FDA Briefing Document

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

January 15, 2020 (PM Session)

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. The new drug application (NDA) 209653 for oxycodone extended-release oral tablets 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 has been brought 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.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 Division Director Memorandum/Division Memorandum

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: December 16, 2019

FROM: Rigoberto Roca, MD
Acting Director
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience, CDER, FDA

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

RE: Overview of the January 15, 2020 AADPAC/DSaRM Meeting to Discuss NDA 209653

At this joint meeting of AADPAC and DSaRM, we will be discussing an application from Intellipharmaceutics for a new extended-release formulation of oxycodone, designed with properties intended to deter abuse. The proposed indication is the management of pain severe enough to require daily, around-the clock-long-term opioid treatment and for which alternative treatment options are inadequate. This is the second cycle for this NDA, which was initially submitted November 25, 2016, and was presented to AADPAC and DSaRM on July 26, 2017. Deficiencies in the application were identified that precluded its approval. As discussed at the July 26, 2017 meeting, the major deficiencies were lack of Category 2 and 3 human abuse potential studies to fully describe the abuse-deterrent properties of the formulation, as well as concerns about the safety of certain excipients in the formulation. The Applicant has resubmitted their application with a new formulation and has stated that they have addressed the deficiencies.

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. To address this public health epidemic, FDA has announced a comprehensive review of our approach to opioid medications. This multi-year action plan focuses on new and existing policies to help

curb abuse, addiction, and overdose of these drugs, while continuing to make them available to patients in need of effective pain relief.

One potentially important step towards the goal of creating safer opioid analgesics has been the development of opioids that are formulated to deter abuse. In April 2015, the Agency issued a final guidance to assist industry in the development of opioid drug products with potentially abuse-deterrent properties. The "Guidance for Industry: Abuse-Deterrent Opioids, Evaluation and Labeling[1]" explains the Agency's current thinking regarding studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, makes recommendations about how those studies should be performed and evaluated, and discusses how to describe those studies and their implications in product labeling.

There have been ten opioid analgesics approved that have been labeled with abuse-deterrent properties as described in the guidance, nine extended-release products and one immediate-release product. The extended-release products approved with labeling language describing studies conducted in support of abuse-deterrent properties are OxyContin (oxycodone extended-release tablets), Targiniq (oxycodone and naloxone extended-release tablets), Embeda (morphine sulfate and naltrexone extended-release capsules), Hysingla ER (hydrocodone extended-release tablets), Morphabond (morphine sulfate extended-release tablets), Xtampza ER (oxycodone extended-release capsules), Troxyca ER (oxycodone and naltrexone extended-release capsules), Arymo ER (morphine sulfate extended-release tablets), and Vantrela ER (hydrocodone extended-release tablets). The immediate-release product is Roxybond (oxycodone HCl immediate-release tablets). The NDAs for Targiniq, Troxyca ER, and Vantrela ER have been withdrawn by the Sponsors and are not currently being marketed.

The results of the Applicant's in vitro physical and chemical manipulation studies from both NDA review cycles will be presented during this meeting, as well as the newly submitted human abuse potential studies assessing abuse potential by the oral and nasal routes. The Applicant conducted their in vitro and human studies using relevant comparators that may provide context for their findings, and we ask that you look at the Applicant's findings in the context of the data presented. You will be asked to discuss whether the Applicant has demonstrated abuse-deterrent properties for their product that would support labeling, whether the benefits of the product at issue outweigh its risks, and whether it should be approved. You will also be asked to discuss how this product would fit into the armamentarium of already approved oxycodone extended-release products labeled with abuse-deterrent properties, and whether you have any concerns regarding the public health impact of approving this product.

These are clearly difficult questions for which there are no easy answers. We are asking that you provide your expertise, your experience and your best insights in order to help us find a reasonable and responsible path forward. Your advice and recommendations will be essential in assisting us with addressing this complex and critical public health concern. We are grateful that you have agreed to join us for this important discussion and look forward to seeing you at the meeting.

[1] Guidance for Industry: Abuse-deterrent opioids, evaluation and labeling; https://www.fda.gov/media/84819/download

Draft Points to Consider

1. Has the Applicant demonstrated that oxycodone extended-release tablets have properties that can be expected to deter abuse by the IV route of administration?

2. Are there sufficient data to support inclusion of language regarding abuse-deterrent properties in the product label for the IV route of administration?

3. Do you have any concerns regarding the public health impact of approving oxycodone extended-release tablets? If so, what are they?

4. Should oxycodone extended-release tablets be approved?

2 Background

NDA #	NDA 209653 Resubmission
Applicant	Intellipharmaceutics
Date of Submission	February 28, 2019
PDUFA Goal Date	August 28, 2019
Proprietary Name	Aximris XR
Proposed Established or Proper Name	Oxycodone Hydrochloride Extended-Release Tablets
Dosage Form(s)	Oral Extended-release tablets: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
Applicant Proposed Indication(s)/Population(s)	**Indication:** Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate **Populations:** Adults and opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg of oxycodone orally or its equivalent
Applicant's Initially Proposed Dosing Regimen(s)	• For opioid-naïve and opioid non-tolerant patients, initiate with 10 mg tablets orally every 12 hours • Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals • Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse

Oxycodone Hydrochloride Extended-Release Tablets is a solid, oral, opioid drug product formulated to incorporate abuse-deterrent technologies utilizing a combination of physical and chemical barriers delivery system. The proposed indication is the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

This New Drug Application (NDA) was initially submitted to the FDA on November 25, 2016 under NDA 209653 as a 505(b)(2) application referencing the Agency's prior findings of safety and efficacy for the listed drug, OxyContin (NDA 22272). The safety and efficacy of oxycodone extended-release tablets is based on the demonstration of bioequivalence to OxyContin. Because oxycodone extended-release tablets demonstrated bioequivalence with the Listed Drug, the Agency did not require the Applicant to conduct new clinical efficacy or clinical studies.

In the original NDA submission, the Applicant conducted in vitro assessments to assess the products abuse liability; however, it did not conduct studies to assess the human abuse potential via the oral and nasal routes of abuse. *As per the guidance for industry: HAP studies (Abuse Deterrent Opioids: Evaluation and Labeling[2]),* all relevant routes of abuse must be studied for a product that is intended to have abuse-deterrent properties.

Of note, one of the excipients in the original formulation was FD&C Blue No. 1 Aluminum Lake Dye. It was intended to impart abuse-deterrent properties to the formulation based on the blue color, however its role was not studied nor was support for this submitted in the orginial NDA. Also, the risks of this excipient administered by unintended routes of administration were not assessed by the Applicant. The Applicant subsequently removed this excipient from the formulation and the current submission uses the new formulation without this excipient for the HAP studies.

On July 26, 2017, the original NDA was discussed at a combined meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). The committees were asked to discuss the overall benefit-risk profile of oxycodone HCL ER and whether the applicant had demonstrated abuse-deterrent properties that would support labeling. (see below for additional information on the meeting)

The Agency did not approve the first cycle application and issued a Complete Response (CR) on September 22, 2017. The major deficiencies were: 1) the lack of human abuse potential studies to characterize the abuse potential by all relevant route of abuse; 2) the presence of excipients (particularly FD&C Blue No. 1 Aluminum Lake Dye) without an adequate rationale for inclusion, assessment of the risks associated with administration of the product by untintended routes, and 3) product quality concerns related to insufficient analytical methods.

On February 28, 2019, the Applicant submitted their Complete Response to the NDA. The submission included the following new information:

- Two human abuse-potential studies with Oxycodone Hydrochloride Extended-Release Tablets:

    1. A randomized, double-blind, active- and placebo-controlled, 5-way crossover study to determine the abuse potential and pharmacokinetics of ground IPC Oxycodone HCl Extended-Release Tablets compared to crushed Oxycodone Immediate-Release Tablets, Ground OxyContin Tablets, and Placebo when administered Intranasally to Non-Dependent, Recreational Opioid Users
    2. A randomized, double-blind, placebo- and active-controlled crossover study to evaluate the Oral Abuse Potential and Pharmacokinetics of Manipulated

[2] Guidance for Industry: Abuse-deterrent opioids, evaluation and labeling; https://www.fda.gov/media/84819/download

Oxycodone HCl Extended-Release Tablets Compared with Oxycodone Immediate-Release Tablets, Manipulated OxyContin Tablets, and Placebo in Non-Dependent Recreational Opioid Users

- The Applicant stated that the function of of FD&C Blue No. 1 Aluminum Lake Dye excipient was solely to impart color and the material did not have any release-controlling properties. Therefore, the Applicant removed the dye. The newly submitted HAP studies were conducted on the batches without dye.

- The Applicant conducted additional risk assessments including excipient exposure risk via various routes of abuse.

Throughout this document, oxycodone extended-release tablets may be referred to as Aximris, Aximris XR, Rexista, or IPC oxycodone HCl extended-release tablets.

2.1 Advisory Committee Meeting

On July 26, 2017, the original NDA was discussed at a combined meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). The committees were asked to discuss the overall benefit-risk profile of oxycodone HCL ER and whether the applicant had demonstrated abuse-deterrent properties that would support labeling.

The Summary Minutes of the questions posed to the committees are reproduced below.[3] Additional detail can be found in the meeting transcript. [4]

Questions to the Committee:

1. **DISCUSSION:** The Applicant submitted only Category 1 (in vitro) studies to support labeling of Oxycodone HCl ER tablets for abuse deterrence and is seeking labeling for abuse-deterrent properties only for the IV route of abuse. The product contains excipients that are intended to deter abuse by other routes. Discuss whether it is appropriate to consider labeling this product for abuse-deterrent properties for a single route without a complete assessment of all relevant routes of abuse.

   Committee Discussion*: The majority of the committee agreed that it was not appropriate to consider labeling this product with abuse-deterrent properties for a*

[3] https://www.fda.gov/media/107124/download.

[4] https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm536646 htm

single route without a complete assessment of all relevant routes of abuse. The majority of the committee also agreed Category 2 and Category 3 studies are necessary to complete the assessment of abuse-deterrent properties. The committee agreed with the need for the sponsor to conduct further studies in accordance with the Guidance for Industry on Abuse Deterrent Opioids, as the sponsors of the other approved products with labeling for abuse deterrent properties have done. Some committee members agreed that without such a complete assessment, there would likely be confusion among health care providers and patients who might think that the product could deter abuse through other routes of administration. In addition, this could create difficulty for prescribers to determine if there was a risk that the product would be abused only intravenously, and not by other routes.

2. **DISCUSSION:** As presented earlier today, excipients in a drug product must have a purpose, and many oral formulations have excipients that pose health risks if injected. As discussed at previous advisory committee meetings, there have been concerns raised that the presence of excipients in abuse-deterrent formulations of products intended for oral use have resulted in additional toxicity to those who abuse these products by non-oral routes. This product contains a nasal irritant, sodium lauryl sulfate (SLS), and a blue dye, that, according to the Applicant, are intended to deter abuse by the nasal and oral routes, however, no data have been provided to support these claims.
    a. Discuss any concerns you may have regarding this product and the presence of excipients that have been included to deter abuse.
    b. Discuss whether it is acceptable to include excipients in this product that increase the potential risk to those who may abuse the drug via certain non-IV routes of abuse, and that have not been shown or are not intended to contribute to the proposed IV abuse-deterrent claim being sought by the Applicant.
    c. Discuss whether it is possible to determine an acceptable level of risk for excipients that may be toxic by unintended routes of administration for this product?

***Committee Discussion**: The majority of the committee members agreed that there were concerns regarding the safety and the potential toxicity that may be caused by the excipients that have been included to deter abuse. Some committee members commented that some of the excipients in this product act as active pharmacological agents and dose-response data should be required like with other active pharmacologic ingredients. Additionally, most committee members had major concerns regarding the effects the blue dye would have when ingested and used in large amounts, and stated the need for long term data on various body sizes as well as how it will affect the GI system. Some committee members expressed concerns about the lack of data on whether the blue dye excipient would actually deter abuse, and pointed out that it may attract abusers. One committee member suggested the need for data examining tolerability to the increased viscosity of this product among patients who use it orally as directed. One committee member expressed concerns that it was inappropriate to use blue dye to stain and shame abusers, noting that addiction is a*

mental illness. Overall, the committee noted that there has been no assessment for benefit or harm of the blue dye when taken orally or when abused nasally or intravenously, and that there is no evidence of proven deterrent effect of the blue dye.

3. **DISCUSSION:** Although the Applicant is not currently seeking a nasal or oral abuse-deterrent claim, discuss the type of data that would be necessary to support a claim that blue dye has deterrent effects for the intravenous, nasal, or oral routes of abuse for this product. Discuss if it is acceptable to predict intranasal or oral abuse-deterrent effects from Category 1 studies alone for this product.

   Committee Discussion*: The majority of the committee stated that it was not acceptable to predict intranasal or oral abuse-deterrent effects from Category 1 studies alone for this product and agreed on the need for Category 2 and 3 studies. These committee members also agreed that the best way to evaluate abuse-deterrent properties would be to use the guidance provided by the FDA. Some committee members suggested the use of dose-response curves and drug liking studies., It was recommended that the Sponsor conduct Category 1-like studies examining the use of household chemicals other than water for the removal of the blue dye from the skin., It was also suggested that opioid users be interviewed and focus groups be used to document attitudes and opinions regarding whether or not the blue dye might have deterrent effects for the intravenous, nasal, or oral routes of abuse for this product. Other committee members suggested studying how this product actually deterred abuse in potential users and current opioid abusers.*

4. **VOTE**: Has the Applicant demonstrated that oxycodone extended-release tablets have properties that can be expected to deter abuse by the IV route of administration?

   Vote Result: Yes: 4 No: 19 Abstain: 0

   Committee Discussion*: The majority of the committee agreed that the Applicant did not demonstrate that oxycodone extended-release tablets have properties that can be expected to deter abuse by the IV route of administration. Some committee members who voted "Yes" noted that they voted based on the strict interpretation of the question and not in the full context of drug product. Some committee members who voted "Yes" also noted that it can be expected to deter abuse because of the difficulty in syringeability of the drug product since it becomes highly viscous.*

5. **VOTE:** Are there sufficient data for this product to support inclusion of language regarding abuse-deterrent properties in the product label for the IV route of administration?

   Vote Result: Yes: 0 No: 23 Abstain: 0
   Committee Discussion*: The committee unanimously agreed that there are not sufficient data for this product to support inclusion of language regarding abuse-deterrent properties in the product label for the IV route of administration. The majority of committee members agreed that Category 2 and 3 studies as well as human*

safety data are needed to make a determination on labeling this drug product as abuse deterrent. Please see the transcript for details of the committee discussion.

6. **VOTE:** Should this drug product, Oxycodone HCl ER tablets, be approved?

   Vote Result: Yes: 1 No: 22 Abstain: 0

   Committee Discussion: *The majority of the committee agreed that the product, Oxycodone HCL ER tablets, should not be approved. The majority of the committee agreed that safety and efficacy data for patient oral use, as well as in reference to all routes of abuse are needed to approve Oxycodone HCl ER tablets. The committee member who voted "Yes" stated that despite concerns with the blue dye, he did not believe that this drug is any less safe than what is currently on the market.*

3 Summary of In-Vitro Abuse-Deterrent Findings for Oxycodone Extended-Release Tablets

DATE: October 18, 2019

FROM: Renishkumar Delvadia, Ph.D.,
Julia Pinto, Ph.D.
Ramesh Sood, Ph.D.

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

RE: Background Document: In vitro category 1 abuse-deterrent studies, NDA 209653, extended-release oxycodone hydrochloride tablet

The proposed drug product is an extended-release (ER) tablet formulation containing 10, 15, 20, 30, 40, 60 and 80 mg oxycodone hydrochloride (also referred to as test tablets). The abuse- deterrent properties of the drug product are imparted by excipients which act as gelling agents. All tablet strengths share an identical product design. The lowest 10 mg and the highest 80 mg product strengths were selected to conduct most of the in vitro abuse-deterrent studies. The comparator product was FDA approved oxycodone extended-release 80 mg tablets (referred to as comparator tablet). In vitro Category 1 abuse-deterrent studies are conducted to assess the relative difficulty and effectiveness of various potential manipulation methods to defeat the drug product's abuse-deterrent properties. Note that initial formulation of the test product also contained a blue dye intended to deter abuse, which was removed in the revised formulation that is the subject of the current submission; the comparative dissolution studies demonstrate that the revised formulation product has similar dissolution properties as

the original formulation product. Therefore, the removal of the blue dye is not expected to change the product performance. Only the key methods, outcome, and conclusion of the in vitro studies relevant to the revised formulation are summarized below.

A. Physical Manipulation (Particle Size Reduction):

From the 10 common household tools tested, seven tools can be used to reduce the test tablets into fine particles; while only five tools can be used to reduce the comparator tablets into fine particles (crushing and grinding). Further, when the most efficient tool was used to manipulate the tablets, the test tablets can be reduced into much finer particles than the comparator tablets. The optimal particle size reduction approach was used to prepare the powder samples used in subsequent in vitro studies. Note that resistance to particle size reduction is not one of the product's intended mechanisms for abuse deterrence.

B. Large Volume Extraction Using Various Solvents Study Results: Solvent volume of 30 mL or greater is typically referred to as large volume in this summary report.

Extraction in model solvents: This part of the study tested all the test product strengths. Conditions considered included volume of solvent, solvent temperature, and type of solvent. In general, all strengths of the test product showed lower or similar extraction compared to the comparator product. The solvent temperature significantly impacted the extraction rate of both test and comparator products.

Extraction in twenty various solvents: This study expanded on the previous study to include more solvents, both ingestible and non-ingestible. The study also included two physical forms of the tablets, referred to as forms A (not manipulated) and B (manipulated); tablets were not pre-treated with heat.

- *Tablet form A*: Agitation condition and temperature significantly impacted the extraction recoveries for all test products; recoveries were dependent on the type of solvent. When analytical variations are considered, the test product had similar or lower extraction efficiency than comparator product, except for one out of the 20 solvents tested (referred to as solvent 3). Solvent 3, a household solvent, was the most effective solvent to extract oxycodone only from the test products, while it still had poor extraction efficiency for comparator product.

- *Tablet Form B*: The extraction of oxycodone was significantly easier from tablet form B compared to tablet form A. Changing both temperature and agitation impacted the oxycodone extraction efficiency for both test and comparator products. However, there was no apparent difference between the comparator and the test products when analytical variations are considered. Except for one non-ingestible solvent, all other tested solvents were very efficient in extraction and had 60% to 100% of oxycodone recoveries for both test and comparator products by 15 minutes.

C. Small Volume Extractability and Syringeability Studies:

Small volume (typically 10 mL or less) extractions were conducted to assess the potential for syringeability and injectability of the manipulated product. The Applicant's definition of syringeable is for a sample to be withdrawn, within 2 minutes, into the syringe at 20% or more of the test solvent volume used in each test. This part of the study was conducted on 10 mg and 80 mg test products and 80 mg comparator tablets. Ingestible solvents of varying pH's and polarity were tested. Testing also included both pre-treated (typically exposed to heat in oven or microwave for a certain duration) and non-pre-treated, intact and manipulated tablets, presented to the different volume of the solvents at both room temperature and elevated temperature. Without pretreatment, neither the test nor the comparator product was syringeable due to high viscosity. At the correct combination of testing conditions, the test product samples were similar or less syringeable than comparator tablet samples. Under a certain pre-treatment condition around 52% of oxycodone present in the 80 mg test product could be isolated and potentially injected.

D. Multiple Tablet Extractability and Syringeability Studies:

These in vitro syringeability studies conducted by extraction from pre-treated manipulated tablets using 30 mL volume of potential ingestible test solvents, with the increasing number of manipulated tablets (both test and comparator products) presented to the extraction medium. The experiment started with a single tablet and the number of tablets increased by two in each the subsequent experiments until the solution is no longer syringeable due to high viscosity. The test product had overall less amount of drug extracted/syringeable compared to the comparator product as the number of ground tablets are increased. For the solvent that resulted in maximum syringeable amount, the average recovery of oxycodone from the test product ranged between 24% to 35% for one to eleven pre-treated 80mg ground tablets and from 9% to 18% for thirteen to nineteen ground 80 mg pre-treated test tablets respectively; the maximum amount of oxycodone hydrochloride extracted in the syringe from the multiple tablets of 80 mg test product was around 255 mg using one of the tested and ingestible solvents. The number of tablets before the solution became un-syringeable was higher for the comparator product than the test product.

E. Effect of Various Physical Manipulations on Dissolution:

Varying extents of physical manipulations progressively increase the oxycodone dissolution rate from both the test product and comparator products. However, overall the test product tablet samples still retained some extended-release characteristics.

F. Complex Extraction and Isolation study:

It is possible that some abusers will attempt to isolate the oxycodone base using very specific solvents/reagents and multi-step complex extraction/precipitation methods that are typically used in a laboratory setting. When tested using complex extraction and isolation procedures, oxycodone base can be extracted with similar or lower purity and yield from the test product samples than from the comparator tablet samples.

G. Vaporization Study:

Supported by the study results, vaporization is not efficient for the comparator product and it appears slightly less efficient for the test product. Vaporization study yielded maximum volatized recoveries of 5.9% from the test product.

4 Summary of Nonclinical Data

The Applicant is cross-referencing the Agency's previous finding of safety and efficacy for OxyContin to support this application, therefore no new toxicology studies for oxycodone were required. As such, the drug product labeling will be virtually identical to that of OxyContin with respect to pharmacology (mechanism of action), pregnancy, and nonclinical toxicology.

There are no safety concerns with the new drug product formulation when the drug product is used as labeled via the intended oral route of administration. The Applicant addressed the potential for intranasal, smoking, and vaping abuse by evaluating the excipients using a literature-based approach. Based on the limited information available for the excipients, potential for irritation and respiratory tract toxicity were identified, although a quantitative prediction of risk was not possible.

In addition, the Applicant conducted studies to characterize the potential toxicological effects of the drug product if it were to be manipulated for intravenous abuse. The Applicant attempted to identify compounds in the syringeable material from their product and compare the chemical profile to that of syringeable material from OxyContin under the same conditions. However, the methods were restricted to lower molecular weight compounds only ($\leq$ 400-600 atomic mass units depending on the method), not fully validated to ensure accuracy of chemical identification or quantitation of those compounds, and higher molecular weight (MW) compounds were not evaluated. While there are a number of limitations in their analysis, the chemical composition of the low MW entities in the syringeable material was relatively similar, though not identical, to that from the currently approved OxyContin drug product. Based on toxicological risk assessments of the identified lower MW compounds, the Applicant has concluded that the compounds in the syringeable material from their drug product would be highly unlikely to pose significant health risks to a person who injects the material, either once or repeatedly. However, because the Applicant did not measure larger MW compounds that may also be potentially present in the syringeable material, such as polyethylene oxide, we cannot state that there is no risk of thrombotic microangiopathy or other uncharacterized toxicity from the excipients in this drug product. Further, given the large number of lower MW compounds identified (>60), the differences in excipients in the proposed drug product compared to the referenced drug product, and the lack of validated data on either product, a definitive comparison of the toxicological profile between products and a conclusion that there are likely no significant potential health risks cannot be made. Based on the data available to date, if approved, the proposed AXIMRIS drug product labeling will include a description of the potential adverse effects that could occur if the product were

manipulated for use via an unintended route of administration that is similar to that present in Section 9 of the OxyContin labeling.

5 Summary of Clinical Pharmacology Findings

First Cycle Clinical Pharmacology findings of IPC oxycodone HCl ER tablets

The comparative bioavailability / bioequivalence (BA/BE) studies between IPC oxycodone HCl ER tablets and the listed drug OxyContin tablets were evaluated under both fasted and fed conditions, at low dose strength (10 mg) and high dose strength (80 mg) in Studies 1878, 1879, 656-15-80, and 655-15-80. The results show that IPC oxycodone HCl ER tablets met the BE criteria for C_{max}, AUC_t, and AUC_{inf} to OxyContin tablets under both fasted and fed conditions. The point estimate of the geometric mean ratio (IPC oxycodone ER / OxyContin) and the corresponding 90% confidence intervals for oxycodone C_{max}, AUC_t and AUC_{inf} fell within the 80 - 125% BE limits. The median Tmax values for IPC oxycodone HCl ER tablets 10 mg or 80 mg under fasted or fed conditions were similar to that of OxyContin.

The multiple dose PK study (Study oxy-80-184) show that steady state AUC ($AUC_{0\text{-}tau,\ ss}$), steady state maximum concentrations ($C_{max,\ ss}$), average concentrations over the dosing interval (C_{avg}) and Tmax after multiple dosing are comparable between IPC oxycodone ER tablets and OxyContin tablets. With BID dosing, steady state is achieved within one day for IPC oxycodone ER tablets, similar to OxyContin tablets

The single dose IPC oxycodone ER 10 mg, 15 mg, 20mg, 30 mg, 40 mg, 60 mg, and 80 mg tablets show dose-proportional increase in oxycodone C_{max} and AUC values (Study oxy-10-80-185).

The food effect study (Study oxy-80-186) showed that IPC oxycodone ER tablets result in comparable Cmax and overall exposure (AUC_t, and AUC_{inf}) following the administration of single dose of 80 mg tablet between fed and fasted state. The median T_{max} of IPC oxycodone ER tablets under fed conditions (5.0 h) is comparable to fasted condition (4.7 h). Therefore, IPC oxycodone ER tablets may be taken without regard to food intake.

Second Cycle Clinical Program: Abuse potential assessment of IPC oxycodone HCl ER tablets

The abuse-deterrence assessment consisted of two clinical studies to evaluate the human abuse potential and pharmacokinetics (PK) via intranasal (IN) and oral routes of administration in studies OXC3/2/0816 and OXC3/4/1117, respectively. In this review, for both abuse-potential studies, PK observations were included. The PK observations must be supported by pharmacodynamic (PD) endpoints to understand whether the PK differences are clinically meaningful. Refer to the Controlled Substance Staff memorandum in Section 7 of this document for the Agency's analysis of the PD endpoints. The Applicant's human abuse potential (HAP) studies, as well as the Applicant's and Agency's clinical pharmacology findings are described and discussed below.

I)Intranasal Human Abuse Potential Study OXC3/2/0816

The applicant conducted "A Randomized, Double-Blind, Active- and Placebo-Controlled, 5-Way Crossover Study to Determine the Abuse Potential and Pharmacokinetics of Ground IPC Oxycodone HCl Extended-Release Tablets Compared to Crushed Oxycodone Immediate-Release Tablets, Ground OxyContin Tablets, and Placebo When Administered Intranasally to Non-Dependent, Recreational Opioid Users". After naloxone challenge and drug discrimination phase, non-dependent recreational opioid users (n=32) received the following treatments in a crossover fashion:

Treatment Periods:

- Treatment A: IPC oxycodone ER (30 mg) tablet, ground
- Treatment B: Oxycodone IR (30 mg) tablet, crushed
- Treatment C: OxyContin ER (30 mg) tablet, ground
- Treatment D: Placebo, matched to IPC Oxycodone ER tablet, ground
- Treatment E: Placebo [microcrystalline cellulose（MCC) powder], to approximate bulk of crushed oxycodone IR tablet, crushed and OxyContin tablet, ground

For the manipulated condition, IPC Oxycodone ER 30 mg, placebo-matched tablets, and OxyContin 30 mg tablets were ground with a grinder using standardized methods. Roxicodone 30 mg tablets were crushed and ground by standardized methods using a glass mortar and pestle.

Clinical Pharmacology Results:
The mean ± SD plasma concentration time profiles of oxycodone after manipulation and IN treatments are shown in Figure 1. The PK parameters and PK parameter ratios are shown in Table 1.

Figure 1. The mean ± SD plasma concentration time profiles of oxycodone after manipulation and IN administration of IPC oxycodone HCl ER ground, oxycodone IR crushed, and OxyContin ER ground. The mean PK profiles from 0-6 h after drug administration is represented as the smaller graph within the figure.

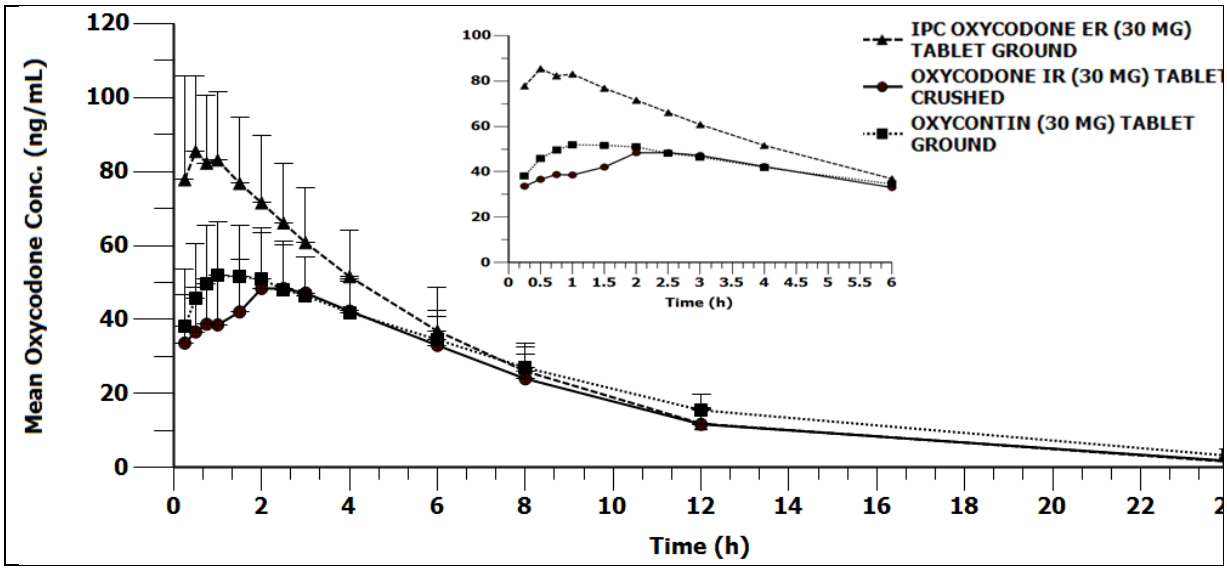


Table 1. The PK parameters after manipulation and IN administration of IPC oxycodone ER ground, oxycodone IR crushed, and OxyContin ground.

PK Parameters	**IPC oxycodone ER 30 mg Ground (N=31)** **Trt. A**	**Oxycodone IR 30 mg Crushed (N=32)** **Trt. B**	**OxyContin 30 mg Ground (N=32)** **Trt. C**	**Ratio IPC oxycodone ER Ground / Oxycodone IR Crushed** **Trt. A / Trt. B**	**Ratio IPC oxycodone ER Ground / OxyContin Ground** **Trt. A / Trt. C**
C_{max} (ng/mL)	92 (22)	55 (11)	56 (14)	1.67	1.64
$AUC_{0\text{-}1\ h}$ (ng × h/mL)	71 (17)	32 (10)	40 (13)	2.22	1.78
$AUC_{0\text{-}2h}$ (ng × h/mL)	148 (32)	75 (22)	91 (25)	1.97	1.63
$AUC_{0\text{-}t}$ (ng × h/mL)	580 (137)	454 (89)	521 (100)	1.28	1.11
$AUC_{0\text{-}inf}$ (ng × h/mL)	589 (140)	466 (93)	549 (102)	1.26	1.07
T_{max} (h)	0.50 [0.25 – 2.00]	2.00 [0.25 – 6.00]	1.00 [0.25 – 3.00]		
$t_{1/2}$ (h)	4.0 (0.5)	4.3 (0.6)	5.3 (1.5)		

Source: Modified from Sponsor's Table 27, Clinical Study Report OXC3/2/0816

Pharmacokinetic comparison between treatments:

Ground IPC oxycodone ER tablets versus crushed Oxycodone IR tablets: The manipulation and IN administration of ground IPC oxycodone ER tablets was associated with higher Cmax, earlier Tmax, higher partial AUCs, and overall-systemic-exposure (AUCinf) compared to the crushed oxycodone IR tablets.

- The ground IPC oxycodone ER tablets were associated with 67% higher Cmax, 122% and 97% higher partial AUCs ($AUC_{0\text{-}1h}$ and $AUC_{0\text{-}2h}$, respectively), 26% higher $AUC_{inf,}$ and 1.5 h earlier median Tmax compared to crushed oxycodone IR tablets.

Ground IPC oxycodone ER tablets versus ground OxyContin tablets: The manipulation and IN administration of ground IPC oxycodone ER tablets was associated with higher Cmax, earlier Tmax, higher partial AUCs, but similar overall-systemic-exposure (AUC_{inf}) compared to the ground OxyContin tablets.

- The ground IPC oxycodone ER tablets were associated with 64% higher Cmax, 78% and 63% higher partial AUCs ($AUC_{0\text{-}1h}$ and $AUC_{0\text{-}2h}$, respectively) and 0.5 h earlier median Tmax compared to ground OxyContin tablets.

II) Oral Human Abuse Potential Study OXC3/4/1117: The Applicant conducted "A Randomized, Double-Blind, Placebo- and Active-Controlled Crossover Study to Evaluate the Oral Abuse Potential and Pharmacokinetics of Manipulated Oxycodone HCl Extended-Release Tablets Compared with Oxycodone Immediate-Release Tablets, Manipulated OxyContin Tablets, and Placebo in Non-Dependent Recreational Opioid Users". After naloxone challenge and drug discrimination phase, non-dependent recreational opioid users (n=40) received the following treatments in a crossover fashion:

Treatment Period:

- Treatment A: IPC Oxycodone ER (40 mg) tablet, milled-in solution
- Treatment B: IPC Oxycodone ER (40 mg) tablet, intact
- Treatment C: IR oxycodone (40 mg) tablet, crushed-in solution
- Treatment D: OxyContin (40 mg) tablet, milled-in solution
- Treatment E: Placebo

For the manipulated condition, oxycodone IR 40 mg, oxycodone IR 30 mg tablets were crushed (multiple tablets crushed at a time and equivalent of single 40 mg dose weighed out) and dissolved in 20 mL solutionand administered via oral syringe. For OxyContin 40 mg, OxyContin 40 mg tablets were ground and dissolved in a solution and administered orally. For placebo (oral syringe), MCC was dissolved in 20 mL solution and administered orally.

Clinical Pharmacology Results:
The mean ± SD plasma concentration time profiles of oxycodone of different oral treatments are shown in Figure 2. The PK parameters and PK parameter ratios are shown in Table 2.

Figure 2. The mean ± SD plasma concentration time profiles of oxycodone after oral administration of IPC oxycodone ER tablets intact, and after manipulation and oral administration of IPC oxycodone ER tablets milled-in solution, oxycodone IR tablets crushed-in solution, and OxyContin tablets milled-in solution. The mean PK profiles from 0-6 h after drug administration is represented as the smaller graph within the figure.

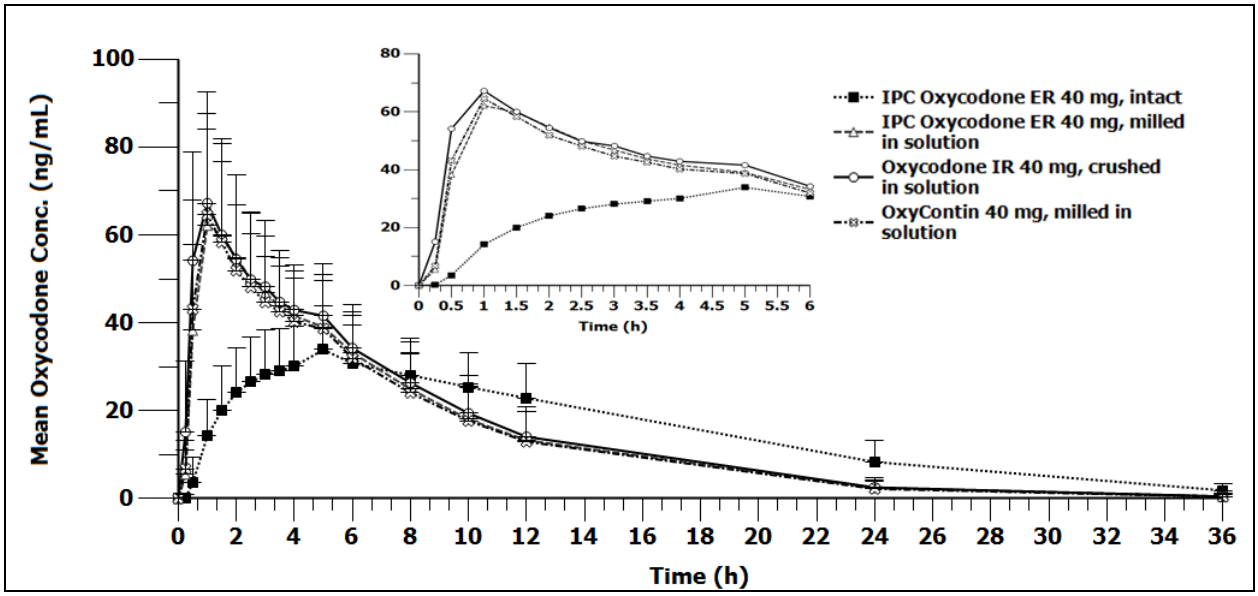


Table 2. The PK parameters of oxycodone after oral administration of IPC oxycodone ER tablets intact, and manipulation and oral administration of IPC oxycodone ER tablets milled-in solution, oxycodone IR tablets crushed-in solution, and OxyContin tablets milled-in solution.

PK Parameters	IPC Oxycodone ER 40 mg, milled in solution (N=40) Trt. A	IPC Oxycodone ER 40 mg, intact (N=40) Trt. B	Oxycodone IR 40 mg crushed in solution (N=40) Trt. C	OxyContin 40 mg milled in solution (N=40) Trt. D	Ratio (IPC oxycodone ER milled in solution / IPC Oxycodone ER, intact Trt. A / Trt. B	Ratio (IPC oxycodone ER milled in solution / Oxycodone IR crushed in solution Trt. A / Trt. C	Ratio (IPC oxycodone ER milled in solution / OxyContin milled in solution Trt. A / Trt. D
Cmax (ng/mL)	67(20)	36 (9)	74 (24)	70 (21)	1.86	0.91	0.96
AUC $_{0\text{-}1\ h}$ (ng ×h/mL)	32 (13)	5 (4)	42 (17)	34 (15)	6.40	0.76	0.94
AUC $_{0\text{-}2\ h}$ (ng ×h/mL)	91 (31)	25 (12)	102 (34)	93 (30)	3.64	0.89	0.98
AUC $_{0\text{-}4\ h}$ (ng ×h/mL)	185 (52)	80 (29)	198(57)	183 (46)	2.31	0.93	1.01
AUC $_{0\text{-}t}$ (ng ×h/mL)	503 (144)	554 (144)	534 (148)	491 (137)	0.91	0.94	1.02
AUC $_{0\text{-}inf}$ (ng ×h/mL)	510 (147)	568 (150)	540 (151)	497 (140)	0.90	0.94	1.03
Tmax (h)	1.3 [0.5 – 5.0]	5.0 [1.1 – 12.0]	1.0 [0.3 – 5.1]	1.0 [0.5 – 5.0]			
t1/2 (h)	4.8 (0.8)	6.3 (1.9)	4.7 (0.8)	4.7 (0.8)			

Source: Modified from Sponsor's Table 27, Clinical Study Report OXC3/4/1117

Pharmacokinetic comparison between treatments:

Milled in solution IPC oxycodone ER tablets versus intact IPC Oxycodone ER tablets: The manipulation and oral administration of milled and dissolved in solution IPC oxycodone ER was associated with higher peak and early exposure compared with intact IPC Oxycodone ER, indicating that the ER mechanism was compromised with manipulation.

- The milled and dissolved in solution IPC oxycodone ER was associated with 86% higher Cmax; 540%, 264 % and 131% higher partial AUCs ($AUC_{0\text{-}1h,}$ $AUC_{0\text{-}2h,}$ and $AUC_{0\text{-}4h,}$ respectively) and 3.7 h earlier median Tmax (1.3 h milled versus 5 h intact) compared to intact IPC Oxycodone ER. The overall systemic exposure ($AUC_{0\text{-}inf}$) was similar between two treatments.

Milled in solution IPC oxycodone ER tablets versus crushed in solution Oxycodone IR tablets: The manipulation and oral administration of milled and dissolved in solution IPC

oxycodone ER was associated with lower partial $AUC_{0\text{-}1h}$, but similar Cmax, partial $AUC_{0\text{-}2h}$ and $AUC_{0\text{-}4h}$, overall systemic exposure ($AUC_{0\text{-}inf}$), and median Tmax compared to manipulation and oral administration of crushed in solution oxycodone IR.

Milled in solution IPC oxycodone ER tablets versus milled in solution OxyContin tablets: The manipulation and oral administration of milled and dissolved in solution IPC oxycodone ER was associated with similar rate (Cmax, Tmax) and extent of systemic exposure (partial AUCs and AUC_{inf}) of oxycodone as that of manipulation and oral administration of milled in solution OxyContin.

Agency's Summary of PK findings of abuse potential studies:

- The manipulated and IN administered IPC oxycodone ER tablets were associated with higher systemic exposure compared to the manipulated oxycodone IR tablets. Similar findings of higher Cmax, earlier Tmax, higher partial AUCs were observed for manipulated and IN administered IPC oxycodone ER tablets compared to manipulated and IN administered OxyContin tablets.

- The manipulated and orally administered IPC oxycodone ER tablets were associated with higher systemic exposure compared to intact IPC oxycodone ER tablets, indicating that the ER mechanism was compromised with manipulation.

- The manipulated and orally administered IPC oxycodone ER tablets were associated with approximately similar systemic exposure compared to the manipulated and orally administered oxycodone IR tablets or OxyContin tablets.

6 Summary of Clinical Data for Oxycodone Extended-Release Tablets

No efficacy studies were conducted to support the NDA. The Applicant plans to rely on Agency's prior findings of safety and efficacy for the listed drug, Oxycontin.

6.1 Safety

In the discussion below, the study drug (i.e., oxycodone HCL ER abuse deterrent formulation) may be referred to as IPC (Intellipharmaceutics Corp) oxycodone HCL ER tablets.

First cycle Clinical Program Overview: The clinical program for oxycodone extended-release tablets consisted of seven Phase 1 pharmacokinetic studies using the original formulation that contained FD&C Blue No. 1 Aluminum Lake Dye.

The safety information collected in the pharmacokinetic studies was limited due to the fact that most were single-dose studies conducted in healthy volunteers who were naltrexone-blocked (blocking any opioid-related effects). No new safety signals were identified during the review of the oxycodone extended-release application beyond what is already known for OxyContin.

Second Cycle Clinical Program Overview: The formulation in the second cycle was the same as the original formulation except that the FD&C Blue No. 1 Aluminum Lake Dye was removed. The abuse-deterrence assessment consisted of two clinical studies to evaluate the human abuse liability potential and pharmacokinetics (PK) via intranasal (IN) and oral routes of administration in studies OXC3/2/0816 and OXC3/4/1117, respectively. Subjects in these studies were not naltrexone blocked, so opioid-effects could be detected.

I) Intranasal Human Abuse Potential Study OXC3/2/0816: The Applicant conducted "A Randomized, Double-Blind, Placebo- and Active-Controlled Crossover Study to Evaluate the Oral Abuse Potential and Pharmacokinetics of Manipulated Oxycodone HCl Extended-Release Tablets Compared with Oxycodone Immediate-Release Tablets, Manipulated OxyContin Tablets, and Placebo in Non-Dependent Recreational Opioid Users". See the Clinical Pharmacology discussion above for the detailed description of the study.

