FDA Briefing Document

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

June 26, 2018

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought pharmacokinetic data, and results of studies evaluating the abuse of Remoxy (oxycodone extended release) oral capsule 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.

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

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

June 26, 2018

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DIVISION DIRECTOR MEMO

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: May 21, 2018

FROM: Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, 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 Open Session, June 26, 2018 AADPAC/DSaRM Meeting to Discuss NDA 22324

At this joint meeting of AADPAC and DSaRM, we will be discussing an application from Pain Therapeutics, Inc. for a new extended-release formulation of oxycodone, designed with properties intended to deter abuse by the oral, nasal, and intravenous routes. 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.

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," 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.

We have heard concerns that the approval of new opioid analgesics increases the prescribing and availability of these products, and may contribute to an increase in misuse and abuse. A recent article published in the journal Anesthesiology reports the results of a study that examined dispensed prescription patterns for opioids and approval of new opioid analgesics in order to investigate whether the introduction of these new drugs increased overall opioid prescribing. In summary, although there has been a dramatic increase in prescriptions dispensed for opioid analgesics since 1997 as well as an increasing number of opioid analgesic approvals, the number of opioid prescriptions dispensed has declined since 2012 despite an increasing number of approvals. (http://anesthesiology.pubs.asahq.org/article.aspx?articleid=2675976)

There are currently ten opioid analgesics labeled with abuse-deterrent properties as described in the guidance, nine extended-release products and one immediate-release product. The extended-release products 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).

When a product intended to have abuse-deterrent properties fails to demonstrate those properties in pre-approval studies, it is important for prescribers to understand the product performance to be able to make an informed decision about the role of the product in their practice of pain management. There is one product, Apadaz (benzhydrocodone/acetaminophen) immediate-release tablets that has labeling describing the negative results of studies that were conducted to assess properties of the formulation that were intended to deter abuse. The labeling includes negative study results from in vitro testing and human abuse potential studies that state the studies failed to demonstrate properties expected to deter abuse based on endpoints specified in the above-mentioned guidance. The label also includes language describing the results of additional secondary endpoints that are not described in the guidance, and for which the clinical significance is unknown.

The results of the Applicant's efficacy and safety studies, in vitro physical and chemical manipulation assessments, and in vivo human abuse potential studies will be presented during this meeting. You will hear presentations from the Applicant and the Agency regarding these

findings. FDA will present an analysis of prescribing patterns for oxycodone products and other opioids.

Based on feedback from prior advisory committee meetings, the Agency is now requesting that Applicants address the safety of excipients when administered by unintended routes, that is abused by the IV or nasal route. You will hear a presentation by FDA on this issue that discusses the of the safety of excipients and how this relates to unintended routes of abuse.

You will be asked to discuss whether the Applicant has provided adequate support for 1) the safety and efficacy of Remoxy in the intended population, and 2) labeling the abuse-deterrent properties for their product, and 3) whether the benefits of the product at issue outweigh its risks, and whether it should be approved.

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.

Draft Points to Consider

1. Has the Applicant demonstrated that Remoxy is expected to be safe and effective in the intended population for the proposed indication?

2. Has the Applicant demonstrated that Remoxy has properties that can be expected to deter abuse by the:

    a. Oral route of administration?
    b. Nasal route of administration?
    c. IV route of administration?

3. Are there sufficient data to support inclusion of language regarding abuse-deterrent properties in the product label for the:
    a. Oral route of administration?
    b. Nasal route of administration?
    c. IV route of administration?

4. Does the committee have concerns regarding of the safety of exposure to the excipients in this product if administered by the unintended routes?

5. Does the committee have concerns regarding the impact of Remoxy on public health?

6. Should Remoxy be approved?

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: May 21, 2018

FROM: Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, 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. Additionally, another immediate-release opioid analgesic that did not demonstrate abuse-deterrent properties has been approved with labeling language describing its negative study results.

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, 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, 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 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, 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.

Apadaz, approved in February 2018, is an immediate-release opioid approved with labeling language describing the negative results of studies conducted to assess properties intended to deter abuse. Apadaz is a combination of benzhydrocodone, a prodrug of the opioid agonist hydrocodone, and acetaminophen. In vitro data demonstrate that Apadaz is not expected to reduce abuse by the intravenous route or by smoking. In vivo data demonstrate that Apadaz is not expected to deter abuse by the oral or nasal routes.

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 nor are they less addictive. 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."

Abuse-Deterrent Opioids — Evaluation and Labeling

Guidance for Industry

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

Clinical Medical
April 2015

Abuse-Deterrent Opioids — Evaluation and Labeling

Guidance for Industry

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

Clinical Medical
April 2015

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Abuse-Deterrent Opioids — Evaluation and Labeling
Guidance for 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.

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:	May 21, 2018
Drug Utilization Analyst(s):	Daniel Bak, PharmD Drug Utilization Data Analyst Division of Epidemiology II
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Associate Director:	Judy Staffa, Ph.D., R.Ph. Associate Director for Public Health Initiatives Office of Surveillance and Epidemiology
Product Name(s):	Remoxy (Oxycodone ER)
Application Type/Number:	NDA 022324
Applicant/Sponsor:	Pain Therapeutics Inc.
OSE RCM #:	2018-504

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EXECUTIVE SUMMARY

On June 26, 2018, the Anesthetics and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DsARM) will meet to discuss and evaluate data for a New Drug Application (NDA) of an oxycodone extended-release formulation formulated to have abuse-deterrent properties. In support of this upcoming meeting, this review intends to provide context for the committee to better understand recent utilization of oxycodone ER products and other opioid analgesics with and without abuse-deterrent formulations (ADF).

In the outpatient retail pharmacy setting, the number of prescriptions dispensed for oxycodone ER products decreased 31% from approximately 4.9 million prescriptions in 2013 to 3.4 million prescriptions in 2017. Prescriptions for single-ingredient oxycodone ER accounted for an estimated 7% (3.4 million prescriptions) of total oxycodone prescriptions dispensed in 2017. Single-ingredient oxycodone IR and oxycodone IR combination products have accounted for the two most dispensed oxycodone prescriptions each year throughout the time examined.

The number of prescriptions dispensed for extended-release/long-acting (ER/LA) opioid analgesic products decreased 19% from nearly 21.4 million prescriptions in 2013 to 17.5 million prescriptions in 2017. Of the total ER/LA opioid analgesic prescriptions, oxycodone ER accounted for approximately 20% (3.4 million prescriptions) in 2017.

The number of prescriptions dispensed for ADF opioid analgesic products decreased 22% from approximately 4.9 million prescriptions in 2013 to 3.8 million prescriptions in 2017. Of the 3.8 million prescriptions dispensed for ADF opioid analgesics in 2017, reformulated OxyContin (oxycodone ER) accounted for the majority of total prescriptions at nearly 88% (3.4 million prescriptions).

Our findings suggest use for oxycodone ER products has gradually decreased during recent years. Among abuse-deterrent opioid analgesics, reformulated OxyContin accounted for the highest proportion of total prescriptions dispensed in 2017.

1 INTRODUCTION

On June 26, 2018, the Anesthetics and Analgesic Drug Products Advisory Committee (AADPAC)) and the Drug Safety and Risk Management Advisory Committee (DsARM) is scheduled to meet to discuss whether the data submitted for a New Drug Application (NDA) for an extended-release formulation of oxycodone with intended abuse-deterrent properties is sufficient for approval and for labeling of properties to deter abuse. To create context for the upcoming meeting, this review examines the extent of use of marketed extended-release oxycodone and other opioid analgesic products with and without formulations designed to deter abuse.

1.1 BACKGROUND

On June 2008, Pain Therapeutics submitted a New Drug Application (NDA) 022324 for an extended-release formulation of oxycodone with intended abuse-deterrent properties. The proposed formulation was designed to prevent tampering when subjected to various physical and chemical manipulation by abusers. The proposed indication for oxycodone ER is for the management of moderate-to-severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.[i]

2 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct these analyses. Detailed descriptions of the databases are included in **Appendix B**.

2.1 DATA SOURCES

The IQVIA, National Sales Perspectives (NSP) database was used to obtain the nationally estimated number of bottles and packages sold for extended-release oxycodone from the manufacturer to all U.S. channels of distribution, from 2013 through 2017. The sales distribution data represent the amount of product sold from manufacturers to pharmacies and other settings of care; it does not reflect what is being sold to or administered to patients directly.

The IQVIA National Prescription Audit (NPA) database was used to obtain the nationally estimated number of prescriptions dispensed for extended-release/long-acting and other opioid analgesics with abuse-deterrent formulations from U.S. outpatient retail pharmacies, from 2013 through 2017, annually.

2.2 MOLECULES INCLUDED[ii]

Table 1 provides the list of molecules included in this review:

Oral Oxycodone Immediate-Release (IR) Analgesic		
Active Ingredient	**Brand Name**	**Initial U.S Approval**
Oxycodone IR	Roxicodone	August 31, 2000
	Oxaydo	June 17, 2011
	(Roxybond)	April 20, 2017
Oxycodone-Acetaminophen IR	Percocet	June 25, 1999
	Roxicet	Feburary 25, 1980
	Tylox	December 12, 1984
Oxycodone-Aspirin IR	Percodan	April 12, 1950
Oxycodone-Ibuprofen IR	Combunox	November 26, 2004
Transdermal Extended-Release/Long-Acting Opioid (ER/LA) Analgesic		
Active Ingredient	**Brand Name**	**Initial U.S Approval**
Buprenorphine	Butrans	June 30, 2010
Fentanyl	Duragesic	August 7, 1990
Oral Extended-Release/Long-Acting Opioid (ER/LA) Analgesic		
Active Ingredient	**Brand Name**	**Initial U.S Approval**
Buprenorphine	Belbuca,	October 23, 2015
Hydrocodone ER	Zohydro	October 25, 2013
	(Hysingla)	November 20, 2014
	(Vantrela)	January 17, 2017
Hydromorphone ER	Exalgo	March 1, 2010
Methadone	Dolophine	August 13, 1947
	Methadose	March 14, 1973
Morphine ER	MS Contin	May 29, 1987
	Kadian	July 3, 1996
	Avinza	March 20, 2002
	(Morphabond)	October 2, 2015
	(Arymo)	January 9, 2017
Morphine-Naltrexone ER	(Embeda)	August 13, 2009
Oxycodone ER	(OxyContin)	December 12, 1995 (Original) April 5, 2010 (Reformulated)
	(Xtampza)	April 26, 2016
Oxycodone-Acetaminophen ER	Xartemis	March 11, 2014
Oxycodone-Naloxone ER	(Targiniq)	July 23, 2014
Oxycodone-Naltrexone ER	(Troxyca)	August 19, 2016
Oxymorphone ER	Opana ER	June 22, 2006 (Original) December 9, 2011(Reformulated)
Tapentadol ER	Nucynta ER	August 25, 2011

Brand name products in parenthesis indicate opioid medications with FDA-approved labeling describing abuse-deterrent properties.

