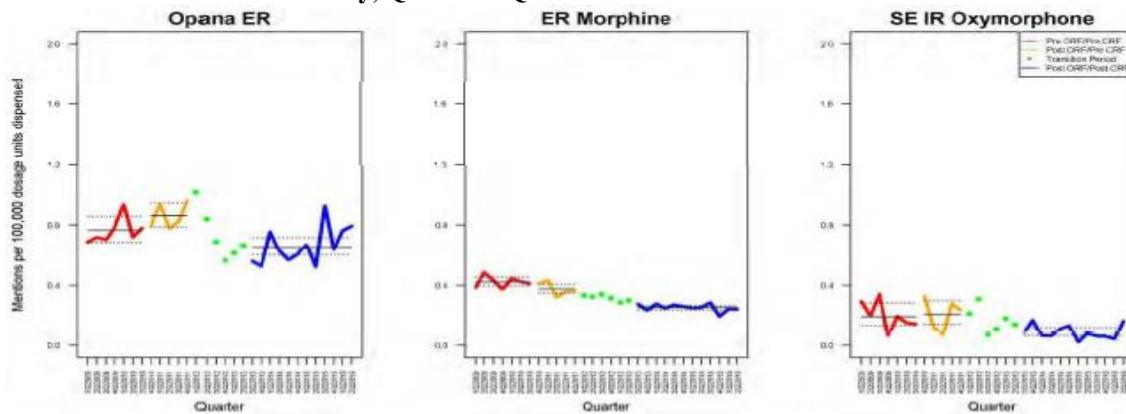
Source: RADARS® PC study report (November 2016)

Table K9. Overdose rates per 100,000 population covered—comparison of means model, RADARS® Poison Center study, Q1 2010 – Q2 2016

Drug Group	Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)	p-value for Percentage Change	Interaction p-value
Opana ER	Pre ORF/Pre CRF	0.0254 (0.0221,0.0292)	Post ORF/Post CRF over Pre ORF/Pre CRF	-22.0% (-34.8%, -6.6%)	0.007*	N/A
	Post ORF/Pre CRF	0.0491 (0.0437,0.0552)	Post ORF/Pre CRF over Pre ORF/Pre CRF	93.3% (61.4%, 131.5%)	<0.001	N/A
	Post ORF/Post CRF	0.0198 (0.0177,0.0223)	Post ORF/Post CRF over Post ORF/Pre CRF	-59.6% (-65.7%, -52.4%)	<0.001	N/A
ER Morphine	Pre ORF/Pre CRF	0.1347 (0.1254,0.1447)	Post ORF/Post CRF over Pre ORF/Pre CRF	-23.9% (-30.7%, -16.4%)	<0.001	0.811
	Post ORF/Pre CRF	0.1354 (0.1245,0.1472)	Post ORF/Pre CRF over Pre ORF/Pre CRF	0.5% (-10.0%, 12.2%)	0.930	<0.001
	Post ORF/Post CRF	0.1025 (0.0965,0.1090)	Post ORF/Post CRF over Post ORF/Pre CRF	-24.2% (-31.7%, -16.0%)	<0.001	<0.001
SE IR Oxymorphone	Pre ORF/Pre CRF	0.0024 (0.0017,0.0034)	Post ORF/Post CRF over Pre ORF/Pre CRF	-31.7% (-58.0%, 11.0%)	0.124	0.614
	Post ORF/Pre CRF	0.0035 (0.0025,0.0050)	Post ORF/Pre CRF over Pre ORF/Pre CRF	47.6% (-10.7%, 144.0%)	0.129	0.322
	Post ORF/Post CRF	0.0016 (0.0012,0.0023)	Post ORF/Post CRF over Post ORF/Pre CRF	-53.7% (-71.3%, -25.5%)	0.002	0.595

Source: RADARS® PC study report (November 2016)

Figure K6. Overdose rates per 100,000 dosing units dispensed—comparison of means model, RADARS® Poison Center study, Q1 2010 – Q2 2016



Source: RADARS® PC study report (November 2016)

Table K10. Overdose rates per 100,000 dosing units dispensed—comparison of means model, RADARS® Poison Center study, Q1 2010 – Q2 2016

Drug Group	Period	Estimate (95% CI)	Comparison	Percentage change (95% CI)	p-value for Percentage Change	Interaction p-value
Opana ER	Pre ORF/Pre CRF	0.7657 (0.6855,0.8552)	Post ORF/Post CRF over Pre ORF/Pre CRF	-14.5% (-26.0%,-1.3%)	0.033*	N/A
	Post ORF/Pre CRF	0.8605 (0.7838,0.9447)	Post ORF/Pre CRF over Pre ORF/Pre CRF	12.4% (-2.8%, 29.9%)	0.114**	N/A
	Post ORF/Post CRF	0.6543 (0.5962,0.7160)	Post ORF/Post CRF over Post ORF/Pre CRF	-24.0% (-33.3%,-13.3%)	<0.001	N/A
ER Morphine	Pre ORF/Pre CRF	0.4216 (0.3940,0.4512)	Post ORF/Post CRF over Pre ORF/Pre CRF	-40.1% (-45.2%,-34.5%)	<0.001	<0.001
	Post ORF/Pre CRF	0.3760 (0.3473,0.4071)	Post ORF/Pre CRF over Pre ORF/Pre CRF	-10.8% (-19.7%,-1.0%)	0.032***	0.011
	Post ORF/Post CRF	0.2526 (0.2384,0.2676)	Post ORF/Post CRF over Post ORF/Pre CRF	-32.8% (-39.1%,-25.9%)	<0.001	0.139
SE IR Oxymorphone	Pre ORF/Pre CRF	0.1948 (0.1345,0.2821)	Post ORF/Post CRF over Pre ORF/Pre CRF	-55.4% (-72.9%,-26.7%)	0.001	0.014
	Post ORF/Pre CRF	0.2075 (0.1451,0.2968)	Post ORF/Pre CRF over Pre ORF/Pre CRF	6.5% (-36.3%, 78.3%)	0.810	0.845
	Post ORF/Post CRF	0.0868 (0.0622,0.1211)	Post ORF/Post CRF over Post ORF/Pre CRF	-58.2% (-74.3%,-31.8%)	<0.001	0.021

Source: RADARS® PC study report (November 2016)

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