Clinical Safety Findings: There were no deaths or serious adverse events (SAEs). One subject discontinued in the Treatment Phase in the IPC oxycodone ER ground treatment group due to vomiting.

Overall, the highest incidence of adverse events (AEs) occurred in the IPC oxycodone ER ground group at approximately 91%, followed by the OxyContin ground group with an AE incidence of approximately 66%. Oxycodone IR crushed had an overall AE incidence of approximately 59%. Placebo IPC and Placebo IR/OxyContin experienced AE incidences of approximately 44% and 9%, respectively.

As shown in Table 3, below, there was a higher incidence of nausea (25%), dizziness (22%), headache (19%), and generalized pruritus (19%) in the IPC treatment group compared to other treatment groups where the incidence for these events was <10%, which probably explains the higher incidence of AEs in the IPC oxycodone ER ground group compared to other treatment groups. This higher incidence of AEs in the IPC oxycodone ER ground group is likely because the IPC oxycodone ER ground group had a higher Cmax and shorter Tmax compared to oxycodone IR crushed and OxyContin ER ground.

There was a slightly higher incidence of nasal congestion in IPC oxycodone ER ground compared to other comparators except for Placebo IPC. The Agency does not consider this to be clinically meaningful as there is no correlation between this finding and the clinical endpoints in the HAP study. In addition, comparing intranasal manipulated Aximris XR 30 mg to intranasal manipulated OxyContin 30 mg, the mean Emax values were not statistically significantly different ($p \geq 0.1455$) with respect to Drug Liking VAS (86.5 versus 85.9, respectively) , Take Drug Again VAS (78.0 versus 80.8, respectively), High VAS (78.8 versus 72.5, respectively), and Overall Drug Liking VAS (79.2 versus 81.3, respectively) so the adverse events reported as a result of intranasal use do not appear to have any meaningful deterrent effect.

The table below displays the incidence of adverse events in the intranasal study by System Organ Class and MedDRA preferred terms which occurred with a frequency greater than 10% in any treatment group.

Table 3. Treatment Emergent Adverse Events >10% Any Treatment Group Intranasal HAP Study

System Organ Class Preferred Term	IPC Oxycodone ER 30 mg Ground N=32	Oxycodone IR 30 mg Crushed N=32	OxyContin 30 mg Ground N=32	Placebo IPC Oxycodone ER N=32	Placebo Oxycodone IR/OxyContin N=32
	n (%)	n (%)	n (%)	n (%)	n (%)
Psychiatric disorders					
Euphoric mood	13 (41)	13 (41)	15 (47)	0	0
Respiratory, thoracic and mediastinal disorders					
Nasal congestion	5 (16)	0	4 (12)	7 (22)	1 (3)
Throat irritation	4 (12)	1 (3)	4 (12)	4 (12)	0
Nervous system disorders					
Somnolence	5 (16)	7 (22)	5 (16)	0	2 (6)
Headache	6 (19)	3 (9)	3 (9)	2 (6)	0
Dizziness	7 (22)	1 (3)	2 (6)	0	0
Skin and subcutaneous tissue disorders					
Generalized pruritus	6 (19)	3 (9)	3 (9)	0	0
Pruritus	1 (3)	5 (16)	4 (12)	0	0
Gastrointestinal disorders					
Nausea	8 (25)	2 (6)	3 (9)	0	0

Source: Applicant's table 30 Clinical Study Report OXC3/2/0816, pages 110-111, modified by Agency clinical reviewer; IR=immediate release; ER=extended-release; percentages rounded

II) Oral Human Abuse Potential Study OXC3/4/1117: The Applicant conducted a study titled, "A Randomized, Double-Blind, Placebo- and Active-Controlled Crossover Study to Evaluate the Oral Abuse Potential and Pharmacokinetics of Manipulated Oxycodone HCl Extended-Release Tablets Compared with Oxycodone Immediate-Release Tablets, Manipulated OxyContin Tablets, and Placebo in Non-Dependent Recreational Opioid Users". See the Clinical Pharmacology discussion above for a description of the study.

Clinical Safety Findings: There were no deaths, serious adverse events (SAEs), or discontinuations due to adverse events in the Treatment Phase of the study.

Overall, the highest incidence of adverse events (AEs) occurred in the oxycodone IR crushed treatment group at approximately 97%, followed by IPC milled in solution and OxyContin milled in solution with an incidence of approximately 95% each. The IPC intact product experienced an incidence of approximately 72% and the lowest incidence of AEs was placebo at approximately 25%.

In general, subjects in the IPC oxycodone ER intact treatment group experienced a lower incidence of AEs compared to other treatment groups except placebo.

The table below displays adverse events by System Organ Class and MedDRA preferred terms for the oral human abuse potential study occurring with a frequency greater than 10%.

Table 4. Treatment Emergent Adverse Events >10% Any Treatment Group Oral HAP Study

System Organ Class Preferred Term	IPC Oxycodone ER 40 mg Milled N=40	IPC Oxycodone ER 40 mg Intact N=40	Oxycodone IR 40 mg Crushed N=40	OxyContin 40 mg Milled N=40	Placebo N=40
	n (%)	n (%)	n (%)	n (%)	n (%)
Psychiatric disorders					
Euphoric mood	34 (85)	19 (47)	32 (80)	34 (85)	4 (10)
Skin & Subcutaneous tissue disorders					
Generalized pruritus	16 (40)	8 (20)	18 (45)	15 (37)	0
Pruritus	7 (17)	4 (10)	10 (25)	7 (17)	1 (2)
Nervous system disorders					
Somnolence	11 (27)	7 (17)	11 (27)	7 (17)	1 (2)
Dizziness	9 (22)	2 (5)	9 (22)	6 (15)	2 (5)
Headache	5 (12)	2 (5)	2 (5)	1 (2)	3 (7)
Paresthesia	2 (5)	0	1 (2)	5 (12)	0
Gastrointestinal disorders					
Dry mouth	14 (35)	8 (20)	11 (27)	11 (27)	2 (5)
Nausea	1 (2)	1 (2)	4 (10)	2 (5)	0
General disorders and administration site conditions					
Feeling of relaxation	2 (5)	3 (7)	3 (7)	5 (12)	1 (2)
Feeling hot	4 (10)	1 (2)	3 (7)	1 (2)	0

Source: Applicant's Table 23, Clinical Study Report, p. 102-103, modified by Agency clinical reviewer; IR=immediate release; ER=extended-release; percentages rounded

Agency's Summary of Clinical Safety findings of abuse potential studies: No new safety signals were identified during the review of the oxycodone ER tablets application beyond what is already known for oxycodone products. There were no deaths or serious adverse events.

Benefit-Risk Assessment

Aximris XR is an extended-release oxycodone drug product formulated to incorporate abuse-deterrent technologies utilizing a combination of physical and chemical barriers, 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.

Chronic pain is a serious medical condition which can affect function, quality of life, and poses a significant public health concern. The annual societal cost in medical expenses and missed work due to issues related to chronic pain is considerable.

Abuse and misue of opioids has become a national public health crisis. Extensive prescribing of opioid analgesics for pain has resulted in widespread availability of

prescription opioids in the community which have contributed to high rates of opioid abuse, overdose, addiction, and death. Efforts to address the opioid epidemic are of critical public health importance and a highest FDA priority.

The goal of chronic pain treatment is to control pain with minimal side effects from pain medication. Though there are many treatment options available, opioids remain a key component of a multi-modal approach to the medical management of chronic pain in some patients. Of the available FDA- approved prescription opioids with abuse- deterrent (AD) labeling, only two extended-release oxycodone-containing products, OxyContin and Xtampza, are currently marketed in the US.

For Aximris XR, collective results from syringeability/extractability studies have shown that under certain conditions, abuse by the IV route is expected to be deterred compared to immediate-release oxycodone. Neither nasal nor oral abuse deterrence was demonstrated for Aximris XR.

Benefits and Risks to Patients Using Aximris XR as Labeled:

The safety and efficacy of oxycodone extended-release tablets (Aximris XR) is based on the demonstration of bioequivalence to OxyContin. When used as labeled, this product carries similar benefits and risks as OxyContin and other approved extended-release oxycodone products.

Opioids carry serious risks for numerous safety concerns including abuse, misuse, addiction, and intentional or accidental overdose which may result in respiratory depression and death. All opioids are regulated under a Risk Evaluation and Mitigation Strategy (REMS) in an effort to monitor and mitigate these risks[5](also see Sections 8.3 and 10.5 of this document)

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.

At a joint meeting of the Drug Safety and Risk Management and the Anesthetic and Analgesic Drug Products Advisory Committees held on June 11-12, 2019, FDA sought public input on the clinical utility and safety concerns associated with the higher range of opoid analgesic dosing in the outpatient setting. The Agency was interested in better understanding the current clinical use and situations that may warrant use of higher doses of opioid analgesics, as well as the magnitude and frequency of harms associated with higher doses relative to lower doses of opioid analgesics.[6] Extended-release opioids are available in higher dosage strengths than immediate-release opioids, and are often prescribed to patients who require higher doses of opioids to control their pain.

[5] https://www.fda.gov/drugs/information-drug-class/opioid-analgesic-risk-evaluation-and-mitigation-strategy-rems

[6] https://www.fda.gov/advisory-committees/advisory-committee-calendar/june-11-12-2019-joint-meeting-drug-safety-and-risk-management-advisory-committee-and-anesthetic-and

At the meeting, the majority of committee members agreed that although there are greater risks associated with higher daily doses or higher dosage strengths of opioid analgesics relative to lower daily doses or dosage strengths, there is a clinical need for higher range dosing of opioid analgesics in certain patient populations with chronic pain conditions such as those receiving hospice or palliative care, those with debilitating illnesses such as cancer, complex neurological, or musculoskeletal conditions, and others.

The committees acknowledged the complexity of this issue, and noted that negative impacts on both patient and public health may ensue if the Agency were to take a regulatory action that resulted in reduced prescribing, access to, or use of higher dosage strenghs to treat chronic pain conditions in certain patient populations who have a clinical need. The committees agreed that there are many uncertainties, for example illicit opioid use and addiction stemming from higher doses or dosage units, and additional data is needed to address these. Refer to the meeting materials for additional information.[4]

The well known risks associated with opioids are serious and must be taken into consideration when prescribing these drugs. There are patients for whom only opioid analgesics will treat their pain, even with the implementation of multimodal pain treatment. In this setting, proper patient selection, education, proper prescribing, and ongoing follow-up are crucial to ensure the benefits of these drugs outweigh the risks.

Risks of Not Using the Drug as Labeled: Aximris is for oral use only. Abuse of Aximris poses a risk of overdose and death. The risk is increased with concurrent use of Aximris with alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved Aximris enhances drug release and increases the risk of overdose and death.

Based on in vitro and clinical human abuse potential studies, this product can be expected to have some degree of abuse deterrence by the IV route. Studies did not support abuse deterrence by the oral or nasal route.

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

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

Benefits and Risks to Public Health: Abuse-deterrent opioid formulations are developed to increase barriers for misuse and abuse, which is a benefit to the public health.

Although Aximris XR failed to demonstrate abuse deterrence for oral and nasal routes, it did demonstrate IV abuse-deterrent properties. Even when one considers that the IV abuse

deterrence can be overcome under certain conditions, the addition of an IV abuse-deterrent formulation adds to already available abuse-deterrent products.

The Agency is aware of the risks of potential unintended adverse consequences with introduction of abuse-deterrent formulations such as a shift to more dangerous routes of abuse or abusers using tampering methods that could result in harmful effects. This became very clear during the postmarketing review and advisory committee meeting for Opana ER.[7] The Agency has not identified unique features of the Aximris XR formulation that would result in new unintended consequences, however the Agency closely monitors for these risks post-approval.

The Agency is also cognizant of the public health concern of potentially approving another opioid and adding new opioids into the marketplace. A recent study[8] found that approval of new branded opioid products alone does not appear to be a primary driver of increased opioid prescribing. Moreover, this same article found that the number of opioid analgesic prescriptions dispensed has declined since 2012, despite an increasing number of opioid analgesic approvals.

Conclusion: The risks and benefits of extended-release, abuse-deterrent opioids have been discussed. Aximris XR appears to have similar risks and benefits to other approved abuse-deterrent, extended-release opioid products. All opioids carry serious, labeled risks for numerous safety concerns including addiction, abuse, misuse, and intentional or accidental overdose, which may result in respiratory depression and death. Opioids are regulated under a Risk Evaluation and Mitigation Strategy (REMS) in an effort to monitor and mitigate these risks. Extended-release opioid analgesics provide a benefit to certain patient populations in which opioid analgesics are the only effective treatment for their pain.

[7] https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-meeting-time-and-public-participation-information-joint-meeting-drug-safety-and-risk

[8] Chai G, et al, New Opioid Analgesic Approvals and Outpatient Utililzation of Opioid Analgesics in the United States, 1997 through 2015, Anesthesiology, Volume 128, No 5, May 2018, pages 953-966.

7 Controlled Substance Staff Memorandum

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:	September 24, 2019
To:	Rigoberto Roca, M.D., Acting Director Division of Anesthesiology, Addiction Medicine and Pain Medicine
Through:	Dominic Chiapperino, Ph.D., Director Silvia Calderon, Ph.D., Senior Pharmacologist Controlled Substance Staff
From:	James M. Tolliver, Ph.D., Pharmacologist Controlled Substance Staff
Subject:	BACKGROUND DOCUMENT on Oral Human Abuse Potential (HAP) Study OXC3/4/1117 and Intranasal Human Abuse Potential Study OXC/2/0816 Submitted Under NDA 209-653. Prepared for the FDA Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Meeting, January 15, 2020. Sponsor: Intellipharmaceutics Corp.

Background

Intellipharmaceutics Corp. submitted oral human abuse potential (HAP) study OXC3/4/1117 and intranasal HAP study OXC/2/0816 under NDA 209653 in support of Aximris XR (Oxycodone HCl) extended-release tablets. Aximris XR tablets were designed to have abuse-deterrent properties. Oral and intranasal HAP studies conducted as part of a pre-market abuse-deterrent assessment are generally thought to be predictive of the likelihood that the abuse-deterrent properties of a formulation will deter or reduce the abuse of the product when taken via the oral or intranasal routes of abuse. A description of studies OXC3/4/1117 and OXC/2/0816, along with relevant findings, are provided below.

Description of Oral HAP Study OXC3/4/1117

Study OXC3/4/1117 was a single-dose, randomized, double-blind, active- and placebo-controlled, 5-way crossover study comprising a Screening Visit, Qualification Phase

(Naloxone Challenge and Drug Discrimination Tests), Treatment Phase, and Follow-up. Completer population consisted of 40 non-dependent, recreational opioid users.

The primary objectives of the study were:

- To evaluate the abuse potential of intact and manipulated Aximris XR 40 mg tablets relative to manipulated oxycodone IR 40 mg tablets and placebo following oral administration in non-dependent, recreational opioid users.
- To evaluate the PK profile of intact and manipulated Aximris XR 40 mg tablets relative to crushed oxycodone IR tablets following oral administration in non-dependent, recreational opioid users.

The secondary objectives of the study were:

- To evaluate the abuse potential and PK profile of manipulated Aximris XR 40 mg compared to manipulated OxyContin 40 mg in non-dependent, recreational opioid users.
- To evaluate the safety of orally administered intact and manipulated Aximris XR ER tablets relative to crushed oxycodone IR tablets, manipulated OxyContin, and placebo in non-dependent, recreational opioid users.

The determination of relative abuse potential was assessed using subjective measures that are based on visual analogue scales (VAS), which are used in the Drug Discrimination Phase and Treatment Phase. Some of the key VAS measures used included the following:

- Bipolar 0-100 mm “at the moment” Drug Liking VAS anchored on the left by “Strong Disliking” (score of 0), in the center by "Neither Like Nor Dislike" (score of 50), and on the right by "Strong Liking” (score of 100). Subjects are asked to respond to the statement *“At this moment, my liking for this drug is.”*
- Unipolar 0-100 mm "at the moment" High VAS anchored on the left by "Not at All" (score of 0) and on the right by “Extremely” (score of 100). Subjects are asked to respond to the statement “*At this moment, I feel high.”*
- Global bipolar 0-100 mm Take Drug Again VAS required subjects to reflect back over their experience at 12 hours and 24 hours post-dosing for each treatment. The VAS was anchored on the left by “Definitely Not” (score of 0), in the center by "Neutral" (score of 50) and on the right by “Definitely So” (score of 100). Subjects were asked to respond to the statement *“I would take this drug again.”*
- Global bipolar 0-100 mm Overall Drug Liking VAS also required subjects to reflect back over their experience at 12 hours and 24 hours post-dosing for each treatment. The VAS was anchored on the left by “Strong Disliking” (score of 0), in the center by "Neither Like or Dislike" (score of 50) and on the right by “Strong Liking” (score of 100). Subjects responded to the statement “Overall, my liking for this drug is...”
- The Ease of Snorting VAS is intended to assess the difficulty of snorting the study drugs. Subjects responded to the statement “Snorting the drug was...” The question was scored using a 0 to 100 point, unipolar VAS anchored on the left with “very easy” (score of 0) and anchored on the right with “very difficult” (score of 100).

Besides demonstrating non-dependence to opioids via the naloxone challenge test, subjects had to distinguish between oral crushed oxycodone IR 40 mg in solution and placebo solution in the Drug Discrimination test. Qualification criteria included:

- Peak score (Emax) in response to oxycodone IR 40 mg greater than that of placebo on Drug Liking and Take Drug Again visual analog scale (VAS; difference of at least 15 points). An Emax score of at least 75 points on Drug Liking VAS and Take Drug Again VAS must have been indicated in response to oxycodone IR.
- Acceptable placebo response based on Drug Liking VAS Emax and Take Drug Again VAS Emax (i.e., score between 40 and 60 points, inclusive).
- Able to complete the subjective measure assessments and had acceptable overall responses as judged by the investigator or designee.
- Able to tolerate oxycodone IR 40 mg as judged by the investigator or designee based on available safety data (e.g., no emesis within 2 hours following dosing).
- General behavior suggested that the subject could successfully complete the study, as judged by the research site staff.

Subjects successfully completing the Qualification Phase were randomized in the Treatment phase to 1 of the 10 treatment sequences. Each treatment was administered in a randomized, double-blind, triple-dummy fashion following a fasting period of at least 8 hours. Each study drug administration was separated by a washout interval of at least 72 hours. Subjects received single oral doses of each of the following treatments on Day 1 of each treatment period (1 per treatment period):

- Aximris XR 40 mg, manipulated, in solution
- Aximris XR 40 mg, intact
- Oxycodone IR (Roxicodone®) 40 mg, manipulated in solution
- OxyContin® 40 mg, manipulated, in solution
- Placebo

For purposes of examining the pharmacokinetics of plasma oxycodone blood samples were taken pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, and 36 hours post-dosing. Pharmacokinetic assessment centered on maximum oxycodone plasma concentration (Cmax), time to Cmax, and drug exposure over the first hour post-dosing as reflected under the oxycodone plasma concentration versus time curve for first area (AUC0-1hr).

Drug Liking VAS and High VAS were assessed at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, and 24 hours post-dosing. High VAS was also measured pre-dosing. Take Drug Again VAS and Overall Drug Liking VAS were taken at 12 hours and 24 hours post-dosing. Maximum effect, designated Emax, for Drug Liking VAS and Take Drug Again VAS constituted the primary endpoints.

Pharmacodynamic parameters determined included but were not limited to:

- Emax = maximum effect observed
- TEmax = time to maximum effect (Emax)
- AUE0-1hr = area under the effect curve out to 1 hour post-dosing.

Statistical analyses of pharmacodynamic endpoints were conducted by the CDER Office of Biostatistics. The Applicant's analysis results were verified using various statistical methods.

Findings for Study OXC3/4/1117

1. With respect to the primary subjective measures of Drug Liking VAS and Take Drug Again VAS, the positive comparator, manipulated Oxycodone IR 40 mg in solution, produced mean Emax values that were greater than placebo by more than 15 points ($p < 0.0001$), thereby validating the study.

2. Oral manipulated Aximris XR 40 mg produced a mean (SD) Cmax of oxycodone of 67.20 (20.32) ng/mL with a median Tmax of 1.30 hours. In contrast, oral Oxycodone IR 40 mg resulted in a mean (SD) Cmax of 74.05 (23.55) ng/mL with a median Tmax of 1.03 hours. Mean (SD) oxycodone exposure over the first hour post-dosing as indicated by AUC0-1hour following oral manipulated Aximris XR and oral Oxycodone IR were 31.57 (12.83) and 41.63 (16.59) ng*h/mL, respectively. These pharmacokinetic findings do not support a deterrent effect of Aximris XR to oral abuse.

3. The following pharmacodynaminc findings suggest that Aximris XR will not have a deterrent effect to oral abuse.

    a. Oral manipulated Aximris XR produced a mean Emax of Drug Liking that was not statistically significantly different ($p \geq 0.6222$) from that produced by oral manipulated Oxycodone IR (90.4 versus 89.7, respectively).
    b. Oral manipulated Aximris XR produced a mean Emax of Take Drug Again that was not statistically significantly different ($p \geq 0.8669$) from that produced by oral manipulated Oxycodone IR (85.8 versus 81.0, respectively).
    c. Oral manipulated Aximris XR produced a mean Emax of High that was not statistically significantly different ($p \geq 0.4413$) from that produced by oral manipulated Oxycodone IR (81.7 versus 82.2).
    d. Oral manipulated Aximris XR produced a mean Emax of Overall Drug Liking that was not statistically significantly different ($p \geq 0.942$) from that produced by either oral manipulated Oxycodone IR (83.8 versus 77.3, respectively).
    e. Oral manipulated Aximris XR produced mean Emax values that were statistically significantly higher than that of oral placebo for Drug Liking VAS (90.4 versus 52.5, respectively), Take Drug Again (85.8 versus 51.9, respectively), High VAS (81.7 versus 4.9, respectively), and Overall Drug Liking (83.8 versus 51.7, respectively).

Under the secondary objective (exploratory analysis) of comparing oral manipulated Aximris XR 40 mg in solution to oral manipulated OxyContin 40 mg in solution, the mean Emax values were not statistically significantlly different ($p \geq 0.4413$) with respect to Drug Liking VAS (90.4 versus 89.8, respectively) , Take Drug Again VAS (85.8 versus 83.0, respectively), High VAS (81.8 versus 80.6, respectively), and Overall Drug Liking VAS (83.8 versus 82.0, respectively). The statistical analysis plan did not take into account multiple comparison.

Description of Intranasal HAP Study OXC/2/0816

Study OXC/2/0816 was a single-dose, randomized, double-blind, active- and placebo-controlled, 5-way crossover study comprising a Screening Visit, Qualification Phase (Naloxone Challenge and Drug Discrimination Tests), Treatment Phase, and Follow-up/early termination visit.

Subjects consisted of opioid users who had used opioids non-therapeutically (i.e., for psychoactive effects) at least 10 times in the past year and used opioids at least once in the 12 weeks before Screening. They were also required to have had experience with intranasal non-therapeutic opioid use on at least 3 occasions in the year prior to Screening.

The primary objectives of this study were:

- To evaluate the abuse potential of manipulated Aximris XR tablets, compared to manipulated oxycodone immediate-release (IR) and placebo when administered intranasally to nondependent, recreational opioid users.
- To evaluate the pharmacokinetic (PK) profile of manipulated Aximris XR tablets relative to manipulated oxycodone IR when administered intranasally to non-dependent, recreational opioid users.

The secondary objectives of this study were:

- To evaluate the abuse potential of ground Aximris XR tablets compared to ground OxyContin when administered intranasally to non-dependent, recreational opioid users.
- To evaluate the PK profile of ground Aximris XR ER relative to ground OxyContin when administered intranasally to non-dependent, recreational opioid users.

The determination of relative abuse potential was assessed using subjective measures that are based on visual analogue scales (VAS), in the Drug Discrimination Phase and Treatment Phase. The VAS measures, as described earlier in this section, were the same measures used in Study OXC3/4/1117.

In the Qualification Phase subjects were required to demonstrate non-dependence to opioids in the Naloxone Challenge Test. In the Drug Discrimination Test subjects received a single 30 mg intranasal dose of crushed oxycodone IR (Roxicodone) and matching placebo in a randomized, double-blind, crossover manner, each separated by approximately 24 hours, to ensure that they were able to discriminate the positive drug effects of the active control from placebo and safely tolerate the dose planned for the Treatment Phase. Specific criteria that subjects were required to satisfy entering the Treatment Phase are listed below.

- Peak score (Emax) in response to intranasally administered 30 mg oxycodone IR greater than that of placebo on Drug Liking and Take Drug Again VAS (difference of at least 15 points). An Emax score of at least 75 points on Drug Liking VAS and Take Drug Again VAS must have been indicated in response to oxycodone IR.
- Acceptable placebo response based on Drug Liking VAS Emax and Take Drug Again VAS Emax (ie, score between 40 and 60 points, inclusive).

- Ability to complete the PD assessments and had acceptable overall responses as judged by the investigator or designee.
- Was able to tolerate 30 mg oxycodone IR administered intranasally as judged by the investigator or designee based on available safety data (e.g., no emesis within 2 hours following dosing and no sneezing/attempts to blow their nose within 1-hour post dosing), and ability to insufflate the entire volume of crushed study drug.
- General behavior suggested that the subject could successfully complete the study, as judged by the research site staff.

Following qualification, eligible subjects were randomized to 1 of 10 treatment sequences in the Treatment Phase. Each treatment was administered in a randomized, double-blind, crossover manner following a fasting period of at least 8 hours, and a washout interval of at least 3 days separated each treatment administration. Intranasal treatments are listed below.

- Aximris XR (30 mg) tablet, manipulated
- Oxycodone IR (30 mg) tablet, manipulated
- Oxycodone ER (OxyContin 30 mg) tablet, manipulated
- Placebo, matched to Aximris XR tablet, manipulated
- Placebo (to approximate oxycodone IR tablet, manipulated/OxyContin, manipulated)

Treatments were self-administered by subjects while they were seated, under the supervision of study personnel. Study drugs were provided in dark dosing containers with a straw to assist insufflation. Subjects were permitted to use both nares to administer the treatments. Any residual amounts remaining following dosing (excluding negligible trace amounts) were weighed and the percent insufflated was calculated.

Blood samples were taken pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours post-dosing in order to examine the pharmacokinetics of oxycodone following each drug treatment. Endpoints included Cmax, Tmax, and AUC0-1hour.

Drug Liking VAS and High VAS were assessed at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, and 24 hours post-dosing. High VAS was also measured pre-dosing. Take Drug Again VAS and Overall Drug Liking VAS were taken at 12 hours and 24 hours post-dosing. Emax, was determined for all subjective measures. The co-primary endpoints were the Emax for Drug Liking and Take Drug Again. The time to achieve Emax, namely Tmax was also determined.

Statistical analyses of pharmacodynamic endpoints were conducted by the CDER Office of Biostatistics. The Applicant's analysis results were verified using various statistical methods.

Findings for Study OXC/2/0816

1. With respect to the primary subjective measures of Drug Liking VAS and Take Drug Again VAS, the positive comparator, intranasal manipulated Oxycodone IR 30 mg produce mean Emax values that were greater than intranasal placebo by more than 15 points ($p < 0.0001$), thereby validating the study.

2. Intranasal manipulated Aximris XR 30 mg produced a mean (SD) Cmax of oxycodone of 92.01 (21.80) ng/mLwith a median Tmax of 0.50 hours. In contrast, intranasal manipulated Oxycodone IR 30 mg resulted in a mean (SD) Cmax of 55.42 (11.38) ng/mL with a median Tmax of 2.00 hours. Total mean (SD) oxycodone exposure as indicated by AUC0-infinity following intranasal manipulated Aximris XR and manipulated Oxycodone IR were 589.37 (140.17) and 465.73 (93.17) ng*h/mL, respectively. These pharmacokinetic findings do not support a deterrent effect of Aximris XR to intranasal abuse.

3. The following pharmacodynaminc findings suggest that Aximris XR will not have a deterrent effect to intranasal abuse.

    a. Intranasal manipulated Aximris XR produced a mean Emax of Drug Liking that was not statistically significantly different ($p \geq 0.5226$) from that produced by intranasal manipulated Oxycodone IR (86.5 versus 86.3, respectively).
    b. Intranasal manipulated Aximris XR produced a mean Emax of Take Drug Again that was not statistically significantly different ($p \geq 0.0924$) from that produced by intranasal manipulated Oxycodone IR (78.0 versus 84.8, respectively).
    c. Intranasal manipulated Aximris XR produced a mean Emax of High that was not statistically significantly different ($p \geq 0.1050$) from that produced by intranasal manipulated Oxycodone IR (78.8 versus 71.6).
    d. Intranasal manipulated Aximris XR produced a mean Emax of Overall Drug Liking that was not statistically significantly different ($p \geq 0.0724$) from that produced by intranasal manipulated Oxycodone IR (79.2 versus 86.0, respectively).
    e. Manipulated Aximris XR produced mean Emax values that were statistically significantly higher than that of placebo for Drug Liking VAS (86.5 versus 51.1, respectively), Take Drug Again (78.0 versus 49.0, respectively), High VAS (78.8 versus 3.1, respectively), and Overall Drug Liking (79.2 versus 50.1, respectively).

4. Under the secondary objective (exploratory analysis) of comparing intranasal manipulated Aximris XR 30 mg to intranasal manipulated OxyContin 30 mg, the mean Emax values were not statistically significally different ($p \geq 0.1455$) with respect to Drug Liking VAS (86.5 versus 85.9, respectively) , Take Drug Again VAS (78.0 versus 80.8, respectively), High VAS (78.8 versus 72.5, respectively), and Overall Drug Liking VAS (79.2 versus 81.3, respectively). The statistical analysis plan did not take into account multiple comparison.

8 Overview of Postmarketing Requirements (PMRs)

8.1 Abuse-Deterrent Opioid Analgesics PMRs

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: December 16, 2019

FROM: Rigoberto Roca, MD
Acting Director
Division of Anesthesiology, Addiction Medicine and Pain Medicine
Office of Neuroscience, CDER, FDA

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

RE: Postmarketing Requirements (PMRs) for Opioid Analgesics Labeled with Abuse-Deterrent Properties

---

The following PMRs are currently required for all approved opioid analgesics labeled with abuse-deterrent properties, in order to assess the known serious risks of misuse and abuse by determining whether the properties intended to deter misuse and abuse of the product actually result in a meaningful decrease in misuse and abuse, and their consequences of addiction, overdose, and death, in the community. The following studies are conducted according to a schedule agreed upon with the Agency.

xxxx-1 Conduct a descriptive study to collect meaningful baseline data to support subsequent formal epidemiologic assessments of the abuse-deterrence of TRADENAME. The descriptive study should include data on the following:

1) Utilization of TRADENAME and selected comparators. Reports should include nationally-projected quarterly dispensing data, overall and by age group and census region;

AND

2) Abuse of TRADENAME and related clinical outcomes. These assessments should utilize multiple data sources in different populations to establish the scope and patterns of abuse for TRADENAME as well as mutually agreed-upon, selected comparators to provide context.

   - Data should include route-specific abuse outcomes, be nationally-representative or from multiple large geographic areas, and use meaningful measures of abuse.

   Additional information, either qualitative or quantitative, from sources such as internet forums, spontaneous adverse event reporting, or small cohort studies may also be included to help better understand abuse of this drug, including routes and patterns of abuse in various populations.

   Formal hypothesis testing is not necessary during this phase, but provide information on the precision of abuse-related outcome estimates (e.g., 95% confidence intervals for quarterly estimates) and calculate utilization-adjusted outcome estimates where possible.

In addition, following satisfactory completion of PMR xxxx-1, FDA intends to require that you conduct the following:

Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of TRADENAME actually result in a meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in the post-approval setting. The studies should allow FDA to assess the impact, if any, attributable to the abuse-deterrent properties of TRADENAME and should incorporate recommendations contained in guidance for industry: *Abuse-Deterrent Opioids—Evaluation and Labeling*, available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm334743.pdf.. Assessing the impact of the formulation with abuse deterrent properties on the incidence of clinical outcomes, including overdose and death, is critical to fulfilling this PMR. Any studies using electronic healthcare data should use validated outcomes and adhere to guidelines outlined in FDA's guidance for industry and FDA staff: *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data* available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm243537.pdf.

Additional specific details of this postmarketing requirement, including a timetable and annual reporting requirements, will be described more fully after completion of and review of data for PMR xxxx-1.

8.2 ERLA PMRs

M E M O R A N D U M

DATE: December 16, 2019

FROM: Rigoberto Roca, MD
Acting Director
Division of Anesthesiology, Addiction Medicine and Pain Medicine
Office of Neuroscience, CDER, FDA

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

RE: Postmarketing Requirements (PMRs) for Extended-Release/Long-Acting Opioid Analgesics

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

The following PMRs are required for all approved ERLA opioid analgesics labeled with abuse-deterrent properties, in order to assess the known serious risks of misuse and abuse by determining whether the properties intended to deter misuse and abuse of the product actually result in a meaningful decrease in misuse and abuse, and their consequences of addiction, overdose, and death, in the community. The following studies are conducted according to a schedule agreed upon with the Agency.

1. In order to provide the baseline data to support the hypothesis-testing studies required under 2 (below), conduct a descriptive study that analyzes data on the following:

    3) utilization of TRADENAME and selected comparators. Reports should include nationally-projected quarterly retail dispensing, overall and by age group and census region; AND

    4) abuse of TRADENAME and related clinical outcomes. These studies should utilize multiple data sources in different populations to establish the scope and patterns of abuse for TRADENAME as well as mutually agreed-upon, selected comparators to provide context.

        - Data should include route-specific abuse outcomes, be nationally-representative or from multiple large geographic areas, and use meaningful measures of abuse.

        - Additional information, either qualitative or quantitative, from sources such as internet forums, spontaneous adverse event reporting, or small cohort studies may also be included to help better understand abuse of this drug, including routes and patterns of abuse in various populations.

        - Formal hypothesis testing is not necessary during this phase, but provide information on the precision of abuse-related outcome estimates (e.g. 95% confidence intervals for quarterly estimates) and calculate utilization-adjusted outcome estimates where possible.

2. Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of TRADENAME actually result in a meaningful decrease

in misuse and abuse, and their consequences, addiction overdose, and death, in post-approval settings. The studies should allow FDA to assess the impact, if any, attributable to the abuse-deterrent properties of TRADENAME and should incorporate recommendations contained in Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry (April 2015). Assessing the impact of the abuse-deterrent formulation on the incidence of clinical outcomes, including overdose and death, is critical to fulfilling this PMR. Any studies using electronic healthcare data should use validated outcomes and adhere to guidelines outlined in FDA's Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.

8.3 ERLA REMS

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

Date:	**December 16, 2019**
To:	**Members of the Joint Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management (DSaRM) Advisory Committee**
From:	**Division of Risk Management (DRISK)** **Office of Medication Error Prevention and Risk Management (OMEPRM)** **Office of Surveillance and Epidemiology (OSE)**
Drug Name:	**oxycodone hydrochloride**
Application Number:	**NDA 209653**
Subject:	**Risk Evaluation and Mitigation Strategy (REMS)**

If approved, oxycodone hydrochloride extended-release oral tablets (NDA 209653), will be required to become a member of the Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of the drug outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. The Opioid Analgesic REMS is a shared system REMS that was initially

approved as the Extended-Release (ER) and Long-Acting (LA) (ER/LA) REMS in July 2012 and expanded in September 2018 to include all application holders of IR opioid analgesics that are expected to be used in the outpatient setting and that are not already covered by another REMS program.

The Opioid Analgesic REMS is intended to reduce risks and improve safe use of opioid analgesics while continuing to provide access to these medications for patients in pain. The central component of the Opioid Analgesics REMS is an education program for healthcare providers (HCPs), including prescribers, nurses, and pharmacists, involved in the treatment and monitoring of patients with pain. Under the Opioid Analgesic REMS, application holders[9] are required to make education programs available to HCPs. The application holders are meeting this requirement by providing educational grants to accredited continuing education (CE) providers who offer training to HCPs at no or nominal cost. The training must include successful completion of a knowledge assessment and proof of successful program completion.

To be considered compliant with the Opioid Analgesic REMS, the CE courses are required to include the content and messages of a "blueprint" developed by FDA for this purpose. The currently approved FDA Blueprint, *FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain,* focuses on the fundamentals of acute and chronic pain management and provides a contextual framework for the safe prescribing of opioid analgesics. This includes principles related to the acute and chronic pain management; non-pharmacologic treatments for pain; and pharmacologic treatments for pain (both non-opioid analgesic and opioid analgesic). The FDA Blueprint covers basic information about addiction medicine and opioid use disorder. The core messages are directed to prescribers, pharmacists, and nurses, but are also relevant for other HCPs who participate in the management of pain.[10]

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

Attachments:
See Appendix – FDA Blueprint

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

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

9 Office of Surveillance and Epidemiology Reviews

9.1 Drug Utilization Review

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

Drug Utilization Review

Date:	December 16, 2019
Reviewer:	Tracy Pham, Pharm.D. Division of Epidemiology II
Team Leader:	Rajdeep Gill, Pharm.D. Division of Epidemiology II
Deputy Director for Drug Utilization:	LCDR Grace Chai, Pharm.D. Division of Epidemiology II
Associate Director for Public Health Initiatives:	Judy Staffa, Ph.D., R.Ph. Office of Surveillance and Epidemiology
Subject:	Outpatient Retail Utilization Patterns of Opioid Analgesics: Advisory Committee Meeting on a New Drug Application for a Single-Ingredient Oxycodone Extended-Release Product with Formulation Properties Designed to Deter Abuse
Drug Name(s):	Opioid Analgesics
Application Type/Number:	Multiple
Applicant/Sponsor:	Multiple
OSE RCM #:	2019-938

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

Table of Contents

EXECUTIVE SUMMARY

A joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) will be held to discuss the overall risk benefit profile and the approvability of a proposed new drug application (NDA) for an oxycodone extended-release (ER) product with formulation properties designed to deter abuse. In preparation for this joint advisory committee (AC) meeting and to provide context for the AC discussion, this review examined the national utilization patterns of opioid analgesics, with a focus on single-ingredient oxycodone ER, in the U.S. retail setting from 2014 through 2018.

Based on prescription dispensing data from U.S. retail pharmacies, an estimated 15.5 million prescriptions were dispensed for extended-release/long-acting (ER/LA) opioid analgesics, accounting for approximately 9% of the total 169 million prescriptions dispensed for any opioid analgesics in 2018. The most frequently dispensed ER/LA opioid analgesics were morphine ER at 33%, fentanyl transdermal patch at 20%, single-ingredient oxycodone ER at 19%, and methadone at 13% of dispensed prescriptions in 2018. Among the opioid analgesics with formulation properties designed to deter abuse, single-ingredient oxycodone ER accounted for 88% of dispensed prescriptions in 2018. Although frequently dispensed from the retail pharmacies, the number of prescriptions dispensed for single-ingredient oxycodone ER decreased by 36% from 4.7 million prescriptions in 2014 to 3 million prescriptions in 2018.

Family practice/general practice/internal medicine specialists were the top prescribers, accounting for 41% of prescriptions dispensed for single-ingredient oxycodone ER from the retail pharmacies in 2018. Based on office-based physicians survey data in 2018, single-ingredient oxycodone ER was primarily prescribed for the diseases of the musculoskeletal system and connective tissue such as low back pain.

In summary, utilization of single-ingredient oxycodone ER decreased over the past five years. In 2018, single-ingredient oxycodone ER accounted for 19% of prescriptions dispensed for all ER/LA opioid analgesics, following prescriptions dispensed for morphine ER (33%) and fentanyl transdermal patches (20%), but has accounted for the vast majority of the prescriptions dispensed for any opioid analgesics with formulation properties designed to deter abuse throughout the examined time.

1 INTRODUCTION

A New Drug Application (NDA) was submitted for the approval of a single-ingredient oxycodone ER product with formulation properties designed to deter abuse for a proposed indication for the management of moderate to severe pain when a continuous around the clock analgesic is needed for an extended period of time. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) is bringing this application to a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), and the Drug Safety and Risk Management Advisory Committee (DSaRM). The AC panel will discuss whether the data submitted by the Applicant are sufficient to support the approval and labeling of the product with the formulation properties expected to deter abuse. In preparation for the AC meeting, DAAAP requested the Division of Epidemiology II (DEPI II) to provide utilization data for opioid analgesics, with a focus on single-ingredient oxycodone ER, as background information to provide context to the AC discussion.

2 METHODS AND MATERIALS

2.1 PRODUCTS INCLUDED

The following opioid analgesics, including products with formulation properties designed to deter abuse, are included in the analyses of the review, which focused on opioid analgesics largely dispensed through retail pharmacies. Due to the different indications and settings of care, the review analyses excluded: 1) opioid analgesics with injectable, topical, and suppository formulations, 2) Medication-Assisted Therapy (MAT) products (e.g. buprenorphine and methadone), 3) opioid-containing cough/cold products, and 4) migraine products containing an opioid, aspirin, butalbital, and/or caffeine.

Extended-Release/Long-Acting Formulation (ER/LA)	**Immediate-Release Formulation (IR)**
• Buprenorphine Transdermal • Buprenorphine Oral Strip • Fentanyl Transdermal • Hydrocodone • Hydromorphone • Methadone (excluding products used as MAT) • Morphine • Morphine-Naltrexone • Oxycodone • Oxycodone-Acetaminophen (Xartemis® XR was withdrawn from marketing in October 2018.[1]) • Oxymorphone • Tapentadol • Tramadol <u>Abuse-deterrent formulations</u>[2] o OxyContin® and its generics o Targiniq™ ER (oxycodone/naloxone) o Embeda® (morphine/naltrexone ER) o Hysingla® ER (hydrocodone ER) o MorphaBond™ ER (morphine) o Xtampza® ER (oxycodone) o Arymo® ER (morphine) o RoxyBond™ (oxycodone ER)	• Butorphanol • Codeine • Codeine-Acetaminophen • Hydrocodone-Acetaminophen • Hydrocodone-Ibuprofen • Hydromorphone • Levorphanol • Meperidine • Meperidine-Promethazine • Morphine • Opium • Oxycodone • Oxycodone-Acetaminophen • Oxycodone-Ibuprofen • Oxymorphone • Pentazocine-Acetaminophen • Pentazocine-Naloxone • Propoxyphene • Propoxyphene-Acetaminophen • Tapentadol • Tramadol • Tramadol-Acetaminophen • Transmucosal Immediate-Release Fentanyl (TIRF)

The following opioid analgesic products were not included in the analyses.

- Targiniq™ ER (oxycodone-naloxone ER) had not been marketed since approval and was withdrawn from marketing in October 2018.[1]

[1] Food and Drug Administration. *Endo Pharmaceuticals, Inc., et al.; Withdrawal of Approval of 10 New Drug Applications*. 83 Federal Register 209 (29 October 2018): 54355-54356. Accessed May 2019. Available at: https://www.govinfo.gov/content/pkg/FR-2018-10-29/pdf/2018-23528.pdf

[2] https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/abuse-deterrent-opioid-analgesics

- Troxyca® ER (oxycodone-naltrexone) had not been marketed since approval and was withdrawn from marketing in April 2018.[3]
- RoxyBond™ (oxycodone ER) has not been marketed in the U.S. since approval in April 2017. [4]

2.2 DATA SOURCES USED

Proprietary databases available to the FDA were used to conduct the drug utilization analyses in this review. See Appendix B for full database descriptions.