3 RESULTS

3.1 DETERMINING SETTINGS OF CARE

In 2017, approximately 77% of all oxycodone ER products were distributed to U.S. outpatient retail pharmacies, followed by 22% to non-retail pharmacies, and 2% to mail-order/specialty pharmacies.[1] Accordingly, we focused our efforts on the outpatient retail pharmacies. Data from other settings of care were not included.

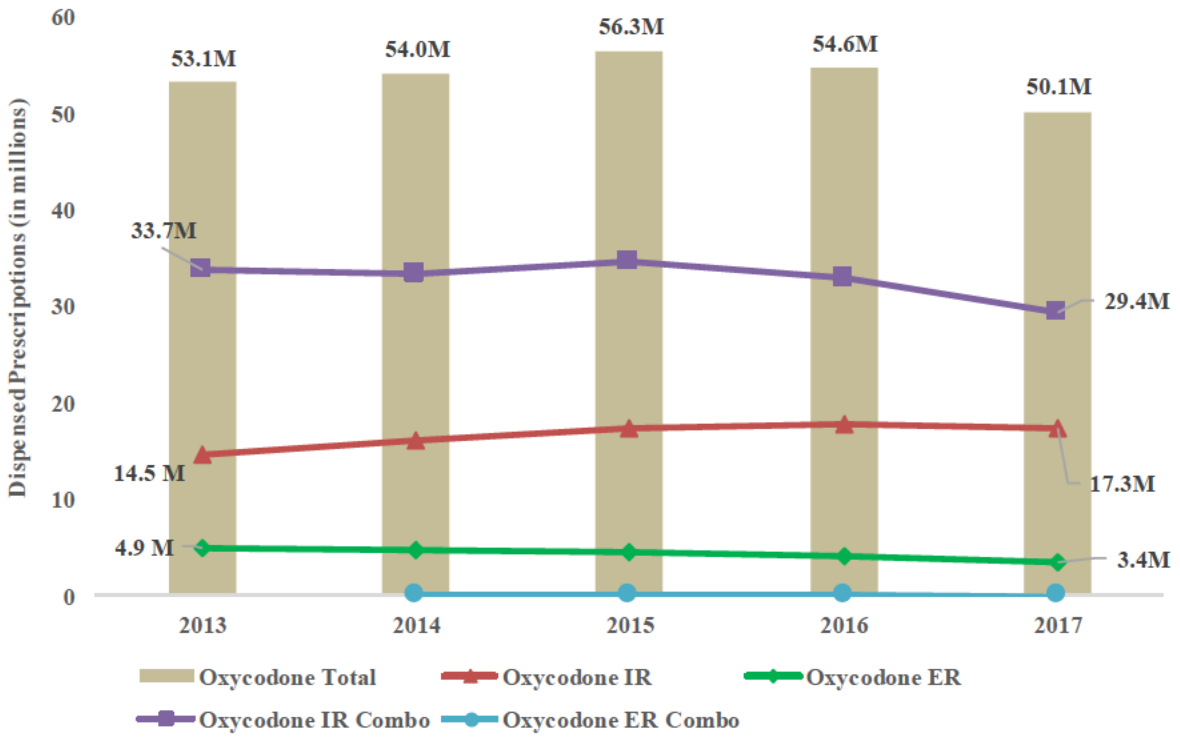
3.2 PRESCRIPTION DATA

3.2.1 Oxycodone Products

Figure 1 below and Table 2 in Appendix A shows the nationally estimated number of dispensed prescriptions for oxycodone products from U.S. outpatient retail pharmacies from 2013 through 2017, annually. Approximately 50-56 million prescriptions of oxycodone products were dispensed annually from 2013 through 2017. The number of prescriptions dispensed for oxycodone ER products decreased 31% from approximately 4.9 million prescriptions in 2013 to 3.4 million prescriptions in 2017. Of the total number of prescriptions dispensed for oxycodone in 2017, prescriptions dispensed for oxycodone IR combination products accounted for the majority at approximately 59% (29.4 million prescriptions), followed by single-ingredient oxycodone IR at 35% (17.3 million prescriptions), single-ingredient oxycodone ER at 7% (3.4 million prescriptions), and combination oxycodone ER at <0.5% (2700 prescriptions).

[1] IQVIA, National Sales Perspectives™ (NSP) database. 2013-2017. Extracted April 2018. 2018-504 NSP Remoxy.xlsx

Figure 1. Nationally Estimated Number of Prescriptions for Oxycodone Products from U.S. Outpatient Retail Pharmacies, from January 2013 Through December 2017, Annually.



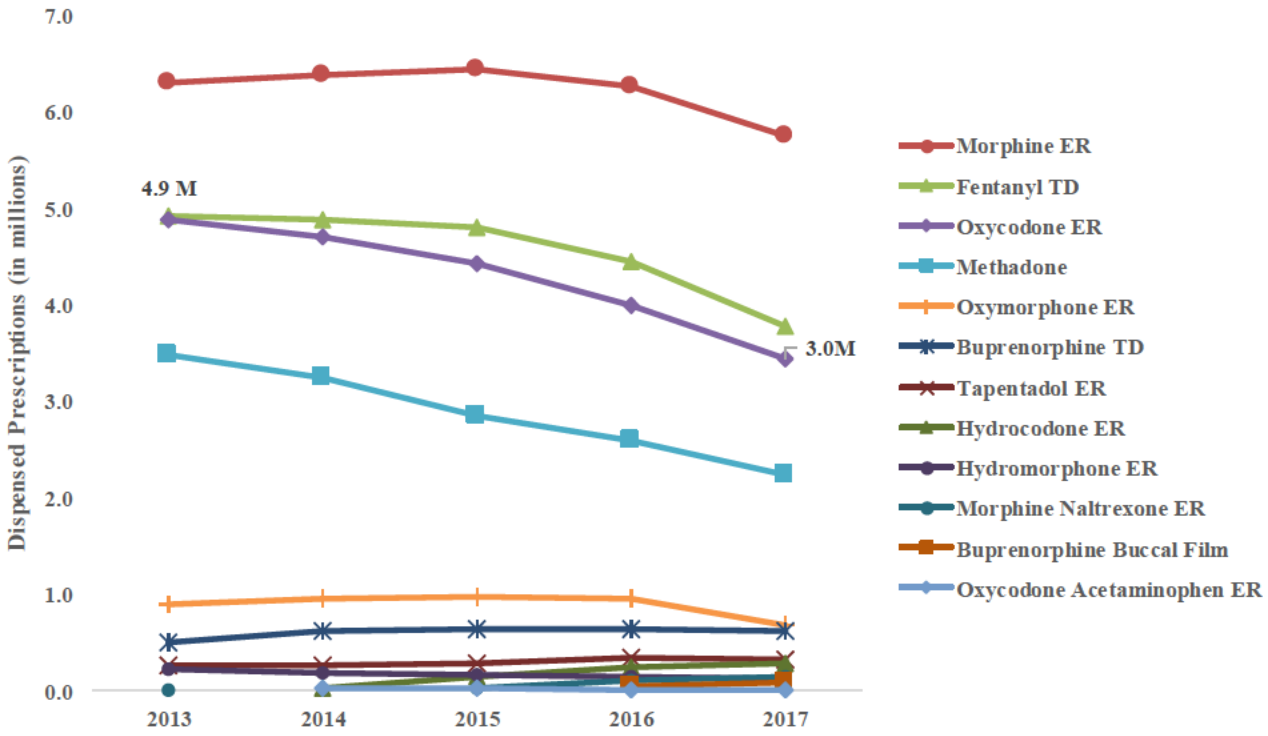
Source: IQVIA, National Prescription Audit™, Years 2013-2017. Data Extracted April 2018. File: 2018-504 NPA Remoxy xlsx
*Immediate-Release (IR) formulations include oral solid tablets/capsules and oral liquids
**Extended-Release/Long-Acting (ER/LA)

3.2.2 ER/LA Opioid Analgesics

Figure 2 below and Table 3 in Appendix A shows the nationally estimated number of dispensed prescriptions for extended-release/long-acting (ER/LA) opioid analgesics from U.S. outpatient retail pharmacies from 2013 through 2017, annually. Over the given time period, the number of prescriptions dispensed for ER/LA opioid analgesic products decreased 19% from nearly 21.4 million prescriptions in 2013 to 17.5 million prescriptions in 2017.

In 2017, morphine ER accounted for the largest proportion at approximately 33% (5.7 million prescriptions) of total ER/LA opioid analgesic prescriptions, followed by fentanyl at 22% (3.8 million prescriptions), and oxycodone ER at 20% (3.4 million prescriptions).

Figure 2. Nationally Estimated Number of Dispensed Prescriptions for Extended-Release/Long-Acting (ER/LA) Opioid Analgesics from U.S. Outpatient Retail Pharmacies, 2013-2017, Annually



Source: IQVIA, National Prescription Audit™, Years 2013-2017. Data Extracted April 2018. File: 2018-504 NPA Remoxy xlsx

[1] Zohydro Approved October 2013; Hysingla November 2014

[2] Embeda was withdrawn from the market in March 2011 because of stability issues. It was approved with a manufacturing supplement in November 2013.