2.2.1 Determining Settings of Care

The IQVIA National Sales Perspectives™ (NSP) database was used to determine the primary setting of care for the utilization of opioid analgesics based on the estimated number of bottles or packages of these products sold from manufacturers to various settings of care in 2018.

2.2.2 Prescription Data

The Symphony Health PHAST™ Prescription Monthly database was used to provide the estimated number of prescriptions dispensed for any opioid analgesics from U.S. retail pharmacies from 2014 through 2018. Data on the top ten prescriber specialties for single-ingredient oxycodone ER in 2018 were also obtained from this database.

2.2.3 Indications for Use

The Syneos Health Research & Insights LLC., TreatmentAnswers™ with Pain Panel database was used to provide the estimated number of mentions for the use of single-ingredient oxycodone ER in association with a diagnosis (ICD-10-CM) as reported by U.S. office-based physician surveys in 2018. Estimates of drug use mentions are obtained from surveys of a sample of 3,200 office-based physicians with 115 pain specialists reporting on patient activity during one day per month. These survey data provide an insight into the prescriber intent, but are not directly linked to dispensed prescriptions. A drug use mention indicates that a specific drug was mentioned in association with a diagnosis during an office visit, but it does not necessarily result in a prescription being generated.

3 RESULTS

In 2018, approximately 71% of bottles or packages of opioid analgesics were sold to retail setting; therefore, this review examined the utilization of opioid analgesics from U.S. retail pharmacies.[5]

3.1 PRESCRIPTION DATA

In 2018, an estimated 15.5 million presriptions (9% of total 169 million opioid analgesic prescriptions) were dispensed for ER/LA opioid analgesics from U.S. retail pharmacies. Morphine ER accounted for

[3] Food and Drug Administration. *Mallinckrodt Inc. et al.; Withdrawal of Approval of Five New Drug Applications*. 83 Federal Register 63 (2 April 2018): 14016-14017. Accessed May 2019. Available at: https://www.govinfo.gov/content/pkg/FR-2018-04-02/pdf/2018-06579.pdf

[4] Daiichi Sankyo, Inc. RoxyBond™ Annual Report (18 June 2018) and Quarterly Periodic Adverse Drug Experience Reports (6 August 2018, 13 November 2018, and 28 March 2019). April 20, 2017 through January 19, 2019. Silver Spring: Document Archiving, Reporting and Regulatory Tracking System (DARRTS) Electronic Document Room (EDR).

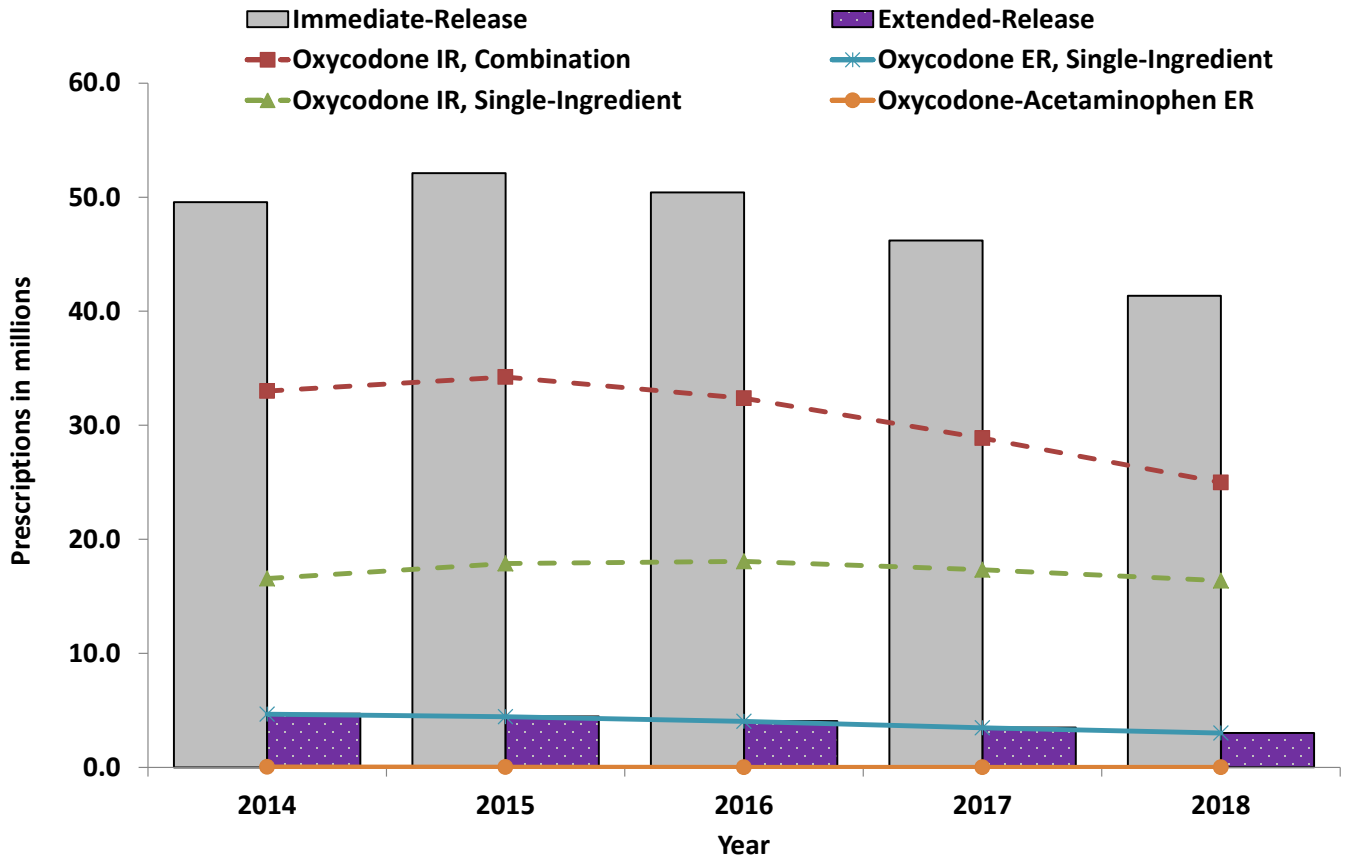
[5] Source: IQVIA National Sales Perspectives™ 2018. Data extracted June 2019.

33% (5 million prescriptions) of prescriptions dispensed for ER/LA opioid analgesics in 2018, followed by fentanyl transdermal patch at 20% (3 million prescriptions), single-ingredient oxycodone ER at 19% (3 million prescriptions), and methadone at 13% (2 million prescriptions). Similar trends were observed for the study period from 2014 through 2017. See Table 1 in Appendix A.

In 2018, an estimated 44 million total oxycodone analgesic prescriptions were dispensed; of these, combination oxycodone-containing IR products accounted for 56% (25 million prescriptions), followed by single-ingredient oxycodone IR at 37% (16 million prescriptions) and single-ingredient oxycodone ER at 7% (3 million prescriptions). See Figure 1 below and Table 2 in Appendix A.

The number of prescriptions dispensed for combination oxycodone-containing IR products peaked in 2015 at 34 million prescriptions, and decreased by 27% to 25 million prescriptions in 2018. The number of prescriptions dispensed for single-ingredient oxycodone IR remained relatively steady from 2014 to 2018. In contrast, the number of prescriptions dispensed for single-ingredient oxycodone ER decreased by 36% from 5 million prescriptions in 2014 to 3 million prescriptions in 2018.

Figure 1. Estimated number of prescriptions dispensed for oxycodone-containing analgesics by formulation from U.S. retail pharmacies, 2014-2018



Source: Symphony Health PHAST™ Prescription Monthly. 2014-2018. Data extracted June 2019.

In 2018, an estimated 3.4 million prescriptions were dispensed for opioid analgesics with formulation properties designed to deter abuse. Of these prescriptions, approximately 88% (3 million prescriptions)

were dispensed for single-ingredient oxycodone ER (OxyContin® and its generics, and Xtampza® ER). Single-ingredient hydrocodone ER (Hysingla® ER) with an estimated 199,000 prescriptions, and morphine-containing ER (Embeda®, MorphaBond™ ER, and Arymo® ER) with an estimated 195,000 prescriptions accounted for the remaining 12% of prescriptions dispensed in 2018. See Table 3 in Appendix A.

3.2 PRESCRIBER SPECIALTIES

In 2018, family practice/general practice/internal medicine specialists accounted for approximately 41% of total prescriptions dispensed for single-ingredient oxycodone ER from U.S. retail pharmacies. Anesthesiologists and physical medicine and rehabilitation specialists followed at 19% and 11%, respectively, of prescriptions dispensed in 2018. See Table 4 in Appendix A.

3.3 INDICATIONS FOR USE

As reported by U.S. office-based physician surveys in 2018, the diseases of the musculoskeletal system and connective tissue (M00-M99) such as post-laminectomy syndrome, not elsewhere classified (M96.1) and low back pain (M54.5) were the top diagnoses (62% of total drug use mentions) associated with the mentions for the use of single-ingredient oxycodone ER. The diseases of the nervous system (G00-G99) such as chronic pain syndrome (G89.4) and multiple sclerosis (G35), and neoplasms (C00-D49) followed at 12% and 10%, respectively, of total mentions for the use of single-ingredient oxycodone ER in 2018. See Table 5 in Appendix A.

4 DISCUSSION

This review examined the outpatient retail utilization of opioid analgesics, with a focus on single-ingredient oxycodone ER, to provide background for an Advisory Committee to discuss the efficacy, safety, and approvability of a NDA for single-ingredient oxycodone ER with formulation properties designed to deter abuse for the indication for the management of moderate to severe pain. Our findings showed that ER/LA opioid analgesics accounted for 9% of the total 169 million opioid analgesic prescriptions dispensed from retail pharmacies in 2018. Morphine ER, fentanyl transdermal patch, single-ingredient oxycodone ER, followed by methadone were the top four dispensed ER/LA opioid analgesics. Single-ingredient oxycodone ER accounted for the vast majority of prescriptions dispensed among opioid analgesics with formulation properties designed to deter abuse. However, the outpatient retail utilization of single-ingredient oxycodone ER decreased by 36% from 2014 to 2018. Findings from this review should be interpreted within the context of the known limitations of the databases used. Dispensed prescription estimates are nationally projected based on a sample of prescriptions claims from U.S. retail pharmacies. Summarization of these projected estimates across time periods and/or products may lead to differences in prescription count due to rounding attributable to the projection methodology utilized. Moreover, the utilization patterns of opioid analgesics in the retail setting might not represent the utilization patterns in other settings of care such as inpatient and clinic settings, which were not examined in this review.

Based on survey data in 2018, office-based physicians reported the use of single-ingredient oxycodone ER primarily in association with the diseases of the musculoskeletal system and connective tissue such as low back pain. The diagnoses data were obtained from surveys of a sample of 3,200 office-based physicians with 115 pain specialists reporting on patient activity during one day per month. Although physician survey data provide an insight into the prescriber's intent, they are not directly linked to

dispensed prescriptions. Due to the small sample sizes captured with correspondingly large confidence intervals, these data should be interpreted with caution and may not be representive of national trends.

5 CONCLUSIONS

Morphine ER, fentanyl transdermal patch, single-ingredient oxycodone ER, followed by methadone were the top four ER/LA opioid analgesics dispensed from U.S. retail pharmacies during the examined time of 2014 through 2018. Single-ingredient oxycodone ER accounted for the vast majority of prescriptions dispensed among opioid analgesics with formulation properties designed to deter abuse. However, the utilization of single-ingredient oxycodone ER decreased by 36% over the past five years to an estimated 3 million prescriptions dispensed in 2018.

6 APPENDIX A: TABLES

Table 1. Estimated number of prescriptions dispensed for opioid analgesics from U.S. retail pharmacies, 2014-2018

	Year									
	2014		2015		2016		2017		2018	
	TRxs	%	TRxs	%	TRxs	%	TRxs	%	TRxs	%
Total Opioid Analgesics	242,741,922	*100.0%*	225,443,624	*100.0%*	213,004,879	*100.0%*	191,775,620	*100.0%*	168,902,461	*100.0%*
Immediate-Release	220,656,303	*90.9%*	203,662,859	*90.3%*	192,373,106	*90.3%*	173,666,805	*90.6%*	153,431,091	*90.8%*
Extended-Release or Long-Acting	22,085,619	*9.1%*	21,780,765	*9.7%*	20,631,773	*9.7%*	18,108,815	*9.4%*	15,471,370	*9.2%*
Morphine	6,351,187	*28.8%*	6,461,754	*29.7%*	6,226,481	*30.2%*	5,662,726	*31.3%*	5,050,683	*32.6%*
Fentanyl Transdermal Patch	4,882,885	*22.1%*	4,813,205	*22.1%*	4,449,737	*21.6%*	3,762,324	*20.8%*	3,035,015	*19.6%*
Oxycodone	4,666,576	*21.1%*	4,439,236	*20.4%*	4,037,387	*19.6%*	3,473,526	*19.2%*	3,001,903	*19.4%*
Methadone	3,335,990	*15.1%*	3,062,344	*14.1%*	2,740,901	*13.3%*	2,351,950	*13.0%*	2,013,980	*13.0%*
Tramadol	725,109	*3.3%*	693,604	*3.2%*	668,341	*3.2%*	606,748	*3.4%*	574,169	*3.7%*
Buprenorphine Transdermal Patch	612,384	*2.8%*	640,155	*2.9%*	643,710	*3.1%*	596,455	*3.3%*	533,685	*3.4%*
Oxymorphone	991,877	*4.5%*	1,017,040	*4.7%*	980,619	*4.8%*	712,973	*3.9%*	353,397	*2.3%*
Hydrocodone	38,570	*0.2%*	157,054	*0.7%*	242,501	*1.2%*	279,718	*1.5%*	268,119	*1.7%*
Tapentadol	263,171	*1.2%*	285,316	*1.3%*	339,524	*1.6%*	321,511	*1.8%*	233,247	*1.5%*
Buprenorphine Oral Strip	--	--	--	--	46,412	*0.2%*	84,389	*0.5%*	162,286	*1.0%*
Morphine-Naltrexone	1	*<0.1%*	27,487	*0.1%*	109,297	*0.5%*	134,777	*0.7%*	144,778	*0.9%*
Hydromorphone	186,003	*0.8%*	163,566	*0.8%*	139,778	*0.7%*	119,011	*0.7%*	100,095	*0.6%*
Oxycodone-Acetaminophen	31,866	*0.1%*	20,004	*0.1%*	7,085	*<0.1%*	2,707	*<0.1%*	13	*<0.1%*

Source: Symphony Health PHAST™ Prescription Monthly, 2014-2018. Data extracted June 2019.

* Targiniq™ ER (oxycodone-naloxone ER), Troxyca® ER (oxycodone-naltrexone), and RoxyBond™ (oxycodone ER) were not included from othe analysis because they had not been marketed in the U.S. since approval and were withdrawn from marketing. Due to the different indications and settings of care, the analysis also excluded: 1) opioid analgesics with injectable, topical, and suppository formulations, 2) Medication-Assisted Therapy (MATs) products (e.g. buprenorphine and methadone), 3) opioid-containing cough/cold products, and 4) migraine products containing an opioid, aspirin, butalbital, and/or caffeine.

Table 2. Estimated number of prescriptions dispensed for hydrocodone-containing, oxycodone-containing, or morphine analgesics from U.S. retail pharmacies, 2014-2018

	Year									
	2014		2015		2016		2017		2018	
	TRxs	%	TRxs	%	TRxs	%	TRxs	%	TRxs	%
Total Hydrocodone-Containing Analgesics	112,049,311	*100.0%*	91,262,115	*100.0%*	83,833,233	*100.0%*	74,041,864	*100.0%*	63,726,045	*100.0%*
Hydrocodone IR, Combination	112,010,741	*100.0%*	91,105,061	*99.8%*	83,590,732	*99.7%*	73,762,146	*99.6%*	63,457,926	*99.6%*
Hydrocodone ER	38,570	*<0.1%*	157,054	*0.2%*	242,501	*0.3%*	279,718	*0.4%*	268,119	*0.4%*
Total Oxycodone-Containing Analgesics	54,265,278	*100.0%*	56,558,994	*100.0%*	54,462,506	*100.0%*	49,671,817	*100.0%*	44,358,483	*100.0%*
Oxycodone IR, Combination	33,005,473	*60.8%*	34,229,615	*60.5%*	32,364,280	*59.4%*	28,861,721	*58.1%*	24,980,556	*56.3%*
Oxycodone IR	16,561,363	*30.5%*	17,870,139	*31.6%*	18,053,754	*33.1%*	17,333,863	*34.9%*	16,376,011	*36.9%*
Oxycodone ER	4,666,576	*8.6%*	4,439,236	*7.8%*	4,037,387	*7.4%*	3,473,526	*7.0%*	3,001,903	*6.8%*
Oxycodone-Acetaminophen ER	31,866	*0.1%*	20,004	*<0.1%*	7,085	*<0.1%*	2,707	*<0.1%*	13	*<0.1%*
Total Morphine	8,348,813	*100.0%*	8,464,590	*100.0%*	8,195,206	*100.0%*	7,569,151	*100.0%*	6,915,185	*100.0%*
Morphine ER	6,351,187	*76.1%*	6,461,754	*76.3%*	6,226,481	*76.0%*	5,662,726	*74.8%*	5,050,683	*73.0%*
Morphine IR	1,997,626	*23.9%*	2,002,836	*23.7%*	1,968,725	*24.0%*	1,906,425	*25.2%*	1,864,502	*27.0%*

Source: Symphony Health PHAST™ Prescription Monthly, 2014-2018. Data extracted June 2019.

* Targiniq™ ER (oxycodone-naloxone ER), Troxyca® ER (oxycodone-naltrexone), and RoxyBond™ (oxycodone ER) were not included from othe analysis because they had not been marketed in the U.S. since approval and were withdrawn from marketing. Due to the different indications and settings of care, the analysis also excluded: 1) opioid analgesics with injectable, topical, and suppository formulations, and 2) opioid-containing cough/cold products.

Table 3. Estimated number of prescriptions dispensed for opioid analgesics with formulation properties designed to deter abuse from U.S. retail pharmacies, 2014-2018

	Year									
	2014		2015		2016		2017		2018	
	TRxs	%	TRxs	%	TRxs	%	TRxs	%	TRxs	%
Total Opioid Analgesics with Formulation Properties Designed to Deter Abuse	4,666,577	*100.0%*	4,553,979	*100.0%*	4,311,042	*100.0%*	3,828,947	*100.0%*	3,396,362	*100.0%*
OxyContin® (Oxycodone ER) and its generics	4,666,576	*100.0%*	4,439,236	*97.5%*	4,029,174	*93.5%*	3,385,585	*88.4%*	2,698,816	*79.5%*
Xtampza® ER (Oxycodone ER)	--	--	--	--	8,213	*0.2%*	87,941	*2.3%*	303,087	*8.9%*
Hysingla® ER (Hydrocodone ER)	--	--	87,256	*1.9%*	164,358	*3.8%*	211,571	*5.5%*	199,126	*5.9%*
Embeda® (Morphine-Naltrexone ER)	1	*<0.1%*	27,487	*0.6%*	109,297	*2.5%*	134,777	*3.5%*	144,778	*4.3%*
MorphaBond™ ER (Morphine ER)	--	--	--	--	--	--	2,561	*0.1%*	35,464	*1.0%*
Arymo® ER (Morphine ER)	--	--	--	--	--	--	6,512	*0.2%*	15,091	*0.4%*

Source: Symphony Health PHAST™ Prescription Monthly, 2014-2018. Data extracted June 2019.

* Targiniq™ ER (oxycodone-naloxone ER) and RoxyBond™ (oxycodone ER) were not included from othe analysis because they had not been marketed in the U.S. since approval and were withdrawn from marketing.

Table 4. Estimated number of prescriptions dispensed for single-ingredient oxycodone extended-release (ER), stratified by top 10 prescriber specialties, from U.S. retail pharmacies, 2018

	2018	
	TRxs	%
Total Single-Ingredient Oxycodone ER	**3,001,903**	***100.0%***
Family Practice/General Practice/Internal Medicine	**1,243,872**	***41.4%***
Anesthesiology	**565,988**	***18.9%***
Physical Medicine and Rehabilitation	**323,551**	***10.8%***
Pain Medicine	**162,305**	***5.4%***
Medical Oncology	**94,463**	***3.1%***
Orthopedics	**79,035**	***2.6%***
Nurse Practitioner	**65,485**	***2.2%***
Neurology	**59,044**	***2.0%***
Emergency Medicine	**25,550**	***0.9%***
Geriatrics	**21,250**	***0.7%***
All Other Specialties	**361,360**	***12.0%***

Source: Symphony Health PHAST™ Prescription Monthly. 2018. Data extracted June 2019.

*Symphony Health assigned specialty and specialty group in PHAST™ Prescription Monthly based on the description and information provided from various groups of practice specialties who collected the practitioner records. Certain title or designation such as physician assistants were mapped under the specialty that they practice in. For example, a physician assistant working in family medicine would report under family medicine.

Table 5. Estimated number of mentions for the use of single-ingredient oxycodone extended-release (ER) in association with a diagnosis (ICD-10-CM) as reported by U.S. office-based physician surveys, 2018

	2018		
	Uses (000)	95% CI	%
Total Single-Ingredient Oxycodone ER	**1,134**	**923 - 1,345**	***100.0%***
M00-M99 Diseases of the musculoskeletal system and connective tissue	**702**	**536 - 868**	***61.9%***
M96.1 Postlaminectomy syndrome, not elsewhere classified	**142**	**67 - 216**	***20.2%***
M54.5 Low back pain	**128**	**57 - 199**	***18.2%***
M48.0 Spinal stenosis	**77**	**22 - 131**	***10.9%***
M54.1 Radiculopathy	**75**	**21 - 129**	***10.7%***
M54.2 Cervicalgia	**47**	**4 - 89**	***6.6%***
M47.8 Other spondylosis	**41**	**1 - 81**	***5.9%***
M51.3 Other thoracic, thoracolumbar and lumbosacral intervertebral disc degeneration	**34**	**<0.5 - 70**	***4.8%***
M54.9 Dorsalgia, unspecified	**31**	**<0.5 - 66**	***4.4%***
M25.5 Pain in joint	**29**	**<0.5 - 62**	***4.1%***
M19.0 Primary osteoarthritis of other joints	**22**	**<0.5 - 51**	***3.1%***
All Others	**78**	**23 - 133**	***11.1%***
G00-G99 Diseases of the nervous system	**132**	**60 - 205**	***11.7%***
G89.4 Chronic pain syndrome	**65**	**15 - 116**	***49.2%***
G35 Multiple sclerosis	**30**	**<0.5 - 64**	***22.5%***
G90.5 Complex regional pain syndrome I (CRPS I)	**10**	**<0.5 - 29**	***7.3%***
G58.9 Mononeuropathy, unspecified	**10**	**<0.5 - 29**	***7.2%***
G89.3 Neoplasm related pain (acute) (chronic)	**8**	**<0.5 - 26**	***6.3%***
G89.2 Chronic pain, not elsewhere classified	**7**	**<0.5 - 23**	***5.2%***
G54.1 Lumbosacral plexus disorders	**3**	**<0.5 - 14**	***2.3%***
C00-D49 Neoplasms	**111**	**45 - 177**	***9.8%***
S00-T88 Injury, poisoning and certain other consequences of external causes	**84**	**27 - 142**	***7.4%***
D57.4 Sickle-cell thalassemia	**14**	**<0.5 - 37**	***1.2%***
All Others	**91**	**31 - 150**	***8.0%***

Source: Syneos Health Research & Insights LLC., TreatmentAnswers™. 2018. Data extracted June 2019.

*Diagnosis data are not directly linked to dispensed prescriptions but are obtained from surveys of a sample of 3,200 office-based physicians reporting on patient activity during one day per month. Syneos recommends caution interpreting results where projected drug use mentions fall below 100,000 because the sample size may be very small with correspondingly large confidence intervals and may not provide reliable national estimates of use.

7 APPENDIX B: DATABASE DESCRIPTIONS

IQVIA National Sales Perspectives™ (NSP)

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and 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.

The manufacturer sales distribution data do not provide an estimate of direct patient use but do provide a national estimate of units sold from the manufacturer to various retail and non-retail settings of care. The amount of product purchased by these settings of care may be a possible surrogate for use if we assume that facilities purchase drugs in quantities reflective of actual patient use.

Symphony Health PHAST™ Prescription Monthly

PHAST Prescription Monthly is a syndicated view of U.S. retail, mail order and long-term care pharmacy prescription activity, updated on a monthly basis. PHAST Prescription Monthly covers over 54,000 retail pharmacies in the sample including mail order and specialty pharmacies. The dispensed prescriptions in the sample represent approximately 92% of all U.S. retail prescriptions (cash, Medicaid, commercial) as well as 69% of all U.S. mail order prescriptions. The retail and mail order prescriptions are projected to the national level.

Syneos Health Research & Insights LLC., TreatmentAnswers™ with Pain Panel

Syneos 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.

9.2 Epidemiology Review

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

Epidemiology Review
Misuse and Abuse of Oxycodone and Other Opioids in the United States

Date:	August 1, 2019
Reviewer(s):	Matthew Daubresse, MHS, DrPH (candidate) *Drug Abuse Team* *Division of Epidemiology II*
Quality Control:	Cynthia Kornegay, PhD *Drug Abuse Team* *Division of Epidemiology II* Yulan Ding, PhD *Drug Abuse Team* *Division of Epidemiology II*
Secondary Reviewer:	Tamra Meyer, PhD, MPH Drug Abuse Team Lead *Division of Epidemiology II*
Tertiary Reviewer:	Judy Staffa, PhD, RPH Associate Director for Public Health Initiatives *Office of Surveillance and Epidemiology*
Subject:	Review of recent epidemiologic data on misuse and abuse of oxycodone
Drug Name(s):	Aximris XR (formerly Rexista)
Application Type/Number:	NDA #209653
Applicant/sponsor:	Intellipharmaceutics Corp.
OSE RCM #:	2019-867

TABLE OF CONTENTS

ABBREVIATIONS

AAPCC: American Association of Poison Control Centers
AD: Abuse-Deterrent
ASI-MV: Addiction Severity Index-Multimedia Version
CDC: Centers for Disease Control and Prevention
DIM: Drug-Involved Mortality
ED: Emergency Department
ER: Extended-release
FDA: U.S. Food and Drug Administration
ICD-10: International Statistical Classification of Diseases and Related Health Problems-10th Revision
IR: Immediate-release
NAVIPPRO: National Addictions Vigilance Intervention and Prevention Program
NDA: New Drug Application
NPDS: National Poison Data System
NEISS-CADES: National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance
NSDUH: National Survey on Drug Use and Health
NVSS-M: National Vital Statistics System-Mortality
OSE: Office of Surveillance and Epidemiology
OTP: Opioid Treatment Program
PCC: Poison Control Center
PMR: Post-market Requirement
RADARS: Researched Abuse, Diversion, and Addiction-Related Surveillance
RMPDC: Rocky Mountain Poison and Drug Center
SAMHSA: Substance Abuse and Mental Health Services Administration
SKIP: Survey of Key Informants' Patients
SUD: Substance Use Disorders
TCP: Treatment Center Program
US: United States

EXECUTIVE SUMMARY

Aximris XR is an extended-release (ER) formulation of oxycodone designed to deter abuse via non-oral routes through modified physical and chemical properties. This review is intended to provide advisory committee members with an informed perspective regarding the potential morbidity and mortality associated with Aximris XR, based on recent patterns of misuse, abuse, and overdose death for marketed oxycodone products and other opioids. Given the formulation of the product under consideration, we provide more detailed information on the abuse, misuse, and deaths associated with extended-release (ER) oxycodone, when the data allow a distinction between immediate-release (IR) and ER formulations. The following points synthesize data from multiple data sources which collect information related to opioid misuse, abuse, and overdose deaths in the general population and among patients entering or being assessed for substance use disorder treatment in the United States (US).

- Scale of misuse and abuse of prescription opioid analgesics
  Based on a general population survey of non-institutionalized individuals ages 12 years and older, prescription opioids were the largest category of approved pharmaceutical products to be misused or abused by Americans in 2017. Approximately 11.1 million individuals reported misuse in the past year and 1.7 million individuals met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria for substance use disorders of prescription opioids. Comparatively, an estimated 886,000 individuals ages 12 years and older reported past year use of heroin and 14.5 million individuals reported substance abuse disorders for alcohol in 2017.

- Relative frequency of misuse and abuse of oxycodone and other selected opioids
  In 2017, the most frequently misused opioid analgesics by individuals in the general US population were hydrocodone (6.3 million), oxycodone (3.7 million), and tramadol (1.8 million). Among patients entering treatment for opioid use disorders in 2016 and 2017, past-month abuse of heroin was most prevalent (60%), followed by oxycodone (32%), and hydrocodone (25%). In a separate population of individuals entering or being assessed for substance abuse treatment, the proportion of all respondents reporting past-month abuse was highest for buprenorphine, hydrocodone, heroin, and oxycodone. The percentage of patients entering substance abuse treatment who reported oxycodone abuse in the past month decreased from 2013 through 2018, however the magnitude of this decrease varied by data source.

- Routes of abuse for oxycodone and other selected opioids
  From 2012 through 2017, 80% of single-substance exposure calls to poison control centers for oxycodone abuse occurred through the oral route. Among people entering or being assessed for treatment for substance use disorders, oxycodone abuse via swallowing whole (62%) and snorting (36-39%) were most prevalent. Administration of oxycodone via injection appeared less common (16-17%) compared to other prescription opioids such as hydromorphone (53-65%), morphine (35-51%), and oxymorphone (34-42%).

- Morbidity and mortality involving oxycodone and other selected opioids
  From 2016 through 2017, there were an estimated49,609 Emergency Department (ED) visits per year involving non-medical use of oxycodone either alone or in conjunction with other agents. Of these visits, approximately 39% lead to unresponsiveness, cardiac arrest or respiratory failure/distress. From 2011 through 2016, deaths involving oxycodone, as reported in the literal text on US death certificates, increased 11% (2011: 5587; 2016: 6199), whereas deaths involving morphine and heroin increased 52% and 301%, respectively.

In evaluating any new oxycodone-containing product for approval, it is essential to consider the public health risks as well as potential benefits. Misuse, abuse, and deaths involving oxycodone

products continue to occur, and while most abuse of oxycodone occurs via the oral route, intranasal and IV abuse of oxycodone is commonly reported by individuals entering or being assessed for treatment for substance use disorders. Published studies have suggested that currently available ADF opioids, primarily reformulated OxyContin, reduce abuse of these products by unintended routes to some extent, but the results of FDA-required protocol-driven post-marketing studies evaluating ADF effectiveness are still forthcoming. In addition, much uncertainty remains about the broader public health impact of ADF opioids. Low market uptake, a complex and changing opioid landscape, and limitations in the available data have presented challenges to understanding the net public health impact of these products.

1 INTRODUCTION

During 2017, opioids were associated with 47,600 deaths in the US, 35% of which involved a prescription opioid.[1,2] Given the persistent contribution of prescription opioid analgesics to the burden of opioid-related morbidity and mortality in the US, FDA aims to evaluate the impact of new opioid drug approval on public health at the time of approval.[3] This review is designed to provide advisory committee members with a basis for considerations regarding the public health impact of new opioid drug approvals on the population at-large.

Opioid analgesic formulations with AD properties have been proposed to promote several positive public health outcomes, such as reductions in: product-specific abuse, transitions to riskier routes of abuse, diversion, and deaths from overdose. These questions have been explored in a number of published epidemiologic studies, mostly relating to the reformulation of OxyContin with abuse deterrent properties.[4,5,6,7,8,9,10] Most of these studies suggest that OxyContin's reformulation was associated with decreases in abuse, particularly through non-oral routes. However, collectively, these studies are subject to significant limitations. In addition to limitations with regard to data quality, methods, and the ability to make clear causal inferences regarding the effect of the AD properties, the majority of these studies did not have published protocols with pre-specified analytic plans.[11] The FDA has determined that "transparency about study design and analysis before execution is critical for ensuring confidence in the results".[12] FDA requires sponsors of approved AD opioid analgesic products to conduct epidemiologic studies under PMRs to monitor the abuse of these products and to evaluate the effects of the AD properties on the patterns of route-specific abuse of these products in the community. According to the 2015 guidance issued by FDA, sponsors of approved products with AD labeling claims based on premarketing studies must conduct studies to "determine whether a product with AD properties results in meaningful reductions in abuse, misuse and related adverse clinical outcomes, including addiction, overdose, and death" in the community.[13]

We focused this review on the misuse, abuse, morbidity and mortality associated with oxycodone products and other selected opioids to provide context for our results. We expect these data to assist advisory committee members in weighing the potential harms and benefits associated with approval of the product under discussion.

1.1 REGULATORY HISTORY

Aximris XR is an AD formulation of extended-release (ER) oxycodone, intended to impede tampering via non-oral routes.

1.2 APPROVED ABUSE-DETERRENT LABELING FOR RELATED PRODUCTS

OxyContin and Xtampza are extended-release (ER), single-ingredient, formulations of oxycodone with AD labeling currently marketed in the US. Four categories of studies contribute to the approved labeling in the Drug Abuse and Dependence (9.2) section.[13] These products are marketed with AD labeling based on Category 1-3 premarket studies of in-vitro manipulation and

extraction (Category 1), pharmacokinetic studies (Category 2), and clinical abuse potential studies (Category 3).[13] In April 2010, FDA approved a reformulated version of OxyContin which has physiochemical AD properties. On August 5, 2010, the sponsor stopped shipping original OxyContin tablets to pharmacies and began shipping only reformulated OxyContin. FDA approved AD labeling in April 2013 stating the original OxyContin formulation was withdrawn for "reasons of safety or effectiveness."[14] FDA has since approved other multi-ingredient AD ER formulations of oxycodone such as Targiniq (oxycodone-naloxone ER) and Troxyca (oxycodone-naltrexone ER), however the sponsors withdrew the NDAs for these products prior to marketing.[15]

Post-market studies (Category 4) assess whether introduction of the AD formulation reduces abuse, misuse, and related adverse events such as addiction, overdose, and death in the general US population. Some opioid analgesic products have Drug Abuse and Dependence (9.2) labeling that describes expected AD properties based on pre-market studies, there are currently no products with category 4 labeling. Upon approval, FDA assigned the sponsors of opioid products with AD labeling based on pre-market studies, PMRs for category 4 studies. These post-market category 4 studies are currently ongoing. Details regarding precise labeling language for currently approved ADF products are available on the FDA website.[16,17]

2 REVIEW METHODS AND MATERIALS

2.1 OVERVIEW AND FRAMEWORK

We examined several data sources to describe the misuse, abuse, morbidity, and mortality associated with oxycodone and other selected opioids in recent years. These data sources collect information from the general population and individuals entering or being assessed for substance abuse treatment. We summarized our findings using the framework outlined in **Table 1**. We provide a more detailed description of each data source and our analytic approach in the sections below. Unless otherwise indicated, we used standard regulatory definitions of misuse and abuse:[18,19]

Misuse: the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse

Abuse: the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect

Table 1. Review framework and data sources

Characteristic assessed	Population and data sources used	Use of data source(s)
Scale of misuse and abuse of prescription opioid analgesics	General population National Survey on Drug Use and Health (NSDUH), 2015-2017	Estimated number of individuals in the general US population reporting misuse and abuse of prescription opioids
	General population National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES, 2016-2017)	Estimated number of ED visits resulting from non-medical use of prescription opioid analgesics
Relative frequency of misuse and abuse of oxycodone and other selected opioids	General population NSDUH, 2015-2017	Prevalence of misuse for specific opioids in general population

	General population National Poison Data System (NPDS) exposure calls to Poison Control Centers (PCCs), 2012-2017	Drug exposures from calls to PCCs by product
	Population with opioid or substance use disorders (OUD/SUD) RADARS Treatment Center Program (TCP), 2013-2017 Inflexxion National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™) Addiction Severity Index-Multimedia Version® (ASI-MV®), 2013-2018	Proportion of patients with opioid or substance use disorders (OUD/SUD) reporting past thirty-day abuse of specific products
Routes of abuse for oxycodone and other selected opioids	General population NPDS PCC, 2012-2017	Routes of abuse for single-substance exposure calls
	Population with OUD/SUD RADARS TCP, 2016-2017 Inflexxion NAVIPPRO™ ASI-MV®, 2016-2017	Product-specific routes of abuse among people entering or being assessed for SUDs RADARS TCP and NAVIPPRO™
Morbidity and mortality involving oxycodone and other selected opioids	General population NEISS-CADES, 2016-2017	Assess outcomes such as need for healthcare intervention associated with specific opioids
	General population Drug-involved Mortality (DIM) data for overdose deaths, 2011-2016	Assess outcomes such as overdose deaths associated with specific opioids

2.2 NATIONAL SURVEY ON DRUG USE AND HEALTH

Data Source

The National Survey on Drug Use and Health (NSDUH) is an annual, federally-funded survey sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA) that collects information regarding drug, alcohol, and tobacco use, the prevalence of mental health disorders, and treatment in the general US population. The strengths of the NSDUH survey include: in-person data collection, a stable survey design which captures temporal changes in outcomes, and a multi-stage probability sampling design which provides nationally representative estimates of illicit and prescription drug use, misuse, and abuse.

The NSDUH provides state and country-level estimates for non-institutionalized residents of the US who are aged 12 years and older. Individuals residing within institutional facilities (e.g., jails, nursing homes) and those without a permanent address (e.g., homeless individuals) are not covered in the survey. The NSDUH is conducted in a face-to-face manner and the interview response rate in 2017 was 50% which included 68,032 completed interviews. For the years 2015 through 2017, NSDUH began to include more detailed data on use and misuse of specific prescription opioid analgesic subtypes. NSDUH defines misuse of a drug as the following: "use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told." NSDUH defines dependence and abuse using the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria and combines both into the broad category of "substance use disorders."[20,21]

Analysis

We extracted data from the 2017 survey that related to misuse or abuse/dependence of

prescription opioid analgesics overall, as well as by subtype. We also extracted analagous data for heroin, as this is currently the only illicit opioid for which SAMHSA is collecting responses. Weighted estimates of abuse and/or misuse were compared to estimates from the 2015 and 2016 survey years, where possible. We reported past-year weighted estimates of abuse/dependence of heroin and prescription opioids, relative to other commonly used substances in the US in 2017. We also reported estimates of past-year misuse of opioids, by subtype. All values were reported in numbers of individuals in thousands, percent of the total population, and percent of any past-year users. We highlighted statistically significant changes from 2015 to 2017.

2.3 AMERICAN ASSOCIATION OF POISON CONTROL CENTERS (AAPCC), NATIONAL POISON DATA SYSTEM (NPDS)

Data Source

NPDS is a database managed by the American Association of Poison Control Centers (AAPCC), and derived from a nationwide network of Poison Control Centers (PCCs) that receives calls from individuals, healthcare professionals, and other interested persons in the general US popoulation regarding exposures to prescription drugs, over-the-counter medications as well as unapproved products.[22] A strength of the NPDS data is its ability to record detailed drug exposure information based on self-reported information from callers, which carries its own set of limitations.

In 2017, there were over 2.6 million calls to PCCs, the majority of which (2.1 million) were human exposure calls. Of these human exposure calls, 60% were for individuals under the age of 20.[23] Almost 80% of calls related to an unintentional exposure, 19% were for intentional exposures, and the remainder for other reasons. Analgesics, including opioids were the most common substances involved in human exposures, accounting for 11% of calls (N=283,784).

Within NPDS, calls for exposures may result in documentation of an event, provision of information, or advice regarding medical management, and AAPCC staff managing these calls undergo training in the efforts to standardize documentation across centers. Documentation of calls includes detail on the drug(s), patient characteristics, route of exposure, reported reasons for exposure, level of care received (e.g., admitted to critical care unit vs. treated and released), medical outcomes (e.g., death,. no effect) and other more curated variables, such as “relatedness” requiring manual chart review to determine the relatedness of the reported exposure to the outcomes of interest. Reasons for use are categorized into groups by AAPCC, and include such categories as “intentional”,“unintentional,” the former encompassing the subgroups of intentional misuse, abuse, suspected suicide or intent that is suspected to be intentional but cannot be categorized further (unknown intent). Additional detail regarding the definition of these variables is provided in Appendix A.

Analysis

In our review of NPDS, we assessed calls for oxycodone and selected other opioids of interest (i.e., hydrocodone, morphine, and heroin). We limited our search to “closed” intentional exposure cases reported for humans (i.e., exposures and outcomes validated by NPDS) and restricted our analysis to individuals 12 years of age and older. Drug codes (i.e., “generic” and/or “product” codes) used to search NPDS for exposures involving oxycodone and other opioids, including both single-ingredient and combination products, were obtained from Micromedex™ as well as the online lookup tool available through NPDS. We restricted our date range to capture a recent six year period for which all cases had been closed (i.e., no unverified or “open” cases). To fully capture the frequency of opioid products involved in calls to PCCs, we examined drug exposure mentions in lieu of calls. Therefore, if a call involved more than one unique oxycodone product, for example, each product was counted as an exposure.

Search parameters used for oxycodone and the comparator drugs of interest are summarized below in **Table 2**.

Table 2. NPDS Search parameters- oxycodone and comparators	
Report name	Case Log (Generic Code/Product Code)
Month/year of query	4/2019
Date range for query	1/1/2012- 12/31/2017
Call type	Exposure
Case status	Closed
Species	Human
Exposure Reason	Intentional
Minimum Age	12 (years)

Analysis of NPDS consisted of three components: evaluation of intentional exposures by exposure type, trends in intentional exposures, and route of administration among single substance-exposure calls. Analyses were performed independently by two analysts to optimize accuracy of results, with any discrepancy resolved by detailed review of processes.

To examine the overall burden of intentional drug exposures by exposure type, we aggregated data for the six-year period and stratified by exposure type (abuse, misuse, suicide, unknown). We then calculated an average call rate per million individuals using Census Bureau estimates of the US population size for those 12 years and older from 2012 through 2017.[24] For exposure trends, we presented annual counts of intentional abuse exposures stratified by opioid type. In the NPDS data, route of administration is not captured for each substance reported in the call. To describe route of administration for oxycodone and other opioids during this six-year period, we restricted our data to calls involving only a single substance, therefore these analyses could be described as calls or exposures. However, multiple routes can be reported for a single substance. For these cases, we counted each route mentioned by the caller separately. As a result, the totals for each individual route may exceed the total number of exposures for that product.

2.4 RESEARCHED ABUSE, DIVERSION, AND ADDICTION-RELATED SURVEILLANCE (RADARS®) SYSTEM TREATMENT CENTER PROGRAM (TCP)

Data Source
The RADARS® TCP surveys individuals entering treatment in private and public opioid dependence treatment programs with a total of 185 participating sites from 46 states and Washington, DC during the year 2017. This data source provides information on self-reported specific products and routes of abuse in a specialized segment of the population with presumably more advanced disease severity with respect to opioid dependence or addiction.[25]

RADARS® TCP includes data from two distinct programs: the RADARS® System Opioid Treatment Program (OTP), and the RADARS® System Survey of Key Informants' Patients Program (SKIP). The OTP surveys a convenience voluntarily recruited sample of patients enrolling in public medication-assisted treatment programs from 69 sites in 32 states. On average, this represents 33% of the population per quarter based on respondent three-digit ZIP code. The SKIP surveys patients seeking treatment at a private treatment facility and covers 116 sites in 39 states. On average, this represents 28% of the population per quarter based on respondent three-digit ZIP code. Surveys in both settings are self-administered and include questions about prescription or illicit drugs used in the past month for "getting high" (i.e., abuse). Surveys also include questions relating to the primary source of the drug and route of abuse.

Analysis
FDA obtains two analytic reports from RADARS® TCP every six months through an ongoing contract with the Rocky Mountain Poison and Drug Center (RMPDC). The first report contains the total number and percentage of respondents endorsing abuse of specific products and routes of abuse between January 2016 and December 2017. The second report contains the number and percent of respondents endorsing abuse of specific opioids in each calendar year (2013 through 2017). In this report, numerators represent the total number of endorsements and denominators represent the total number of respondents for that year. For this review, we first examined the percent of respondents endorsing past-month abuse and route of administration from 2016 through 2017. Subsequently, we examined trends in the percentage of respondents endorsing abuse from 2013 through 2017. At the time of this review we lacked RADARS® TCP data from 2018. We restricted this analysis to sites participating in 75% or more of calendar quarters in the study period and excluded careless responses. We found similar overall trends when examining data from all treatment sites that conducted assessments from 2013 through 2017. RADARS® considers surveys with 24 or more opioid item endorsements or endorsements of 9 or more consecutive items, careless responses.

2.5 NATIONAL ADDICTIONS VIGILANCE INTERVENTION AND PREVENTION PROGRAM (NAVIPPRO™)

Data Source
The National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™) is a surveillance system that consists of multiple data streams related to drug abuse. One of these streams is derived from administration of a computerized survey instrument, the Addiction Severity Index-Multimedia Version® (ASI-MV®), which measures addiction severity and includes questions relating to use or abuse of specific products. ASI-MV® is administered to a convenience sample of adults seeking treatment or being assessed for substance use disorder treatment at participating facilities. Adoption and use of the ASI-MV® varies by state and locality. In 2018, NAVIPPRO included a total of 390 treatment sites in 36 states.

Analysis
FDA obtains two analytic reports from the NAVIPPRO™ ASI-MV® every six months through an ongoing contract with Inflexxion. Each report contains two prevalence estimates for each opioid: 1) the prevalence of abuse among all ASI-MV® respondents and 2) the prevalence of abuse among ASI-MV® respondents reporting prescription opioid abuse.

The first report contains information on respondents endorsing abuse of specific opioids and routes of abuse between January 2016 and December 2017. The second report provides estimates of abuse for specific opioids in each calendar year from 2013 through 2018. In this report, numerators represent the total number of endorsements and denominators represent the total number of assessments in that calendar year. Data on heroin abuse was present in the first report, but not in the trend report.

For this review, we first assessed the prevalence of abuse and route of administration for each opioid from 2016 through 2017. Subsequently, we assessed analogous data by route of administration. We then examined trends in the prevalence of abuse from 2013 through 2018 among a consistent panel of sites that contributed data in each quarter. After restriction, only 65 of an average 462 sites remained, therefore we re-examined the data using all sites.

2.6 NATIONAL ELECTRONIC INJURY SURVEILLANCE SYSTEM -- COOPERATIVE ADVERSE DRUG EVENT SURVEILLANCE (NEISS-CADES)

Cases and national estimates of the number of ED visits for drug-related adverse events were based on data from the NEISS-CADES project, a national stratified probability sample of approximately 60 hospitals with a minimum of six beds and a 24-hour ED in the US and its territories. The NEISS-CADES project, which has been described in detail elsewhere, is a joint effort of the Centers for Disease Control and Prevention (CDC), the US Consumer Product Safety Commission, and the US Food and Drug Administration.[26,27,28,29] In brief, trained coders located at each participating hospital review clinical records of every ED visit to identify clinician-diagnosed drug related adverse events, to report up to four medications implicated in each adverse event, and to record narrative descriptions of the incident (including clinical diagnoses and manifestations). Drugs captured in NEISS-CADES include: prescription and over-the-counter medications, vaccines/immunizations, vitamins/minerals, and herbal/complimentary nutritional products. The sample weights include adjustments for changes in the hospital population (e.g., non-response, mergers, and closures) and for the annual number of ED visits in the US.

NEISS-CADES has historically focused exclusively on ED visits due to use of medications for a therapeutic indication, or unintended medication exposures by young children. However, in 2016 NEISS-CADES surveillance activities were expanded to represent the full spectrum of pharmaceutical-related harm, encompassing ED visits resulting from therapeutic use, and in addition, self-harm and non-medical use. Non-medical use includes visits for abuse, therapeutic misuse, and overdoses without indication of intent. Appendix B provides the definitions for the intents of drug use (non-medical, therapeutic, and self-harm).

Analyses of 2016-2017 NEISS-CADES data were conducted and provided to FDA by the CDC Division of Healthcare Quality Promotion. Cases included ED visits in 2016 and 2017 for harms from single-ingredient or combination oxycodone-containing analgesic products as well as ED visits for harms from other prescription opioid products. ED visits in 2016-2017 for harms from single-ingredient or combination hydrocodone-containing or morphine-containing analgesic products were provided for context. Cases involving opioid-containing cough medications were excluded.

2.7 NATIONAL VITAL STATISTICS SYSTEM – MORTALITY (NVSS-M) AND DRUG-INVOLVED MORTALITY (DIM) LINKED DATA

In the U.S., states are responsible for collecting vital statistics, including information on live births, deaths, and fetal deaths. The federal government collects these data from each state and collates them to populate the National Vital Statistics System (NVSS). For a more granular analysis of specific drugs involved in deaths, Drug-involved mortality (DIM) data combine information extracted from the death certificate literal text with the cause-of-death, demographic, and geographic information from the NVSS-Mortality files (NVSS-M).

We obtained DIM data for oxycodone and other opioids from a recently published journal article[30] and the method used to extract information on DIM has been previously described. [31] We provide a brief description of this method here. The information written on the death certificate by the medical certifier on the cause, manner, circumstances, and other factors contributing to the death is referred to as the literal text fields. Drug mentions identified using literal text data are extracted from three fields on the death certificate: 1) cause of death from Part I, 2) significant conditions contributing to death from Part II, and 3) a description of how the injury occurred from Box 43.

The literal text information has been processed to allow for the identification of cases of drug-involved mortality, i.e., mortality cases having at least one literal text mention of a drug, drug class, or exposure not otherwise specified, excluding mentions where information in the literal text suggests that the drug was not involved in the death. The drug or substance mentioned in a literal text field is assumed to be involved in the death unless contextual information indicates otherwise. Additional information on these variables is provided in Appendix C.

In NVSS-M, cause of death is captured by ICD-10 codes, where no information on specific drug involvement is available. Overdose deaths were defined using ICD-10 underlying cause-of-death codes: X40–X44 (accidental self-poisoning), X60–X64 (intentional self-poisoning), X85 (homicide), and Y10–Y14 (undetermined poisonings). These data were limited to U.S. residents. From the article, we abstracted information on all overdose deaths where oxycodone, hydrocodone, morphine and heroin were mentioned in the literal text as contributing to the death from January 1, 2011 through December 31, 2016. The selected ICD-10 codes limit deaths to those caused by acute intoxication from drugs (i.e., overdose) as opposed to chronic exposure or adverse effects experienced due to therapeutic or prophylactic dosages. For overdose deaths involving these substances, we examined trends in the annual number of opioid involved drug overdose deaths and the annual age-adjusted rate of overdose deaths per 100,000 population stratified by opioid.

3 RESULTS

3.1 NSDUH

In 2017, prescription opioids were the largest category of approved pharmaceutical products to be misused or abused by Americans. Over 90 million individuals in the general US population were estimated to have used prescription opioid analgesics during the previous year. In the NSDUH, “misuse" is defined as “use in any way not directed by a doctor, including use without a prescription of one’s own; use in greater amounts, more often, or longer than told.”

Approximately 11 million people, or 4.1% of the total population, reported prescription opioid misuse in 2017 (**Table 3/Figure 1**). Comparatively, an estimated 886,000 individuals ages 12 years and older reported past year use of heroin. Among individuals reporting any past-year use of a prescription opioid analgesic, the most frequently misused products were oxymorphone, buprenorphine, and methadone, respectively misused in 36%, 32% and 20% of individuals who reported past-year use of each opioid (**Table 3**).

Table 3. NSDUH 2017: Reported past year use or misuse of prescription pain relievers, by active ingredients, individuals aged 12 and older*

Active Pharmaceutical Ingredient	Past-Year Any Use (thousands)	Past-Year Misuse (thousands)	Misuse in Total Population % (SD)	Misuse in Past-Year Among Any Users % (SD)
Any	90,799	11,077	4.1 (0.10)	12.2 (0.30)
Hydrocodone	51,979**	6,262**	2.3** (0.08)	12.0 (0.39)
Oxycodone	26,720	3,735	1.4 (0.06)	14.0 (0.56)
Tramadol	18,485	1,753	0.6 (0.05)	9.5 (0.66)
Codeine***	26,870	2,832	1.0 (0.06)	10.5 (0.55)
Morphine	6,231	501	0.2 (0.02)	8.0 (0.85)
Fentanyl****	2,046	245	0.1 (0.01)	12.0 (1.82)
Buprenorphine	2,414	766	0.3 (0.03)	31.7 (2.81)

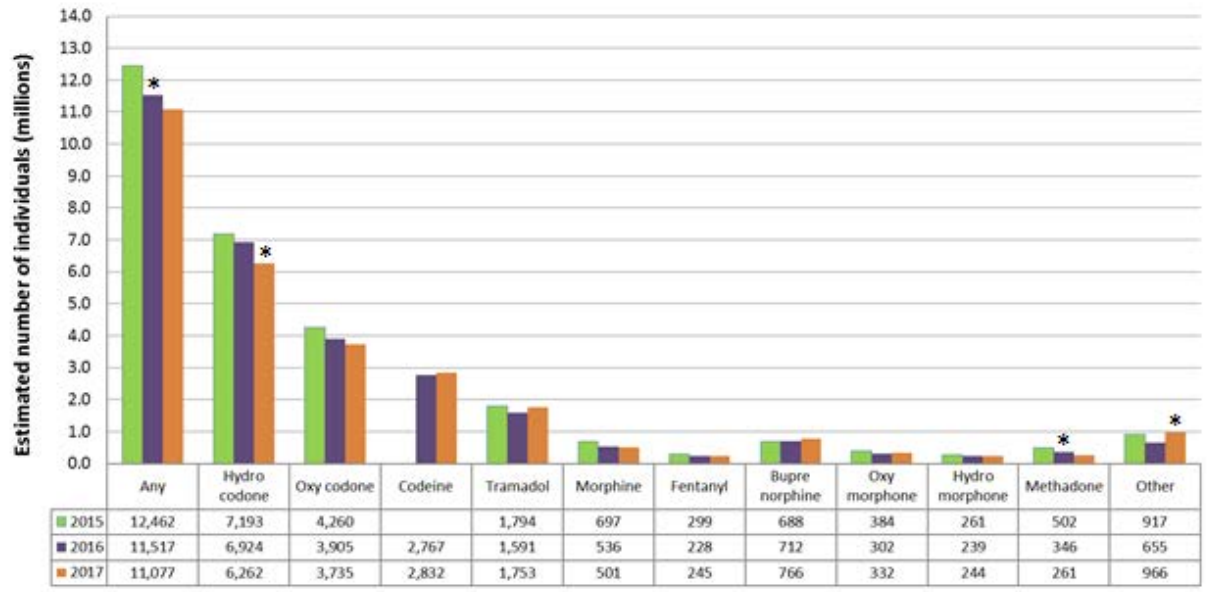
Oxymorphone	917	332	0.1 (0.02)	36.2 (4.56)
Demerol®	1,202	116	0.0 (0.01)	9.6 (2.75)
Hydromorphone	1,941	244	0.1 (0.01)	12.6 (1.86)
Methadone	1,341	261	0.1 (0.02)	19.5 (3.09)
Other	24,220	966**	0.4** (0.03)	4.0** (0.33)

SD: standard deviation
*see Appendix D for drug product and category descriptions
**represents statistically significant changes relative to 2016
***product-specific information first available in 2016
****estimate does not include illicit fentanyl

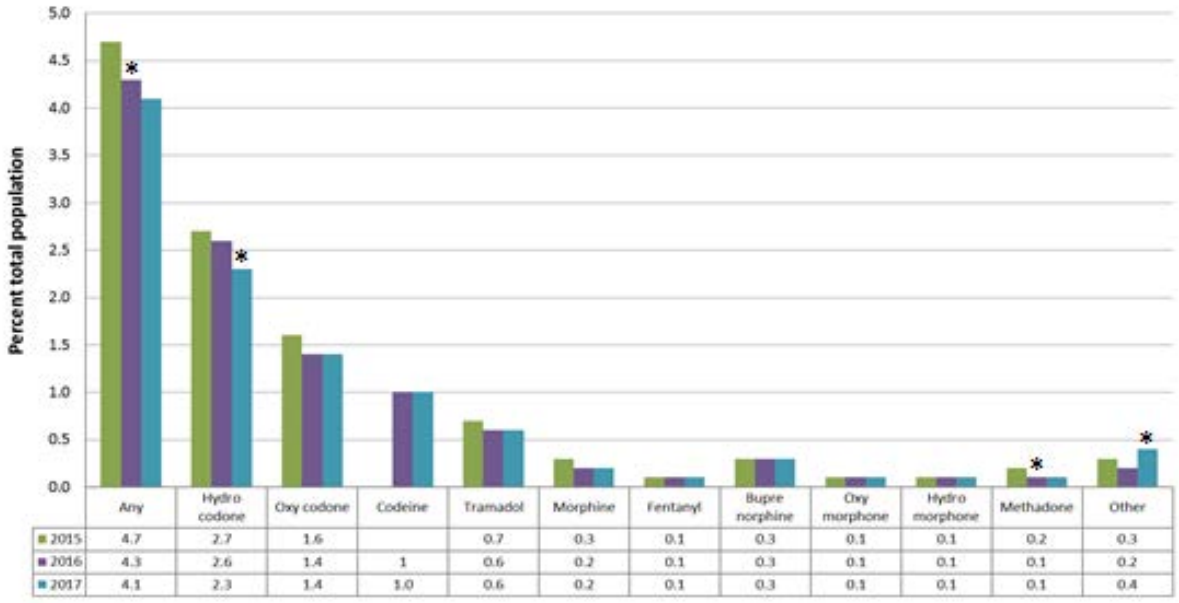
Source: SAMHSA detailed tables, Tables 1.97A-B Available from: https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2017/NSDUHDetailedTabs2017.pdf Accessed on 4/20/2019. Note: NSDUH defines misuse of a drug as the following: "use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told"

In 2017, the top three most frequently misused opioid analgesic products in the general population were hydrocodone, oxycodone and codeine, with estimated misuse in 6.3 million, 3.7 million and 2.8 million individuals, respectively (**Table 3/Figure 1**). The estimated number of individuals who used or misused hydrocodone was statistically significantly lower in 2017 compared to 2016. Products in the "other" opioid category have statistically significantly lower estimates of misuse compared to 2016. Figures 1 and 2 present numeric and percentage estimates of opioid misuse from 2015 to 2017.

Figure 1. NSDUH 2015-2017:
Past-year misuse of prescription opioid analgesics, individuals ≥12 years



	Any	Hydro codone	Oxy codone	Codeine	Tramadol	Morphine	Fentanyl	Bupre norphine	Oxy morphone	Hydro morphone	Methadone	Other
2015	12,462	7,193	4,260		1,794	697	299	688	384	261	502	917
2016	11,517	6,924	3,905	2,767	1,591	536	228	712	302	239	346	655
2017	11,077	6,262	3,735	2,832	1,753	501	245	766	332	244	261	966

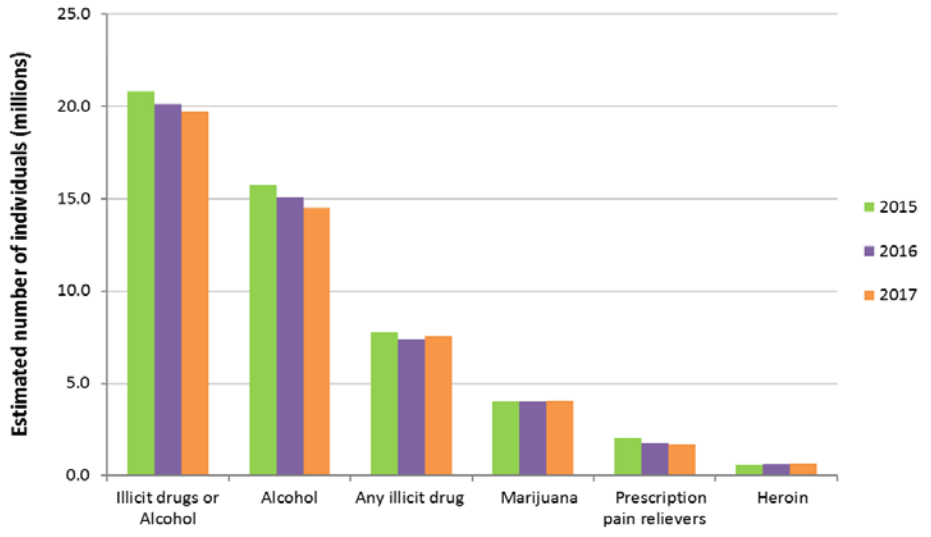


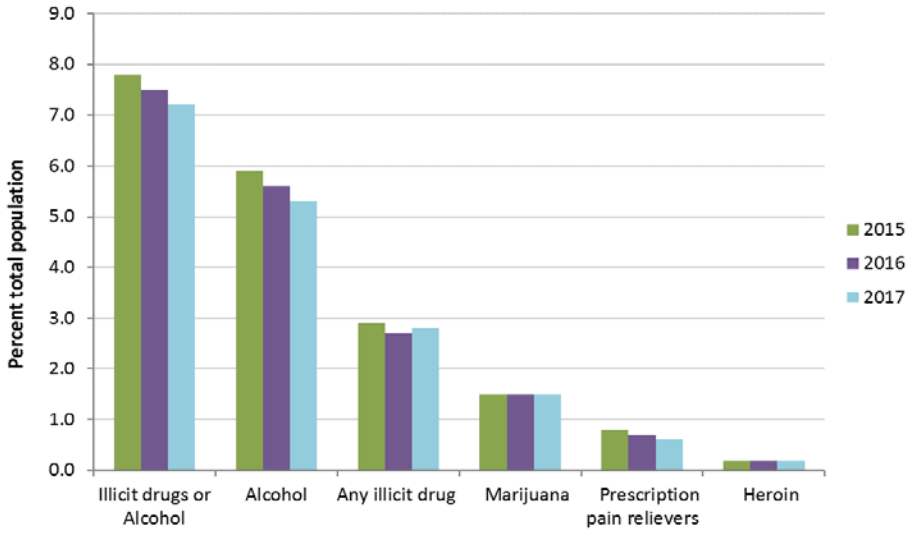
	Any	Hydro codone	Oxy codone	Codeine	Tramadol	Morphine	Fentanyl	Bupre norphine	Oxy morphone	Hydro morphone	Methadone	Other
2015	4.7	2.7	1.6		0.7	0.3	0.1	0.3	0.1	0.1	0.2	0.3
2016	4.3	2.6	1.4	1	0.6	0.2	0.1	0.3	0.1	0.1	0.1	0.2
2017	4.1	2.3	1.4	1.0	0.6	0.2	0.1	0.3	0.1	0.1	0.1	0.4

NSDUH: National Survey on Drug Use and Health
*represents statistically significant changes relative to prior year
Source: SAMHSA detailed tables, Tables 1.97 A-B, 1.97D. Available from:
https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016 htm#tab1-97A.
https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2017/NSDUHDetailedTabs2017.pdf
Accessed on 4/20/2019. Note: NSDUH defines misuse of a drug as the following: "use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told."

In 2017, an estimated 1.7 million or 0.6% of the total population age 12 years or older appeared to meet criteria for prescription pain reliever use disorders, second only to marijuana (4.1 million) and alcohol (14.5 million) in terms of frequency of abuse/dependence for the substances assessed by NSDUH. No significant changes in the relative frequency of abuse/dependence for these substances were observed from 2016 to 2017 (**Figure 2**).

Figure 2. NSDUH 2015-2017:
Past-year abuse/dependence (substance use disorders), illicit drugs or alcohol, individuals ≥12 years*





NSDUH: National Survey on Drug Use and Health
*No statistically significant differences between adjacent years
Source: SAMHSA detailed tables, Tables 5.2 A-B, 5.2 D. Available from:
https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016 htm#tab1-97A.
https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2017/NSDUHDetailedTabs2017.pdf
p1200
Accessed on 4/15/2019.

3.2 AAPCC NPDS

Over the period 2012-2017, a total of 62,002 calls reporting intentional exposure to any oxycodone product among individuals ≥12 years of age were received by U.S Poison Control Centers (PCCs) (**Table 4**). Over the same time frame, U.S. PCCs received a total of 85,501 hydrocodone, 10,945 morphine, and 32,385 heroin calls for intentional drug exposures. Population-adjusted rates of calls for drug products varied depending upon the type of intentional exposure. Across all intentional exposure calls of the opioids examined, hydrocodone and oxycodone-involved exposure call rates were highest (52.5 and 38.1 calls per million, respectively). Among intentional abuse exposure calls, exposure call rates were highest for heroin and oxycodone (14.2 and 6.8 calls per million, respectively). Across exposure types, rates of exposure calls involving IR combination oxycodone products were higher than rates of exposure calls involving ER oxycodone (**Table 4**).

Table 4. AAPCC NPDS 2012-2017:
Number of intentional drug exposure calls by exposure type, individuals 12 years of age and older (Population-adjusted rate*)

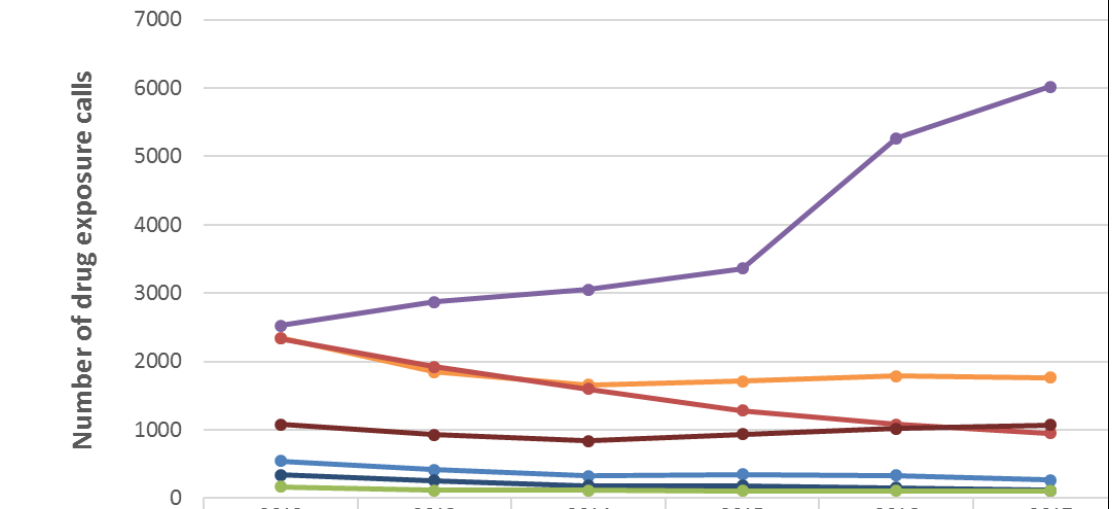
	Specific Oxycodone Products					Other Opioids		
Exposure Type	Oxycodone All	ER	IR, SE	IR, Combination Ingredient	Oxycodone NOS	Hydrocodone	Morphine	Heroin
All intentional**	62002 (38.1)	5084 (3.1)	2633 (1.6)	23436 (14.4)	30849 (19.0)	85501 (52.5)	10945 (6.7)	32385 (19.9)
Abuse	11113 (6.8)	1232 (0.8)	723 (0.4)	3281 (2.0)	5877 (3.6)	9180 (5.6)	2233 (1.4)	23105 (14.2)
Misuse	8148 (5.0)	674 (0.4)	444 (0.3)	3381 (2.1)	3649 (2.2)	11350 (7.0)	1409 (0.9)	2894 (1.8)

Suicide	37896 (23.3)	2743 (1.7)	1251 (0.8)	15104 (9.3)	18798 (11.6)	59860 (36.8)	6316 (3.9)	5148 (3.2)
Unknown	4845 (3.0)	435 (0.3)	215 (0.1)	1670 (1.0)	2525 (1.6)	5111 (3.1)	987 (0.6)	1238 (0.8)

AAPCC: American Association of Poison Control Centers; ER: extended-release; IR: immediate-release; NPDS: National Poison Data System; SE: single-entity; NOS: Not otherwise specified
*Average call rate per 1 million census population for those 12 years and older, 2007-2017
https://wonder.cdc.gov/Bridged-Race-v2017.HTML
**Includes suicide attempt, other, misuse/abuse

Figure 3 depicts trends in drug exposures among PCC calls for intentional abuse. From 2012 through 2017, the number of drug exposure calls for ER oxycodone remained low and slightly declined from 343 to 114 abuse exposure calls. During this time period, oxycodone abuse exposure calls declined from 2344 to 1762 exposures. Heroin abuse exposure calls increased overall, but almost doubled from 3363 calls in 2015 to 6018 calls in 2017. The number of abuse exposure calls involving IR SE oxycodone declined slightly from 168 in 2012 to 108 in 2017.

Figure 3. AAPCC NPDS 2012-2017:
Intentional abuse exposure calls for oxycodone vs. other opioids, individuals 12 years of age and older



	2012	2013	2014	2015	2016	2017
Heroin	2528	2874	3056	3363	5266	6018
Any Oxycodone	2344	1851	1658	1714	1784	1762
Hydrocodone	2336	1926	1599	1283	1082	954
NOS oxycodone	1080	927	841	938	1017	1074
Morphine	542	418	323	346	334	270
ER oxycodone	343	257	181	184	153	114
IR SE oxycodone	168	117	116	105	109	108

AAPCC: American Association of Poison Control Centers; NPDS: National Poison Data System; IR: Immediate Release; SE: Single Entity; ER: Extended Release

As noted earlier, due to current limitations in NPDS, routes of exposure for individual drugs could be assessed only for patients with single-substance exposures. For patients with single-

substance abuse exposure calls, most calls for oxycodone products overall occurred via ingestion (74-89%) (**Table 5**). A non-trivial percentage of single-substance abuse exposure calls indicated injection of ER (12%) and single-entity oxycodone IR products (13%), though this was substantially lower than the percentage of such exposures indicating injection of morphine products (22%) or heroin (55%).

Table 5. AAPCC NPDS, 2012-2017:
Percentage (%) of single-substance abuse exposure calls reporting specific exposure routes for oxycodone and selected other opioids^ among individuals 12 years of age and older

	Oxycodone Products					Other Opioids		
Route	Oxycodone Any, % (N= 4023)	ER, % (N= 533)	IR, SE, % (N= 343)	IR, Combination Ingredient, % (N= 1203)	Oxycodone NOS, % (N= 1944)	Hydrocodone, % (N= 3336)	Morphine, % (N= 867)	Heroin, % (N= 13713)
Ingestion	80.2	73.5	73.5	88.9	77.9	96.4	70.2	14.5
Inhalation /nasal	11.5	14.1	14.3	7.3	12.9	2.9	5.2	14.6
Parenteral (injection)	8.8	12.0	12.8	4.8	9.6	1.1	22.0	54.5
Other*	0.6	0.8	0.9	0.7	0.4	0.2	1.5	1.2
Unknown	1.0	1.3	0.9	0.4	1.3	0.3	3.3	17.4

AAPCC: American Association of Poison Control Centers; ER: extended-release; IR: immediate-release; NPDS: National Poison Data System; SE: single-entity; ^Routes are represented as percentage of exposure calls reporting a specific route over all of the single-substance exposures for the opioid. A single-substance exposure call may be associated with more than one exposure route, thus the sum for total route of exposure may be greater than the sum for total number of single-substance exposure calls, thus the total % for each column may exceed 100%; * "Other" includes exposure routes categorized as bite/sting, dermal, ocular, vaginal, rectal, and/or other

3.3 RADARS® TCP

From 2016 through 2017, assessments of individuals with opioid use disorders (OUD) entering private and public treatment programs participating in the RADARS® surveillance program indicated that past-month abuse of heroin was most prevalent, followed by oxycodone, and hydrocodone—with 60%, 32%, and 25% of respondents reporting past-month abuse of these products, respectively (**Table 6**). Of the opioids assessed in the RADARS® surveillance program, oxycodone was the most commonly snorted opioid. Among patients reporting past-month abuse of oxycodone, 36% administered it via snorting, 23% via chewing, and 16% via injecting. Chewing was more commonly associated with abuse of Buprenorphine (25%), Tapentadol (25%), Tramadol (26%) and Hydrocodone (30%). Injecting was more commonly associated with abuse of Oxymorphone (34%), Morphine (35%), Fentanyl (45%), Hydromorphone (53%), and Heroin (63%) (**Table 6**).

Table 6. RADARS® TCP, 2016-2017:
Percent respondents with past-month abuse and by route* of administration

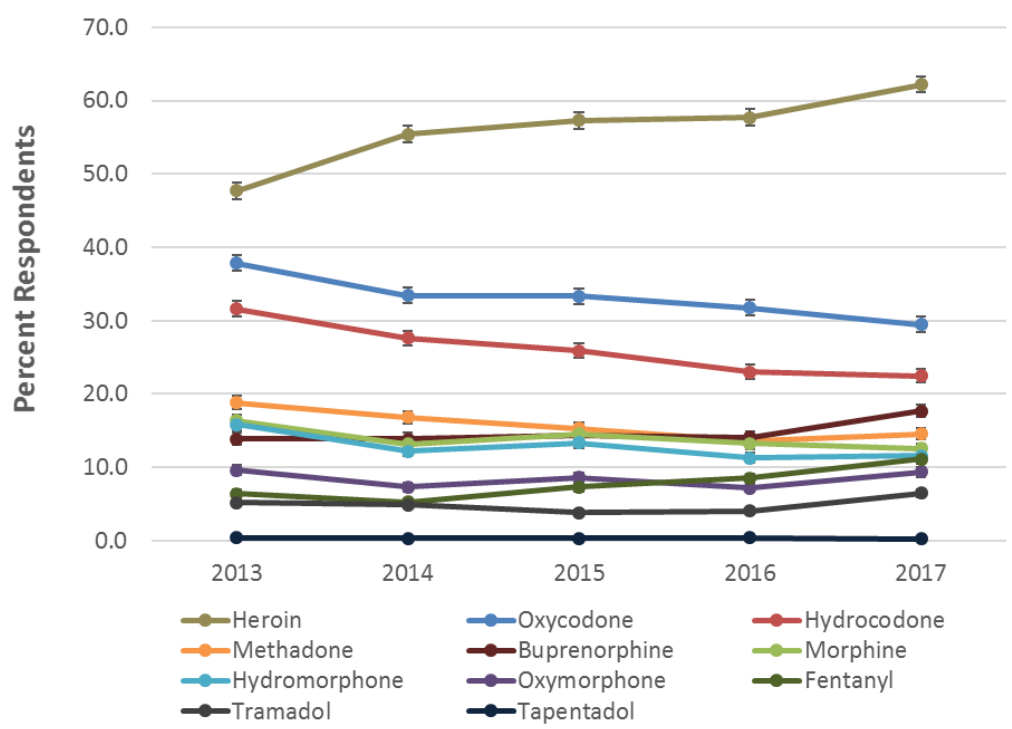
	Past-Month Abuse, Unadjusted					
Opioids of Interest	N	% Respondents (95% CI)	Chewed %	Smoked %	Snorted %	Injected %
Hydrocodone	4,524	24.5 (23.9, 25.2)	30.2	1.2	21.0	3.1
Oxycodone	5,853	31.7 (31.1, 32.4)	23.1	4.2	36.3	15.6
Tramadol	1,064	5.8 (5.4, 6.1)	25.8	1.1	10.2	2.8
Morphine	2,497	13.5 (13.1,14.0)	17.4	2.2	21.3	35.2

Fentanyl**	2,102	11.4 (10.9, 11.9)	17.2	8.3	17.2	44.9
Buprenorphine	3,299	17.9 (17.3, 18.4)	24.6	2.3	15.5	16.1
Oxymorphone	1,614	8.8 (8.3, 9.2)	12.8	2.2	29.8	33.5
Hydromorphone	2,214	12.0 (11.5, 12.5)	9.4	1.7	18.8	52.7
Methadone	2,626	14.2 (13.7,14.7)	22.3	0.9	7.5	5.6
Tapentadol	73	0.4 (0.3, 0.5)	24.7	4.1	17.8	12.3
Heroin	11,026	59.8 (59.1, 60.5)	0.8	12.7	32.2	63.3

CI: confidence interval
*respondents may report multiple opioids and multiple routes per opioid
**excludes illicit fentanyl

Between 2013 and 2017, the percent of respondents reporting past-month abuse of heroin increased from 48% to 62% (**Figure 4**). During this time, the percent of respondents reporting past-month abuse oxycodone, hydrocodone, and morphine declined. The percentage of respondents reporting past-month abuse of oxycodone decreased from 38% in 2013 to 30% in 2017.

Figure 4. RADARS® TCP:
Percent respondents with past-month abuse by year, 2013-2017*



*among sites participating in 75% or more of calendar quarters in the study period and excluding careless responses

3.4 NAVIPPRO™

Between January 1, 2016 and December 31, 2017, there were 114,307 assessments in the NAVIPPRO™ ASI-MV. Of those, 27,882 (24.34%) indicated abuse of an opioid product. From 2016 through 2017, assessments of individuals entering or being assessed for substance abuse

treatment in the NAVIPPRO™ treatment center surveillance program indicated that the percent of all respondents reporting past-month abuse was highest for buprenorphine, hydrocodone, heroin, and oxycodone—with 13%, 10%, 10%, and 10%, respectively (**Table 7**). Buprenorphine, hydrocodone, oxycodone, and methadone were some of the most commonly abused opioids among patients specifically reporting prescription opioid abuse.

Table 7. NAVIPPRO™ ASI-MV®, 2016-2017: Prevalence of past-month abuse

Opioids of Interest	N	All respondents % (95% CI)	Respondents reporting prescription opioid abuse % (95% CI)
Hydrocodone	11,736	10.4 (10.3, 10.6)	43.7 (43.1, 44.3)
Oxycodone	11,189	9.8 (9.6, 10.0)	40.2 (39.6, 40.8)
Tramadol	2,036	1.8 (1.8, 1.9)	8.0 (7.7, 8.4)
Morphine	2,164	1.9 (1.9, 2.0)	8.3 (8.0, 8.7)
Fentanyl	1,268	1.1 (1.1, 1.2)	5.0 (4.7, 5.2)
Buprenorphine	14,805	13.0 (12.8, 13.2)	53.2 (52.6, 53.8)
Oxymorphone	2,599	2.3 (2.3, 2.4)	10.2 (9.8, 10.6)
Meperidine	282	0.3 (0.2,0.3)	1.1 (1.0,1.2)
Hydromorphone	2,056	1.9 (1.8, 1.9)	8.1 (7.8, 8.4)
Methadone	6,128	5.6 (5.5, 5.7)	24.9 (24.4, 25.4)
Tapentadol	98	0.1 (0.1, 0.1)	0.4 (0.3, 0.5)
Heroin	11,164	9.8 (9.6, 10.0)	---

NAVIPPRO: National Addictions Vigilance Intervention and Prevention Program; ASI-MV: Addiction Severity Index-Multimedia Version; CI: confidence interval

Routes of administration varied across opioids (**Table 8**). Most people reporting hydrocodone and oxycodone abuse reported using via swallowing whole (hydrocodone: 82%; oxycodone: 62%) and snorting (hydrocodone: 26%; oxycodone: 39%). A similar proportion of people who abused oxycodone reported injecting (17%) and chewing (17%).

Chewing was most prevalent among respondents reporting abuse of hydrocodone (20%), whereas swallowing whole was most common among respondents abusing tramadol (84%) and hydrocodone (82%). Snorting was most common with oxymorphone (51%) and oxycodone (39%) abuse, whereas injection was most common with heroin (68%) and hydromorphone (65%) abuse.

Table 8. NAVIPPRO™ ASI-MV®, 2016-2017: Percent of past-month abuse by route of administration*

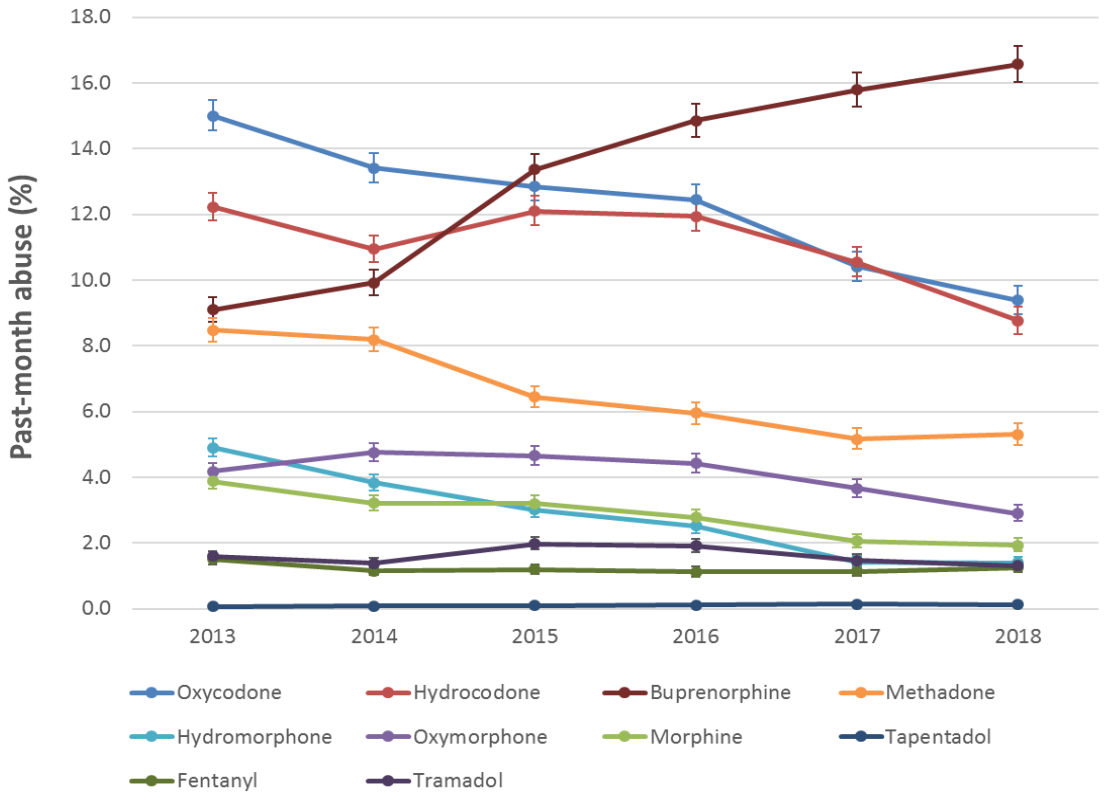
Opioids of Interest	Swallowed Whole		Chewed		Snorted		Injected	
	N	%	N	%	N	%	N	%
Hydrocodone	9,566	81.5	2,399	20.4	3,031	25.8	239	2.0
Oxycodone	6,903	61.7	1,856	16.6	4,369	39.1	1,859	16.6
Tramadol	1,699	83.5	197	9.7	157	7.7	27	1.3
Morphine	791	36.6	219	10.1	480	22.2	1,104	51.0
Fentanyl	60	4.7	34	2.7	114	9.0	384	30.3
Buprenorphine	2,014	13.6	734	5.0	2,357	15.9	2,183	14.8

Oxymorphone	498	19.2	134	5.2	1,329	51.1	1,094	42.1
Meperidine	139	49.3	23	8.2	39	13.8	55	19.5
Hydromorphone	497	24.2	105	5.1	409	19.9	1,327	64.5
Methadone	3,649	59.6	516	8.4	845	13.8	458	7.5
Tapentadol	59	60.2	10	10.2	4	4.1	7	7.1
Heroin	32	0.3	---	---	2,596	23.3	7,627	68.3

NAVIPPRO: National Addictions Vigilance Intervention and Prevention Program; ASI-MV: Addiction Severity Index-Multimedia Version; CI: confidence interval
*% reporting that route among people reporting abuse of the specific product or substance

Figure 5 depicts trends in past-month abuse by opioid from 2013 through 2018 among treatment sites reporting at least one assessment per quarter. The prevalence of buprenorphine abuse among all respondents increased from 9% in 2013 to 17% in 2018. During this period, rates of oxycodone abuse decreased from 15% to 9%. From 2016 through 2018, declines in hydrocodone abuse were similar to declines in the prevalence of oxycodone abuse. We found similar overall trends when examining data from all treatment sites that conducted assessments from 2013 through 2018.

Figure 5. NAVIPPRO™® ASI-MV®, 2013-2018;
Prevalence of past-month abuse by opioid (N=65 Sites)*



*restricted to sites reporting results from at least one assessment per quarter 2013-2018; heroin data unavailable

3.5 NEISS-CADES

From 2016 through 2017, there were an estimated 267,020 ED visits per year for harms attributed to use of any prescription opioid product, of which nearly half (100,313) involved oxycodone-containing products, specifically. Among ED visits associated with non-medical use of a prescription opioid product, 39% (N=49,609) involved an oxycodone product (**Table 9**).

Table 9. National estimates of ED visits for harms from use of oxycodone-containing and other prescription opioid products, by intent of drug use, 2016-2017[a]

Opioid Product	Cases	Average Annual Estimate		
	No.	No.	% of Total Estimate[d]	95% CI
Non-medical Use of any Prescription Opioid[b] (Total Average Annual Estimate = 127,177 ED Visits)				
Oxycodone-containing Product	**1,478**	**49,609**	**39.0**	**(32.7 - 45.3)**
Hydrocodone-containing Product	376	14,901	11.7	(6.1 - 17.3)
Morphine-containing Product	212	7,814	6.1	(4.0 - 8.3)
Therapeutic Use of any Prescription Opioid[c] (Total Annual Estimate = 103,786 ED Visits)				
Oxycodone-containing Product	**1,069**	**36,997**	**35.6**	**(29.3 - 42.0)**
Hydrocodone-containing Product	540	22,647	21.8	(15.7 - 27.9)
Morphine-containing Product	220	8,175	7.9	(6.2 - 9.5)
Use of any Prescription Opioid for Self-harm (Total Annual Estimate = 36,057 ED Visits)				
Oxycodone-containing Product	**394**	**13,707**	**38.0**	**(30.7 - 45.3)**
Hydrocodone-containing Product	263	9,478	26.3	(19.8 - 32.8)
Morphine-containing Product	52	2,102	5.8	(4.3 - 7.4)

CI: Confidence Interval; ED: Emergency Department
[a]Data are from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project, CDC.
[b]Includes pharmaceutical abuse, therapeutic misuse (use other than as directed by a clinician), and opioid overdoses without indication of intent.
[c]Includes adverse events from therapeutic use (e.g., adverse effects, allergic reactions, medication errors, and unsupervised ingestions by children)
[d] Percent oftotal estimated ED visits for harms from prescription opioid use in 2016-2017, for each intent of drug use
Source: Data provided by the CDC Division of Healthcare Quality Promotion

For nonmedical use visits involving oxycodone, an estimated 41% led to an inpatient admission, transfer to another hospital, or observation admission. An oxycodone product was the only implicated pharmaceutical in over half of ED visits involving nonmedical use of oxycodone (53%); a benzodiazepine was implicated in 31% of visits. Approximately one-fifth of ED visits for nonmedical use of oxycodone products involved concurrent use of alcohol (20%) or marijuana (18%) (**Table 10**).