[3] Belbuca Approved October 2015

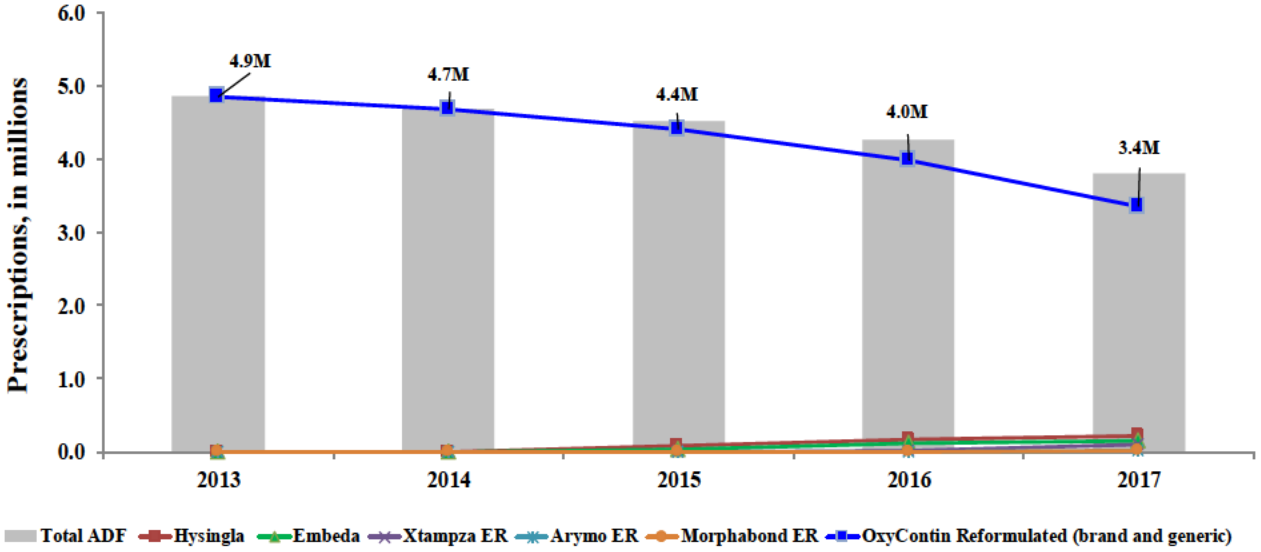
[4] Xartemis XR Approved March 2014

[5] Opana ER was withdrawn from the market in July 2017 following FDA's withdrawal request[iii]

3.2.3 Opioid Analgesics with Abuse Deterrent Formulation

Figure 3 below and Table 4 in Appendix A shows the nationally estimated number of prescriptions dispensed for abuse-deterrent formulation (ADF) opioid analgesic products from U.S. outpatient retail pharmacies from 2013 through 2017, annually. The number of prescriptions dispensed for ADF opioid analgesic products decreased 22% from approximately 4.9 million prescriptions in 2013 to 3.8 million prescriptions in 2017. In 2017, of the total number of prescriptions dispensed for ADF prescriptions, prescriptions for reformulated oxycodone ER accounted for the majority at nearly 88% (3.4 million prescriptions).

Figure 3. Nationally Estimated Number of Prescriptions Dispensed for Abuse-Deterrent Formulation (ADF) Opioid Analgesic Products from U.S. Outpatient Retail Pharmacies, 2013-2017, Annually



Source: IQVIA, National Prescription Audit™, Years 2013-2017. Data Extracted April 2018. File: 2018-504 NPA Remoxy ADF xlsx
Hysingla (hydrocodone ER)[1] - Approved 11/2014
Embeda (morphine/naltrexone ER)[2] - was first approved on August 13, 2009 but was voluntarily withdrawn from the market in March 2011 due to testing that found stability concerns in the manufacturing process. The FDA confirmed that these issues were resolved with its approval of a manufacturing supplement in November 2013[iv].
Xtampza ER (oxycodone ER)[3] – Approved 04/2016
Arymo ER (morphine ER)[4] - Approved 01/2017
Morphabond ER (morphine ER)[5] – Approved 10/2015
OxyContin (oxycodone ER)[6] – Reformulated Version Approved 04/2010
* Products not marketed during study period: RoxyBond (oxycodone IR) – Approved 04/2017, Targiniq (oxycodone/naloxone) – Approved 07/2014, Troxyca (oxycodone/naltrexone ER) – Approved 08/2016, Vantrela (hydrocodone ER) – Approved 01/2017

4 DISCUSSION

An analysis of oxycodone ER and other opioid analgesics with and without abuse-deterrent properties for recent years was performed to provide context for the advisory committees to evaluate the NDA for an extended-release oxycodone with abuse-deterrent properties.

Of the oxycodone products reviewed, single-ingredient oxycodone IR and oxycodone IR combination products have accounted for the two most dispensed oxycodone prescriptions each year throughout the time examined.

Our findings show that prescriptions for oxycodone ER decreased in the past five years. Possible factors that may have contributed to this trend include but are not limited to the

reformulation of OxyContin in August 2010, the introduction of the ER/LA opioid analgesic REMS in 2012, and regulatory actions implemented by federal and local governments and other stakeholders to address the opioid epidemic.

Findings from this review should be interpreted in the context of the known limitations of the databases used. The nationally estimated numbers of dispensed prescriptions provided in this review represent the U.S. outpatient retail pharmacy setting only and may not apply to other important settings of care.

5 CONCLUSION

Our findings suggest use of oxycodone ER products has gradually decreased during recent years, but among abuse-deterrent opioid analgesics, reformulated OxyContin (oxycodone ER) accounted for the highest proportion of total prescriptions dispensed from 2013 through 2017.

6 APPENDICES

6.1 APPENDIX A. TABLES

Table 2. Nationally Estimated Number of Prescriptions for Oxycodone Products from U.S. Outpatient Retail Pharmacies, from January 2013 Through December 2017, Annually.

	2013		2014		2015		2016		2017	
	TRx	%	TRx	%	TRx	%	TRx	%	TRx	%
Grand Total Oxycodone	**53,101,127**	**100.0%**	**54,043,581**	**100.0%**	**56,335,360**	**100.0%**	**54,608,404**	**100.0%**	**50,130,499**	**100.0%**
Oxycodone IR Combination*	33,722,400	63.5%	33,340,684	61.7%	34,575,502	61.4%	32,812,238	60.1%	29,371,411	58.6%
Oxycodone IR Single-Ingredient*	14,513,238	27.3%	15,972,555	29.6%	17,317,048	30.7%	17,801,720	32.6%	17,314,059	34.5%
Oxycodone ER Single-Ingredient**	4,865,489	9.2%	4,699,154	8.7%	4,423,455	7.9%	3,987,452	7.3%	3,442,297	6.9%
Oxycodone ER Combination**	…	…	31,188	<0.5%	19,355	<0.5%	6,994	<0.5%	2,732	<0.5%

Source: IQVIA, National Prescription Audit™, Years 2013-2017. Data Extracted April 2018. File: 2018-504 NPA Remoxy.xlsx

*Immediate-Release (IR) formulations include oral solid tablets/capsules and oral liquids

**Extended-Release/Long-Acting (ER/LA) formulations include oral solid tablets/capsules designed to dissolve for an extended period of time.

Table 3. Nationally Estimated Number of Dispensed Prescriptions for Extended-Release/Long-Acting (ER/LA) Opioid Analgesics from U.S. Outpatient Retail Pharmacies, 2013-2017, Annually.

	2013		2014		2015		2016		2017	
	TRx	%	TRx	%	TRx	%	TRx	%	TRx	%
Grand Total ER/LA Opioid Analgesic Products	**21,446,004**	**100.0%**	**21,287,835**	**100.0%**	**20,761,985**	**100.0%**	**19,757,860**	**100.0%**	**17,461,720**	**100.0%**
Morphine ER	6,288,088	29.3%	6,375,570	29.9%	6,441,121	31.0%	6,256,262	31.7%	5,740,199	32.9%
Fentanyl Transdermal	4,923,139	23.0%	4,881,447	22.9%	4,791,686	23.1%	4,439,684	22.5%	3,769,647	21.6%
Oxycodone ER	4,865,489	22.7%	4,699,154	22.1%	4,423,455	21.3%	3,987,452	20.2%	3,442,297	19.7%
Methadone	3,484,537	16.2%	3,242,281	15.2%	2,846,882	13.7%	2,591,013	13.1%	2,243,191	12.8%
Oxymorphone ER	901,307	4.2%	960,933	4.5%	968,029	4.7%	947,081	4.8%	687,208	3.9%
Buprenorphine Transdermal	497,697	2.3%	613,086	2.9%	643,634	3.1%	645,450	3.3%	610,970	3.5%
Tapentadol ER	259,294	1.2%	264,048	1.2%	289,459	1.4%	343,610	1.7%	328,492	1.9%
Hydrocodone ER[1]	–	–	35,093	<0.5%	149,957	0.7%	240,748	1.2%	288,926	1.7%
Hydromorphone ER	226,452	1.1%	185,035	0.9%	160,632	0.8%	138,126	0.7%	118,591	0.7%
Morphine Naltrexone ER[2]	1	<0.5%	–	–	27,775	<0.5%	110,865	0.6%	139,334	0.8%
Buprenorphine Buccal Film[3]	–	–	–	–	–	–	50,575	<0.5%	90,133	0.5%
Oxycodone Acetaminophen ER[4]	–	–	31,188	<0.5%	19,355	<0.5%	6,994	<0.5%	2,732	<0.5%

Source: IQVIA, National Prescription Audit™, Years 2013-2017. Data Extracted April 2018. File: 2018-504 NPA Remoxy.xlsx

[1] Zohydro Approved October 2013; Hysingla November 2014

[2] Embeda was withdrawn from the market in March 2011 because of stability issues. It was approved with a manufacturing supplement in November 2013.

[3] Belbuca Approved October 2015

[4] Xartemis XR Approved March 2014

Table 4. Nationally Estimated Number of Prescriptions Dispensed for Abuse-Deterrent Formulation (ADF) Opioid Analgesic Products* from U.S. Outpatient Retail Pharmacies, 2013-2017, Annually

	2013	2014	2015	2016	2017
Total ADF	**4,850,154**	**4,686,484**	**4,519,991**	**4,264,525**	**3,806,205**
Hysingla[1]	...	...	85,934	166,208	214,954
Embeda[2]	...	...	27,775	110,865	139,334
Xtampza ER[3]	...	...	...	7,880	88,360
Arymo ER[4]	...	...	...	...	7,080
Morphabond ER[5]	...	...	...	...	2,540
OxyContin Reformulated (brand and generic)[6]	4,850,153	4,686,484	4,406,282	3,979,572	3,353,937

Source: IQVIA, National Prescription Audit™, Years 2013-2017. Data Extracted April 2018. File: 2018-504 NPA Remoxy.xlsx

Hysingla (hydrocodone ER)[1] - Approved 11/2014

Embeda (morphine/naltrexone ER)[2] - was first approved on August 13, 2009 but was voluntarily withdrawn from the market in March 2011 due to testing that found stability concerns in the manufacturing process. The FDA confirmed that these issues were resolved with its approval of a manufacturing supplement in November 2013[v].