Table 10. National estimates of ED visits for non-medical use of oxycodone-containing products, by case characteristics, 2016-2017[a]

Patient and Case Characteristics	Cases	Average Annual Estimate[c]		
	No.	No.	%	95% CI
Patient Age (Years)[b]				
<10	0	--	--	--

10-24	234	7,722	15.6	(13.6 - 17.6)
25-34	386	12,914	26.0	(22.0 - 30.0)
35-44	250	8,427	17.0	(14.5 - 19.5)
45-54	260	9,007	18.2	(15.4 - 20.9)
55-64	243	8,092	16.3	(13.6 - 19.0)
65-74	88	2,949	5.9	(4.6 - 7.3)
>74	16	--	--	--
Patient Sex				
Female	533	19,276	38.9	(35.0 - 42.7)
Male	945	30,333	61.1	(57.3 - 65.0)
Disposition				
Admitted, Transferred, or Held for Observation	584	20,345	41.0	(29.2 - 52.8)
Treated/Released or Left Against Medical Advice	894	29,265	59.0	(47.2 - 70.8)
Number of Implicated Pharmaceuticals				
1	794	26,509	53.4	(48.9 - 58.0)
2	466	15,637	31.5	(28.5 - 34.6)
3	159	5,316	10.7	(8.4 - 13.1)
4	59	2,148	4.3	(2.8 - 5.9)
Implicated Oxycodone Product				
Single-ingredient Oxycodone	836	28,209	56.9	(48.0 - 65.8)
Oxycodone in Combination with Acetaminophen	658	21,787	43.9	(34.6 - 53.2)
Oxycodone in Combination with Aspirin	1	--	--	--
Co-implicated Pharmaceuticals				
>1 Rx Opioid	213	6,815	13.7	(10.4 - 17.1)
Benzodiazepine	462	15,590	31.4	(27.8 - 35.1)
Illicit Drugs/Alcohol				
≥1 Illicit Drug	556	17,357	35.0	(31.2 - 38.8)
Alcohol	303	9,729	19.6	(15.8 - 23.5)
Illicit Drug(s) or Alcohol	732	23,062	46.5	(42.9 - 50.0)
Cocaine	209	5,720	11.5	(8.4 - 14.7)
Fentanyl	22	--	--	--
Heroin	119	3,463	7.0	(4.8 - 9.1)
Marijuana	270	9,136	18.4	(15.5 - 21.3)
Methamphetamine	59	1,945*	3.9*	(1.4 - 6.4)
Other/Unspecified Illicit Drug	48	1,127	2.3	(1.3 - 3.2)
Total	1,478	49,609	100.0	

CI: Confidence Interval; ED: Emergency Department
[a]Data are from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project, CDC. Nonmedical use includes pharmaceutical abuse, therapeutic misuse (use other than as directed by a clinician), and opioid overdoses without indication of intent. Estimates based on <20 cases or total estimates <1,200 are considered statistically unstable and are not shown (--).
[b]Missing for 1 case.
[c]Average annual estimates based on total cases from 2016 through 2017
*Coefficient of variation >30%.

Source: Data provided by the CDC Division of Healthcare Quality Promotion

In 39% of nonmedical use visits involving oxycodone products, the patient experienced cardiac arrest, was unresponsive, or had respiratory failure/distress, and in an additional 32% of visits, the patient experienced altered mental status (**Table 11**).

Table 11. National estimates of ED visits for non-medical use of oxycodone-containing products, by adverse event manifestation, 2016-2017[a]

Adverse Event Manifestation[b]	Cases	Average Annual Estimate[c]		
	No.	No.	%	95% CI
Cardiac Arrest/Unresponsive/Respiratory Failure/Distress	518	19,264	38.8	(29.1 - 48.6)
Severe Allergic Reaction	0	--	--	--
Altered Mental Status	516	15,857	32.0	(26.6 - 37.3)
Injection-related Infection/Reaction	25	1,227*	2.5*	(0.5 - 4.5)
Fall/Injury	42	1,639	3.3	(2.2 - 4.4)
Presyncope/Syncope/Dyspnea	41	1,281*	2.6*	(0.9 - 4.3)
Psychiatric or Other Central Nervous System Effect	48	1,319*	2.7*	(1.0 - 4.3)
Cardiovascular Effect	37	1,256	2.5	(1.7 - 3.4)
Mild-to-Moderate Allergic Reaction	0	--	--	--
Gastrointestinal Effect	37	1,120	2.3	(1.2 - 3.3)
Other/Unspecified Effect	214	6,645	13.4	(9.4 - 17.4)
Total	1,478	49,609	100.0	

CI: Confidence interval; ED: Emergency Department
[a]Data are from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project, CDC. Nonmedical use includes pharmaceutical abuse, therapeutic misuse (use other than as directed by a clinician), and opioid overdoses without indication of intent. Estimates based on <20 cases or total estimates <1,200 are considered statistically unstable and are not shown (--).
[b]Adverse event manifestations were categorized in a mutually exclusive and hierarchical manner based on severity (e.g., a case involving a patient who had depressed consciousness and had a fall would be classified as altered mental status based on the depressed consciousness).
[c]Average annual estimates based on total cases from 2016 through 2017
*Coefficient of variation >30%.
Source: Data provided by the CDC Division of Healthcare Quality Promotion

3.6 NSVSS-M AND DIM

A published report of analyses of NVSS-M and DIM linked databases[30] found that in the five-year period from 2011-2016, there were a total of 33,154 oxycodone, 18,905 hydrocodone, 23,839 morphine, and 61,679 heroin-involved overdose deaths in the U.S. Oxycodone-involved overdose deaths decreased slightly from 5,587 in 2011 to 4,967 in 2013, then increased to 6,199 deaths in 2016**.** The report shows an 52% increase in the number of overdose deaths involving morphine between 2011 and 2016 (2011: 3,290 to 2016: 5,014). During this time period, hydrocodone-involved overdose deaths remained constant ranging from 3,037 overdose deaths in 2012 to 3,299 overdose deaths in 2014. Heroin-involved overdose deaths increased 300% from 4,571 deaths in 2011 to 18,335 deaths in 2016 (**Table 12**).

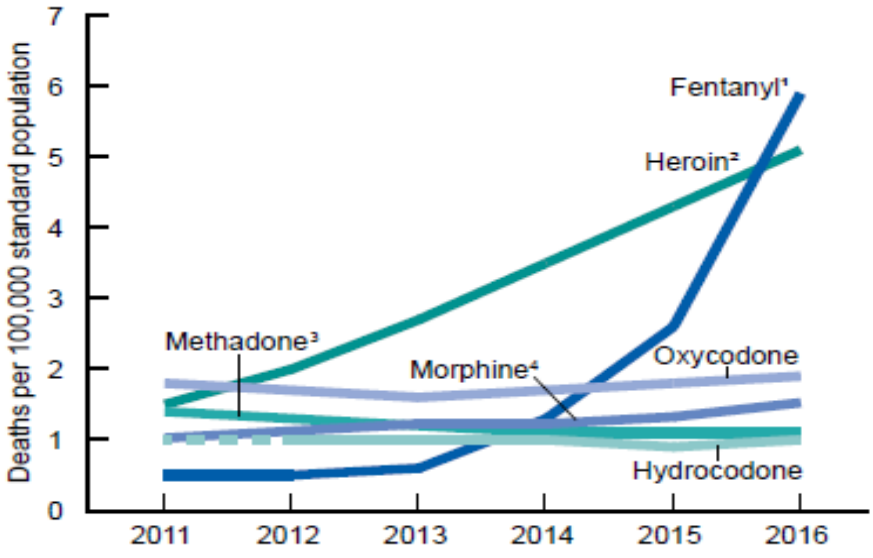
Table 12. Select opioid involved drug overdose deaths by year 2011-2016*

Active Pharmaceutical Ingredient or Substance	2011	2012	2013	2014	2015	2016	Percent change 2011-2016, %	Total
Oxycodone	5,587	5,178	4,967	5,431	5,792	6,199	11.0	33,154
Hydrocodone	3,206	3,037	3,113	3,299	3,051	3,199	-0.2	18,905
Morphine	3,290	3,513	3,772	4,024	4,226	5,014	52.4	23,839
Heroin	4,571	6,155	8,418	10,882	13,318	18,335	301.1	61,679

NOTES: Drug overdose deaths are identified using International Classification of Diseases, Tenth Revision (ICD–10) underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to the referent drug (i.e., the one listed). Deaths involving more than one drug (e.g., a death involving both heroin and cocaine) are counted in both totals. Caution should be used when comparing numbers across years. The reporting of at least one specific drug or drug class in the literal text, as identified using ICD–10 multiple cause-of-death codes T36–T50.8, improved from 75% of drug overdose deaths in 2011 to 85% of drug overdose deaths in 2016.
*Adapted from: Hedegaard H, Bastian BA, Trinidad JP, Spencer M, Warner M. Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2011-2016. Natl Vital Stat Rep. 2018 Dec;67(9):1-14.

From 2011 through 2016, the age-adjusted rate of drug overdose deaths involving heroin more than tripled from 1.5 to 5.1 per 100,000 population. The rate of overdose deaths involving oxycodone decreased from 1.8 in 2011 to 1.6 in 2013 then increased to 1.9 deaths per 100,000 population in 2016 (**Figure 6**).

Figure 6. Age-adjusted rates for drug overdose deaths involving selected opioids, 2011–2016



1 Significant increasing trend for 2013–2016, $p < 0.05$.
2 Significant increasing trend for 2011–2016 with different rates of change over time, $p < 0.05$.
3 Significant decreasing trend for 2011–2014, $p < 0.05$.
4 Significant increasing trend for 2011–2015, $p < 0.05$.
NOTES: Drug overdose deaths are identified using International Classification of Diseases, Tenth Revision underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to the referent drug (i.e., the one listed). Deaths involving more than one drug (e.g., a death involving both heroin and cocaine) are counted in both totals. Caution should be used when comparing numbers across years. The reporting of at least one specific drug in the literal text improved from 73% of drug overdose deaths in 2011 to 85% of drug overdose deaths in 2016.
SOURCE: Hedegaard H, Bastian BA, Trinidad JP, Spencer M, Warner M. Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2011-2016. Natl Vital Stat Rep. 2018 Dec;67(9):1-14.

4 DISCUSSION

4.1 SUMMARY OF THE DATA AND DISCUSSION

Aximris XR is an extended-release (ER) formulation of oxycodone designed to deter abuse via non-oral routes through modified physical and chemical properties. To provide advisory committee members with misuse and abuse information relevant to Aximris, we provide more detailed information related to ER oxycodone products. Although some of these data sources collect information on misuse and abuse at the product- and formulation-level, we have concerns regarding the validity of survey data collected with this degree of granularity because of response bias associated with brand recognition and ordering effects. For data sources with lower potential response bias, we stratified misuse/abuse information by IR/ER formulations of oxycodone.

Scale of misuse and abuse of prescription opioid analgesics

Although national discourse on the opioid epidemic is now dominated by discussion of deaths arising from ultra-potent illicit opioids such as fentanyl,[32] our analysis indicates that prescription opioids continue to contribute substantially to opioid-related adverse outcomes, such as abuse, misuse, ED visits, and overdose deaths. During 2017, an estimated 90 million individuals in the general US population had used prescription opioid analgesics the previous year, 11.1 million had misused them, and 1.7 million individuals met the criteria for abuse or dependence involving prescription opioid analgesics. The same year, approximately 267,000 estimated ED visits in the US were for harms from use of a prescription opioids, of which, nearly 130,000 visits were for non-medical opioid use, and almost 50,000 involved non-medical use of oxycodone products, specifically.

Relative frequency of misuse and abuse of oxycodone and other selected opioids

NSDUH data suggest that the most frequently misused opioid analgesics in the general US population in 2017 were hydrocodone, oxycodone and codeine, with misuse occurring among 6.3 million, 3.7 million and 2.8 million individuals, respectively. Among calls to PCCs from 2012 through 2017, intentional exposures were highest for hydrocodone and oxycodone, at 53 and 38 exposures per one-million census population, respectively. During this time period, intentional abuse exposures for oxycodone declined 25% and calls for heroin increased 138%.

In the RADARS® TCP, we found past-month abuse of heroin was most prevalent during 2016-2017, followed by oxycodone, and hydrocodone—with 60%, 32%, and 25% of respondents reporting past-month abuse of these products, respectively. Between 2013 and 2017, the percent of respondents reporting past-month abuse of heroin increased from 48% to 62%. The percentage of respondents reporting past-month abuse of oxycodone decreased from 38% in 2013 to 30% in 2017. NAVIPPRO™ ASI-MV data from 2016 though 2017, showed buprenorphine (53%), hydrocodone (44%), and oxycodone (40%) were some of the most commonly abused opioids among patients specifically reporting prescription opioid abuse.

Differences in the prevalence of abuse in the RADARS® TCP and NAVIPPRO™ ASI-MV may be explained by several factors, such as differences in the underlying populations, survey format, and methodology. RADARS® TCP represents a population of patients specifically entering treatment for OUD, while the NAVIPPRO™ ASI-MV treatment centers include patients entering or being assessed for treatment for any SUD. Thus, the differences between these two populations should be taken in to account prior to comparing these results. Differences in format, order of survey questions related to specific opioid products, and the inherent potential for product misclassification may also contribute to variation in abuse prevalence between the two surveillance systems.

Routes of abuse for oxycodone and other selected opioids
The AAPCC NPDS and RADARS® TCP/NAVIPPRO™ ASI-MV data depicted somewhat similar pictures regarding alternative routes of abuse, despite differences in population characteristics and capture of these routes. The AAPCC NPDS analysis included people with single-substance abuse exposures resulting in a call to a PCC. The RADARS® TCP/NAVIPPRO™ ASI-MV population is comprised of patients with presumably more advanced substance use disorders. Despite this, oral abuse was the most common route of abuse for prescription opioids in both populations.

For patients in the NPDS with single-substance abuse exposure calls, 74-89% of calls for oxycodone products occurred via ingestion. In NAVIPRO, 62% of respondents reporting ingestion via swallowing whole. Within calls to PCCs, 12% reported injection of ER oxycodone and 13% reported injection of single-entity oxycodone IR products. We found similar proportions of patients reporting oxycodone abuse via injection in RADARS® TCP (16%) and NAVIPRO (17%). In both RADARS® TCP and NAVIPRO a similar proportion of respondents reported snorting (RADARS® TCP: 36%; NAVIPPRO: 39%) and chewing oxycodone (RADARS® TCP: 23%; NAVIPRO: 17%). In the NPDS data only 12% of oxycodone exposures involved snorting and administration via chewing was not captured.

Morbidity and mortality involving oxycodone and other selected opioids
A high frequency of adverse outcomes continues to be reported in association with misuse/abuse of prescription opioids, including oxycodone products. Data from NEISS-CADES from 2016-2017 suggest there are an estimated 49,609 ED visits per year involving non-medical use of oxycodone products, either alone or in conjunction with other agents such as a benzodiazepine; concurrent use of alcohol, marijuana, or illicit drugs was also frequently documented. Over 40% of such visits required observation, admission or transfer to another hospital; and 39% of visits involved patients with cardiac arrest, respiratory failure/distress or non-responsiveness. Mortality data from NVSS-M/DIM for the period 2011-2016 identified a total of 33,154 deaths involving oxycodone, 18,905 deaths involving hydrocodone and 23,839 deaths involving morphine. Deaths involving heroin increased 301% from 2011 through 2016. During this period, deaths from oxycodone overdose fluctuated between 4,967 to 6,199 deaths per year, resulting in an overall increase of 11%.

4.2 LIMITATIONS

NSDUH
Although NSDUH is one of the few resources capable of producing national estimates of prescription drug misuse and abuse, it is subject to the inherent limitations of self-reported data, such as non-response bias, misclassification, and recall bias. NSDUH data often lacks sufficient granularity to examine specific branded products and formulations. Information on route of administration in the NSDUH survey is also limited. Individuals with advanced substance use disorders may be underrepresented in these data, particularly if they become homeless, incarcerated, or enter a residential treatment facility.

AAPCC NPDS
PCC call data does not capture the complete incidence of drug exposures or instances of misuse/abuse related to any substance in the US. These data capture events where the exposure resulted in a call to a PCC. PCC data rely on information shared by the community and healthcare personnel. Substance classifications are identified by PCC staff based on self-reported information from the caller without any biologic confirmation. Drug exposures resulting in

unattended or out-of-hospital death are unlikely to generate a call to a PCC, thus fatal poisonings are expected to be substantially under-reported in PCC call data. Follow-up and medical outcomes are not available for all calls. It is possible that changes in PCC abuse rates are influenced by changes in public and professional awareness of risks associated with specific drugs and other secular trends.

RADARS® TCP and NAVIPPRO™ ASI-MV®

Misclassification of the specific product(s) being abused is an important potential limitation of data collected from people entering or being assessed for substance use disorders treatment. These data are also based on convenience samples and enriched with individuals with advanced substance use disorders who have sought or been referred for treatment or assessment, thus patterns observed in these study populations may not reflect those that exist in a broader population of individuals who abuse drugs.

Numerous other factors such as judicial referral policies and funding for substance use disorders treatment can may affect the probability that an individual who is abusing or addicted to prescription opioids is assessed for treatment and included in the sample. Finally, these data are not geographically representative of all individuals being assessed for substance use disorders treatment in the US and participation by treatment centers varies over time.

NEISS-CADES

NEISS-CADES data can be used to calculate national estimates of ED visits for harms from pharmaceutical use, but NEISS-CADES excludes cases that do not result in an ED visit and cases that result in death before or during ED evaluation. NEISS-CADES also excludes instances of inadequate therapy, drug withdrawal, detoxification treatment, medical clearance, occupational exposures, or adverse events from ED treatment. The quality of these data depends on the completeness and accuracy of medical record documentation by the healthcare provider and providers must record a pharmaceutical drug or drug class (e.g. “prescription opioid”) was implicated in the ED visit. Up to four medications may be recorded as being implicated in a case, but it is possible that other medications were involved, but not recorded. Similarly, concurrent use of illicit drugs or alcohol may not have been documented.

NVSS-M and DIM

The DIM dataset relies on drug mentions in the death certificate literal text to identify cases. Opioid-involved deaths can only be identified when these substances are specifically mentioned on death certificates, thus these findings may underestimate the number of opioid-involved deaths. There were also changes in the percentage of drug overdose deaths with a specific drug mentioned in the literal text over the course of the study period. The percentage of drug overdose deaths with codes T36–T50.8 increased from 75% in 2011 to 85% in 2016, however the study authors obtained similar results after adjusting for this increase in detection.[30]

5 CONCLUSIONS

As new prescription opioid analgesics with AD properties are considered for approval, risks to both patients and the broader community must be weighed against potential benefits. This review examines data related to the public health burden associated with misuse and abuse of oxycodone and other selected opioids in the US. These data suggest that misuse and abuse of prescription opioids remain prevalent in the general US population and among individuals with SUDs. Over the past decade, increases in morbidity and mortality associated with abuse of heroin and fentanyl were much greater than those associated with oxycodone. Despite the limitations of drug abuse data, it appears both IR and ER formulations of oxycodone are abused via swallowing whole, snorting, and injection. Although rates of oxycodone misuse and abuse have declined in recent

years, oxycodone continues to contribute to the overall morbidity and mortality associated with prescription opioid analgesics in the US. Advisory committee members should carefully consider the risks and benefits to patients and the general US population in decisions related to the approval of new oxycodone products.

6 APPENDICES

6.1 APPENDIX A. AAPCC NPDS DEFINITIONS OF EXPOSURE REASONS

Intentional exposure reasons	Definition
Suspected Suicides	"An exposure resulting in the inappropriate use of a substance for self-harm or self-destruction or manipulative reasons"
Abuse	"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", including recreational use of a substance for any effect
Misuse	"An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect"
Unknown	Exposures that are deemed to be intentional although the specific motive is undetermined
Source: American Association of Poison Control Centers. National Poison Data System (NPDS) Data Dictionary. Version 2016.07.11. July 11, 2016	

6.2 APPENDIX B. NEISS-CADES DEFINITIONS FOR INTENT OF DRUG USE

Intent of drug use	Definition
Non-medical	Nonmedical use includes pharmaceutical abuse, therapeutic misuse, and overdoses without indication of intent. Abuse cases involve documented clinician diagnosis of abuse or documented recreational use (e.g., "to get high"). Therapeutic misuse cases involved documented therapeutic intent, but use was not as directed (e.g., taking someone else's prescription medication for pain, intentionally taking larger doses than prescribed). Cases of overdose without indication of intent lack documentation of therapeutic intent, abuse, or self-harm (e.g., patients found unresponsive by paramedics and patients unable or unwilling to provide description of circumstances or intent).
Therapeutic	Therapeutic use includes adverse effects, allergic reactions, medication errors, and unsupervised ingestions by children
Self-harm	Self-harm includes administration of pharmaceuticals to injure or kill oneself
Source: Geller AI, Dowell D, Lovegrove MC, McAninch JK, Goring SK, Rose KO, Weidle NJ, Budnitz DS. U.S. Emergency Department Visits Resulting From Nonmedical Use of Pharmaceuticals, 2016. Am J Prev Med. 2019 May;56(5):639-647. doi: 10.1016/j.amepre.2018.12.009. Epub 2019 Mar 6.	

6.3 APPENDIX C. DESCRIPTION OF THE DRUG-INVOLVED MORTALITY DATA SOURCE

The drug-involved mortality data combine the cause-of-death, demographic, and geographic information from the National Vital Statistics System – Mortality files, with drug-involved mortality information extracted from the death certificate literal text. The method used to extract information on drug-involved mortality has been described previously[31] and is briefly described here. The information written on the death certificate by the medical certifier on the cause, manner, circumstances, and other factors contributing to the death is referred to as the literal text fields. The literal text information had been processed to allow for the identification of cases of drug-involved mortality, i.e., mortality cases having at least one literal text mention

of a drug, drug class, or exposure not otherwise specified, excluding mentions where information in the literal text suggests that the drug was not involved in the death. For example, the drug "METHICILLIN" in the phrase "METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS INFECTION" does not suggest drug involvement in mortality, but rather a type of bacterial infection. Similarly, the phrase "NOT DRUG RELATED" clearly indicates that a death did not involve drugs.

Although the drug-involved mortality data overcome a major limitation of the current coding system for mortality data by enabling the identification of specific drugs, the drug-involved mortality data have other limitations and considerations. These limitations and considerations are described in more detail elsewhere.[31] Most importantly, the quality of data extracted from death certificates depends on the amount and level of detail provided by medical certifiers, and such information can vary by certifier, jurisdiction, and over time. For example, the percentage of drug overdose deaths with codes T36–T50.8 increased each year (75% in 2011, 76% in 2012, 78% in 2013, 81% in 2014, 83% in 2015, and 85% in 2016).[30] Undercounting of deaths with involvement of specific drugs is likely with the drug-involved mortality data.

6.4 APPENDIX D. NSDUH PRODUCT CATEGORIES AND DESCRIPTIONS*

Drug Product Category	Category Description
Hydrocodone	Vicodin®, Lortab®, Norco®, Zohydro® ER, generic hydrocodone, or other similar products
Oxycodone	OxyContin®, Percocet®, Percodan®, Roxicodone®, generic oxycodone, or other similar products
Tramadol	Ultram®, Ultram® ER, Ultracet®, generic tramadol, generic extended-release tramadol, or other similar products
Codeine	Tylenol® with codeine 3 or 4, generic codeine pills, or other similar products);
Morphine	Avinza®, Kadian®, MS Contin®, generic morphine, generic extended-release morphine, or other similar products
Fentanyl	Duragesic®, Fentora®, generic fentanyl, or other similar products
Buprenorphine	Suboxone®, generic buprenorphine, generic buprenorphine plus naloxone, or other similar products
Oxymorphone	Opana®, Opana® ER, generic oxymorphone, generic extended-release oxymorphone, or other similar products
Meperidine	Demerol® or other similar products
Hydromorphone	Dilaudid® or generic hydromorphone, Exalgo® or generic extended-release hydromorphone, or other similar products
Methadone	Methadone or other similar products
Any Other Prescription Pain Reliever	Products containing other active ingredients. Reports of misuse of "any other prescription pain reliever" that correspond only to the specific pain reliever categories shown in the table are excluded from estimates for "any other prescription pain reliever" and are included instead in the relevant pain reliever category. Due to changes in how these reports of misuse of "any other prescription pain reliever" were assigned, the 2016 estimates may differ from previously published estimates.
*Over-the-counter drugs are not included. Source: Center for Behavioral Health Statistics and Quality. (2018). 2017 National Survey on Drug Use and Health: Methodological summary and definitions. Rockville, MD: Substance Abuse and Mental Health Services Administration	

7 REFERENCES

[1] Centers for Disease Control and Prevention, 2018. Drug overdose deaths. Available from: https://www.cdc.gov/drugoverdose/data/statedeaths.html

[2] Centers for Disease Control and Prevention 2018. Prescription Opioid Data. Available from: https://www.cdc.gov/drugoverdose/data/prescribing.html

[3] National Academies of Sciences, Engineering, and Medicine. 2017. Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/24781.

[4] Coplan PM, Chilcoat HD, Butler SF, et al. The effect of an abuse-deterrent opioid formulation (OxyContin) on opioid abuse-related outcomes in the postmarketing setting. Clin Pharmacol Ther. 2016 Sep;100(3):275-86. doi: 10.1002/cpt.390. Epub 2016 Jun 22.

[5] Chilcoat HD, Coplan PM, Harikrishnan V, Alexander L. Decreased diversion by doctor-shopping for a reformulated extended release oxycodone product (OxyContin). Drug Alcohol Depend. 2016 Aug 1;165:221-8. doi: 10.1016/j.drugalcdep.2016.06.009. Epub 2016 Jun 16.

[6] Sessler NE, Downing JM, Kale H, Chilcoat HD, Baumgartner TF, Coplan PM. Reductions in reported deaths following the introduction of extended-release oxycodone (OxyContin) with an abuse-deterrent formulation. Pharmacoepidemiol Drug Saf. 2014 Dec;23(12):1238-46. doi: 10.1002/pds.3658. Epub 2014 Jun 11.

[7] Havens JR, Leukefeld CG, DeVeaugh-Geiss AM, Coplan P, Chilcoat HD. The impact of a reformulation of extended-release oxycodone designed to deter abuse in a sample of prescription opioid abusers. Drug Alcohol Depend. 2014 Jun 1;139:9-17. doi: 10.1016/j.drugalcdep.2014.02.018. Epub 2014 Feb 26.

[8] McNaughton EC, Coplan PM, Black RA, Weber SE, Chilcoat HD, Butler SF. Monitoring of internet forums to evaluate reactions to the introduction of reformulated OxyContin to deter abuse. J Med Internet Res. 2014 May 2;16(5):e119. doi: 10.2196/jmir.3397.

[9] Cassidy TA, DasMahapatra P, Black RA, Wieman MS, Butler SF. Changes in prevalence of prescription opioid abuse after introduction of an abuse-deterrent opioid formulation. Pain Med. 2014 Mar;15(3):440-51. doi: 10.1111/pme.12295. Epub 2013 Dec 11.

[10] Dart RC, Iwanicki JL, Dasgupta N, Cicero TJ, Schnoll SH. Do abuse deterrent opioid formulations work? J Opioid Manag. 2017 Nov/Dec;13(6):365-378.

[11] Food and Drug Administration [Internet]. “Data and Methods for Evaluating the Impact of Opioid Formulations with Properties Designed to Deter Abuse in the Postmarket Setting.” Available from: https://www.fda.gov/Drugs/NewsEvents/ucm540845.htm.

[12] Food and Drug Administration [Internet]. "Framework for FDA's Real-World Evidence Program." Available from: https://www.fda.gov/media/120060/download

[13] Food and Drug Administration [Internet]. "Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry" Available from: https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf.

[14] Federal Register [Internet]. Food and Drug Administration: 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 [updated 2013 Apr 18; cited 2018 May 15]. Available from: https://www.gpo.gov/fdsys/pkg/FR-2013-04-18/pdf/2013-09092.pdf

[15] Food and Drug Administration [Internet]. Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse [updated 2018 Apr 23; cited 2018 May 10]. Available from: https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm338566.htm

[16] Food and Drug Administration [Internet]. Drugs@FDA: FDA Approved Drug Products, New Drug Application 022272 [cited 2018 May 11]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022272s034lbl.pdf.

[17] Food and Drug Administration [Internet]. Drugs@FDA: FDA Approved Drug Products, New Drug Application 208090 [cited 2018, May 11]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process.

[18] Food and Drug Administration [Internet]. "Assessment of Abuse Potential of Drugs: Guidance for Industry" [updated 2017 Jan; cited 2018 May 11]. Available from: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf.

[19] Food and Drug Administration [Internet]. "General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products: Guidance for Industry" [updated 2017 Nov; cited 2018 May 11]. Available from: https://www.fda.gov/downloads/Drugs/.../Guidances/UCM492172.pdf.

[20] Substance Abuse and Mental Health Services Administration [Internet]. "About Population Data/NSDUH" [updated 2016 Jan 14; cited 2018 May 11]. Available from: https://www.samhsa.gov/data/population-data-nsduh/about.

[21] Center for Behavioral Health Statistics and Quality. (2017). *2016 National Survey on Drug Use and Health: Methodological summary and definitions*. Rockville, MD: Substance Abuse and Mental Health Services Administration. Available from: https://www.samhsa.gov/data/sites/default/files/NSDUH-MethodSummDefs-2016/NSDUH-MethodSummDefs-2016.htm#b4-3.

[22] American Association of Poison Control Centers [Internet]. "National Poison Data System" [cited 2018 May 11]. Available from: http://www.aapcc.org/data-system/.

[23] Gummin DD, Mowry JB, Spyker DA, Brooks DE, Osterthaler KM, et al. 2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report. Clin Toxicol (Phila). 2018 Dec 21;:1-203. PubMed PMID: 30576252.

[24] Centers for Disease Control and Prevention. "Bridged-Race Population Estimates 1990-2017 Request" [cited 2018 May 11]. Available from: https://wonder.cdc.gov/Bridged-Race-v2017.HTML.

[25] RADARS® System [Internet]. Available from: https://www.radars.org/.

[26] Shehab N, Lovegrove MC, Geller AI, Budnitz DS, et al. Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. *JAMA* 2016;316:2115-25.

[27] Jhung MA, Budnitz DS, Mendelsohn AB, et al. Evaluation and overview of the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project (NEISS-CADES). *Med Care* 2007; 45(Suppl 2):S96-102.

[28] Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA* 2006; 296:1858–66.

[29] Schroeder TJ, Ault K. National Electronic Injury Surveillance System (NEISS) sample design and implementation from 1997 to present. Washington, DC: US Consumer Products Safety Commission; 2001. Available at: http://www.cpsc.gov/neiss/2001d011-6b6.pdf.

[30] Hedegaard H, Bastian BA, Trinidad JP, Spencer M, Warner M. Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2011-2016. Natl Vital Stat Rep. 2018 Dec;67(9):1-14.

[31] Trinidad JP, Warner M, Bastian BA, Minino AM, Hedegaard H. Using Literal Text From the Death Certificate to Enhance Mortality Statistics: Characterizing Drug Involvement in Deaths. Natl Vital Stat Rep. 2016 Dec;65(9):1-15.

[32] Somerville NJ, O'Donnell J, Gladden RM, et al. Characteristics of Fentanyl Overdose - Massachusetts, 2014-2016. Morb Mortal Wkly Rep. 2017 Apr 14;66(14):382-386. doi: 10.15585/mmwr.mm6614a2.

10 Appendix

10.1 Regulatory History of Abuse-Deterrent Opioid Analgesics

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: December 16, 2019

FROM: Rigoberto Roca, MD
Acting Director
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience, CDER, FDA

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

RE: Regulatory History of Abuse-Deterrent Opioid Analgesics

Regulatory History of Abuse-Deterrent Opioid Analgesics

The growing epidemic of opioid abuse, misuse, and overdose in the United States is deeply concerning. In light of this, the Agency has encouraged drug companies to develop products that can mitigate abuse, while recognizing the importance of maintaining the availability of opioid analgesics for the millions of patients in this country who suffer from pain. The Agency has supported the development of novel formulations through multiple interactions with both the pharmaceutical industry and the academic community.

In April 2015, the Agency issued a final guidance to assist industry in the development of opioid drug products with potentially abuse-deterrent properties. The "Guidance for Industry: Abuse-Deterrent Opioids" explains the Agency's current thinking regarding studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, makes recommendations about how those studies should be performed and evaluated, and discusses how to describe those studies and their implications in product labeling. It is important to keep in mind that 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 this, the Agency intends to take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products.

An effort has been made to improve the product labels for all opioid analgesics to help ensure safe use of these drugs. In April 2014, the Agency finalized the class-wide safety labeling changes (SLC) for all extended-release and long-acting (ERLA) opioid analgesics in order to better describe their risks and benefits and to better ensure safe use. All ERLA opioid analgesics, those with and without abuse-deterrent properties, used for the management of chronic pain now have a harmonized indication, the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate, which is intended to emphasize the need to balance risk with benefit. The safety labeling changes included the indication stated above, a new warning for Neonatal Opioid Withdrawal Syndrome (NOWS), and updated language in the Warnings and Precautions section of the label regarding addiction, abuse, and misuse, life-threatening respiratory depression, accidental ingestion, and drug interactions. On March 22, 2016, a class-wide SLC for immediate-release opioid analgesics was issued, similar to the 2014 SLC for ERLA opioid analgesics. The labeling changes included a boxed warning with information about the risks of misuse, abuse, addiction, overdose and death, and the potential for neonatal opioid withdrawal syndrome (NOWS) with prolonged maternal use of opioids during pregnancy; an updated indication stating that IR opioids should be reserved to manage pain severe enough to require opioid treatment and for which alternative treatment options are inadequate or not tolerated; and clearer information regarding patient monitoring and drug administration. New warnings were also included for all opioids regarding serotonin syndrome and endocrine effects.

A total of ten opioid analgesics have been approved with labeling language describing studies that evaluated their abuse-deterrent properties; nine ERLA opioid analgesic products and one immediate-release opioid analgesic. **Embeda**, approved in 2009, is an extended-release formulation of morphine sulfate with a sequestered opioid antagonist, naltrexone. The naltrexone is intended to be released only if the product is manipulated. In vitro and in vivo data reviewed by the Agency indicate that Embeda has properties that are expected to reduce abuse by the oral (crushing/chewing) and intranasal routes. A human abuse potential study of IV morphine and naltrexone to simulate injection of crushed Embeda demonstrated evidence of abuse deterrence; however, it is unknown whether the results from simulated crushed Embeda can predict a reduction in abuse by the IV route until additional postmarketing data are available. The first formulation of extended-release oxycodone was **OxyContin** approved in 1995. A reformulation of the original OxyContin, approved in 2010, was designed with physicochemical properties intended to deter abuse by being more difficult to prepare for intravenous abuse by syringe and to resist breaking or crushing for intranasal abuse. The original OxyContin is no longer manufactured or marketed in the US. In 2012, language was added to the label describing OxyContin's abuse-deterrent properties based on the Agency's review of in vitro and in vivo studies.

Targiniq ER[11], the second extended-release oxycodone product with abuse-deterrent properties, was approved in 2014. It is a fixed-dose combination drug product consisting of oxycodone and naloxone, an opioid antagonist. Naloxone has low oral bioavailability due to high first pass metabolism and is not intended to reach adequate levels to have an effect in patients taking the medication as prescribed. However, if Targiniq ER is manipulated for abuse by injection or nasal insufflation, the naloxone levels are high enough to antagonize the reinforcing opioid effects. Language in the label includes findings of in vitro studies and human abuse potential studies that indicate that Targiniq ER has pharmacologic properties that are expected to reduce abuse via the intranasal and IV routes of administration.

Hysingla ER, approved in 2014, is the first extended-release formulation of hydrocodone with properties intended to deter abuse. In vitro data demonstrate that Hysingla ER's physicochemical properties can be expected to deter intranasal and intravenous abuse. Data from human abuse potential studies also support that these properties can be expected to deter intranasal abuse and oral abuse when chewed.

Morphabond ER, an extended-release formulation of morphine sulfate, approved in 2015, is the second extended-release morphine product with abuse-deterrent labeling. Morphabond ER has physicochemical properties expected to make abuse via injection difficult. Data from human abuse potential studies as well as in vitro data also support that these properties are expected to reduce abuse by the intranasal route of administration.

Xtampza ER, the third extended-release oxycodone product with abuse-deterrent properties, was approved on April 26, 2016. In vitro data demonstrate that Xtampza ER has physicochemical properties expected to make abuse by injection difficult. The data from pharmacokinetic and human abuse potential studies, along with support from the in vitro data, also indicate that Xtampza ER has physicochemical properties that are expected to reduce abuse via the intranasal route.

Troxyca ER[12]**,** an extended-release formulation of oxycodone hydrochloride with a sequestered opioid antagonist, naltrexone, was approved on August 19, 2016. The naltrexone is intended to be released only if the product is manipulated. In vitro and in vivo data reviewed by the Agency indicate that Troxyca ER has properties that are expected to reduce abuse via the oral (crushing/chewing) and intranasal routes. A human abuse potential study of IV oxycodone and naltrexone to simulate injection of crushed Troxyca ER demonstrated evidence of abuse deterrence; however, it is unknown whether the results from simulated crushed Troxyca ER can predict a reduction in abuse by the IV route until additional postmarketing data are available.

Arymo ER, an extended-release formulation of morphine sulfate, approved in January 2017, is the third extended-release morphine product with abuse-deterrent labeling. In vitro data demonstrate that Arymo ER's physicochemical properties can be expected to make abuse by

[11] Targiniq ER NDA has been withdrawn. FR notice effective November 28, 2018. https://s3.amazonaws.com/public-inspection.federalregister.gov/2018-23528.pdf

[12] Troxyca ER NDA has been withdrawn.. FR notice effective May 2, 2018. https://www.federalregister.gov/documents/2018/04/02/2018-06579/mallinckrodt-inc-et-al-withdrawal-of-approval-of-five-new-drug-applications

injection difficult. As discussed at the August 4, 2016 advisory committee meeting, there were data to support that the formulation could be expected to reduce abuse by the intranasal route, but this information was not included in labeling as it was blocked by exclusivity awarded to Morphabond ER. Although the results of the oral human abuse potential study showed a difference in the Drug Liking endpoint, there was no statistically significant reduction in the response to Take Drug Again. Therefore, it cannot be concluded that Arymo ER has properties that are expected to reduce abuse via the oral route.

Vantrela ER[13], approved in January 2017, is the second extended-release formulation of hydrocodone with properties intended to deter abuse. In vitro data demonstrate that the physicochemical properties of Vantrela ER can be expected to deter intravenous abuse. In vitro and in vivo data demonstrate that Vantrela ER has properties that are expected to reduce abuse via the oral and intranasal routes.

Roxybond, approved in April, 2017, is the first immediate-release opioid approved with labeling language describing properties intended to deter abuse. Roxybond is an immediate-release formulation of oxycodone HCl with physicochemical properties expected to make abuse via injection difficult, and reduce abuse by the intranasal route, based on results of in vitro and in vivo studies.

All Sponsors of opioid analgesics with approved abuse-deterrent language in labeling are required to conduct postmarketing epidemiologic studies to determine whether the properties of their product results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting.
It is important to recognize that abuse-deterrent opioid products are not abuse-proof. As stated in the "Guidance for Industry: Abuse-Deterrent Opioids, "Because opioid products are often manipulated for the 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."

[13] Vantrela ER NDA has been withdrawn. FR notice effective May 2, 2018.
https://www.federalregister.gov/documents/2018/04/02/2018-06579/mallinckrodt-inc-et-al-withdrawal-of-approval-of-five-new-drug-applications

10.2 Labeling for Approved Abuse-Deterrent Opioids

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: December 16, 2019

FROM: Rigoberto Roca, MD
Acting Director
Division of Anesthesiolgoy, Addiction Medicine and Pain Medicine
Office of Neuroscience, CDER, FDA

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

RE: Opioids with Abuse-Deterrent Labeling

Opioids with Abuse-Deterrent Labeling: Section 9.2 Drug Abuse

Based on feedback from previous advisory committee meetings where abuse-deterrent opioid analgesics were discussed, excerpts are included here from the labels of approved opioids analgesics with abuse-deterrent labeling, specifically Section 9.2, which describes the in vitro and in vivo studies conducted to support the abuse-deterrent properties. The products are listed in the order in which they were approved.

EMBEDA (morphine sulfate and naltrexone hydrochloride) extended-release capsules [NDA 022321]

Approval Date: August 13, 2009
Abuse Deterrence Labeling Update: October 17, 2014

Abuse Deterrence Studies

EMBEDA is formulated with a sequestered opioid antagonist, naltrexone HCl, which is released with manipulation by crushing.

In Vitro Testing

In vitro laboratory tests were performed to evaluate the effect of different physical and chemical conditions intended to defeat the extended-release formulation. When EMBEDA is crushed and mixed in a variety of solvents, both morphine sulfate and naltrexone hydrochloride are simultaneously extracted.

Clinical Studies

The abuse potential of EMBEDA when crushed was examined in three studies following administration by the oral (Studies 1 and 2) and intranasal (Study 3) routes. A fourth study was conducted with IV administration of simulated crushed EMBEDA (Study 4). These were randomized, double-blind, single-dose, placebo and active-controlled, crossover studies in non-dependent recreational opioid users. Drug Liking in Studies 1- 3 was measured on a bipolar 100-point Visual Analog Scale (VAS) where 0 represents maximum disliking, 50 represents a neutral response (neither like nor dislike), and 100 represents maximum liking. Drug Liking in Study 4 and Drug High in all studies was measured on a unipolar 100-point VAS where 0 represents no response and 100 represents maximum response. Response to whether the subject would take the study drug again was also measured in two studies (Study 2, Study 3) on a bipolar 100-point VAS where 0 represents the strongest negative response (e.g., 'definitely would not'), 50 represents a neutral response, and 100 represents the strongest positive response (e.g., 'definitely would'). The pharmacokinetics of morphine sulfate and naltrexone hydrochloride were also determined in these abuse potential studies. When EMBEDA was crushed and administered by the oral and intranasal routes, morphine and naltrexone were absorbed with similar median time-to-peak concentration (T_{max}) values of 1 hour following oral administration and approximately 36 minutes following intranasal administration.

Oral Studies

Study 1 compared EMBEDA to IR morphine sulfate. In this study 32 subjects received four treatments: 120 mg/4.8 mg as intact EMBEDA capsules, 120 mg/4.8 mg as crushed EMBEDA in solution, 120 mg IR morphine in solution, and placebo. When EMBEDA was crushed and taken orally, the geometric mean (±SD) values for naltrexone C_{max} and AUC_{inf} were 1073 ± 721 pg/mL and 3649 ± 1868 pg·hr/mL, respectively. The oral administration of crushed EMBEDA was associated with statistically significantly lower mean and median Drug Liking and Drug High scores compared with crushed IR morphine (as summarized in Table 3).

Figure 1 (Study 1) demonstrates a comparison of Drug Liking for crushed EMBEDA compared to crushed IR morphine sulfate when given by the oral route in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in Drug Liking with crushed EMBEDA vs. morphine greater than or equal to the value on the X-axis. Of the 32 subjects who completed the study, approximately 81% of subjects had some reduction in Drug Liking and Drug High with crushed EMBEDA compared to administration of IR morphine sulfate, while approximately 19% had no reduction in Drug Liking or in Drug High. At least a 30% and 50% reduction in Drug Liking with crushed EMBEDA compared to IR morphine was observed in 72% and 56% of subjects, respectively (summarized in Figure 1). At least a 30% and 50% reduction in Drug High with crushed EMBEDA was observed in 56% and 31% of subjects, respectively.

Study 2 compared EMBEDA to ER morphine sulfate. In this study 36 subjects were randomized to receive three treatments in solution: 120 mg/4.8 mg as crushed EMBEDA capsules, 120 mg crushed ER morphine, and placebo. When EMBEDA was crushed and taken orally, the geometric mean (±SD) values for naltrexone C_{max}, $AUC_{0\text{-}2h}$, and AUC_{inf} were 824 ± 469 pg/mL, 1121 ± 561 pg·hr/mL, and 2984 ± 1388 pg·hr/mL, respectively. The oral administration of crushed EMBEDA was associated with statistically significantly lower mean and median Drug Liking, Drug High, and Take Drug Again scores compared with crushed ER morphine (summarized in Table 3).

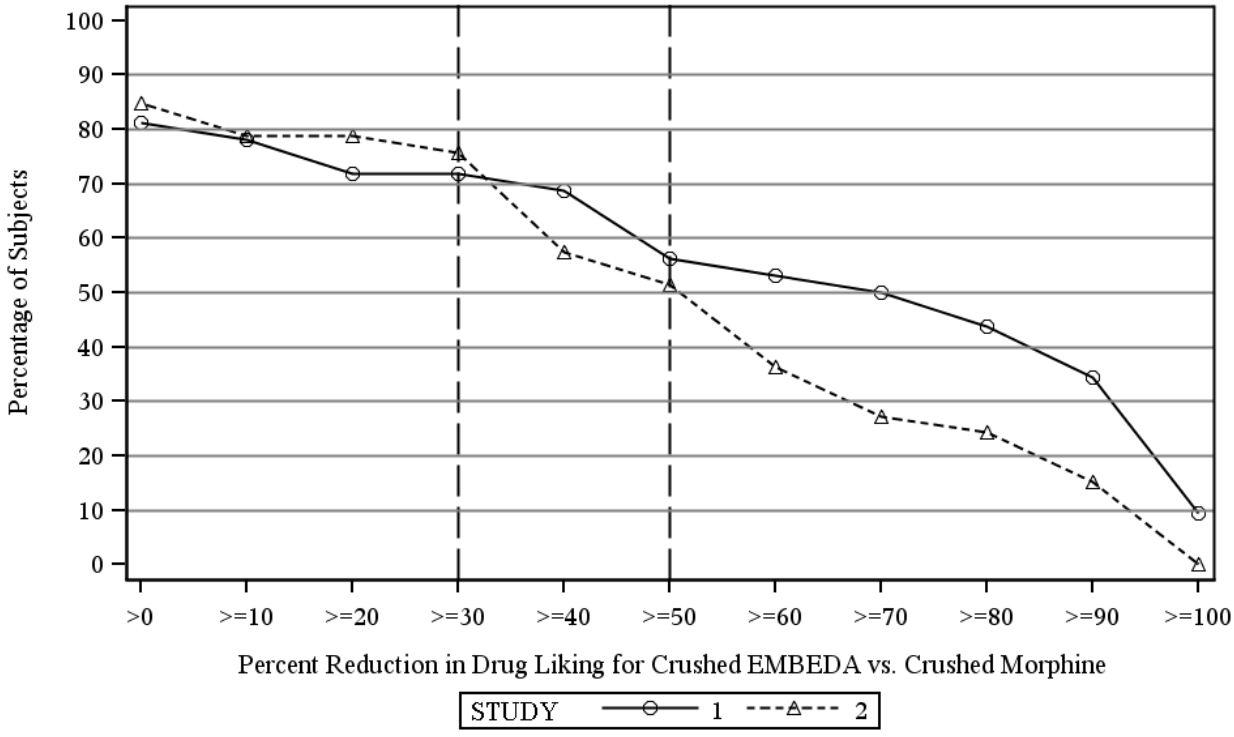
Figure 1 (Study 2) demonstrates a comparison of maximum Drug Liking for crushed EMBEDA compared to crushed ER morphine in subjects who received both treatments. Of the 33 subjects who completed the study, approximately 85% of subjects had some reduction in Drug Liking with crushed EMBEDA compared to administration of crushed ER morphine sulfate, while approximately 15% had no reduction in Drug Liking. Similarly, 100% of subjects showed some reduction in Drug High with crushed EMBEDA compared to crushed ER morphine. At least a 30% and 50% reduction in Drug Liking with crushed EMBEDA compared to crushed ER morphine was observed in 76% and 52% of subjects, respectively (summarized in Figure 1). At least a 30% and 50% reduction in Drug High with crushed EMBEDA was observed in 79% and 64% of subjects, respectively.

Table 3. Summary of Abuse Potential Maximal Responses (E_{max}) with Oral Administration of Crushed EMBEDA Compared to Crushed IR Morphine Sulfate (Study 1) or Crushed ER Morphine (Study 2)

VAS Scale (100 point)		E_{max}	
		Crushed EMBEDA (120 mg/4.8 mg)	Crushed Morphine (120 mg)
Study 1			**Immediate Release**
Drug Liking*	Mean (SE)	68.1 (3.1)	89.5 (2.2)
	Median (range)	62 (50-100)	93 (57-100)
Drug High**	Mean (SE)	54.7 (6.1)	90.2 (2.1)
	Median (range)	64 (0-100)	97 (61-100)
Study 2			**Extended Release**
Drug Liking*	Mean (SE)	65.2 (2.0)	80.6 (2.3)
	Median (range)	65 (51-100)	81 (50-100)
Drug High**	Mean (SE)	29.2 (3.6)	64.1 (3.3)
	Median (range)	27 (0-78)	63 (28-100)
Take Drug Again*	Mean (SE)	58.0 (3.8)	70.6 (4.3)
	Median (range)	58 (9-100)	75 (12-100)

* Presented on bipolar 100-point Visual Analog Scales (VAS) (0=maximum negative response, 50=neutral response, 100=maximum positive response).
**Presented on a unipolar 100-point VAS scale (0=no response, 100=maximum response).
E_{max} = maximal response; ER = extended release; IR = immediate release; SE = standard error.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for EMBEDA vs. Morphine Following Oral Administration in Studies 1 and 2.



Intranasal Study

Study 3 compared intranasal administration of crushed EMBEDA to crushed ER morphine sulfate. In this study, 33 subjects were randomized to receive three treatments: 30 mg/1.2 mg as crushed EMBEDA, 30 mg crushed ER morphine, and crushed placebo. When EMBEDA was crushed and taken intranasally, the geometric mean (±SD) values for naltrexone C_{max}, AUC_{0-2h}, and AUC_{inf} were 1441 ± 411 pg/mL, 1722 ± 441 pg·hr/mL and 3228 ± 846 pg·hr/mL, respectively. Intranasal administration of crushed EMBEDA was associated with statistically significantly lower mean and median Drug Liking, Drug High, and Take Drug Again scores compared with crushed ER morphine (summarized in Table 4).

Figure 2 demonstrates a comparison of maximum Drug Liking for intranasal administration of crushed EMBEDA compared to crushed ER morphine in subjects who received both treatments. Of the 27 subjects who completed the study, approximately 78% of subjects had some reduction in Drug Liking with crushed EMBEDA compared to administration of crushed ER morphine sulfate, while approximately 22% had no reduction in Drug Liking. Similarly, approximately 70% of subjects showed some reduction in Drug High with crushed EMBEDA compared to crushed ER morphine and approximately 30% of subjects had no reduction in Drug High. At least a 30% and 50% reduction in Drug Liking with crushed EMBEDA compared to crushed ER morphine was observed in 63% and 59% of subjects, respectively (summarized in Figure 2). At least a 30% and 50% reduction in Drug High with crushed EMBEDA was observed in 59% and 37% of subjects, respectively.

Table 4. Summary of Abuse Potential Maximal Responses (E_{max}) with Intranasal Administration of Crushed EMBEDA Compared to Crushed ER Morphine Sulfate (Study 3)

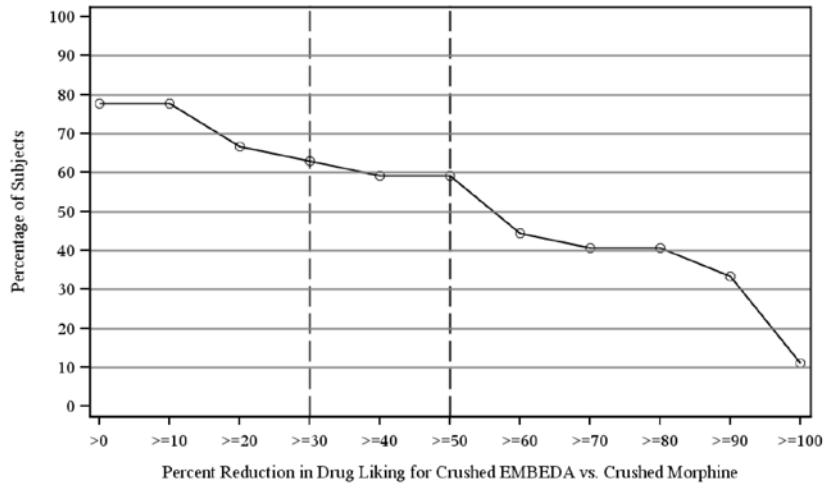
VAS Scale (100 point)		E_{max}	
		Crushed EMBEDA (30 mg/1.2 mg)	Crushed ER Morphine (30 mg)
Drug Liking*	Mean (SE)	69.0 (3.5)	88.4 (3.2)
	Median (range)	66 (50-100)	100 (51-100)
Drug High**	Mean (SE)	48.6 (7.8)	84.4 (3.8)
	Median (range)	51 (-39–100)	100 (42-100)
Take Drug Again*	Mean (SE)	59.1 (5.4)	87.0 (4.0)
	Median (range)	56 (0–100)	100 (12–100)

* Presented on bipolar 100-point Visual Analog Scales (VAS) (0=maximum negative response, 50=neutral response, 100=maximum positive response).

**Presented on a unipolar 100-point VAS scale (0=no response, 100=maximum response).

E_{max} = maximal response; ER = extended release; SE = standard error.

Figure 2: Percent Reduction Profiles for E_{max} of Drug Liking VAS for EMBEDA vs. Morphine Following Intranasal Administration in Study 3.



Simulated IV Study

Study 4, a randomized double-blind, placebo-controlled, three-way cross-over trial in 28 non-dependent recreational opioid users, was performed using 30 mg of intravenous (IV) morphine sulfate alone and 30 mg of IV morphine sulfate in combination with 1.2 mg of IV naltrexone to simulate parenteral use of crushed EMBEDA. These doses were based on the assumption of the complete release of both morphine sulfate and naltrexone hydrochloride upon crushing EMBEDA. Intravenous administration of the combination of morphine sulfate and naltrexone hydrochloride was associated with statistically significantly lower mean and median Drug Liking and Drug High scores (median scores 34 and 23, respectively) compared with morphine alone (median scores 86 and 89, respectively). Three of the 26 subjects who completed the study had no reduction in Drug Liking and all the subjects showed some reduction in Drug High. Intravenous injection of crushed EMBEDA may result in serious injury and death due to a morphine overdose and may precipitate a severe withdrawal syndrome in opioid-dependent patients.

Summary

The in vitro and pharmacokinetic data demonstrate that crushing EMBEDA pellets results in the simultaneous release and rapid absorption of morphine sulfate and naltrexone hydrochloride. These data along with results from the oral and intranasal human abuse potential studies indicate that EMBEDA has properties that are expected to reduce abuse via the oral and intranasal route. However, abuse of EMBEDA by these routes is still possible. Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of EMBEDA on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

A human abuse potential study of intravenous morphine and naltrexone to simulate crushed EMBEDA demonstrated lower Drug Liking and Drug High compared with morphine alone. However, it is unknown whether these results with simulated crushed EMBEDA predict a reduction in abuse by the IV route until additional postmarketing data are available.

EMBEDA contains morphine sulfate, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal and illicit, including fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone. EMBEDA can be abused and is subject to misuse, addiction, and criminal diversion

OXYCONTIN (oxycodone hydrochloride) extended-release tablets [NDA 022272]

Approval Date: April 5, 2010
Abuse Deterrence Labeling Update: April 16, 2013

Abuse Deterrence Studies

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

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

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

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

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

The intranasal administration of finely crushed OXYCONTIN was associated with a numerically lower mean and median drug liking score and a lower mean and median score for take drug again, compared to finely crushed original OxyContin or powdered oxycodone HCl as summarized in Table 4.

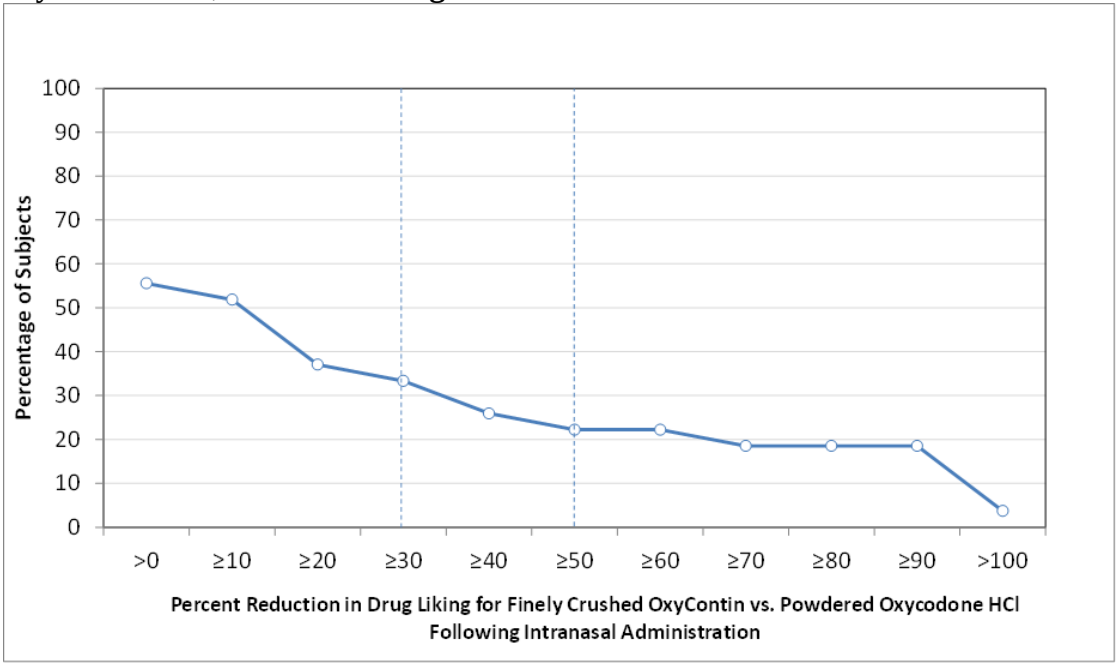
Table 4: Summary of Maximum Drug Liking (E_{max}) Data Following Intranasal Administration

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

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

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

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



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

Summary

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

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

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

TARGINIQ ER[14] (oxycodone hydrochloride and naloxone hydrochloride) extended-release tablets [NDA 205777]
Approval Date: July 23, 2014

Abuse Deterrence Studies
In Vitro Testing
In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the controlled-release formulation of TARGINIQ ER and separating the oxycodone component from naloxone, a potent opioid antagonist. Laboratory test data demonstrate that TARGINIQ ER can be crushed and dissolved in solution. However, complete separation or complete inactivation of naloxone from oxycodone was not achieved despite using various techniques and conditions.

Clinical Abuse Potential Studies
In the clinical abuse potential studies described below, drug-liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was measured on a unipolar scale of 0 to 100 where 0 represents the strongest negative response ("definitely would not take drug again") and 100 represents the strongest positive response ("definitely would take drug again"). Response to subjective feeling of getting "high" was measured on a unipolar scale of 0 to 100, where 0 represents "definitely not" and 100 represents "definitely so".

Study in Non-Dependent, Opioid Abusers (Intranasal (IN) Administration)
In a randomized, double-blind, placebo- and active-controlled, 3-period crossover pharmacodynamic study, 23 non-dependent, opioid abusers with moderate experience with opioids received IN administered TARGINIQ ER 40 mg/20 mg (finely crushed tablets), oxycodone HCl 40 mg powder (active control), and placebo treatments.

IN administration of finely crushed TARGINIQ ER was associated with statistically significant lower maximum drug liking scores ($p < 0.001$) and statistically significant lower maximum scores for take drug again ($p < 0.001$), compared to powdered oxycodone HCl, and was associated with similar mean and median maximum scores for drug liking and take drug again, compared to placebo treatment, as summarized in Table 5.

[14] Targiniq ER is no longer marketed with the NR notice effective November 28, 2018.

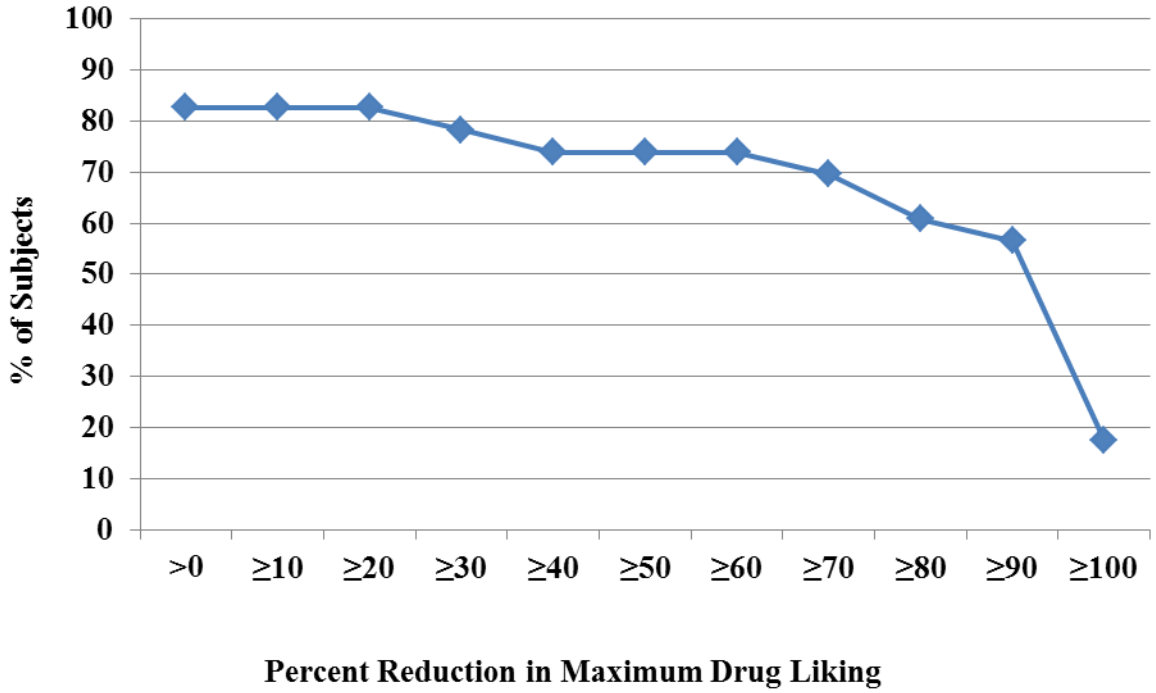
Table 5. Summary of Maximum Drug Liking (E_{max}) and Take Drug Again (E_{max}) Following Intranasal (IN) Administration of TARGINIQ ER, Oxycodone, and Placebo in Non-Dependent, Opioid Abusers (N=23)

VAS		TARGINIQ ER 40 mg/20 mg (finely crushed)	Oxycodone HCl 40 mg (powdered)	Placebo (lactose powder)
Drug Liking*	Mean (SE)	59.1 (2.8)	94.8 (2.2)	53.2 (2.1)
	Median (Range)	51 (50-100)	100 (61-100)	51 (50-100)
Take Drug Again**	Mean (SE)	42.6 (6.4)	93.6 (2.3)	30.7 (6.1)
	Median (Range)	50.0 (0-100)	100 (62-100)	50 (0-100)

VAS: visual analog scale
SE: standard error
* Drug Liking Question text: "At this moment, my liking for this drug is"; scale: 0 = maximum disliking, 50 = neither liking nor disliking (neutral response), 100 = maximum liking.
**Take Drug Again Question text: "I would take this drug again"; scale: 0 = definitely not, 100 = definitely so.

Figure 1 demonstrates a comparison of maximum drug liking for finely crushed TARGINIQ ER compared to powdered oxycodone HCl in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in maximum drug liking for TARGINIQ ER vs. oxycodone HCl powder greater than or equal to the value on the X-axis. Among non-dependent, opioid drug abusers, 78% (n = 18) of subjects had a reduction of at least 30% in maximum drug liking with TARGINIQ ER compared to oxycodone HCl, and approximately 74% (n = 17) of subjects had a reduction of at least 50% in maximum drug liking with TARGINIQ ER compared to oxycodone HCl.

Figure 1. Percent Reduction in Maximum Drug Liking for Finely Crushed TARGINIQ ER 40 mg/20 mg vs. Powdered Oxycodone HCl 40 mg Following Intranasal Administration in Non-Dependent Opioid Abusers



Study in Non-Dependent, Opioid Abusers (Intravenous (IV) Administration)
In a randomized, double-blind, placebo- and active-controlled, 3-period crossover pharmacodynamic study, 22 non-dependent, opioid abusers with moderate experience with opioids received intravenously administered 0.07 mg/kg oxycodone HCl and 0.035 mg/kg naloxone HCl solution (simulated version of TARGINIQ ER), oxycodone HCl (0.07 mg/kg solution; active control) and placebo (saline) treatments.

The intravenous administration of simulated TARGINIQ ER solution was associated with statistically significant lower maximum drug liking scores ($p < 0.001$) and statistically significant lower maximum scores for take drug again ($p < 0.001$), compared to oxycodone solution, and was associated with similar mean and median scores for drug liking and take drug again, compared to placebo treatment, as summarized in Table 6.

Table 6. Summary of Maximum Drug Liking (E_{max}) and Take Drug Again Following IV Administration of Oxycodone HCl + Naloxone HCl (Simulated TARGINIQ ER Solution), Oxycodone HCl, and Placebo in Non-Dependent, Opioid Abusers (N=22)

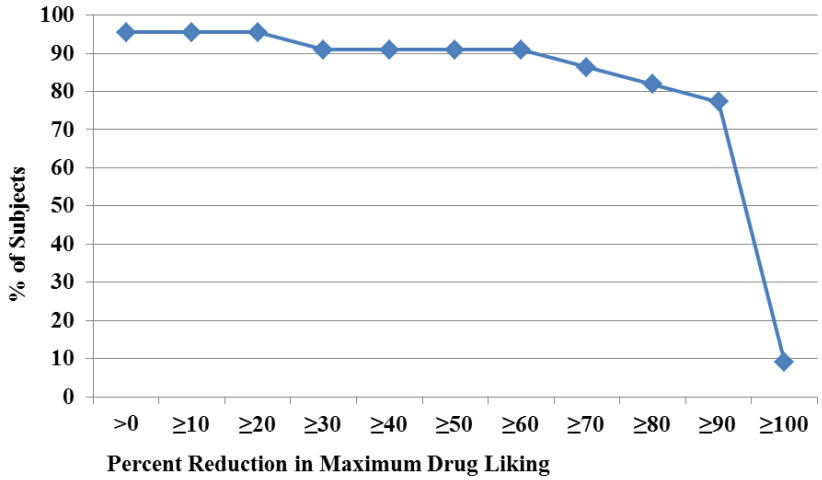
VAS		Oxycodone HCl/ Naloxone HCl 0.07/0.35 mg/kg	Oxycodone HCl 0.07 mg/kg	Placebo saline (0.9% NaCl)
Drug Liking*	Mean (SE)	56.5 (2.8)	96.4 (2.3)	48.7 (2.3)

	Median (Range)	51 (50-100)	100 (50-100)	51.0 (0-53)
Take Drug Again**	Mean (SE)	37.0 (6.2)	82.0 (6.0)	34.5 (5.1))
	Median (Range)	50.0 (0-100)	99.0 (0-100)	50.0 (0-55)

VAS: visual analog scale
SE: standard error
* Drug Liking Question text: "At this moment, my liking for this drug is"; scale: 0 = maximum disliking, 50 = neither liking nor disliking (neutral response), 100 = maximum liking.
**Take Drug Again Question text: "I would take this drug again"; scale: 0 = definitely not, 100 = definitely so; Values obtained at 8 hours post dose.

Figure 2 demonstrates a comparison of maximum drug liking for simulated TARGINIQ ER solution compared to oxycodone HCl solution in subjects who received both treatments. Among non-dependent, opioid drug abusers, approximately 91% (n = 20) of subjects had a reduction of at least 50% in maximum drug liking with TARGINIQ ER compared to oxycodone solution.

Figure 2. Percent Reduction in Maximum Drug Liking for Oxycodone 0.07 mg/kg + Naloxone 0.035 mg/kg (Simulated TARGINIQ ER) vs. Oxycodone HCl 0.07 mg/kg Following Intravenous Administration in Non-Dependent, Opioid Abusers



Study in Opioid-Dependent Subjects
In a randomized, double-blind, placebo- and positive-controlled, 4-period crossover pharmacodynamic study, 29 opioid-dependent, methadone-maintained subjects received orally administered TARGINIQ ER 60 mg/30 mg chewed and intact tablets, oxycodone HCl solution 60 mg (active control) and placebo (chewed and intact tablets and solution) treatments.

The oral administration of TARGINIQ ER, either chewed or intact, was associated with statistically significant lower maximum drug liking scores ($p < 0.001$) and statistically significant lower scores for take drug again ($p < 0.001$), compared to oxycodone solution, and was associated with similar mean and median maximum scores for drug liking and take drug again, compared to placebo treatment, as summarized in Table 7.

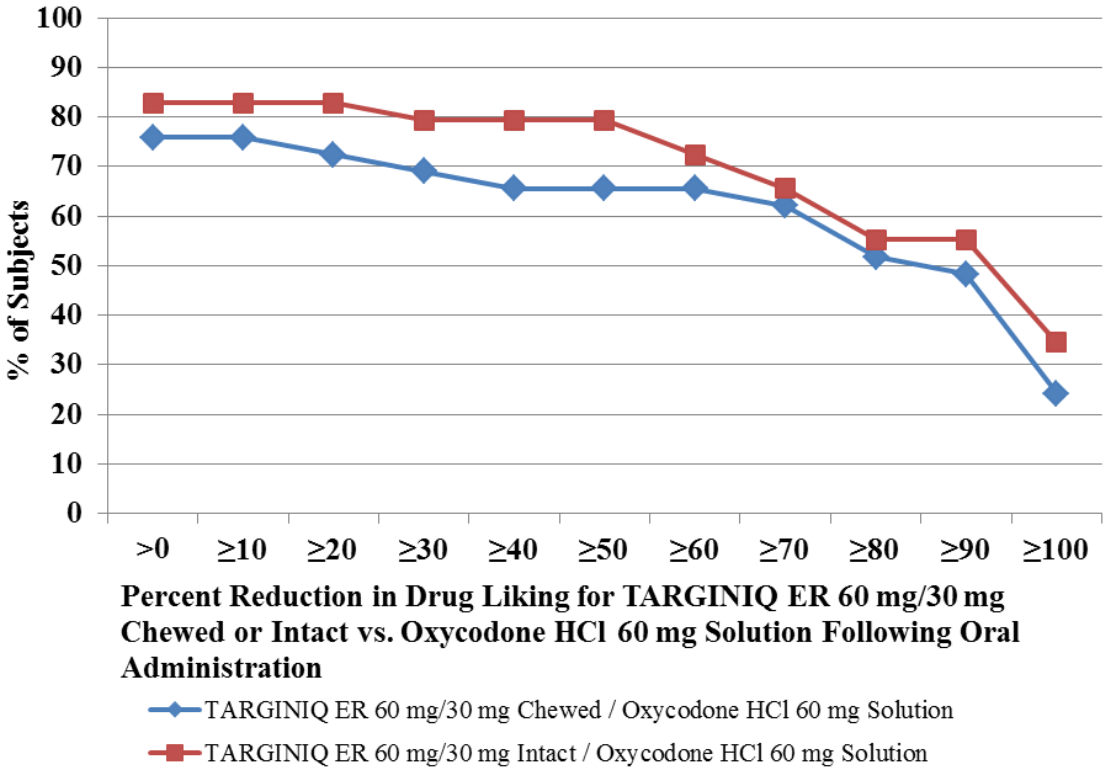
Table 7. Summary of High, Maximum Drug Liking (E_{max}), and Take Drug Again Following Oral Administration of TARGINIQ ER (Intact and Chewed), Oxycodone HCl solution, and Placebo in Opioid-Dependent Subjects (N=29)

VAS		TARGINIQ ER 60 mg/30 mg intact	TARGINIQ ER 60 mg/30 mg chewed	Oxycodone HCl solution 60 mg	Placebo chewed and intact tablet, solution
Drug Liking*	Mean (SE)	54.7 (2.0)	54.6 (3.2)	77.9 (3.8)	54.4 (2.1)
	Median (Range)	51.0 (50-99)	51.0 (0-100)	78.0 (50-100)	51.0 (50-100)
Take Drug Again**	Mean (SE)	38.5 (5.7)	32.6 (5.9)	61.4 (5.9)	41.5 (5.0)
	Median (Range)	50.0 (0-100)	50.0 (0-100)	50.0 (0-100)	50.0 (0-100)
Getting High***	Mean (SE)	20.6 (5.1)	27.7 (6.5)	77.9 (5.0)	20.6 (5.0)
	Median (Range)	1.0 (0-73)	1.0 (0-100)	86.0 (0-100)	1.0 (0-82)

VAS: visual analog scale
SE: standard error
* Drug Liking Question text: "At this moment, my liking for this drug is"; scale: 0 = maximum disliking, 50 = neither liking nor disliking (neutral response), 100 = maximum liking.
**Take Drug Again Question text: "I would take this drug again"; scale: 0 = definitely not, 100 = definitely so; Values obtained at 12 hours post dose.
***Getting High Question Text: "I am feeling high"; scale: 0 = definitely not, 100 = definitely so.

Figure 3 demonstrates a comparison of maximum drug liking (E_{max}) for TARGINIQ ER either chewed or intact compared to oxycodone solution in subjects who received both treatments. Among opioid-dependent subjects, 69.0% (n = 20) had a reduction of at least 30%, and 65.5% (n = 19) of subjects had a reduction of at least 50% in maximum drug liking with chewed TARGINIQ ER tablets compared to oxycodone solution; 79.3% (n = 23) of subjects had a reduction at least 50% in maximum drug liking with intact TARGINIQ ER tablets compared to oxycodone solution.

Figure 3. Percent Reduction in Maximum Drug Liking for TARGINIQ ER 60 mg/30 mg Chewed or Intact vs. Oxycodone HCl 60 mg Solution Following Oral Administration in Opioid-Dependent Subjects



Summary

Based on the *in vitro* study results, it is expected that abuse of oxycodone from physically and chemically manipulated TARGINIQ ER tablets will be deterred by the inability to separate the two active components.

The data from the clinical abuse potential studies indicate that TARGINIQ ER has pharmacologic properties that are expected to reduce abuse via the intranasal and intravenous routes of administration. However, abuse of TARGINIQ ER by these routes is still possible.

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

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

HYSINGLA ER (hydrocodone bitartrate) extended-release tablets [NDA 206627]

Approval Date: November 20, 2014
Abuse Deterrence Studies

HYSINGLA ER is formulated with physicochemical properties intended to make the tablet more difficult to manipulate for misuse and abuse, and maintains some extended release characteristics even if the tablet is physically compromised. To evaluate the ability of these physicochemical properties to reduce the potential for abuse of HYSINGLA ER, a series of in vitro laboratory studies, pharmacokinetic studies and clinical abuse potential studies was conducted. A summary is provided at the end of this section.

In Vitro Testing
In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that HYSINGLA ER resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some extended-release properties despite manipulation. When subjected to an aqueous environment, HYSINGLA ER gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a hypodermic needle.

Clinical Abuse Potential Studies

Studies in Non-dependent Opioid Abusers
Two randomized, double-blind, placebo and active-comparator studies in non-dependent opioid abusers were conducted to characterize the abuse potential of HYSINGLA ER following physical manipulation and administration via the intranasal and oral routes. For both studies, drug liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking, and 100 represents maximum liking. Response to whether the subject would take the study drug again was measured on a unipolar scale of 0 to 100 where 0 represents the strongest negative response ("definitely would not take drug again") and 100 represents the strongest positive response ("definitely would take drug again").

Intranasal Abuse Potential Study
In the intranasal abuse potential study, 31 subjects were dosed and 25 subjects completed the study. Treatments studied included intranasally administered tampered HYSINGLA ER 60 mg tablets, powdered hydrocodone bitartrate 60 mg, and placebo. Incomplete dosing due to granules falling from the subjects' nostrils occurred in 82% (n = 23) of subjects receiving tampered HYSINGLA ER compared to no subjects with powdered hydrocodone or placebo. The intranasal administration of tampered HYSINGLA ER was associated with statistically significantly lower mean and median scores for drug liking and take drug again ($P<0.001$ for both), compared with powdered hydrocodone as summarized in Table 3.

Table 3. Summary of Maximum Scores (E_{max}) on Drug Liking and Take Drug Again VAS Following intranasal Administration of HYSINGLA ER and Hydrocodone Powder in Non-dependent Opioid Abusers

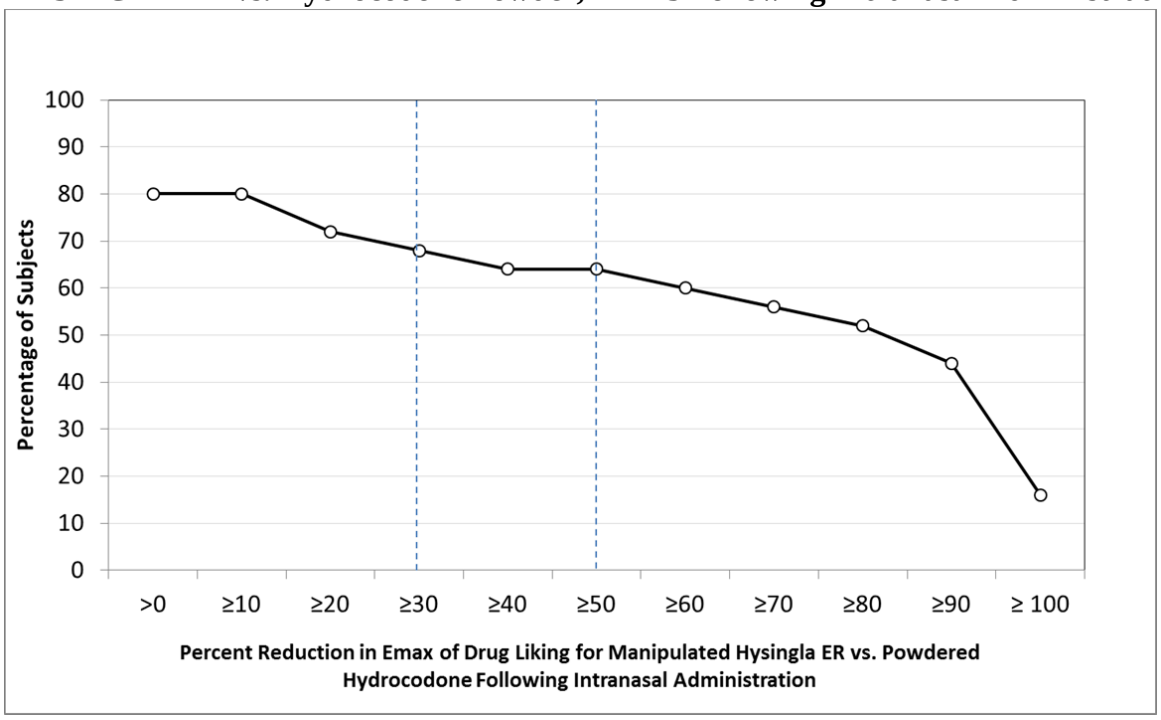
VAS Scale (100 point) *Intranasal (n=25)*	HYSINGLA ER Manipulated	Hydrocodone Powder
Drug Liking*		
Mean (SE)	65.4 (3.7)	90.4 (2.6)
Median (Range)	56 (50–100)	100 (51–100)
Take Drug Again**		
Mean (SE)	36.4 (8.2)	85.2 (5.0)
Median (Range)	14 (0-100)	100 (1-100)

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

Figure 1 demonstrates a comparison of peak drug liking scores for tampered HYSINGLA ER compared with powdered hydrocodone in subjects (n = 25) who received both treatments intranasally. The Y-axis represents the percent of subjects attaining a percent reduction in peak drug liking scores for tampered HYSINGLA ER vs. hydrocodone powder greater than or equal to the value on the X-axis.

Approximately 80% (n = 20) of subjects had some reduction in drug liking with tampered HYSINGLA ER relative to hydrocodone powder. Sixty-eight percent (n = 17) of subjects had a reduction of at least 30% in drug liking with tampered HYSINGLA ER compared with hydrocodone powder, and approximately 64% (n = 16) of subjects had a reduction of at least 50% in drug liking with tampered HYSINGLA ER compared with hydrocodone powder. Approximately 20% (n = 5) of subjects had no reduction in liking with tampered HYSINGLA ER relative to hydrocodone powder.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for Manipulated HYSINGLA ER vs. Hydrocodone Powder, N = 25 Following Intranasal Administration



Oral Abuse Potential Study

In the oral abuse potential study, 40 subjects were dosed and 35 subjects completed the study. Treatments studied included oral administrations of chewed HYSINGLA ER 60 mg tablets, intact HYSINGLA ER 60 mg tablets, 60 mg aqueous hydrocodone bitartrate solution, and placebo.

The oral administration of chewed and intact HYSINGLA ER was associated with statistically lower mean and median scores on scales that measure drug liking and desire to take drug again ($P<0.001$), compared to hydrocodone solution as summarized in Table 4.

Table 4. Summary of Maximum Scores (E_{max}) on Drug Liking and Take Drug Again VAS Following Oral Administration of HYSINGLA ER and Hydrocodone Solution in Non-dependent Recreational Opioid Users

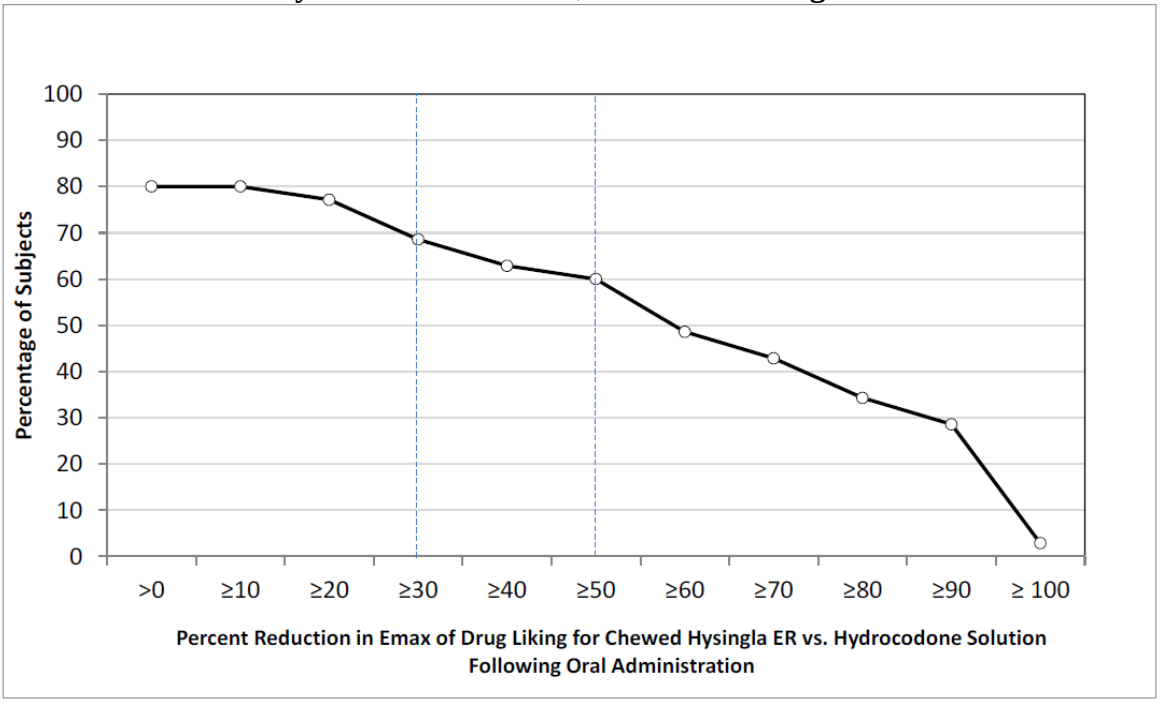
VAS Scale (100 point)	HYSINGLA ER		Hydrocodone
Oral (n=35)	**Intact**	**Chewed**	**Solution**
Drug Liking*			
Mean (SE)	63.3 (2.7)	69.0 (3.0)	94.0 (1.7)
Median (Range)	58 (50–100)	66 (50–100)	100 (51–100)
Take Drug Again**			
Mean (SE)	34.3 (6.1)	44.3 (6.9)	89.7 (3.6)
Median (Range)	24 (0-100)	55 (0-100)	100 (1-100)

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

Figure 2 demonstrates a comparison of peak drug liking scores for chewed HYSINGLA ER compared with hydrocodone solution in subjects who received both treatments orally. The Y-axis represents the percent of subjects attaining a percent reduction in peak drug liking scores for chewed HYSINGLA ER vs. hydrocodone solution greater than or equal to the value on the X-axis.

Approximately 80% (n = 28) of subjects had some reduction in drug liking with chewed HYSINGLA ER relative to hydrocodone solution. Approximately 69% (n = 24) of subjects had a reduction of at least 30% in drug liking with chewed HYSINGLA ER compared with hydrocodone solution, and approximately 60% (n = 21) of subjects had a reduction of at least 50% in drug liking with chewed HYSINGLA ER compared with hydrocodone solution. Approximately 20% (n = 7) of subjects had no reduction in drug liking with chewed HYSINGLA ER relative to hydrocodone solution.