Xtampza ER (oxycodone ER)[3] – Approved 04/2016

Arymo ER (morphine ER)[4] - Approved 01/2017

Morphabond ER (morphine ER)[5] – Approved 10/2015

OxyContin (oxycodone ER)[6] – Reformulated Version Approved 04/2010

* Products not marketed during study period: RoxyBond (oxycodone IR) – Approved 04/2017, Targiniq (oxycodone/naloxone) – Approved 07/2014, Troxyca (oxycodone/naltrexone ER) – Approved 08/2016, Vantrela (hydrocodone ER) – Approved 01/2017

6.2 APPENDIX B. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IQVIA, National Sales Perspectives™: Retail and Non-Retail

The IQVIA National Sales Perspectives (NSP) 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.

IQVIA National Prescription Audit™

The IQVIA National Prescription Audit (NPA) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over 3.7 billion prescription claims per year, captured from a sample of the universe of approximately 59,900 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 93% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 45 – 75% (varies by class and geography) of mail service pharmacies and approximately 71 – 83% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

6.3 REFERENCES

[i] DARRTS: NDA 209653, User Fee/Coversheet; New/NDA; Form 3674, Supporting Document 1/eCTD0001, dated 11/25/2016.

[ii] U.S. Food and Drug Administration: Drugs@FDA. Accessed May 11, 2017. Website: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

[iii] Endo International News Release. "Endo Provides Update on OPANA® ER". Accessed May, 2017. Website: http://investor.endo.com/news-releases/news-release-details/endo-provides-update-opanar-er

[iv] U.S. Food and Drug Administration News Release. "FDA approves labeling with abuse-deterrent features for third extended-release opioid analgesic. Accessed June 2017. https://wayback.archive-it.org/7993/20161022101255/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm419288.htm

[v] U.S. Food and Drug Administration News Release. "FDA approves labeling with abuse-deterrent features for third extended-release opioid analgesic. Accessed June 2017. https://wayback.archive-it.org/7993/20161022101255/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm419288.htm

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

M E M O R A N D U M

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Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Summary of Clinical Data for Oxycodone Extended Release Capsules (NDA 22324)

Summary of Clinical Data for Oxycodone Extended-Release Capsules

The proposed indication for oxycodone extended-release (ER) capsules is for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The safety and efficacy of oxycodone ER capsules is based on demonstration of bioequivalence to the listed drug, Roxicodone (NDA 021011) for this 505(b)(2) New Drug Application. One adequate and well-controlled Phase 3 clinical trial was required to support the safety and efficacy of oxycodone ER capsules. This study (PTI-821-CO) supports the efficacy of this reformulation of oxycodone. Safety information was collected from two Phase 3 clinical trials and two human abuse potential studies. No new safety signals were identified in study subjects during review of the oxycodone ER capsules application beyond what is already known for oxycodone-containing products.

Several clinical pharmacology studies have been conducted with Remoxy ER (PTI-821, oxycodone ER capsules) and reviewed. The aggregate clinical pharmacology data in healthy volunteers show that plasma concentrations of oxycodone increased in a dose-proportional manner when Remoxy ER (5 mg – 40 mg) was taken with food. In pharmacokinetic (PK) studies, after a single dose of Remoxy ER 30 mg, oxycodone reached peak plasma concentrations of 27.2 ng/mL at 4.5 hours. Steady-state, peak plasma concentrations after Remoxy ER 30 mg taken with food were 43.9 ng/mL at 4.75 hours and the area under the curve for the dosing interval, AUC0-12 was 218.2 hr•ng/mL after a single dose and 378.7 hr•ng/mL at steady state. Food-effect was evaluated and an increase of 50 - 90% oxycodone Cmax was observed with different meals. In vitro and in vivo studies showed that Remoxy ER is not susceptible to alcohol dose dumping. In a relative bioavailability study in fasted volunteers, (Study B45011039), a 3-fold increase in Cmax was noted when Remoxy ER was chewed and swallowed orally compared to a cohort administered intact drug product.

Two human abuse potential studies conducted in opioid-experienced, non-dependent volunteers included a clinical pharmacology component.

Oral Abuse Potential Study B4501016:

Study B4501016 evaluated the abuse potential of intact and chewed Remoxy (40 mg) compared to crushed oxycodone HCl IR tablets (40 mg) and placebo administered orally to non-dependent, recreational opioid users. Subjects who successfully completed a naloxone challenge were randomized into the drug discrimination phase to assess continued eligibility for the treatment phase which included 4 treatment periods while fasting, with each period separated by a washout of a minimum of 120 hours (5 days) but not to exceed 14 days. Summary data are shown in Figure 1 and Table 1.

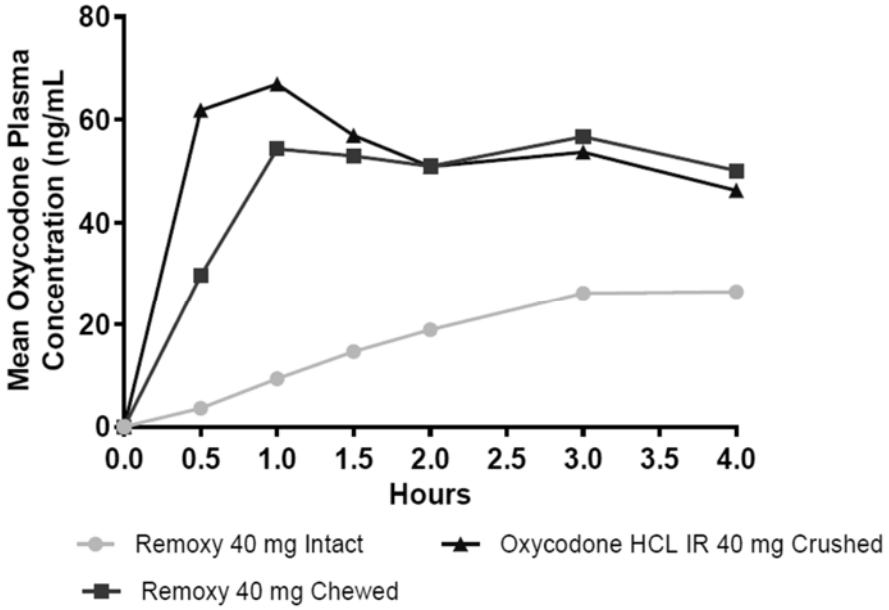


Figure 1: Mean concentration profile of oxycodone following oral administration of different treatments in Study B4501016.

Source: Excerpt from Clinical Pharmacology Review Dated 8/31/2016

Table 1: Summary Statistics of Oxycodone Pharmacokinetics in Study B4501016.

	Intact Remoxy 40 mg	**Chewed Remoxy 40 mg**	**Crushed IR Oxycodone HCl 40 mg**
Cmax [ng/mL]	30.3 (31)	**64.4(23)**	82.1 (28)
Tmax [hr]	4.33 (2.2-12.2)	**2.15 (0.7-5.2)**	1.15 (0.6-6.2)
AUC0-1h [ng hr/mL]	2.38 (77)	20.39 (66)	39.335 (41)
AUC0-2h [ng hr/mL]	14.67 (41)	71.78 (40)	97.834 (31)
AUC0-3h [ng hr/mL]	35.33 (33)	124.6 (31)	148.49 (28)
AUC0-12h [ng hr/mL]	249.3 (26)	420.0 (19)	402.8 (18)
AUCinf [ng hr/mL]	493.4 (22)	521.9 (22)	463.5 (20)
AUClast [ng hr/mL]	402.6 (22)	503.3 (21)	455.6 (19)

Geometric mean (geometric %CV) for all except: median (range) for Tmax; arithmetic mean (±SD) for t½.

Source: CSR B4501016, Table 32 and 33.

In the fasted state, the Cmax of oxycodone, following chewing and swallowing of Remoxy was approximately twice that of intact Remoxy. The earlier Tmax and the high relative bioavailability compared to intact product indicate that the proposed product may not deter oral abuse by chewing. The Applicant compared the PK parameters of chewed product to crushed IR product to show lower exposure (Cmax and partial AUC). The Cmax of crushed Remoxy is approximately 25% lower compared to the IR product taken orally after crushing. Refer to the Controlled Substance Staff (CSS) review in this background package for the pharmacodynamic (PD) aspects of Remoxy taken intact and chewed in study B4501016.

Intranasal Abuse Potential Study PTI-821-CO8:

A Category 3 pharmacokinetic/pharmacokynamic (PK/PD) study, PTI-821-C08, was submitted to support claims of intranasal (IN) abuse deterrence for Remoxy ER. The primary objective of this study was to determine the relative abuse potential of Remoxy ER (or PTI-821) compared to ground oxycodone immediate-release (IR) tablets and placebo when self-administered intranasally by nondependent, recreational opioid users. A secondary objective was to compare the PK of Remoxy 40 mg IN with that of ground oxycodone IR 40 mg IN. In an exploratory manner, the PK and selected PD of Remoxy 40 mg IN was also compared with the PK and selected PD of ground OxyContin ER 40 mg IN. Refer to the CSS review in this background package for the PD aspects of the study.

Following a minimum 48-hour washout period from the drug discrimination test, subjects began Treatment Period 1. For each of the 4 treatment periods, subjects were randomized to 1 of 4 treatment sequences. Each subject received a total of 4 or 5 treatments. Subjects were required to fast for at least 8 hours pre-dose until at least 4 hours post-administration. The 4 study treatments, indicated below, were separated by a minimum 72-hour washout period:

- Treatment A = Right nostril: Remoxy 40 mg (Manipulated), Left nostril: oxycodone matched placebo powder.
- Treatment B = Right nostril: Remoxy 40 mg (Intact), Left nostril: oxycodone matched placebo powder.
- Treatment C = Right nostril: Remoxy matched placebo gel, Left nostril: oxycodone IR 40 mg powder.
- Treatment D = Right nostril: Remoxy matched placebo gel, Left nostril: oxycodone matched placebo powder.

Following an approximately 72-hour washout from the last treatment in the Treatment Phase, approximately 20 subjects were to participate in an exploratory fifth treatment arm. During the exploratory fifth treatment arm, subjects received the following:

- Treatment E = Left nostril: OxyContin ER 40 mg powder.

Relevant pharmacokinetic parameters showing the systemic exposure of oxycodone over time following the treatments are described in Table 2 and Figure 2 below. After IN

administration of oxycodone IR powder 40 mg, the mean Cmax was 65 ng/mL and occurred at a median Tmax of 1.6 hours. After IN administration of PTI-821 with and without manipulation, the mean Cmax values were 12.3 ng/mL and 15.3 ng/mL, respectively, and occurred at approximately a median Tmax of 3 hours.

Table 2: Summary Statistics of Pharmacokinetic Parameters (Geometric Mean (%CV)) of Oxycodone from Study PTI-821-C08.