Figure 2. Percent Reduction Profiles for E_{max} of Drug Liking VAS for Chewed HYSINGLA ER vs. Hydrocodone Solution, N = 35 Following Oral Administration



The results of a similar analysis of drug liking for intact HYSINGLA ER relative to hydrocodone solution were comparable to the results of chewed HYSINGLA ER relative to hydrocodone solution. Approximately 83% (n = 29) of subjects had some reduction in drug liking with intact HYSINGLA ER relative to hydrocodone solution. Eighty-three percent (n = 29) of subjects had a reduction of at least 30% in peak drug liking scores with intact HYSINGLA ER compared to hydrocodone solution, and approximately 74% (n = 26) of subjects had a reduction of at least 50% in peak drug liking scores with intact HYSINGLA ER compared with hydrocodone solution. Approximately 17% (n = 6) had no reduction in drug liking with intact HYSINGLA ER relative to hydrocodone solution**.**

Summary

The in vitro data demonstrate that HYSINGLA ER has physical and chemical properties that are expected to deter intranasal and intravenous abuse. The data from the clinical abuse potential studies, along with support from the in vitro data, also indicate that HYSINGLA ER has physicochemical properties that are expected to reduce intranasal abuse and oral abuse when chewed. However, abuse of HYSINGLA ER by the intravenous, intranasal, and oral routes is still possible.

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

HYSINGLA ER contains hydrocodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. HYSINGLA ER can be abused and is subject to misuse, addiction, and criminal diversion

MORPHABOND (morphine sulfate) extended-release tablets [NDA 206544]

Approval Date: October 2, 2015

Abuse Deterrence Studies

MORPHABOND is formulated with inactive ingredients that make the tablet more difficult to adulterate for misuse and abuse while maintaining extended-release characteristics even if the tablet is subjected to physical manipulation, and/or chemical extraction. To evaluate the ability of the abuse-deterrent technology to reduce the potential for abuse of MORPHABOND, a series of in vitro laboratory manipulation, extraction, and syringeability, studies was conducted. An in vivo clinical abuse potential study was also conducted. The results of these studies are summarized below. Overall, the results indicate that MORPHABOND has properties that are expected to reduce abuse or misuse via injection or insufflation; however, abuse by these routes is still possible.

In Vitro Testing

MORPHABOND has been tested in vitro using methods of manipulation that drug abusers commonly use for preparation of extended-release opioids for administration by various routes, including oral consumption, intranasal insufflation, injection, and smoking. Abusers may manipulate extended-release opioids in order to prepare the tablets for oral, intranasal, or intravenous administration. The laboratory test data demonstrated that, relative to morphine sulfate extended-release tablet, MORPHABOND has increased resistance to cutting, crushing, or breaking using a variety of tools. When subjected to a liquid environment the manipulated MORPHABOND formulation forms a viscous material that resists passage through a needle.

Clinical Studies

A randomized, double-blind, double-dummy, placebo-controlled, single-dose four-way crossover study in 25 non-dependent recreational opioid users with a history of intranasal drug abuse was performed to determine the relative bioavailability and abuse potential of crushed intranasal MORPHABOND 60 mg tablets compared with crushed intranasal morphine sulfate extended-release tablet 60 mg tablets, and intact orally administered MORPHABOND 60 mg tablets. The intact oral tablets were included as a reference for evaluating abuse potential after manipulation and administration via an unintended route.

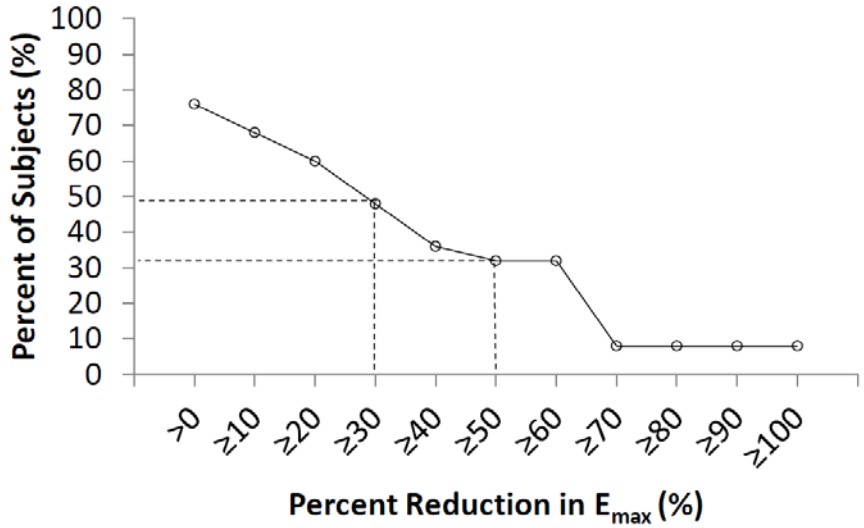
Drug liking was measured on a 100 mm bipolar visual analog scale (VAS) where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking, and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale of 0 to 100 where 50 represents a neutral response, 0 represents the strongest negative response (‘definitely would not take drug again’) and 100 represents the strongest positive response (‘definitely would take drug again’). Intranasal administration of crushed MORPHABOND was associated with statistically significantly lower drug liking (E_{max}) scores ($P < 0.0001$), and significantly lower willingness to take the drug again (E_{max}) scores ($P = 0.034$), compared to crushed extended-release morphine (Table 2). Drug liking and take drug again scores for crushed intranasal

MORPHABOND were not significantly different from those of MORPHABOND taken orally intact. These data are consistent with the similar relative bioavailability after crushed intranasal and intact oral administration of MORPHABOND that support retention of its extended release properties when manipulated compared to morphine sulfate extended-release tablets

Table 2.	**Summary of Maximum Drug Liking (E_{max}) and Take Drug Again (E_{max}) Following Administration of MORPHABOND, morphine sulfate extended-release tablet, and Placebo in Recreational Opioid Users (n=25)**				
		Crushed Intranasal MORPHABOND 60 mg	**Crushed Intranasal morphine sulfate extended-release tablet 60 mg**	**Placebo**	**Crushed Intranasal morphine sulfate extended-release tablet vs. Crushed Intranasal MORPHABOND Difference of LS Means (95% CI)**
Drug Liking (E_{max})	Mean (SEM)	71.7 (2.87)	85.3 (2.42)	54.3 (1.63)	13.65 (7.80, 19.51)
	Median (Range)	72 (50-100)	85 (56-100)	51 (50-80)	
Take Drug Again (E_{max})	Mean (SEM)	66.4 (3.76)	76.4 (4.17)	49.1 (2.21)	9.96 (0.77, 19.14)
	Median (Range)	64.0 (38-100)	75.0 (17-100)	50.0 (0-64)	

Figure 1 demonstrates a comparison of peak drug liking scores for crushed MORPHABOND compared to crushed extended-release morphine in subjects who received both treatments intranasally. Seventy-six percent of subjects (n = 19) experienced some reduction in E_{max} of Drug Liking VAS with crushed MORPHABOND compared with crushed extended-release morphine, 48%; (n = 12) experienced at least a 30% reduction in E_{max} and 32% (n = 8) experienced at least a 50% reduction in E_{max} of drug liking.

Figure 1. Percent Reduction Profiles for E_{max} of Drug Liking for MORPHABOND vs. Morphine Sulfate ER Tablets (n=25), Following Intranasal Administration



Summary

The in vitro data demonstrate that MORPHABOND has physiochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from in vitro data, also indicate that MORPHABOND has physicochemical properties that are expected to reduce abuse by the intranasal route of administration. However, abuse by intranasal, intravenous, and oral routes is still possible. Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of MORPHABOND on the abuse liability of the drug.

XTAMPZA ER (oxycodone) extended-release capsules [NDA 208090]

Approval Date: April 26, 2016

Abuse Deterrence Studies

XTAMPZA ER capsules contain microspheres formulated with inactive ingredients intended to make the formulation more difficult to manipulate for misuse and abuse.

In Vitro Testing

In vitro physical and chemical manipulation studies were performed to evaluate the success of different methods of defeating the extended-release formulation.

Results support that, relative to immediate-release oxycodone tablets, XTAMPZA ER is less susceptible to the effects of grinding, crushing, and extraction using a variety of tools and solvents.

XTAMPZA ER resisted attempts to pass the melted capsule contents or the microspheres suspended in water through a hypodermic needle.

Pharmacokinetic Studies

The pharmacokinetic profile of manipulated XTAMPZA ER capsule contents (36 mg; [equivalent to 40 mg oxycodone HCl]) was characterized following oral (two studies) and intranasal (two studies) administration. The studies were conducted in a randomized, cross-over design. In studies assessing manipulation by crushing, the most effective crushing method identified in previous in vitro studies was applied to the product(s).

Oral Pharmacokinetic Studies, Manipulated and Intact XTAMPZA ER

The effect of two types of product manipulation (crushing and chewing) on XTAMPZA ER pharmacokinetics was measured in two studies.

In Oral Pharmacokinetic Study 1, XTAMPZA ER capsule contents were crushed or chewed prior to oral administration in healthy, naltrexone blocked volunteers. The two comparators in this study were intact XTAMPZA ER capsules and an immediate-release solution of oxycodone.

In Oral Pharmacokinetic Study 2, XTAMPZA ER capsule contents were crushed prior to oral administration in healthy, naltrexone-blocked volunteers. The comparators in this study included intact XTAMPZA ER capsules and crushed immediate-release oxycodone tablets.

The pharmacokinetic data displayed in Table 3 illustrate the findings from these two studies. Collectively, the data from the two studies demonstrated that crushing or chewing XTAMPZA ER prior to administration did not increase the maximum observed plasma concentration (C_{max}) or total exposure ($AUC_{0\text{-}INF}$) relative to dosing the intact product under fed conditions. Relative to immediate-release oxycodone, the C_{max} for all XTAMPZA ER treatments was significantly lower and the T_{max} significantly longer, consistent with an extended-release profile.

Table 3: Oxycodone Pharmacokinetic Parameters, Administration of Manipulated Capsule Contents and Intact Capsules (36 mg)

	C_{max} **(ng/mL)**	T_{max} **(hr)**	$AUC_{0\text{-}INF}$ **(hr•ng/mL)**
Treatment	**Oral Pharmacokinetic Study 1**		
Intact XTAMPZA ER Capsules (fed)	62.3 (13.0)	4.0 (1.5-6)	561 (124)
Crushed XTAMPZA ER Capsule Contents (fed)	57.6 (12.6)	4.5 (2.5-6)	553 (134)
Chewed XTAMPZA ER Capsule Contents (fed)	55.6 (10.9)	4.5 (2.5-8)	559 (113)
Immediate-Release Oxycodone Solution (fasted)	115 (27.3)	0.75 (0.5-2)	489 (80.2)
	Oral Pharmacokinetic Study 2		
Intact XTAMPZA ER Capsules (fed)	67.5 (17.6)	3.5 (1.25 – 6.0)	581 (138)
Crushed XTAMPZA ER Capsule Contents (fed)	62.9 (12.6)	4.0 (2.0 – 7.0)	597 (149)
Crushed Immediate-Release Oxycodone Tablets (fed)	79.4 (17.1)	1.75 (0.5-4.0)	561 (146)

Values shown for C_{max} and $AUC_{0\text{-}INF}$ are mean (standard deviation); values shown for T_{max} are median (minimum-maximum).

Nasal Pharmacokinetic Studies

The pharmacokinetic profile following intranasal administration of crushed XTAMPZA ER capsule contents was characterized in two clinical studies.

In Nasal Pharmacokinetic Study 1, XTAMPZA ER capsule contents were crushed and intranasally administered by non-dependent, naltrexone-blocked subjects with a history of

nasal abuse of opioids. The two comparators in this study were intact XTAMPZA ER capsules (oral) and oxycodone HCl powder (intranasal) at an equivalent dose.

In Nasal Pharmacokinetic Study 2, XTAMPZA ER capsule contents were crushed and intranasally administered by non-dependent subjects with a history of nasal abuse of opioids. The two comparators in this study were intact XTAMPZA ER capsules (oral) and crushed oxycodone immediate-release tablets (intranasal) at an equivalent dose.

The results of Nasal Pharmacokinetic Studies 1 and 2 are comparable and both studies demonstrated that intranasal administration of crushed XTAMPZA ER capsule contents did not result in higher peak plasma concentration (C_{max}) or shorter time to peak concentration (T_{max}) than taking XTAMPZA ER orally. The data from Nasal Pharmacokinetic Study 2 are displayed in Table 4 to represent these findings.

Table 4: Pharmacokinetic Parameters, Nasal Pharmacokinetic Study 2:

Treatment	**C_{max} (ng/mL)**	**T_{max} (hr)**	**$AUC_{0\text{-}INF}$ (hr•ng/mL)**
Intact XTAMPZA ER Capsules (oral)	41.0 (10.0)	5.1 (1.6-8.1)	477 (89.6)
Crushed XTAMPZA ER Capsule Contents (nasal)	29.8 (6.6)	5.1 (1.6-12.1)	459 (106)
Crushed Immediate-Release Tablets (nasal)	60.9 (11.9)	2.6 (0.3-6.1)	577 (124)

Values shown for C_{max} and $AUC_{0\text{-}INF}$ are mean (standard deviation); values shown for T_{max} are median (minimum-maximum).

Clinical Studies

Oral Abuse Potential Study:

In the Oral Abuse Potential Study, a randomized, double-blind, active- and placebo-controlled, single-dose, six-way crossover pharmacodynamic study, 61 recreational opioid users with a history of oral drug abuse received orally administered active and placebo treatment. The six treatment arms were intact XTAMPZA ER (36 mg, fed and fasted); chewed XTAMPZA ER (36 mg, fed and fasted); crushed immediate-release oxycodone HCl in water (40 mg, fasted, equivalent to 36 mg of XTAMPZA ER), and placebo. Data for chewed XTAMPZA ER and crushed IR oxycodone in the fasted state are described below.

Drug Liking was measured on a bipolar 100-point Visual Analog Scale (VAS) where 50 represents a neutral response, 0 represents maximum disliking, and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar 100-point VAS where 50 represents a neutral response, 0 represents the strongest negative response (e.g., ‘definitely would not take drug again’) , and 100 represents the strongest positive response (e.g., ‘definitely would take drug again’).

Thirty-eight subjects completed the study. The results are summarized in Table 5. The oral administration of chewed and intact XTAMPZA ER in the fasted state was associated with

statistically lower mean Drug Liking scores compared with crushed immediate-release oxycodone. However, the differences for XTAMPZA ER chewed and intact compared with crushed immediate-release oxycodone for the Take Drug Again scores were small and not statistically significant.

Table 5: Summary of Maximum Drug Liking and Take Drug Again (E_{max}) Following Oral Administration

		XTAMPZA ER Intact (Fasted)	XTAMPZA ER Chewed (Fasted)	Crushed IR Oxycodone (Fasted)	Placebo
Drug Liking* (E_{max})	Mean (SEM)	68.8 (2.11)	73.4 (2.26)	81.8 (1.86)	54.9 (1.37)
	Median (Range)	72 (50-89)	76 (50-95)	83 (50-99)	51 (50-84)
Take Drug Again (E_{max})*	Mean (SEM)	70.2 (2.59)	73.7 (2.42)	75.4 (2.72)	52.7 (2.17)
	Median (Range)	69 (50-98)	74 (50-98)	76 (37-100)	50 (3-95)

* Bipolar scale (0=maximum negative response, 50=neutral response, 100=maximum positive response)
Emax = maximum (peak) effect; ER = extended-release; IR = immediate-release; VAS = visual analogue scale; SEM= standard error of the mean.

Nasal Abuse Potential Study:

In a randomized, double-blind, active- and placebo-controlled, single-dose, four-way crossover pharmacodynamic study, 39 recreational opioid users with a history of intranasal drug abuse received nasally administered active and placebo drug treatment. The four treatment arms were crushed XTAMPZA ER 36 mg dosed intranasally; intact XTAMPZA ER 36 mg dosed orally; crushed immediate-release oxycodone HCl 40 mg (equivalent to 36 mg of XTAMPZA ER) dosed intranasally; and placebo. Data for intranasal XTAMPZA ER and crushed immediate-release oxycodone are described below.

Thirty-six subjects completed the study. Intranasal administration of crushed XTAMPZA ER was associated with statistically lower mean Drug Liking and Take Drug Again scores compared with crushed immediate-release oxycodone (summarized in Table 6).

Table 6: Summary of Maximum Drug Liking and Take Drug Again (E_{max}) Following Intranasal Administration

		XTAMPZA ER Intranasal	Crushed IR Oxycodone Intranasal	Placebo
Drug Liking* (E_{max})	Mean (SEM)	61.8 (2.6)	82.7 (1.8)	54.5 (2.0)
	Median (Range)	59.5 (16-94)	84 (60-100)	51 (28-93)
Take Drug Again* (E_{max})	Mean (SEM)	47.7 (4.6)	71.4 (3.9)	45.9 (2.9)
	Median (Range)	50 (0-100)	78.5 (18-100)	50 (0-97)

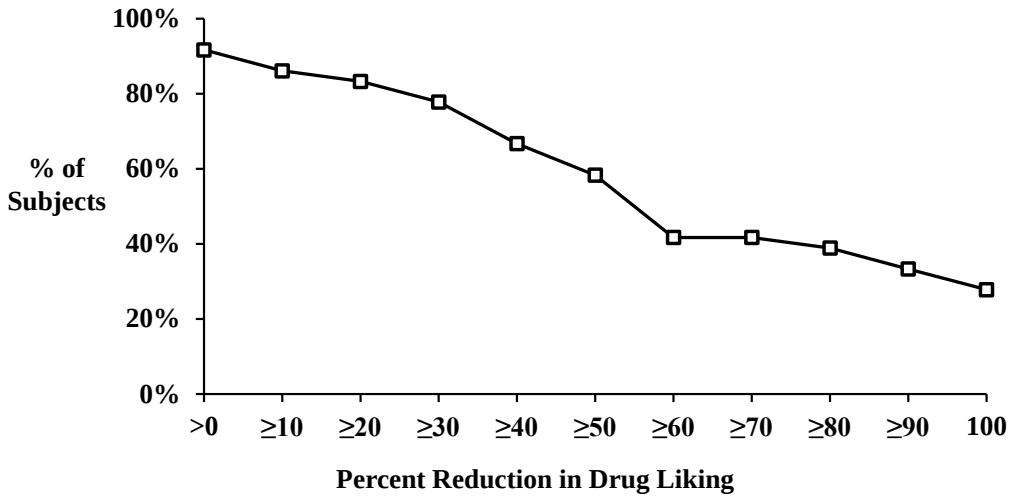
* Bipolar scale (0=maximum negative response, 50=neutral response, 100=maximum positive response).

E_{max} = maximum (peak) effect; ER = extended-release; IR = immediate-release; VAS = visual analogue scale; SEM = Standard error of the mean.

Figure 1 demonstrates a comparison of Drug Liking for intranasal administration of crushed XTAMPZA ER compared to crushed immediate-release oxycodone in subjects who received both treatments (N=36). The Y-axis represents the percent of subjects attaining a percent reduction in drug liking for XTAMPZA ER vs. immediate-release oxycodone greater than or equal to the value on the X-axis. Approximately 92% (n = 33) of subjects had some reduction in drug liking with XTAMPZA ER relative to crushed immediate-release oxycodone HCl. 78% (n = 28) of subjects had a reduction of at least 30% in drug liking with XTAMPZA ER compared to crushed immediate-release oxycodone HCl, and approximately 58% (n = 21) of subjects had a reduction of at least 50% in drug liking with XTAMPZA ER compared to crushed immediate-release oxycodone HCl.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for Crushed XTAMPZA ER vs. Crushed Immediate-release Oxycodone, N=36 Following Intranasal Administration

.



Summary

The in vitro data demonstrate that XTAMPZA ER has physicochemical properties expected to make abuse by injection difficult. The data from pharmacokinetic and human abuse potential studies, along with support from the in vitro data, also indicate that XTAMPZA ER has physicochemical properties that are expected to reduce abuse via the intranasal route. The data from the oral pharmacokinetic studies of manipulated XTAMPZA ER demonstrated a lack of dose dumping with no increase in oxycodone levels compared to intact XTAMPZA ER. Although the results of the oral human abuse potential study showed a difference in the Drug Liking endpoint, there was no statistically significant reduction in the response to Take Drug Again. Therefore, it cannot be concluded that XTAMPZA ER has physicochemical properties that are expected to reduce abuse via the oral route.

However, abuse of XTAMPZA ER by injection and by the nasal route of administration, as well as by the oral route is still possible.

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

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

TROXYCA ER[15] (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules [NDA 207621]
Approval Date: August 19, 2016

Abuse Deterrence Studies
TROXYCA ER is formulated with a sequestered opioid antagonist, naltrexone HCl, which is released with manipulation by crushing.

In Vitro Testing
In vitro laboratory tests were performed to evaluate the effect of different physical and chemical conditions intended to defeat the extended-release formulation. When TROXYCA ER is crushed and mixed in a variety of solvents, both oxycodone HCl and naltrexone HCl are simultaneously extracted.

Clinical Abuse Potential Studies
Two randomized, double-blind active- and placebo-controlled studies were conducted in non-dependent opioid abusers to characterize the abuse potential of oral or intranasal administration of TROXYCA ER following physical manipulation. A third randomized, double-blind, single-dose, placebo and active-controlled study was conducted with IV administration of simulated crushed TROXYCA ER. For these studies, Drug Liking was measured on a bipolar 100-point Visual Analog Scale (VAS) where 0 represents maximum disliking, 50 represents a neutral response (neither like nor dislike), and 100 represents maximum liking. Response to whether the subject would Take Drug Again was measured on a bipolar 100-point VAS where 0 represents strongest negative response (e.g., 'definitely would not take drug again'), 50 represents a neutral response, and 100 represents the strongest positive response (e.g., 'definitely would take drug again').
The pharmacokinetic profiles of oxycodone HCl and naltrexone HCl were also determined in these abuse potential studies. When TROXYCA ER was crushed and administered orally (40 mg/4.8 mg and 60 mg/7.2 mg doses) or intranasally (30 mg/3.6 mg doses), oxycodone HCl and naltrexone HCl were both absorbed rapidly with median time-to-peak concentration (T_{max}) values of approximately 0.6-1 hour and 0.6 hours, respectively, following oral administration and 1.6 hours and 0.3 hours, respectively, following intranasal administration.

Oral Abuse Potential Study
In this study, 31 non-dependent, recreational opioid abusers received all six treatments by the oral route: crushed 40 mg/4.8 mg TROXYCA ER in solution, crushed 40 mg immediate-release (IR) oxycodone HCl in solution, intact 60 mg/7.2 mg TROXYCA ER, crushed 60 mg/7.2 mg TROXYCA ER in solution, crushed 60 mg IR oxycodone HCl in solution, and placebo. When 40 mg/4.8 mg TROXYCA ER and 60 mg/7.2 mg TROXYCA ER were crushed and taken orally, the geometric mean (SD) values for naltrexone HCl C_{max} were 1074 (1463) pg/mL and 1810 (2450) pg/mL respectively; the AUC_{0-2h} values were 1217 (1471) and 2010 (1839) pg·h/mL, and the AUC_{inf} values were 2877 (2834) pg·h/mL and 4695 (3714) pg·h/mL, respectively.

[15] Troxyca ER is no longer marketed with the FR notice effective May 2, 2018.

Oral administration of crushed 40 mg/4.8 mg TROXYCA ER was associated with statistically significantly lower means and medians for Drug Liking and Take Drug Again E_{max} compared with crushed 40 mg IR oxycodone HCl. Oral administration of crushed 60 mg/7.2 mg TROXYCA ER was associated with statistically significantly lower means and medians for Drug Liking E_{max} compared to crushed 60 mg IR oxycodone HCl. The mean and median Take Drug Again E_{max} for crushed 60 mg/7.2 mg TROXYCA ER compared with crushed 60 mg IR oxycodone HCl was numerically lower; however, this finding did not reach statistical significance. The results from this study are summarized in Table 6.

Among the 31 subjects who received both TROXYCA ER and IR oxycodone by the oral route, 74% (23) and 77% (24) experienced some reduction in Drug Liking E_{max} with crushed 40 mg/4.8 mg TROXYCA ER and crushed 60 mg/7.2 mg TROXYCA ER, respectively, compared to crushed IR oxycodone, while 26% (8) and 23% (7) of subjects had no reduction in Drug Liking E_{max} for crushed 40 mg/4.8 mg TROXYCA ER and crushed 60 mg/7.2 mg TROXYCA ER, respectively, compared to crushed IR oxycodone. With crushed 40 mg/4.8 mg TROXYCA ER, 65% (20) of subjects had at least a 30% reduction and 55% (17) of subjects had at least a 50% reduction in Drug Liking E_{max} compared to crushed 40 mg IR oxycodone. With crushed 60 mg/7.2 mg TROXYCA ER, 61% (19) of subjects had at least a 30% reduction and 45% (14) of subjects had at least a 50% reduction in Drug Liking E_{max} compared to crushed 60 mg IR oxycodone.

Table 6. Summary Statistics of Abuse Potential Measures of Drug Liking (E_{max}) and Take Drug Again (E_{max}) following Oral Administration

Bipolar VAS Scale (100 point)		Placebo N=31	TROXYCA ER 40 mg/4.8 mg Crushed N=31	IR Oxycodone 40 mg Crushed N=31	TROXYCA ER 60 mg/7.2 mg Intact N=31	TROXYCA ER 60 mg/7.2 mg Crushed N=31	IR Oxycodone 60 mg Crushed N=31
Drug Liking (E_{max})*	Mean (SE)	51.6 (0.68)	69.5 (3.45)	85.6 (2.94)	59.3 (2.75)	74.3 (3.30)	90.0 (2.46)
	Median (range)	51.0 (50,68)	64.0 (50,100)	94.0 (50,100)	51.0 (50,100)	73.0 (50,100)	100.0 (57,100)
Take Drug Again (E_{max})*	Mean (SE)	45.5 (3.47)	56.7 (6.00)	82.9 (3.66)	47.7 (5.12)	71.1 (5.08)	80.6 (4.56)
	Median (range)	50.0 (0,92)	58.0 (0,100)	90.0 (30,100)	50.0 (0,100)	77.0 (0,100)	90.0 (0,100)

* Presented on bipolar 100-point Visual Analog Scales (VAS) (0=maximum negative response, 50=neutral response, 100=maximum positive response).
E_{max} = maximal response for Drug Liking and Take Drug Again; ER = extended-release; IR = immediate-release; SE = standard error

Intranasal Abuse Potential Study

In this study, 27 non-dependent, recreational opioid abusers with experience with intranasal administration of opioids received all four treatments by the intranasal route: crushed 30 mg/3.6 mg TROXYCA ER, crushed 30 mg IR oxycodone HCl, crushed placebo sugar spheres and crushed placebo lactose tablets. Placebo sugar spheres and placebo lactose tablets were weight matched to TROXYCA ER or IR oxycodone HCl. When TROXYCA ER was crushed and taken intranasally, the geometric mean (SD) values for naltrexone HCl C_{max}, AUC_{0-2h}, and AUC_{inf} were 4372 (1409) pg/mL, 5481 (1472) pg·hr/mL, and 10710 (3213) pg·hr/mL, respectively.

Intranasal administration of crushed TROXYCA ER was associated with statistically significantly lower means and medians for Drug Liking and Take Drug Again E_{max} compared with crushed IR oxycodone HCl (summary statistics for Drug Liking and Take Drug Again in Table 7).

Table 7. Summary Statistics of Abuse Potential Measures for Drug Liking and Take Drug Again with Intranasal Administration of Crushed TROXYCA ER Compared to Crushed IR Oxycodone HCl

VAS Scale (100 point)		Placebo for TROXYCA ER N=27	TROXYCA ER 30 mg/3.6 mg Crushed N=27	Placebo for IR Oxycodone N=27	IR Oxycodone 30 mg Crushed N=27
Drug Liking (E_{max})*	Mean (SE)	51.0 (0.23)	60.3 (2.36)	51.3 (0.65)	93.7 (2.11)
	Median (range)	51.0 (50,56)	55.0 (50,100)	51.0 (50,68)	100.0 (50,100)
Take Drug Again (E_{max})*	Mean (SE)	47.9 (2.92)	58.1 (6.27)	46.5 (3.67)	88.5 (5.18)
	Median (range)	50.0 (0,83)	51.0 (0,100)	50.0 (0,98)	100.0 (0,100)

* Presented on bipolar 100-point Visual Analog Scales (VAS) (0=maximum negative response, 50=neutral response, 100=maximum positive response).
E_{max} = maximal response for Drug Liking and Take Drug Again; ER = extended-release; IR = immediate-release; SE = standard error

Among 27 subjects who received both TROXYCA ER and IR oxycodone by the intranasal route, 93% (25) experienced some reduction in Drug Liking Emax with crushed TROXYCA ER compared to crushed IR oxycodone, while 7% (2) of subjects had no reduction in Drug Liking Emax for crushed TROXYCA ER compared to crushed IR oxycodone. With crushed TROXYCA ER 93% (25) of subjects had at least a 30% reduction in Drug Liking Emax and 85% (23) of subjects had at least a 50% reduction in Drug Liking Emax compared to crushed IR oxycodone.

Simulated IV Abuse Potential Study
This study in non-dependent recreational opioid abusers compared 20 mg IV oxycodone HCl in combination with 2.4 mg IV naltrexone HCl (to simulate parenteral use of crushed TROXYCA ER) to 20 mg of IV oxycodone HCl and placebo; 29 subjects received all three treatments. These doses were based on the assumption of the complete release of both oxycodone HCl and naltrexone HCl upon crushing TROXYCA ER. Intravenous administration of the combination of oxycodone HCl and naltrexone HCl was associated with statistically significantly lower mean and median Drug Liking and Take Drug Again Emax scores (median scores 51 and 50, respectively) compared with oxycodone alone (median scores 97 and 81, respectively). Among 29 subjects, 90% (26) experienced some reduction in Emax of Drug Liking with simulated parenteral use of crushed TROXYCA ER compared to IV oxycodone HCl, while 10% (3) of subjects had no reduction in Drug Liking Emax for simulated parenteral use of crushed TROXYCA ER compared to IV oxycodone HCl.

Summary
The in vitro and pharmacokinetic data demonstrate that crushing TROXYCA ER pellets results in the simultaneous release and absorption of oxycodone HCl and naltrexone HCl. These data along with results from the oral and intranasal human abuse potential studies

indicate that TROXYCA ER has properties that are expected to reduce abuse via the oral and intranasal routes. However, abuse of TROXYCA ER by these routes is still possible.

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

A human abuse potential study of intravenous oxycodone HCl and naltrexone HCl to simulate crushed TROXYCA ER demonstrated lower Drug Liking and Take Drug Again Emax compared with oxycodone HCl alone. However, it is unknown whether these results with simulated crushed TROXYCA ER predict a reduction in abuse by the IV route until additional postmarketing data are available.

TROXYCA ER contains oxycodone HCl, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal and illicit, including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxymorphone, and tapentadol. TROXYCA ER can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.1)]*.

ARYMO ER (morphine sulfate) extended-release tablets [NDA 208603]
Approval Date: January 9, 2017

Abuse Deterrence Studies
ARYMO ER is formulated with inactive ingredients that make the tablet more difficult to manipulate for misuse and abuse.

To evaluate the ability of ARYMO ER to reduce the potential for misuse and abuse, a series of abuse-deterrent in vitro laboratory physical manipulation, chemical extraction, and syringeability studies was conducted. An oral pharmacokinetic study and an oral clinical abuse potential study were also conducted.

In Vitro Testing
In vitro physical and chemical manipulation studies were performed to evaluate the ability of different methods to defeat the extended-release properties. The results of this testing demonstrated that ARYMO ER tablets, in comparison to morphine sulfate extended-release tablets, have increased resistance to cutting, crushing, grinding or breaking using a variety of tools. When subjected to a liquid environment, the manipulated ARYMO ER tablets form a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a hypodermic needle.

Oral Pharmacokinetic Study
The pharmacokinetic profile of manipulated ARYMO ER was characterized following oral administration. The study was conducted in a randomized cross-over design. The pharmacokinetic profile of manipulated and intact ARYMO ER compared to crushed morphine sulfate extended-release was evaluated in 38 subjects after oral administration. The results are summarized in Table 2 and demonstrate that oral ingestion of manipulated ARYMO ER resulted in a higher Cmax, but similar AUC, when compared to intact ARYMO ER. In

addition, manipulated ARYMO ER had a lower Cmax and longer Tmax than crushed morphine sulfate extended-release tablets.

Table 2: Results from Oral Pharmacokinetic Study

PK Parameter	ARYMO ER		Crushed Morphine Sulfate Extended-Release (n = 39)
	Manipulated (n = 38)	Intact (n = 38)	
C_{max} (ng/mL)			
Mean (SD)	28.7 (9.1)	17.8 (6.6)	42.3 (14.3)
Median (Range)	29.2 (12.5, 47.8)	16.7 (8.5, 32.3)	42.2 (14.2, 79.0)
T_{max} (h)			
Median (Range)	2.1 (0.9, 4.2)	4.1 (1.6, 6.1)	0.9 (0.6, 4.1)
$AUC_{0-\infty}$ (h*ng/mL)			
Mean (SD)	159.3 (36.8)	168.0 (53.6)	182.1 (49.9)
Median (Range)	157.1 (94.5, 215.3)	159.4 (80.9, 274.8)	185.5 (61.8, 284.1)

C_{max} = maximum observed plasma concentration; T_{max} = time to achieve the maximum observed plasma concentration; $AUC_{0-\infty}$ = area under the curve, zero to infinity

Oral Clinical Abuse Potential Study

An oral abuse potential study was conducted in 39 subjects who were non-dependent recreational opioid users; 38 subjects completed the study. Treatment arms included manipulated ARYMO ER 60 mg tablets (taken with juice), intact ARYMO ER 60 mg tablets (taken with juice), crushed 60 mg morphine sulfate extended-release tablets (mixed in juice), and placebo.

The study demonstrated that the oral administration of manipulated ARYMO ER resulted in a statistically lower mean drug liking score than the oral administration of crushed morphine sulfate extended-release tablets. However, the difference between manipulated ARYMO ER and crushed morphine sulfate extended-release tablets for Take Drug Again was not statistically significant, indicating that the difference in drug liking scores was not clinically meaningful.

These results are summarized in Table 3.

Table 3: Summary of Maximum Scores (E_{max}) for Drug Liking and Take Drug Again VAS[1] Following Oral Administration of Manipulated and Intact ARYMO ER and Crushed Morphine Sulfate Extended-Release in Non-Dependent Recreational Opioid Users

Parameter	ARYMO ER		Crushed Morphine Sulfate Extended-Release (n = 38)	Placebo (n = 38)
	Manipulated (n = 38)	Intact (n = 38)		
Maximum Drug Liking (E_{max})				
Mean (SD)	68.3 (12.3)	63.2 (10.1)	73.3 (9.8)	53.3 (7.8)
Median (Q1, Q3)	67.0 (61.0, 75.0)	62.0 (56.0, 68.0)	74.0 (68.0, 79.0)	50.0 (50.0, 52.0)
Take Drug Again (E_{max})				
Mean (SD)	62.9 (19.6)	54.8 (20.8)	70.1 (17.5)	51.0 (10.2)
Median (Q1, Q3)	61.5 (51.0, 71.0)	56.0 (50.0, 65.0)	68.0 (56.0, 80.0)	50.0 (50.0, 50.0)

[1] 100 point bipolar VAS (0=maximum negative response, 50=neutral response, 100=maximum positive response)

Summary
The in vitro data demonstrate that ARYMO ER has physical and chemical properties expected to make abuse by injection difficult.

Although the results of the oral human abuse potential study showed a difference in the Drug Liking endpoint, there was no statistically significant reduction in the response to Take Drug Again. Therefore, it cannot be concluded that ARYMO ER has physical and chemical properties that are expected to reduce abuse via the oral route.

Abuse of ARYMO ER by injection, as well as by the oral and nasal routes, is still possible.

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

VANTRELA ER[16] (hydrocodone bitartrate) extended-release tablets [NDA 207975]
Approval Date: January 17, 2017

Abuse Deterrence Studies
VANTRELA ER is formulated with physicochemical properties intended to make the tablet more difficult to manipulate for misuse and abuse.

In Vitro Testing
In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results

[16] Vantrela ER is no longer marketed with the NR notice effective May 2, 2018.

support that VANTRELA ER resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some extended-release properties despite manipulation. When VANTRELA ER was subjected to attempts at small volume extraction, the resulting material was viscous and resisted passage through a hypodermic needle.

Pharmacokinetics of Manipulated Tablets
The pharmacokinetic profile of manipulated VANTRELA ER tablet contents was characterized following oral and intranasal administration. The studies were conducted in a randomized, crossover design and are described in the section on Clinical Abuse Potential Studies. In the oral study assessing manipulation by crushing, the most effective crushing method identified in previous in vitro studies was applied to the product(s). For the intranasal study, VANTRELA ER tablets were manipulated to produce a powder suitable for nasal insufflation.

Oral Pharmacokinetic Data
The effect of product manipulation (crushing) on VANTRELA ER pharmacokinetics was measured in an oral clinical abuse potential study. VANTRELA ER tablets were crushed prior to oral administration in healthy, nondependent recreational opioid users. The two comparators in this study were intact VANTRELA ER tablets and an immediate-release hydrocodone powder.

The pharmacokinetic data displayed in Table 4 illustrate the findings from this study. The data demonstrated that crushing VANTRELA ER tablets prior to administration increased the maximum observed plasma concentration (Cmax) but not the total exposure (AUC0-inf) relative to dosing the intact product. Relative to immediate-release hydrocodone, the Cmax for all VANTRELA ER treatments was significantly lower and the Tmax significantly longer, consistent with an extended-release profile.

Table 4: Hydrocodone Pharmacokinetic Parameters, Oral Administration (45 mg)

Treatment	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}inf}$ (hr*ng/mL)
45 mg Vantrela ER intact	28.77 (6.1)	7.1 (6.1 - 12.0)	584 (124.8)
45 mg Vantrela ER finely crushed	40.78 (10.2)	4.0 (1.8 - 7.0)	586 (138.5)
45 mg immediate-release hydrocodone powder	91.46 (16.8)	0.8 (0.3 - 4.1)	625 (137.3)

Values shown for C_{max} and $AUC_{0\text{-}inf}$ are mean (standard deviation); values shown for T_{max} are median (minimum-maximum).

Nasal Pharmacokinetic Data
The pharmacokinetic profile following intranasal administration of manipulated VANTRELA ER tablet contents was characterized in a nasal clinical abuse potential study. VANTRELA ER tablets were finely milled and intranasally administered by non-dependent subjects with a history of nasal abuse of opioids. Two comparators in this study were intact VANTRELA ER tablets (oral) and immediate-release hydrocodone powder (intranasal) at an equivalent dose.

The results of the study demonstrated that intranasal administration of manipulated VANTRELA ER tablet contents resulted in higher peak plasma concentration (Cmax) and shorter time to peak concentration (Tmax) than taking VANTRELA ER orally and lower Cmax and longer Tmax then taking hydrocodone powder intranasally. The pharmacokinetic data from this nasal clinical abuse potential study are displayed in Table 5 to represent these findings.

Table 5: Hydrocodone Pharmacokinetic Parameters, Nasal and Oral Administration

Treatment	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}inf}$ (hr*ng/mL)
45 mg intact Vantrela ER Tablets (oral)	25.05 (7.18)	9.11 (4.10 -12.12)	568 (172)
45 mg Vantrela ER finely milled (nasal)	56.84 (15.1)	2.62 (1.33 - 7.02)	572 (150)
45 mg immediate-release hydrocodone powder (nasal)	71.28 (30.5)	1.38 (0.60 - 7.07)	579 (163)

Values shown for C_{max} and $AUC_{0\text{-}inf}$ are mean (standard deviation); values shown for T_{max} are median (minimum-maximum).

Clinical Abuse Potential Studies

Two randomized, double-blind active- and placebo-controlled studies were conducted in nondependent opioid abusers to characterize the abuse potential of oral or intranasal administration of VANTRELA ER following physical manipulation. For both studies, Drug Liking was measured on a bipolar drug-liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would Take Drug Again was measured on a bipolar scale of 0 to 100 where 0 represents the strongest negative response (“definitely would not take drug again”), 50 represents a neutral response, and 100 represents the strongest positive response (“definitely would take drug again”).

Oral Abuse Potential Study

In a randomized, double-blind, placebo- and active-controlled, 4-period crossover study in nondependent opioid abusers, 35 of the 49 enrolled subjects completed all treatment conditions: 45 mg VANTRELA ER (intact), 45 mg VANTRELA ER (finely crushed), 45 mg hydrocodone bitartrate powder (immediate release (IR) condition), and placebo.

The oral administration of finely crushed VANTRELA ER was associated with statistically significantly lower mean scores for Drug Liking and Take Drug Again ($P<0.001$ for both), compared with powdered hydrocodone as summarized in Table 6.

Table 6: Summary of Maximum Drug Liking (E_{max}) and Take Drug Again (E_{max}) Following Oral Administration

Measure	Statistic	Placebo (N=35)	Hydrocodone IR 45 mg (N=35)	VANTRELA ER 45 mg (finely crushed) (N=35)	VANTRELA ER 45 mg (intact) (N = 35)
Drug Liking	Mean (SE)	53.4 (1.80)	85.0 (2.31)	65.6 (2.46)	54.5 (1.02)
	Median (Range)	51.0 (50-100)	88.0 (50-100)	60.0 (50-98)	51.0 (50-70)
Take Drug Again	Mean (SE)	46.3 (2.88)	75.1 (3.04)	55.9 (3.53)	48.5 (2.77)
	Median (Range)	50.0 (0-98)	74.0 (42-100)	56.0 (2-97)	50.0 (1-100)

Intranasal Abuse Potential Study

In a randomized, double-blind, placebo-and active-controlled, 5-period crossover study in nondependent opioid abusers, 34 of the 45 subjects enrolled completed all treatment conditions: intranasal administration of 45 mg VANTRELA ER (finely milled), intranasal administration of 45 mg hydrocodone bitartrate powder (immediate release condition), oral administration of 45 mg VANTRELA ER (intact), and intranasal administration of placebo.

The intranasal administration of finely milled VANTRELA ER was associated with statistically significantly lower mean and median scores for Drug Liking and Take Drug Again (P<0.001 for both), compared with powdered hydrocodone administered intranasally, as summarized in Table 7.

Table 7: Summary of Maximum Drug Liking (E_{max}) and Take Drug Again (E_{max}) Following Intranasal Insufflation

Measure	Statistic	Placebo IN (N=34)	Hydrocodone IR 45 mg (N=34)	VANTRELA ER 45 mg Finely Milled (N=34)
Drug Liking	Mean (SE)	58.6 (1.94)	80.2 (2.16)	72.8 (2.35)
	Median (Range)	52.0 (50-90)	79.0 (57-100)	72.5 (50-100)
Take Drug Again	Mean (SE)	56.4 (2.13)	75.5 (2.57)	67.5 (3.45)
	Median (Range)	50.0 (34-90)	76.5 (43-100)	67.0 (30-100)

The in vitro data demonstrate that VANTRELA ER has physical and chemical properties that are expected to make intravenous abuse difficult. The data from the in vitro studies and clinical abuse potential studies indicate that VANTRELA ER has physicochemical properties that are expected to reduce abuse via the oral route and the intranasal route. However, abuse of VANTRELA ER by the intravenous, nasal, and oral routes is still possible.