Parameter	Treatment A: Intranasal Remoxy 40 mg (Manipulated) n = 35	Treatment B: Intranasal Remoxy 40 mg (Intact) n = 36	Treatment C: Intranasal Oxycodone IR 40 mg Powder n = 36	Treatment E: Intranasal Ground OxyContin ER 40 mg n = 20
T_{max} (h)	3.07 (0.75-8.12)[a]	3.1 (1.1-8.07)[a]	1.6 (0.28-5.1)[a]	0.875 (0.25-6.07)[a]
C_{max} (ng/mL)	12.3 (108)	15.3 (70)	64.7 (28)	66.4 (25)
AUC_{last} (h*ng/mL)	132 (108)	152 (64)	460 (28)	628 (18)
AUC_{inf} (h*ng/mL)	147 (98)[b]	169 (64)[b]	467 (28)	678 (21)
$AUC_{0-0.5}$ (h*ng/mL)	0.805 (98)	0.949 (123)	14.2 (34)	16.6 (50)
AUC_{0-1} (h*ng/mL)	3.22 (96)	3.64 (88)	37.7 (27)	46.1 (32)
AUC_{0-2} (h*ng/mL)	11.6 (93)	13.2 (83)	84.5 (31)	104 (26)
AUC_{0-3} (h*ng/mL)	22.7 (90)	25.5 (75)	133 (30)	158 (24)
AUC_{0-4} (h*ng/mL)	34.1 (92)	39.3 (67)	183 (28)	210 (23)

a: Median (Range); all others are geometric mean (%CV); b: n = 34

Source – DCN: 4005734 Pharmacokinetic Report, an appendix to the Study report PTI-821-C08

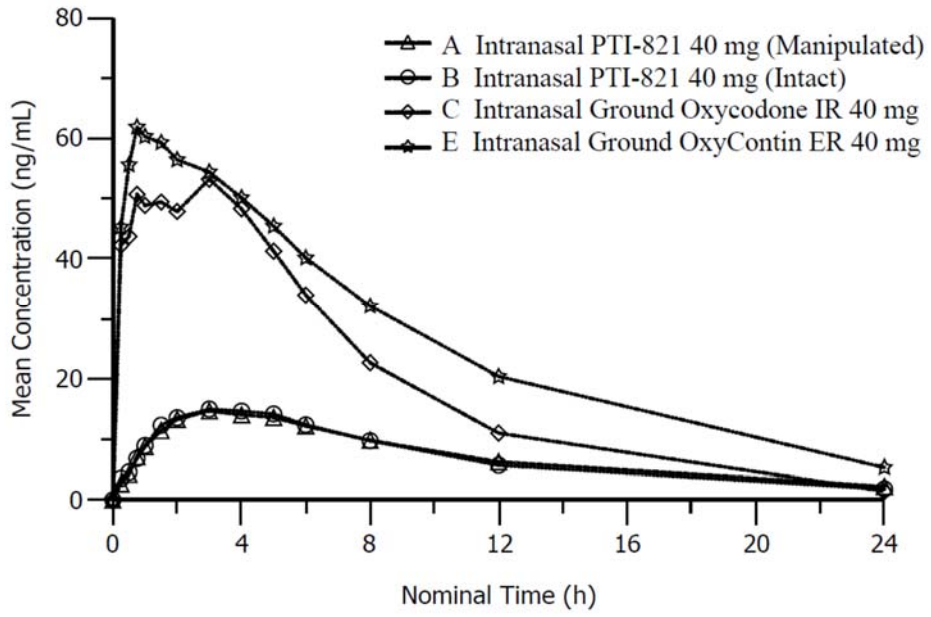


Figure 2: Mean concentration profile of oxycodone following intranasal administration of different treatments in Study PTI-821-CO8.

Source: Study report PTI-821-C08

Intransal administration of both manipulated and intact Remoxy gel resulted in lower oxycodone Cmax, partial AUCs and overall AUCs compared to the equivalent dose of ground oxycodone IR tablets. The difference in oxycodone bioavailability is also demonstrated by all tabulated parameters having 90% confidence intervals that are below 80% (See Tables 3 and 4 below).

Table 3: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Oxycodone Comparing Intranasal PTI-821 40 mg (Manipulated, Test) (Treatment A) vs. Intranasal Oxycodone IR 40 mg Powder, Reference (Treatment C).

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]	
	Test	Ref	(Test/Ref)	Lower	Upper
ln(C_{max})	11.9329	64.7364	18.43	14.91	22.80
ln(AUC_{last})	129.4768	461.8865	28.03	23.00	34.17
ln(AUC_{inf})	145.5857	468.7692	31.06	25.53	37.78
ln($AUC_{0-0.5}$)	0.7973	14.1921	5.62	4.38	7.20
ln(AUC_{0-1})	3.1629	37.7089	8.39	6.81	10.33
ln(AUC_{0-2})	11.3771	84.8873	13.40	10.89	16.49
ln(AUC_{0-3})	22.2785	133.1958	16.73	13.71	20.40
ln(AUC_{0-4})	33.2725	183.4810	18.13	15.02	21.90

[a] Geometric Mean for PTI-821 40 mg (Manipulated) (Test) and Oxycodone IR 40 mg Powder (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
Source: Appendix 16.1.13.2, PTI-821-08 PK Report, Tables 4, 5, 6, 7, 8

Table 4: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Oxycodone Comparing Intranasal PTI-821 40 mg (Intact, Test) (Treatment B) vs. Intranasal Oxycodone IR 40 mg Powder, Reference (Treatment C).

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]	
	Test	Ref	(Test/Ref)	Lower	Upper
ln(C_{max})	14.9164	64.7364	23.04	18.65	28.46
ln(AUC_{last})	148.5358	461.8865	32.16	26.41	39.16
ln(AUC_{inf})	166.1148	468.7692	35.44	29.15	43.08
ln($AUC_{0-0.5}$)	0.9404	14.1921	6.63	5.18	8.48
ln(AUC_{0-1})	3.5832	37.7089	9.50	7.72	11.69
ln(AUC_{0-2})	12.9114	84.8873	15.21	12.38	18.69
ln(AUC_{0-3})	24.9211	133.1958	18.71	15.36	22.79
ln(AUC_{0-4})	38.3699	183.4810	20.91	17.33	25.23

[a] Geometric Mean for PTI-821 40 mg (Intact) (Test) and Oxycodone IR 40 mg Powder (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval
Source: Appendix 16.1.13.2, PTI-821-08 PK Report, Tables 4, 5, 6, 7, 8

The CSS review indicates that the methodology for IN administration of Remoxy ER capsules was acceptable although administering IN Remoxy gel was reported to be more difficult than insufflation of oxycodone powder. The PK results of Study PTI-821-CO8 demonstrate that IN

administration of Remoxy ER with or without manipulation may result in significantly lower plasma oxycodone concentrations compared to IN administration of IR oxycodone product.

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: May 21, 2018

To: Sharon Hertz, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Dominic Chiapperino, Ph.D., Director
Silvia Calderon, Ph.D., Lead Pharmacologist
Controlled Substance Staff

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

Subject: OPEN SESSION BACKGROUND DOCUMENT on Oral Human Abuse Potential Study B4501016 and Intranasal Human Abuse Potential Study PTI-821-C08 Submitted Under NDA 22-324. Prepared for the FDA Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee Meeting, June 26, 2018. Sponsor: Pain Therapeutics

Background Document

Pain Therapeutics has submitted an oral human abuse potential (HAP) study B4501016 and an intranasal HAP study PTI-821-C08 under NDA 22-324 in support of Remoxy (oxycodone hydrochloride (HCl)) extended-release (ER) capsules. These studies are designed on the premise that Remoxy ER capsules have abuse-deterrent properties based in physical/chemical barriers to abuse of this capsule formulation by selected routes of abuse including chewing and insufflation. HAP studies, used as part of the abuse-deterrent pre-market assessment, are generally thought to be predictive of the likelihood that proposed abuse deterrent properties in a new drug product formulation will deter or reduce the abuse of the product when taken through selected routes (oral and intranasal) of abuse.

Descriptions of HAP studies B4501016 and PTI-821-C08, along with relevant findings, are provided below. Statistical analyses of pharmacodynamic measures were conducted by the CDER Office of Biostatistics.

Description of Study B4501016

Study B4501016 is a randomized, double-blind, triple-dummy, placebo and active-controlled, single-dose, 4-way crossover study having a Screening Visit, Naloxone Challenge Phase, Drug Discrimination Phase, Treatment Phase, and End-of-Study Visit.

Primary Objective: To determine the relative abuse potential of intact and chewed PF-00345439 (Oxycodone Extended-Release Capsules) compared to crushed oxycodone HCl immediate release (IR) tablets and placebo administered orally to non-dependent, recreational opioid users.

The determination of relative abuse potential is 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:

- Unipolar 0-100 mm "at the moment" Drug Liking VAS anchored on the left by "0: Not at All" and on the right by "100: Extremely." Subjects are asked to respond to the statement, *"At this moment, my liking for this drug is..."*
- Unipolar 0-100 mm High VAS anchored on the left by "0: Not at All" and on the right by "100: Extremely." Subjects are asked to respond to the statement "*I am feeling high…"*
- Unipolar 0-100 mm Take Drug Again VAS anchored on the left by "0: Definitely Not" and on the right by "100: Definitely So." Subjects are asked to respond to the statement, *"I would take this drug again."*
- Unipolar 0-100 mm Overall Drug Liking VAS anchored on the left by "0: Not at All" and on the right by "100: Extremely." Subjects are asked to respond to the statement, *"Overall, my liking for this drug is."*

During the Drug Discrimination Phase, subjects randomly received 1 of the 3 treatments, 1 treatment per day, over 3 consecutive days (Days 1 - 3), in a fasted state and double-blind fashion:

- Oxycodone HCl IR 20 mg (e.g., 4 × 5 mg) tablets crushed in solution, and
- Oxycodone HCl IR 40 mg (e.g., 2 × 5 mg + 1 × 30 mg) tablets crushed in solution, and
- Placebo solution.

To be eligible for the Treatment Phase, subjects were required during the Drug Discrimination Phase to:

1. Distinguish oxycodone HCl IR 20 mg from placebo on select subjective drug measures (i.e., ≥ 20 point maximum score on visual analogue scales (VAS) collected within the 2-hour post-dosing period for Drug Liking and Drug High).
2. Distinguish oxycodone HCl IR 40 mg from oxycodone IR 20 mg on select subjective drug measures (i.e., ≥ 20 point maximum score on visual analogue scales (VAS) collected within the 2-hour post-dosing period for Drug Liking and High).
3. Display an acceptable placebo response, defined as a VAS response between 0 to 10 inclusive for Drug Liking.
4. Tolerate study treatments safely (i.e., oxygen saturation of hemoglobin [SpO2] ≥ 90%, no episodes of vomiting within the first 2 hours post-dose).

5. Demonstrate general behavior suggestive that the subject could successfully complete the study, as judged by the study center staff.

The Treatment Phase consisted of 4 periods each involving a 2-night confined stay. Each period was separated by a washout period of a minimum 5 days, not to exceed 14 days. Treatments were administered in a randomized (Williams Square design), double-blind, double-dummy crossover fashion, under fasted (8 hours prior to and 2 hours following treatment) conditions. Treatments were as follows:

- Placebo
- Remoxy ER capsules, 40 mg, Intact
- Remoxy ER capsules, 40 mg, Chewed
- Oxycodone HCl IR tablets, 40 mg, Crushed

Oxycodone plasma pharmacokinetic parameters were determined from blood samples taken pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dosing. Oxycodone PK parameters that were evaluated included, but were not limited to, the following:

- Cmax = Maximum oxycodone plasma level achieved following treatment
- Tmax = Time to achieve Cmax
- AUC0-2hours = Area under the oxycodone plasma concentration curve over the first two hours post-dosing reflecting a measure of drug exposure.

Pharmacodynamic measures included, but were not limited to, the VAS for Drug Liking, High, Take Drug Again, and Overall Drug Liking. The primary measures were Drug Liking VAS and High VAS, conducted at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours post-dosing. Take Drug Again VAS and Overall Drug Liking VAS were assessed at hour 24 after dosing.

Pharmacodynamic parameters determined included but were not limited to:

- Emax = maximum effect observed
- TEmax = time to maximum effect (Emax)
- AUE0-2hr = area under the effect curve out to 2 hours post-dosing.

Primary endpoints were the Emax and the AUE0-2hr for both Drug Liking and High.

Statistical analyses of pharmacodynamic endpoints were conducted by the CDER Office of Biostatistics. Statistical model used was a mixed-effects model with period, sequence, and treatment as fixed effects and subjects as a random effect. All tests were one-sided with $\alpha = 0.025$. Statistical analyses of pharmacodynamic endpoints were assessed using data from 46 completers.

Findings Regarding Study B4501016

1. With respect to Drug Liking VAS, High VAS, Take Drug Again VAS, and Overall Drug Liking VAS, the positive comparator, oxycodone HCl IR 40 mg, had mean Emax values that were statistically significantly larger compared to placebo ($p < 0.0001$), thereby validating the study.

2. The least square mean (LSmean) for Emax of Drug Liking of chewed Remoxy 40 mg of 63.0 was not statistically significantly different from the LSmean of 69.9 for oxycodone HCL IR 40 mg ($p = 0.0533$). The median TEmax of Drug Liking were 1.1 and 1.5 hours following treatments with oxycodone HCL IR 40 mg and chewed Remoxy 40 mg, respectively. As evidenced from mean response to Drug Liking versus time curves, much of the rise in Drug Liking was achieved within 30 minutes and 1 hour following oxycodone HCL IR 40 mg and chewed Remoxy 40 mg, respectively. The mean (AUE0-2hrs) post-dosing for Drug Liking was statistically significantly larger following oxycodone HCl IR 40 mg compared to chewed Remoxy 40 mg ($p < 0.0001$).

3. Even though chewed Remoxy 40 mg had statistically significantly lower mean (63.1) of Emax of High than crushed oxycodone HCl IR (70.7) ($p=0.0043$), it failed to demonstrate a minimum of 5% reduction in mean of Emax of High for chewed Remoxy 40 mg compared to crushed oxycodone HCl IR 40 mg ($p=0.0667$). Median TEmax values of High following oxycodone HCl IR 40 mg and chewed Remoxy 40 mg were 1.0 and 2.0 hours, respectively. As evidenced from mean response of High versus time curves, much of the rise in High was achieved within 1 and 1.5 hours following oxycodone HCl IR 40 mg and chewed Remoxy 40 mg, respectively. The mean of AUE0-2hrs for High was statistically significantly larger following oxycodone HCl IR 40 mg compared to chewed Remoxy 40 mg ($p < 0.0001$).

4. The LSmean Emax of 63.5 produced by chewed Remoxy 40 mg was not statistically significantly different from LSmean of 65 following oxycodone HCl IR 40 mg for unipolar Take Drug Again VAS at 24 hours ($p=0.4064$).

5. The LSmean of 60.5 following chewed Remoxy 40 mg for unipolar Overall Drug Liking VAS was not statistically significantly different from that of 64.3 produced by oxycodone HCl IR 40 mg ($p=0.2165$).

6. The statistical analysis results also showed that chewed Remoxy 40 mg had a statistically significantly larger mean Emax than intact Remoxy 40 mg, and intact Remoxy 40 mg had a statistically significantly larger mean than placebo for Drug Liking Emax, High Emax, and Overall Drug Liking VAS and Take Drug Again VAS at 24 hours ($p \leq 0.0116$).

7. Chewed Remoxy 40 mg produced a Cmax of plasma oxycodone that was approximately twice that of intact Remoxy 40 mg (64.4 versus 30.3 ng/mL) and 78% of that produced by oxycodone HCl IR 40 mg crushed (64.4 versus 82.1 ng/mL). The calculated median Tmax for Chewed Remoxy was 2.15 hours, which was half that following intact Remoxy (4.33 hours) and about twice that following oxycodone HCl IR. An examination of the mean oxycodone plasma concentration as a function of time following active treatments shows that the majority of the rise in mean oxycodone plasma concentration following chewed Remoxy was achieved within 1 hour post-dosing.

Description of Study PTI-821-C08

Study PTI-821-C08 was a randomized, double-blind, placebo- and active-controlled, 4-way crossover study. The study included a Screening visit, Qualification Phase, Treatment Phase, and Follow-up visit.

Primary objective was to determine the relative abuse potential of Remoxy ER capsules compared to ground oxycodone HCl IR tablets and placebo when self-administered intranasally by nondependent, recreational opioid users having intranasal opioid use experience at least three times within the last 12 months.

Pharmacodynamic measures were conducted on the completer population consisting of 36 subjects.

During the Qualification Phase, subjects underwent a Naloxone Challenge to ensure that they were not physically dependent on opioids. Subjects were also subjected to a Drug Discrimination Test to ensure that they could differentiate between the effects of 40 mg manipulated intranasal IR oxycodone and intranasal placebo on selective pharmacodynamic measures such as Drug Liking VAS.

Subjects who successfully completed the Naloxone Challenge and Drug Discrimination tests remained in the clinic and began the Treatment Phase following a minimum 48-hour washout period. For each of the 4 treatment periods, subjects were randomized to 1 of 4 treatment sequences where each subject received the 4 treatments. For each of the 4 treatment periods, a double-dummy design was used and subjects received an intranasal treatment (active or placebo). Intranasal treatments are described below.

- Remoxy ER capsules, 40 mg, Manipulated
- Remoxy ER capsules, 40 mg, Intact
- Oxycodone HCl IR tablets, 40 mg, Crushed/Powder
- Placebo

Subjects were instructed to self-administer the study medications to the nostrils within 5 minutes. Remoxy gel was applied using a foam swab applicator. Oxycodone IR 40 mg powder was insufflated using a straw. The amount of time needed for intranasal administration was recorded. Subjects who were unable to self-administer the entire intranasal treatment were allowed to continue in the study. The amount applied or snorted was recorded.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose for purposes of examining the plasma pharmacokinetics of oxycodone. Maximum oxycodone plasma concentration (Cmax) following each active treatment was determined.

During the Treatment Phase, pharmacodynamic measures included, but were not limited to, Drug Liking VAS, High VAS, Take Drug Again VAS, Overall Drug Liking VAS, and Ease

of Snorting/Application. The primary measure, Drug Liking VAS, and the secondary measure, High VAS, were conducted at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours post-dosing. Take Drug Again VAS and Overall Drug Liking VAS were assessed at 12 and 24 hours after dosing. A description of the High VAS used in this study is found on page 2 of this document. However, descriptions of Drug Liking VAS (primary measure), Take Drug Again VAS, Overall Drug Liking VAS, and Ease of Snorting/Application VAS, as specifically used in this study, are provided below.

- Bipolar 0-100 mm At the Moment Drug Liking VAS anchored on the left by "0: Strong Disliking", in the center by "50: Neither Like nor Dislike" and on the right by "100: Strong Liking." Subjects are asked to respond to the statement, *"Do you like the drug effect you are feeling now?"*
- Bipolar 0-100 mm Take Drug Again VAS was anchored on the left by "0: Definitely Would Not", in the center by "50: Do Not Care" and on the right by "100: Definitely Would." Subjects are asked to respond to the question, *"Would you want to take the drug you just received again, if given the opportunity?"*
- Bipolar 0-100 mm Overall Drug Liking VAS was anchored on the left with "strong disliking" (score of 0); "neither like nor dislike" (score of 50) in the middle; and anchored on the right with "strong liking" (score of 100). Subjects were required to respond to the statement *"Overall, my liking for this drug is."*
- Bipolar 0-100 mm Ease of Snorting/Application VAS anchored on the left with "very difficult (score of 0); "neither easy nor difficult (score of 50); and anchored on the right with "very easy" (score of 100). Depending on the treatment administered (i.e., powder or gel), subjects responded to the statements: *"Snorting the drug was…"* and *"Application of the drug was..."*

Pharmacodynamic parameters determined included, but were not limited to, Emax and TEmax.

Statistical analyses of pharmacodynamic endpoints were conducted by the CDER Office of Biostatistics. Statistical model used was a mixed-effects model with period, sequence, and treatment as fixed effects and subjects as a random effect. For data for measures for which this model was not satisfied alternative statistical analyses were conducted. All tests were one-sided. Statistical analyses of pharmacodynamic endpoints were assessed using data from 36 completers.

<u>Findings Regarding Study PTI-821-C08</u>

1. With respect to Drug Liking VAS, High VAS, Take Drug Again VAS, and Overall Drug Liking VAS, the positive comparator, intranasal oxycodone HCl IR 40 mg, had mean Emax values that were statistically significantly larger compared to placebo ($p < 0.0001$), thereby validating the study.