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

VANTRELA ER contains hydrocodone bitartrate, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal and illicit, including fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone. VANTRELA ER can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1)]*.

ROXYBOND (oxycodone hydrochloride) immediate-release tablets [NDA 209777]

Approval Date: April 20, 2017

Abuse Deterrence Studies

ROXYBOND is formulated with inactive ingredients that make the tablet more difficult to manipulate for misuse and abuse even if the tablet is subjected to physical manipulation and/or chemical extraction. To evaluate the ability of the abuse-deterrent technology to reduce the potential for abuse of ROXYBOND, a series of in vitro laboratory manipulation, extraction, and syringeability studies were conducted. An in vivo intranasal clinical abuse potential study was also conducted.

In Vitro Testing

ROXYBOND has been tested in vitro using methods of manipulation that drug abusers commonly use for preparation of opioids for administration by various routes, including oral consumption, intranasal insufflation, and injection.

Abusers may manipulate prescription opioids in order to prepare the tablets for oral, intranasal, or intravenous administration. The laboratory test data demonstrated that, relative to oxycodone immediate-release tablets, ROXYBOND has increased resistance to cutting, crushing, grinding, or breaking using selected tools. In addition, the intact and manipulated tablets resisted extraction in selected household and laboratory solvents under various conditions, including selected pre-treatments. Relative to oxycodone immediate-release tablets, the formulation forms a viscous material that resists passage through a needle; it was also more difficult to prepare solutions suitable for intravenous injection.

Clinical Abuse Potential Studies

A randomized, double-blind, double-dummy, placebo-controlled, single-dose four-way crossover study in 29 non-dependent recreational opioid users with a history of intranasal drug abuse was performed to determine the relative bioavailability and abuse potential of crushed intranasal ROXYBOND 30 mg tablets compared with crushed intranasal 30 mg oxycodone immediate-release tablets and intact orally administered ROXYBOND 30 mg tablets. Intact oral ROXYBOND tablets were included as a reference for evaluating abuse potential after manipulation and administration via an unintended route.

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

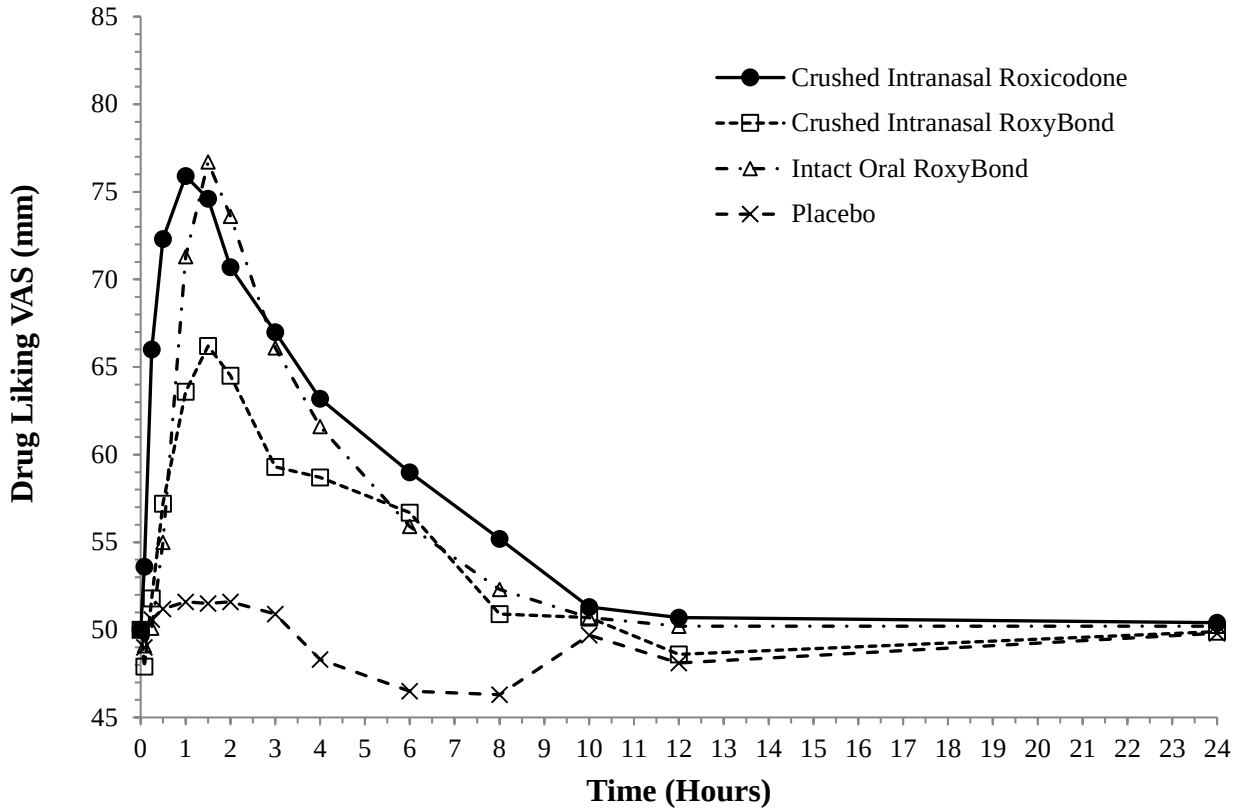
The pharmacokinetic profiles of oxycodone were also determined in this study (Table 2). When crushed and insufflated, ROXYBOND showed a lower peak oxycodone plasma concentration (C_{max} ~28% reduction) and a 35% longer time to peak plasma concentration (T_{max}) relative to crushed and insufflated oxycodone immediate-release tablets. Similar results were demonstrated when crushed and insufflated ROXYBOND was compared to intact oral ROXYBOND with a reduction in C_{max} and a longer time to T_{max}. Intact oral ROXYBOND resulted in a C_{max} of oxycodone similar to that of crushed and insufflated oxycodone immediate-release tablets, with a similar T_{max}.

Table 2	**Summary of Plasma Oxycodone Pharmacokinetic Parameters From the Intranasal Abuse Potential Study (n=31)**		
Treatment or Comparison	**C_{max} (ng/mL) LS Mean**	**AUC_{0-t} (ng*hr/mL) LS Mean**	**T_{max} (hr) Median**
Crushed, Insufflated oxycodone immediate-release tablets 30 mg	55.56	330.77	1.7
Crushed, Insufflated ROXYBOND 30 mg	40.04	309.21	2.3
Intact, oral ROXYBOND	56.97	265.38	1.3
AUC_{0-t} = Area under the plasma concentration vs time curve from 0 to last measurable concentration.			

Compared to crushed intranasal oxycodone immediate-release tablets, intranasal administration of crushed ROXYBOND was associated with statistically significantly lower drug liking (E_{max}) and take drug again (E_{max}) scores, as summarized in Table 3. Similar reductions in drug liking and willingness to take the drug again were reported for crushed intranasal ROXYBOND relative to intact oral ROXYBOND. These data are consistent with the slowing of the intended immediate-release properties of ROXYBOND when manipulated then insufflated compared to taking ROXYBOND orally intact. No statistically significant differences in Emax of Drug Liking or Take Drug Again were observed between crushed intranasal oxycodone immediate-release tablets and intact oral ROXYBOND.

Table 3.		**Summary of Maximum Drug Liking (E_{max}), and Take Drug Again (E_{max}), Following Administration of ROXYBOND, Oxycodone Immediate-release Tablets, and Placebo in Recreational Opioid Users (N=29)**			
VAS		Crushed Intranasal ROXYBOND 30 mg	Crushed Intranasal Oxycodone immediate-release tablets 30 mg	Intact Oral ROXYBOND 30 mg	Placebo
Drug Liking (E_{max})	Mean (SD)	71.1 (12.01)	82.9 (11.55)	81.5 (11.49)	53.4 (6.34)
	Median (Range)	71 (50 to 100)	82 (50 to 100)	82.00 (56 to 100)	51.0 (50 to 77)
Take Drug Again (E_{max})	Mean (SD)	62.2 (24.51)	82.1 (16.44)	77.3 (18.11)	41.9 (20.09)
	Median (Range)	62.0 (3 to 99)	86.0 (37 to 100)	81.0 (13 to 100)	50.0 (0.0 to 78)

Figure 1. Mean Drug Liking VAS Scores Over Time (N=29)



The majority of subjects (86%; n=25) experienced some reduction in E_{max} of Drug Liking VAS with crushed intranasal ROXYBOND compared with crushed intranasal oxycodone immediate-release tablets, whereas 59% (n=17) experienced at least a 30% reduction in E_{max} of drug liking and 21% (n=6) experienced at least a 50% reduction in E_{max} of drug liking.

Summary

The in vitro data demonstrate that ROXYBOND has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from in vitro data, also indicate that ROXYBOND has physicochemical properties that are expected to reduce abuse by the intranasal route of administration. However, abuse by the intranasal, oral, and intravenous route is still possible.

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

10.3 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

Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

Clinical Medical
April 2015

TABLE OF CONTENTS

Abuse-Deterrent Opioids — Evaluation and Labeling Guidance for Industry[1]

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 controls[6] 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 Cmax 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 means[18] between crushed, chewed, or otherwise modified *T* and *C* with an abuse deterrence margin on drug liking VAS. That is, test

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

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,

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

where $\delta_2 \ge 15$.

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:

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

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,

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

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

$H_0 : p^* \leq 50\%$ 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

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

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 the $median(ptr) \leq DR\%$, 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 postmarket[20] 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-deterrence. 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-deterrent 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-deterrent 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.

10.4 Guidance for Industry: Opioid Analgesic Drugs – Considerations for Benefit-Risk Assessment Framework

Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Sharon Hertz at 301-796-1225.

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

June 2019
Clinical/Medical

Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

June 2019
Clinical/Medical

TABLE OF CONTENTS

Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish 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

The purpose of this guidance is to describe the benefit-risk assessment framework that the Agency uses in evaluating whether applications for opioid analgesic drugs meet the standard for approval under section 505 of the Federal Food, Drug, and Cosmetic Act. This guidance summarizes the information that should be included in a new drug application for an opioid analgesic drug to facilitate the Agency's benefit-risk assessment.

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

Benefit-risk assessment is the foundation for FDA's regulatory review of human drugs and biologics. These assessments capture the evidence, uncertainties, and reasoning used by FDA to arrive at its regulatory decisions. Additionally, these assessments serve as tools for communicating that information to those interested in a better understanding of FDA's thinking.

[1] This guidance has been prepared by the Division of Anesthesia, Analgesia, and Addiction Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

FDA has developed a benefit-risk assessment framework — a structured, qualitative approach to FDA's benefit-risk assessment[2] formatted as a table (see Figure 1 below).[3] In Figure 1, the factors affecting the benefit-risk assessment are listed on the left side. As reflected in the shaded boxes, the top two factors (*Analysis of Condition* and *Current Treatment Options*) relate to the specific therapeutic area — the current state of knowledge regarding the condition to be treated and the available therapies. The bottom two factors (*Benefit* and *Risk and Risk Management*) are specific to the drug at issue.

FDA assesses risks and benefits of all drugs in the context of the use indicated in the labeling. However, because of the widespread misuse and abuse of prescription opioid analgesic drugs, for this class of drugs, FDA also considers the broader public health effect of opioid analgesic drugs; this involves consideration of the risks related to misuse, abuse, opioid use disorder, accidental exposure, and overdose, for both patients and others. Likewise, FDA considers any properties of a drug expected to mitigate these risks. This guidance describes the various factors that FDA will consider in evaluating the benefits and risks of an opioid analgesic drug. FDA encourages applicants to provide information relevant to these factors.

Figure 1: FDA's Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment		
Benefit-Risk Dimensions		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk* Management		

* For purposes of this figure, *Risk and Risk Management* includes not only risks to the patient when used as indicated but also risks related to the broader public health sometimes described as second-order effects. And, in assessing risks to the broader public health, the Agency is making an assessment relative to other currently available analgesic drugs.

[2] See the Enhancing Benefit-Risk Assessment in Regulatory Decision-Making web page available at https://www fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm.

[3] See the Benefit-Risk Assessment in Drug Regulatory Decision-Making implementation plan available at https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM602885.pdf.

III. BENEFIT-RISK ASSESSMENT

The following sections describe the information that FDA will consider in assessing the benefits and risks of an opioid analgesic drug. Consistent with the benefit-risk assessment framework, FDA considers the benefits and risks to the patient when the drug is used as labeled, as well as the benefits and risks relative to other available therapies for pain. Additionally, FDA considers the public health risks of the drug related to misuse, abuse, opioid use disorder, accidental exposure, and overdose in both patients and nonpatients, as well as any properties of the drug that may mitigate such risks. Note that the risk of opioid use disorder can arise even when a patient is taking an opioid analgesic drug as labeled.

The sections below provide recommendations for information the applicant should provide to assist FDA in its assessment.

A. Benefits to the Patient Using the Drug as Labeled

The Agency will consider questions including the following about benefits to patients who are prescribed the drug and take it as labeled and directed by their prescribers:

- Analgesic efficacy of the drug when used for its proposed indication
  - What is the body of evidence supporting a finding of analgesic drug efficacy?
  - In what patient population(s) was efficacy demonstrated? Why was the patient population chosen for the efficacy study? How does the population studied reflect the proposed indication (i.e., is the proposed indication broader than the population studied)?
  - What is the body of evidence supporting the proposed duration of use for each proposed indication?
- Safety of the drug when used for its proposed indication
  - Does the drug have characteristics that mitigate adverse events associated with opioid analgesic drugs, including respiratory depression, sedation, and constipation? What data support the conclusion that these risks are mitigated?
  - Does the drug have characteristics that mitigate the risk of opioid use disorder when used as labeled? How do the safety data support this?

B. Risks to the Patient Using the Drug as Labeled

In addition to the already known risks associated with opioid analgesic drugs, the Agency will also consider questions including the following about risks to patients who are prescribed this drug and take it as labeled and directed by their prescribers:

- Does this particular drug have any novel risks not typically associated with opioid analgesic drugs? How serious are they? Can they be mitigated through monitoring, patient selection characteristics, or limiting duration of use? Are the novel risks reversible?

- Do the formulation and/or excipients pose risks to patients (e.g., tablets that swell in the gastrointestinal tract, tablets that may adhere to moist mucosal surfaces)? For drugs formulated to have abuse-deterrent properties, are there any adverse events associated with the drug product when used as labeled that are attributable to aversive excipients or excipients intended to impart resistance to manipulation?

- Are there characteristics of the drug that increase or decrease the risk for respiratory depression, sedation, or development of opioid use disorder in patients (e.g., large residual opioid in transdermal systems, high dosage strengths)? Can the risks be mitigated by particular packaging configurations or storage and disposal conditions?

- Is there evidence that adverse events typically associated with opioid analgesic drugs occur at a higher rate or with greater severity with the new drug than expected for similar drugs based on clinical trials or theoretical risks?

C. Effectiveness and Safety Relative to Approved Analgesic Drugs

As part of the benefit-risk assessment for a particular drug and proposed indication, FDA considers the benefits and risks relative to other available therapies for the condition. FDA will consider the questions including the following in assessing effectiveness and safety of an opioid analgesic drug:

- Do any comparative efficacy data exist for the drug relative to approved opioid or nonopioid analgesic drugs? Does this analgesic drug offer any advantages relative to available approved analgesic drugs for each indication, with regard to effectiveness or duration of response?

- Do any comparative safety data exist for the drug relative to approved opioid or nonopioid analgesic drugs? Does this analgesic drug offer any other safety advantages or disadvantages relative to available approved analgesic drugs for each indication (e.g., abuse-deterrent properties, less risk of drug-drug interactions)?

- What is the anticipated benefit-risk balance relative to available approved analgesic drugs for each indication? Do any comparative safety data exist for the drug relative to approved opioid or nonopioid analgesic drugs? Does this analgesic drug offer any other safety advantages or disadvantages relative to available approved analgesic drugs for each indication (e.g., less risk of drug-drug interactions)?

- Does the drug have any other advantages over other available approved analgesic drugs (e.g., can be mixed with food)?

FDA notes that, while the comparative data described above is helpful in applying the benefit-risk framework, superiority to other available treatments is not a requirement for approval under FDA's drug approval authorities.

D. Broader Public Health Effects: Risks and Mitigation of Risks Related to Misuse, Abuse, Opioid Use Disorder, Accidental Exposures, and Overdose

In the overall benefit-risk assessment of opioid analgesic drugs, FDA will consider the positive and negative public health effects of the drug, which includes the drug's potential effect on risks to both patients and nonpatients, such as members of the patient's household (e.g., children, teenagers, visitors, and others). The risks considered include those related to misuse, abuse, opioid use disorder, accidental exposure, and overdose. FDA's evaluation of the broader public health effect of a new opioid analgesic drug is made relative to other currently available analgesic drugs.

- In evaluating ways in which an opioid analgesic drug positively or negatively affects public health FDA will consider the following:

  - Are there characteristics of the drug that increase or decrease the risk of accidental exposure in children (e.g., tablet size, color, flavor, packaging configuration, appearance of topical systems)?

  - Are there characteristics of the drug that increase or decrease the risk of misuse, abuse, opioid use disorder, and related adverse outcomes such as overdose and infectious complications of injection (e.g., abuse-deterrent properties, large residual opioid in transdermal systems, high dosage strengths)? Can the risks be mitigated by particular packaging configurations or storage and disposal conditions?

  - Are there increased or decreased risks associated with the indicated method of delivery (i.e., delivery device)? For example, does the delivery method affect an existing risk or introduce a novel risk?

  - To support the opioid-specific public health benefit-risk evaluation, the applicant should use traditional epidemiologic data sources (e.g., surveys, emergency department visits, poison control center calls) and nontraditional sources (e.g., internet discussion forums and blogs, social media, qualitative/ethnographic studies, law enforcement data) to provide information about how this moiety or similar opioid analgesic drugs are misused and abused in postmarketing settings. These data should address demographic patterns of abuse, the routes by which these drugs are abused, concomitant abuse of other substances, as well as risks of related adverse outcomes (e.g., addiction, fatal and nonfatal overdose, infectious complications of abuse).

- For abuse-deterrent formulations, in addition to considering any potential benefits of such drug products, FDA also will consider the following in terms of opioid-specific public health considerations:

- Potential unintended adverse consequences with introduction of the abuse-deterrent formulation, such as the following:

  - A shift to more dangerous routes of abuse (e.g., nasal to the more dangerous intravenous) based on properties of the formulation.

  - Potential tampering methods that could result in harmful effects, including injection-related harms (e.g., large volume extraction of drug that leads to increased sharing of drug paraphernalia increasing the risk of human immunodeficiency virus and hepatitis transmission).

  - Any other potential safety concerns related to the abuse-deterrent formulation.

- For safety of excipients by unintended routes of administration, FDA will consider the following in terms of opioid-specific public health considerations:

  - Based on a risk assessment of the excipients in the drug, the potential safety concerns for the drug when administered by unintended routes of administration, including intravenous, intranasal, and inhalation.

- For specific populations that may present distinct benefit-risk profiles, FDA will consider the following in terms of opioid-specific public health considerations:

  - The potential for subpopulations where the benefit-risk balance may be unfavorable (e.g., adolescents, patients with mental health and/or substance use disorders, patients with certain other comorbidities). The applicant should include a discussion of anticipated use-specific subpopulations and proposed approaches to mitigate such risks, if present.

E. Risk Management

FDA has determined that a class-wide risk evaluation and mitigation strategy (REMS) is necessary for all opioid analgesic drugs intended for outpatient use to ensure that the benefits of these drugs continue to outweigh the risks.[4] The Opioid Analgesic REMS program requires that training be made available to all health care providers (HCPs) who are involved in the management of patients with pain, including nurses and pharmacists.[5] To meet this requirement, drug companies with approved opioid analgesic drugs provide unrestricted grants to accredited continuing education providers for the development of education courses for HCPs based on

[4] See the Opioid Analgesic Risk Evaluation and Mitigation Strategy web page at https://www fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm. Note that certain opioid analgesic drugs are subject to other REMS. Information on the specific REMS associated with each approved opioid analgesic drug can be found on the FDA's Approved Risk Evaluation and Mitigation Strategies (REMS) web page at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm.

[5] Ibid.

FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain.[6]

To the extent that the safety profile of a drug product may differ from those drug products covered by the class-wide REMS, a product-specific REMS or REMS element may be required. For example, an opioid analgesic drug that must be restricted to use in a monitored inpatient setting may need additional risk mitigation strategies to ensure the drug product does not leave the hospital. In short, the applicant for an opioid analgesic drug should include any proposed REMS that the applicant considers necessary to ensure a drug's benefits outweigh its risks. All sponsors of opioid analgesic drugs should begin discussions with FDA early during drug development regarding product-specific risks and the potential need for additional risk mitigation.

[6] Available at https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_analgesic_2018_09_18_FDA_Blueprint.pdf.

10.5 FDA Blueprint – REMS Memo

Introduction
FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain

Background

In July 2012, FDA approved the Extended-Release and Long-Acting (ER/LA) Opioid Analgesic Risk Evaluation and Mitigation Strategy (ER/LA REMS) to ensure that the benefits of ER and LA opioid analgesics used in the outpatient setting outweigh the risks. That REMS was modified and the new *Opioid Analgesic REMS* includes, in addition to ER/LA opioid analgesics, all immediate-release (IR) opioids used in the outpatient setting that are not already covered by another REMS program. The *Opioid Analgesic REMS* is intended to support other national efforts underway to address the misuse and abuse of prescription opioid analgesics.

As part of the Opioid Analgesic REMS, all opioid analgesic companies must provide the following:

- Education for health care providers (HCPs) who participate in the treatment and monitoring of pain. For the purpose of the Opioid Analgesic REMS, HCPs will include not only prescribers, but also HCPs who participate in the treatment and monitoring of patients who receive opioid analgesics, including pharmacists and nurses.
    - Education will be offered through accredited continuing education (CE) activities. These activities will be supported by unrestricted educational grants from opioid analgesic companies.
- Information for HCPs to use when counseling patients about the risks of ER, LA, and IR opioid analgesic use.

To facilitate the development of CE educational materials and activities as part of the Opioid Analgesic REMS, FDA has also revised the education blueprint — originally designed to facilitate development of CE educational materials under the ER/LA REMS. FDA has completed the revisions to the *FDA Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain* (FDA Blueprint), following publication of a draft version and consideration of received public comments.

The FDA Blueprint contains a high-level outline of the core educational messages that will be included in the educational programs developed under the Opioid Analgesic REMS. The FDA Blueprint focuses on the fundamentals of acute and chronic pain management and provides a contextual framework for the safe prescribing of opioid analgesics. The core messages are directed to prescribers, pharmacists, and nurses, but are also relevant for other HCPs who participate in the management of pain. The course work is not intended to be exhaustive nor a substitute for a more comprehensive pain management course.

Accrediting bodies and CE providers will ensure that the CE activities developed comply with the standards for CE of the Accreditation Council for Continuing Medical Education, [1,2] or another CE accrediting body, depending on the target audience's medical specialty or health care profession.

FDA is making the FDA Blueprint, approved as part of the Opioid Analgesic REMS, available on the REMS@FDA Website (www.fda.gov/REMS), where it will remain posted for use by CE providers as they develop the CE materials and activities. A list of the REMS-compliant CE activities supported by unrestricted educational grants from the opioid analgesic companies to accredited CE providers will be posted at www.opioidanalgesicREMS.com as that information becomes available.

Reasons Why HCP Education Is So Important

Adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse of opioids have emerged as major public health problems. It is critical that HCPs are knowledgeable about the risks associated with opioid analgesics as they pertain to their patients as well as from a public health perspective. The data continue to show problems associated with prescription opioid analgesics.

- In 2015, over 52,404 Americans died from drug poisonings, and of these, 24% or approximately 12,570 deaths involved opioid analgesics.[3]

- Based on the 2016 National Survey on Drug Use and Health (NSDUH), an estimated 11.5 million Americans aged 12 or older misused a prescription pain reliever in the past year — with hydrocodone, oxycodone, and codeine products being the most commonly reported.[4]

- The most common source of pain relievers in the 2016 NSDUH was "a friend or relative" (53%). "A physician's prescription" was the second most common source, reported by approximately 35% of respondents.[5]

The nation is facing competing public health problems: the need to adequately treat a large number of Americans with acute and chronic pain and an epidemic of prescription opioid abuse.

[1] Accreditation Council for Continuing Medical Education. 2016. Accreditation Requirements. Criteria for CME Providers-Accreditation Criteria. Accessed July 2018.

[2] Accreditation Council for Continuing Medical Education. 2016. Accreditation Requirements. Criteria for CME Providers-Standards for Commercial Support. Accessed July 2018.

[3] See https://www.cdc.gov/nchs/data/factsheets/factsheet_drug_poisoning.pdf. Accessed July 2018.

[4] Substance Abuse and Mental Health Services Administration. (2017). *Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health* (HHS Publication No. SMA 17-5044, NSDUH Series H-52). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration.

[5] Ibid.

Described in the 2011 report by the National Academies of Science, Engineering, and Medicine (NASEM), *Relieving PAIN in America, A Blueprint for Transforming Prevention, Care, Education, and Research*,[6] 100 million Americans suffer from common chronic pain conditions; fewer than half of Americans undergoing surgery report adequate pain relief; and 60% of Americans visiting the emergency department with acute painful conditions receive analgesics.

The increasing availability of prescription opioids since the 1990's has been accompanied by an epidemic of opioid addiction. The Substance Abuse and Mental Health Services Administration's *National Survey of Drug Use and Health* has shown that most people who use prescription analgesics "nonmedically" obtain them from friends or family, who it is believed obtained the drugs from a doctor's prescription.[7]

Some of the immediate consequences of untreated or undertreated pain include reduced quality of life, impaired physical function, and high economic costs. Chronic pain is associated with physical disability, fear, anger, depression, anxiety, and reduced ability to carry out the roles of family member, friend, and employee. It is critically important that HCPs have all the information they need to properly treat their patients and safely manage their pain. It is also critical for HCPs to understand when opioid analgesics are the appropriate treatment and how to implement best practices to ensure their patients' safety. A 2017 report by NASEM, *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use,* describes the challenges of providing adequate pain management and calls for the establishment of "comprehensive pain education materials and curricula" for HCPs.[8]

Having broad knowledge about how to manage patients with pain can create the opportunity for HCPs to consider ***all*** options for pain management, including nonpharmacologic and non-opioid pharmacologic options, and to reserve opioids for when non-opioid options are inadequate and when the benefits of the opioids are expected to outweigh the risks. This information can also aid HCPs in identifying and intervening when encountering obstacles that may reduce access to nonpharmacological and non-opioid medication options. Fully informed HCPs can help contribute to national efforts to address opioid addiction and reduce opioid misuse and abuse.

[6] http://www.nationalacademies.org/hmd/Reports/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research.aspx. Accessed July 2018.

[7] https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.pdf, Table 6.53A. Accessed July 2018.

[8] http://nationalacademies.org/hmd/Reports/2017/pain-management-and-the-opioid-epidemic.aspx. Accessed July 2018.

FDA Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain

Purpose of the Opioid Analgesic REMS HCP Educational Effort

Following completion of educational activities under the Opioid Analgesic REMS, HCPs should be knowledgeable about the following.

- The fundamental concepts of pain management, including definitions and mechanisms of pain
- How to assess patients in pain, identifying risk factors for abuse and addiction
- The range of therapeutic options for managing pain, including nonpharmacologic approaches and pharmacologic (non-opioid and opioid analgesics) therapies
- How to integrate opioid analgesics into a pain treatment plan individualized to the needs of the patient
- How to safely and effectively manage patients on opioid analgesics in the acute and chronic pain settings, including initiating therapy, titrating, and discontinuing use of opioid analgesics
- How to counsel patients and caregivers about the safe use of opioid analgesics, including proper storage and disposal
- How to counsel patients and caregivers about the use of naloxone for opioid overdose
- When referral to a pain specialist is appropriate
- The fundamental elements of addiction medicine
- How to identify and manage patients with opioid use disorder

In addition, HCPs will gain an understanding of current information about safe opioid practices and about current Federal[9] and State regulations, national guidelines,[10] and professional organization[11] and medical specialty guidelines on treating pain and prescribing opioids. HCPs will also become familiar with the use of naloxone and with the importance of its availability for use by patients and caregivers both in the community and in the home.

[9] For example, see https://www.deadiversion.usdoj.gov/21cfr/cfr/2106cfrt.htm and https://www.deadiversion.usdoj.gov/21cfr/21usc/829 htm. Accessed July 2018.

[10] For example, see Dowell D, Haegerich TM, Chou R. 2016. CDC Guideline for Prescribing Opioids for Chronic Pain –United States, 2016. MMWR Recomm Rep 2016; 65 (No.RR-1): 1-49. Accessed July 2018.

[11] For example, see Federation of State Medical Boards' Guidelines for the Chronic Use of Opioid Analgesics. Accessed July 2018.

Section 1: The Basics of Pain Management

I. THE NEED FOR COMPREHENSIVE PAIN EDUCATION

The FDA Blueprint was developed with two, competing, U.S. public health concerns in mind, (1) the large number of Americans with acute and chronic pain and (2) the epidemic of prescription opioid abuse.

1. Providing health care providers (HCPs) with a thorough understanding of the risks associated with opioids can give HCPs the opportunity to consider all pain management options, including nonpharmacologic and pharmacologic options, prescribing opioids only when non-opioid options are inadequate and when the benefits of using an opioid are expected to outweigh the risks.

2. When HCPs have information about the risks of opioid misuse and abuse, they will be better able to create opportunities for patient counseling and other strategies to reduce these risks.

II. DEFINITIONS AND MECHANISMS OF PAIN

Pain can be categorized according to its duration, underlying pathophysiology of the original insult, and whether a central sensitization component has developed. An understanding of these different categorizations can help direct therapeutic decisions.

When defining, and classifying pain, the following should be taken into consideration:

1. Biological significance of pain (survival value)
2. Relationship between acute and chronic pain
3. Distinction between nociceptive and neuropathic pain

III. ASSESSING PATIENTS IN PAIN

HCPs should be knowledgeable about how to assess each patient when initiating a pain management program. When appropriate, evidence-based, standardized scales and tools can be used to document pain characteristics and guide management decisions throughout treatment, noting the strengths and weaknesses regarding specificity and sensitivity of these scales.

Important elements of an initial assessment should include the following:

1. Patient history

2. Screening tools to evaluate the known risk factors for development of chronic pain after an acute injury or disease

3. Screening tools to evaluate the known risk factors for opioid use disorder (OUD) or abuse

4. Queries of state prescription drug monitoring programs (PDMPs)

5. Pain assessment scales/tools

6. Functional assessment scales

7. Physical examination

8. Family planning, including information about use of contraceptives, pregnancy intent/status and plans to breastfeed

9. Psychological and social evaluation

10. Diagnostic studies when indicated

Section 2: Creating the Pain Treatment Plan

A comprehensive pain treatment plan should be developed and customized to the needs of the individual patient. The treatment plan should include the types of therapies planned, the goals of treatment, and an explanation of the patient and prescriber roles and responsibilities. The goals of treatment should be based on (1) expected outcomes of pain reduction; (2) improvement in functional outcomes impaired by pain (e.g., activities of daily living); and (3) quality of life.

If HCPs encounter potential barriers to managing patients with pharmacologic and/or nonpharmacologic treatment options, such as lack of insurance coverage or inadequate availability of certain HCPs who treat patients with pain, attempts should be made to address these barriers. The overall treatment approach and plan should be well documented in the patient record, including written agreements and informed consent/patient provider agreements (PPAs) that reinforce patient-provider responsibilities and avoid punitive tones.

I. COMPONENTS OF AN EFFECTIVE TREATMENT PLAN

1. The goals of treatment, including the degree of improvement in pain and function when function has been impaired by pain

2. Possible constituents of the treatment plan, including nonpharmacologic approaches and pharmacologic therapies

3. Patient/prescriber/health care team interactions, including

- Patient responsibilities/compliance with the plan
- Responsibilities of the prescriber and health care team, including patient monitoring
- Plans for reviewing functional goals
- Use of supplemental medication for intermittent increases in pain
- Use of PPAs

II. GENERAL PRINCIPLES OF NONPHARMACOLOGIC APPROACHES

Pain can arise from a wide variety of causes. There are a number of nonpharmacologic and self-management treatment options that have been found to be effective alone or as part of a comprehensive pain management plan, particularly for musculoskeletal pain and chronic pain. Examples include, but are not limited to, psychological, physical rehabilitative, and surgical approaches, complementary therapies,[12] and use of approved/cleared medical devices for pain management. HCPs should be knowledgeable about the range of treatment options available, the types of pain that may be responsive to those options, and when they should be used as part of a multidisciplinary approach to pain management. HCPs should also be aware that not all nonpharmacologic options have the same strength of evidence to support their utility in the management of pain, and some may be more applicable for some conditions than others.

III. GENERAL PRINCIPLES OF PHARMACOLOGIC ANALGESIC THERAPY

A variety of analgesics, including non-opioid and opioid medications, are available for use to manage pain symptoms. HCPs should be well informed about the range of analgesics available and the types of pain that may be responsive to those analgesics.

A. Non-opioid medications

When using non-opioid medications in pain management, HCPs should be knowledgeable about the following:

1. Mechanism of action of analgesic effect
2. Indications and uses for pain management
3. Routes of administration and formulations used in pain management
4. Initial dosing, dose titration, dose tapering (when appropriate) for analgesia
5. Contraindications
6. Adverse events, with emphasis on labeled warnings
7. Drug interactions — both pharmacodynamic and pharmacokinetic

B. Opioid analgesic medications

Opioid analgesic medications can be used successfully as a component of pain management. However, opioids carry risks not present with most non-opioid analgesics, specifically the risks

[12] For example, see https://nccih.nih.gov. Accessed July 2018.

of addiction, abuse and misuse, which can lead to respiratory depression, overdose and death. Therefore, it is the responsibility of HCPs to be knowledgeable, not just about the presence of such risks, but about how to weigh these risks before prescribing an opioid and about how to properly manage patients who are prescribed opioids, both for short-term and long-term use. When using opioid analgesics as part of pain management, HCPs should be knowledgeable about the following:

1. General precautions
   a. Even at prescribed doses, opioid analgesics carry the risk of misuse, abuse, opioid use disorder, overdose, and death
   b. Importance of the appropriate use of PDMPs[13] and their use as a clinical decision support tool
   c. DSM-5 (R) criteria (or the most recent version) for OUD and the concepts of abuse (taking an opioid to get high) vs. misuse (taking more than prescribed for pain or giving to someone else in pain)[14]
   d. The concepts of tolerance and physiological dependence and how they differ from OUD (addiction)
   e. Recognition that some opioid analgesics (e.g., Transmucosal Immediate Release Fentanyl products, some ER/LA products) are safe only for opioid-tolerant patients

2. Mechanism of action and analgesic effect

3. Types of opioids (full agonists, partial agonists)

4. Indications and uses for pain management

5. Range of opioid analgesic products available for pain management and their related safety concerns
   a. Routes of administration including oral, transmucosal, transdermal
   b. Release characteristics of immediate release (IR), extended-release (ER), long-acting (LA)
   c. Abuse-deterrent formulations (ADFs)
      - Definition of ADF based on the FDA guidance for industry, *Abuse-Deterrent Opioids – Evaluation and Labeling*[15]
      - Recognition that all ADFs have the same potential for addiction and overdose death as non-abuse-deterrent opioids
      - How to understand FDA-approved ADF product labeling

6. Initial dosing, dose titration, dose tapering (when appropriate) for analgesia
   a. Concepts and limitations of the conversion charts in labeling and the limitations of relative potency or equianalgesic dosing tables in literature

[13] SAMHSA Prescription Drug Monitoring Programs: A Guide for Healthcare Providers. Accessed July 2018.

[14] American Psychiatric Association DSM-5-Opioid Use Disorder Diagnostic Criteria. Accessed July 2018.

[15] See FDA guidance for industry *Abuse-Deterrent Opioids —Evaluation and Labeling*. Accessed July 2018.

b. Interindividual variability of response
c. Special populations
    - Pregnant, postpartum, breastfeeding, and neonatal opioid withdrawal syndrome
    - Renal and hepatic impairment
    - Children and adolescents
    - Genetic and phenotypic variations
    - Older adults
    - Sleep disorders
    - Common and uncommon psychiatric disorders

7. Contraindications

8. Adverse Events
    a. Medication errors
    b. Periods of greater risk for significant respiratory depression, including at treatment initiation and with dose increases
    c. Serious adverse drug reactions (including overdose and death)
    d. Labeled warnings
    e. Common adverse drug reactions

9. Drug interactions
    a. Pharmacokinetic interactions based on metabolic pathway
    b. Pharmacokinetic and pharmacodynamic interactions with alcohol
    c. Concerns with particular drug–drug interactions, including, but not limited to:
        - Benzodiazepines and other central nervous system depressants, including alcohol
        - Monoamine oxidase inhibitors
        - Antidiuretic hormone drugs

10. Key safety strategies for use with opioid medications
    a. Dosing instructions including daily maximum
    b. Safe storage to reduce risk of accidental exposure/ingestion by household contacts, especially children/teens and to reduce risk of theft
    c. Naloxone products for use in the home to reduce risk of overdose deaths in patients and household contacts
    d. Proper disposal of used (e.g., transdermal systems) and unused opioids
    e. Pain management after an opioid overdose
    f. Driving and work safety

IV. MANAGING PATIENTS ON OPIOID ANALGESICS

HCPs should be knowledgeable about the appropriate use of opioids in patients with acute and chronic pain, including the importance of balancing potential benefits with the risks of serious adverse outcomes such as overdose and death.

A. Initiating treatment with opioids — acute pain

1. Patient selection — consider when an opioid is an appropriate option and consult the PDMP

2. Dosing — as needed vs. around-the clock dosing, prescribing an appropriate quantity based on the expected duration of pain, i.e., the least amount of medication necessary to treat pain and for the shortest amount of time

3. Naloxone for home use — prescribe and discuss the use of naloxone products and the various means of administration

4. Screening tools for risk of abuse

B. Initiating treatment with opioids — chronic pain

1. Patient selection
   a. Differences in benefit and risk and expected outcomes for patients with chronic pain, palliative care, or end-of-life care
   b. Differences in initiating treatment in opioid nontolerant vs. opioid-tolerant patients

2. Dosing
   a. As needed vs. around-the-clock
   b. How to determine a safe initial dose
   c. Safe conversion from other opioids

3. Considerations in opioid selection
   a. IR or ER/LA
   b. Special precautions with methadone
   c. Products restricted to opioid-tolerant patients

4. When and how to use an opioid or non-opioid analgesic to supplement pain management

C. Ongoing management of patients on opioid analgesics

1. Periodic review of pain and functional goals

2. Review adverse events at each visit
   - Eliciting signs or symptoms of opioid abuse
   - Screening for endocrine function may be recommended

- Importance of adverse event reporting and mechanisms to report

3. Review refill history/review PDMP

4. How to determine when an opioid analgesic is no longer necessary/beneficial

D. Long-term management

1. Evaluation of the patient with worsening pain for changes in underlying condition and for signs of OUD before increasing opioid dosage

2. Changing opioid medications
   - Concept of incomplete cross-tolerance when converting patients from one opioid to another
   - Concepts and limitations of the conversion charts in labeling and the limitations of relative potency or equianalgesic dosing tables in literature

3. Monitoring of patient adherence to the treatment plan, especially regarding misuse and abuse:
   - Perform medication reconciliation — recognize, document, and address aberrant drug-related behavior
   - Determine if nonadherence is due to inadequate pain management
   - Understand the utility and interpretation of urine drug testing (e.g., screening and confirmatory tests) and use as indicated
   - Screen and refer for substance use disorder treatment when concerns arise

E. How to recognize and intervene upon suspicion or identification of an OUD

HCPs should understand how to monitor patients taking opioid analgesics and identify the signs and symptoms of opioid misuse, abuse, and OUD and be knowledgeable about how to begin the process of intervention upon suspicion of an OUD.

F. When to consult with a pain specialist

HCPs should be knowledgeable about when referral to a pain management specialist is indicated, including identifying patients at high risk for OUD and patients unable to achieve adequate pain management.

G. Medically directed opioid tapering

HCPs should be knowledgeable about how to safely taper opioid analgesics, including how to recognize and manage signs and symptoms of opioid withdrawal. HCPs should be knowledgeable about the particular risks associated with tapering during pregnancy.

H. Importance of patient education

HCPs should recognize their role in reducing the risks associated with opioid analgesics through patient education at initiation of an opioid and throughout long-term management.

1. Inform patients about pain management expectations and managing pain through different pharmacologic and nonpharmacologic modalities.

2. Use the *Patient Counseling Guide: What You Need to Know About Opioid Pain Medicines* as part of discussion with patients and caregivers when prescribing opioid analgesics.

3. Counsel the patient about the following:
   a. Importance of adherence to prescribed dosing regimen
   b. Patients should use the least amount of medication necessary to treat pain and for the shortest amount of time
   c. The risk of serious adverse events that can lead to death
   d. The risk of addiction that can occur even when product is used as recommended
   e. Known risk factors for serious adverse events, including signs and symptoms of overdose and opioid-induced respiratory depression, GI obstruction, and allergic reactions, among others
   f. The most common side effects, along with the risk of falls, working with heavy machinery, and driving
   g. When to call the prescriber (e.g., managing adverse events, ongoing pain)
   h. How to handle missed doses
   i. The importance of full disclosure of all medications and supplements to all HCPs and the risks associated with the use of alcohol and other opioids/benzodiazepines
   j. Product-specific concerns, such as not to crush or chew ER products; transdermal systems and buccal films should not be cut, torn, or damaged before use, etc.
   k. How to safely taper dose to avoid withdrawal symptoms
   l. Safe storage and disposal, risks of theft by family members and household visitors
   m. Never share any opioid analgesic with another person
   n. How and when to use naloxone products and their various means of administration
   o. Seeking emergency medical treatment if an opioid overdose occurs
   p. How to report adverse events and medication errors to FDA (1-800-fda-1088 or via http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf)

V. ADDICTION MEDICINE PRIMER

HCPs should be knowledgeable about the basic elements of addiction medicine and be familiar with the definition, neurobiology, and pharmacotherapy of OUDs. In particular, stigmatizing or blaming language should be replaced with language that acknowledges that addiction,

reclassified as *substance use disorder*[16] in the revised Diagnostic Statistical Manual–V, is a disease. The term *opioid use disorder* [17] should be used when referring to the use of opioids, rather than other substances.

It should also be noted that there may be a different approach with a patient who misuses an opioid analgesic by taking the product differently than prescribed for the purpose of managing pain, in contrast to the patient who abuses an opioid analgesic with the intent of getting high. HCPs should be familiar with the following:

1. The neurobiology of OUD (addictive cycle)

2. Use of screening tools to identify patients at risk, based on known risk factors, and to identify patients developing signs of opioid dependence or addiction as early as possible.

3. Management of OUD, including the types of pharmacologic and nonpharmacologic treatments available and when to refer to an addiction medicine specialist.

[16] Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association.

[17] Id.