2. For the primary endpoint Drug Liking Emax, the analysis results show that compared to LSmean of 89.8 produced by oxycodone IR 40 mg, Remoxy 40 mg manipulated and intact had statistically significant 48% and 44% reduction in LSmean, respectively

($p \leq 0.0213$). Both LSmeans of 65.9 and 67.5 produced by Remoxy 40 mg manipulated and intact, respectively, were not statistically significantly similar to LSmean of 54.0 produced by placebo ($p \geq 0.6262$). The median of differences in TEmax for Drug Liking between Remoxy (both manipulated and intact) and oxycodone IR was zero.

3. For the secondary measure of High VAS, the analysis results showed that compared to LSmean of 81.1 produced by oxycodone IR 40 mg, Remoxy 40 mg manipulated and intact had statistically significant 50% and 48% reduction in LSmean, respectively ($p \leq 0.0238$). The LSmeans of 31.1 and 32.2 produced by Remoxy 40 mg manipulated and intact, respectively, were statistically significantly greater than the LSmean of 7.2 produced by placebo ($p < 0.0001$). The median of differences in TEmax for High between Remoxy (both manipulated and intact) and oxycodone IR was zero.

4. For the secondary endpoint of Take Drug Again Emax, the analysis results showed that the mean of 88.6 produced by oxycodone IR 40 mg was statistically significantly greater than those produced by Remoxy 40 mg manipulated and intact (59.6 and 63.4, respectively) ($p < 0.0001$). The mean produced by Remoxy 40 mg intact was statistically significantly different from the mean of 51.6 produced by placebo ($p = 0.0024$). The mean Emax produced by Remoxy 40 mg manipulated compared to that of placebo was border-line insignificant ($p = 0.0506$, two-sided test).

5. For the secondary measure of Overall Drug Liking Emax, the analysis results showed that the mean Emax of 84.4 produced by oxycodone IR 40 mg was statistically significantly greater than those produced by Remoxy 40 mg manipulated and intact (60.9 and 65.3, respectively) ($p < 0.0001$). Both means of Emax produced by Remoxy 40 mg manipulated and intact were statistically significantly different from that produced by placebo ($p \leq 0.0133$).

6. For the Ease of Snorting/Application VAS assessment, lower numerical scores, indicative of greater difficulty in administering intranasal treatments, were reported with the application of Remoxy gel (manipulated or intact) compared to the insufflation of Oxycodone IR 40 mg powder.

7. The geometric mean for maximum oxycodone plasma concentration (Cmax) of 64.7364 ng/mL, achieved following insufflation of Oxycodone IR 40 mg powder, was statistically significantly higher compared to the geometric mean Cmax of 11.9329 ng/mL and 14.9164 ng/mL ($p < 0.0001$ for both comparisons) following gel application of Remoxy manipulated and intact, respectively.

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: May 21, 2018

FROM: Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, 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_{0-2h}, 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).

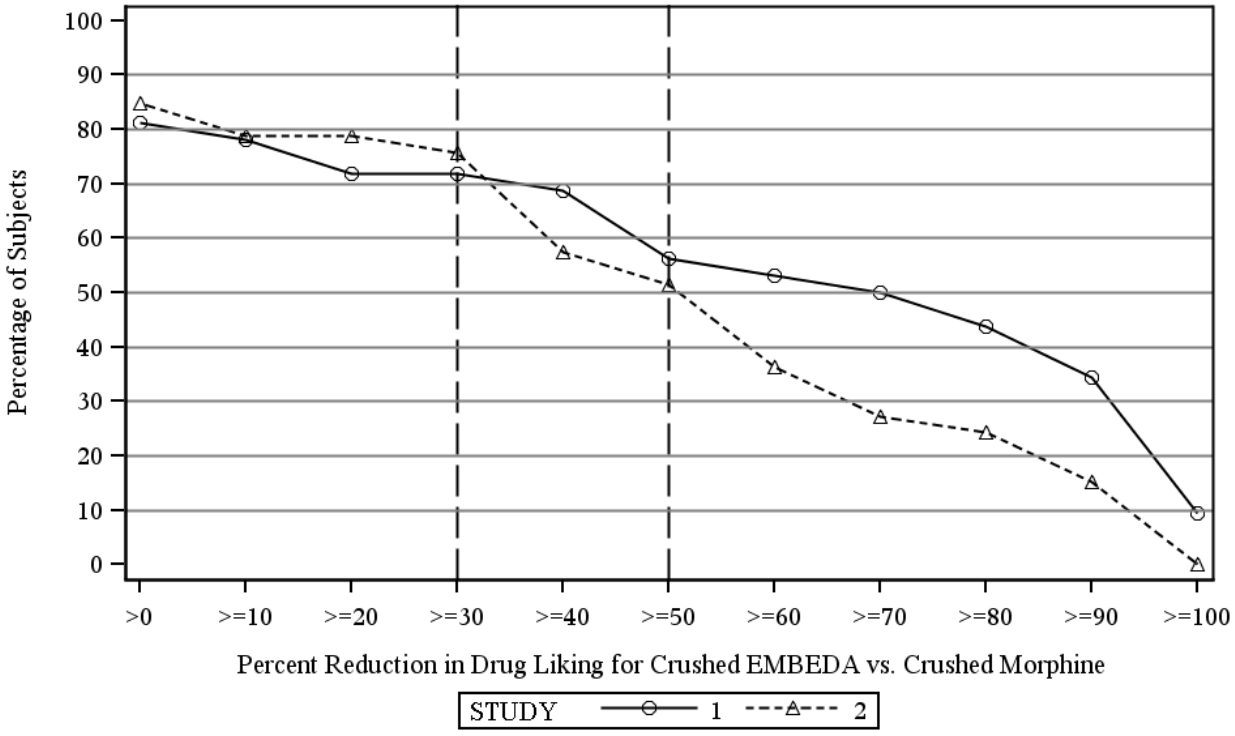
Figure 1 (Study 2) demonstrates a comparison of maximum Drug Liking for crushed EMBEDA compared to crushed ER morphine in subjects who received both treatments. Of the 33 subjects who completed the study, approximately 85% of subjects had some reduction in Drug Liking with crushed EMBEDA compared to 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).

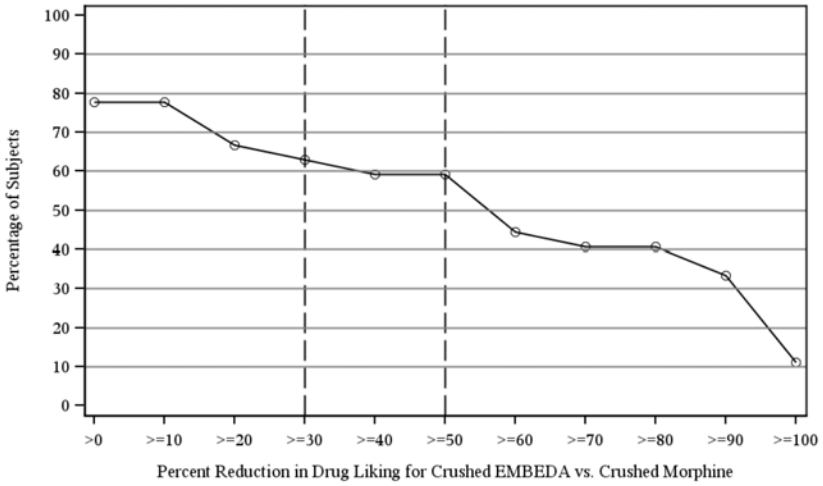
Figure 2 demonstrates a comparison of maximum Drug Liking for intranasal administration of crushed EMBEDA compared to crushed ER morphine in subjects who received both treatments. Of the 27 subjects who completed the study, approximately 78% of subjects had some reduction in Drug Liking with crushed 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

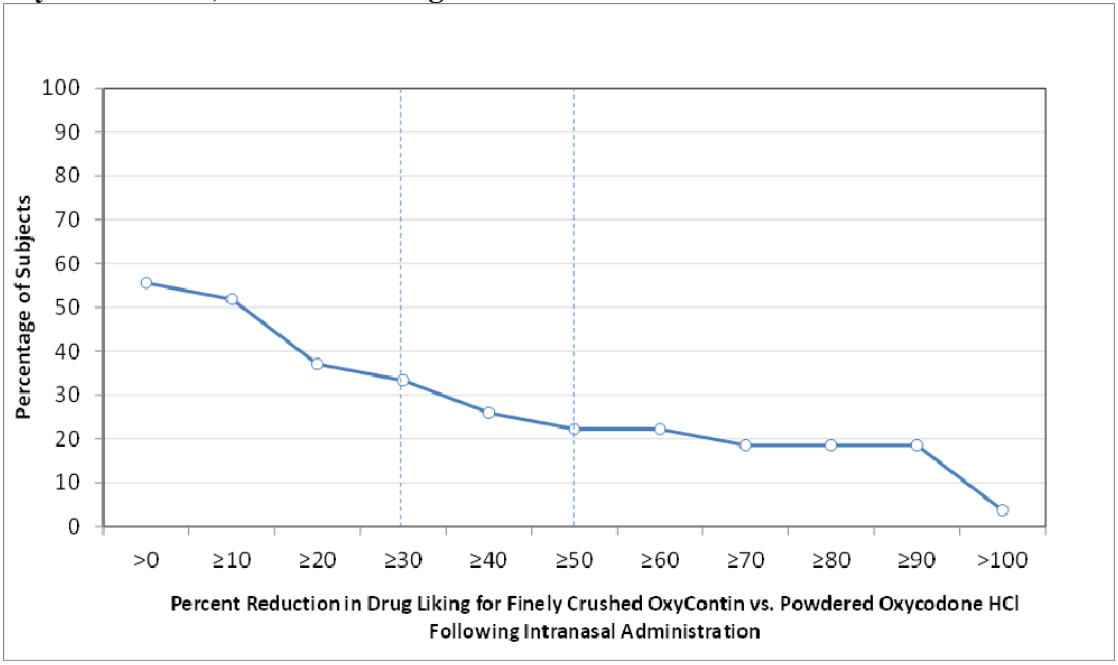
VAS Scale (100 mm)*		OXYCONTIN (finely crushed)	Original OxyContin (finely crushed)	Oxycodone HCl (powdered)
Drug Liking	Mean (SE)	80.4 (3.9)	94.0 (2.7)	89.3 (3.1)
	Median (Range)	88 (36-100)	100 (51-100)	100 (50-100)
Take Drug Again	Mean (SE)	64.0 (7.1)	89.6 (3.9)	86.6 (4.4)
	Median (Range)	78 (0-100)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

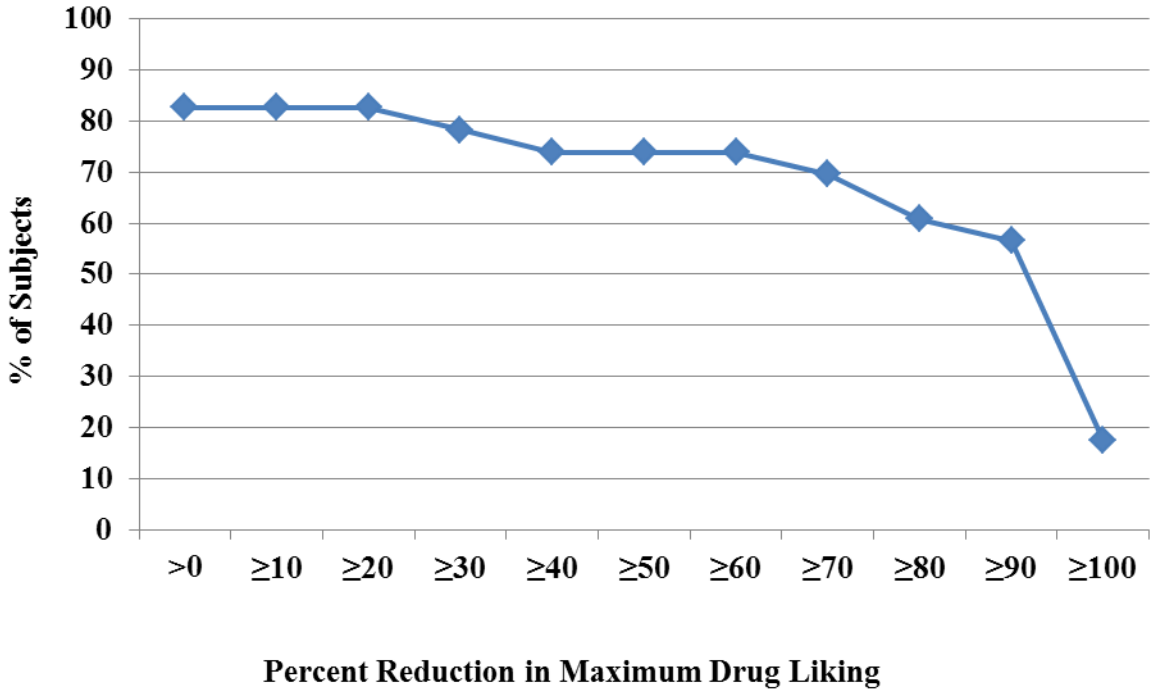
Table 5. Summary of Maximum Drug Liking (E_{max}) and Take Drug Again (E_{max}) Following Intranasal (IN) Administration of TARGINIQ ER, Oxycodone, and Placebo in Non-Dependent, Opioid Abusers (N=23)

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.

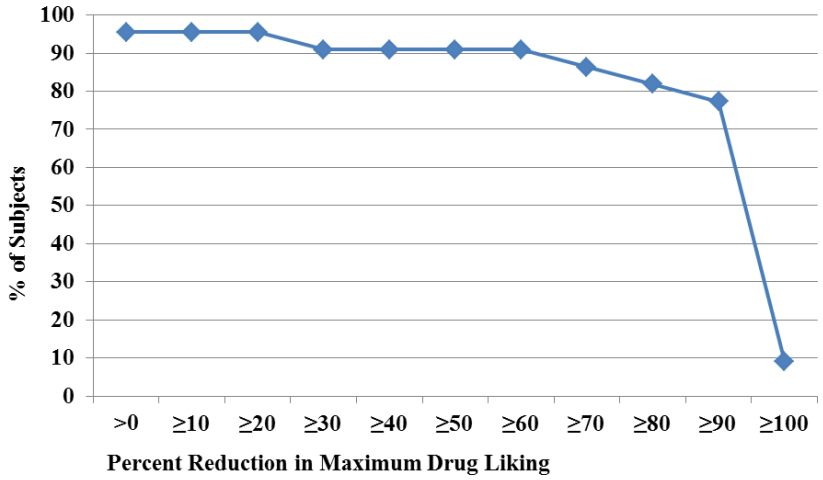
Table 6. Summary of Maximum Drug Liking (E_{max}) and Take Drug Again Following IV Administration of Oxycodone HCl + Naloxone HCl (Simulated TARGINIQ ER Solution), Oxycodone HCl, and Placebo in Non-Dependent, Opioid Abusers (N=22)

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.

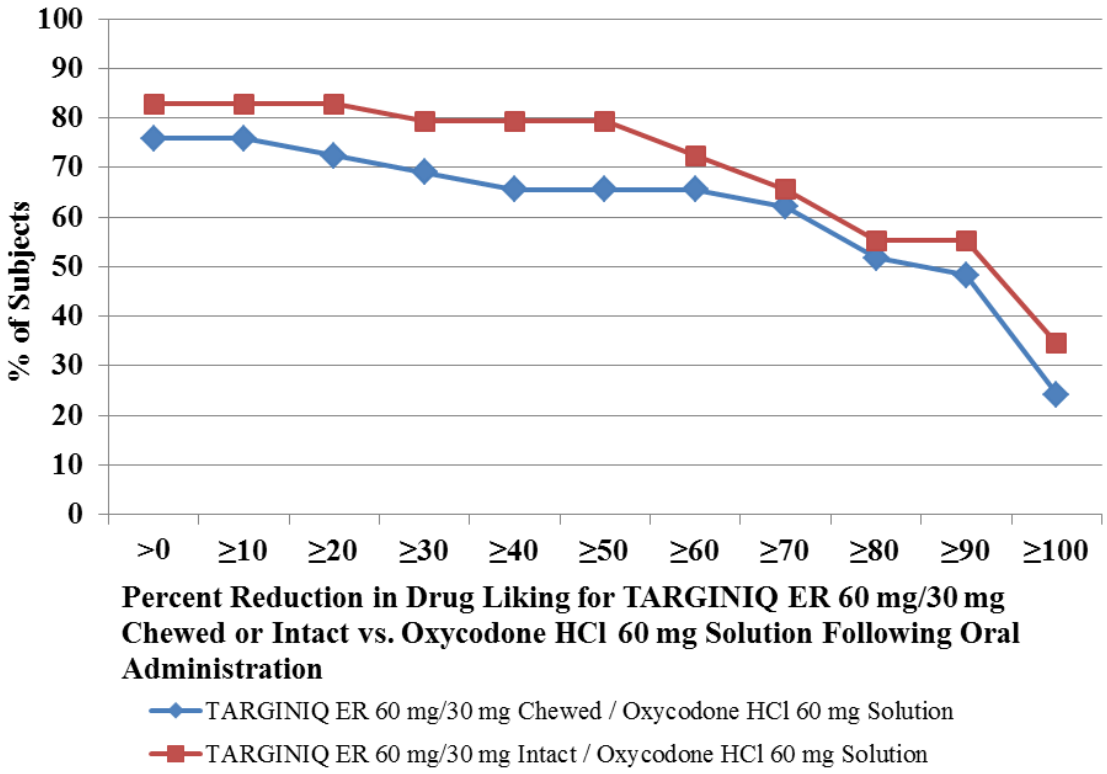
Table 7. Summary of High, Maximum Drug Liking (E_{max}), and Take Drug Again Following Oral Administration of TARGINIQ ER (Intact and Chewed), Oxycodone HCl solution, and Placebo in Opioid-Dependent Subjects (N=29)

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

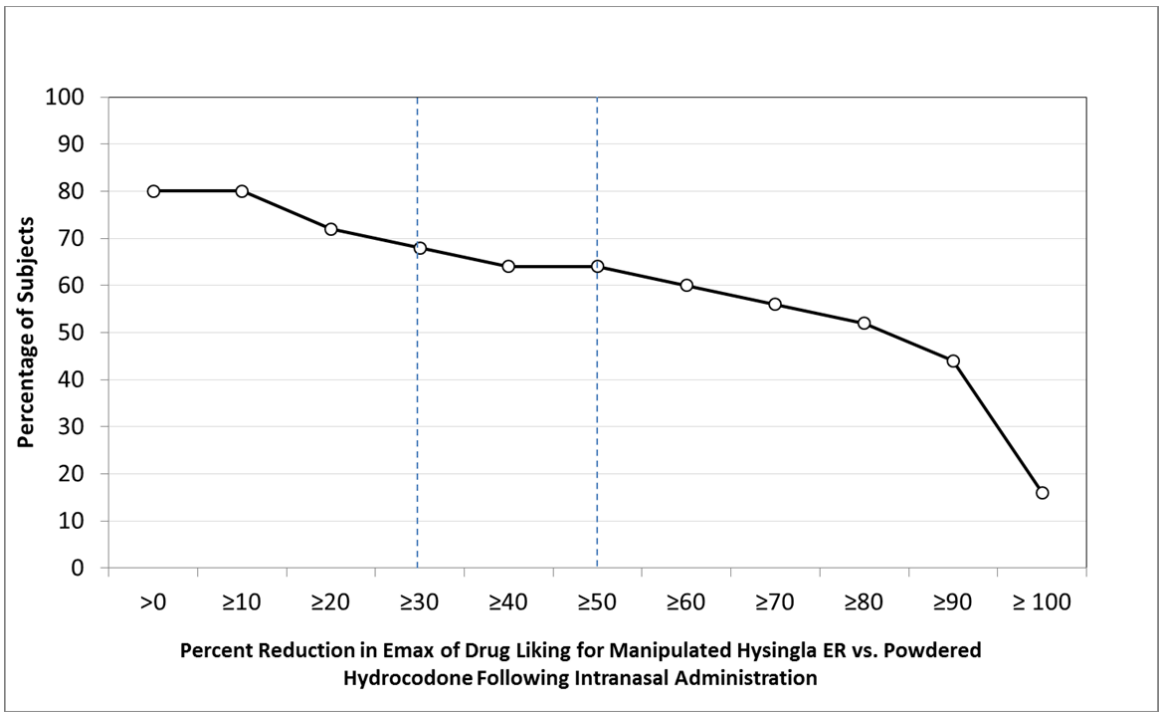
VAS Scale (100 point) *Intranasal (n=25)*	HYSINGLA ER Manipulated	Hydrocodone Powder
Drug Liking*		
Mean (SE)	65.4 (3.7)	90.4 (2.6)
Median (Range)	56 (50–100)	100 (51–100)
Take Drug Again**		
Mean (SE)	36.4 (8.2)	85.2 (5.0)
Median (Range)	14 (0-100)	100 (1-100)

*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

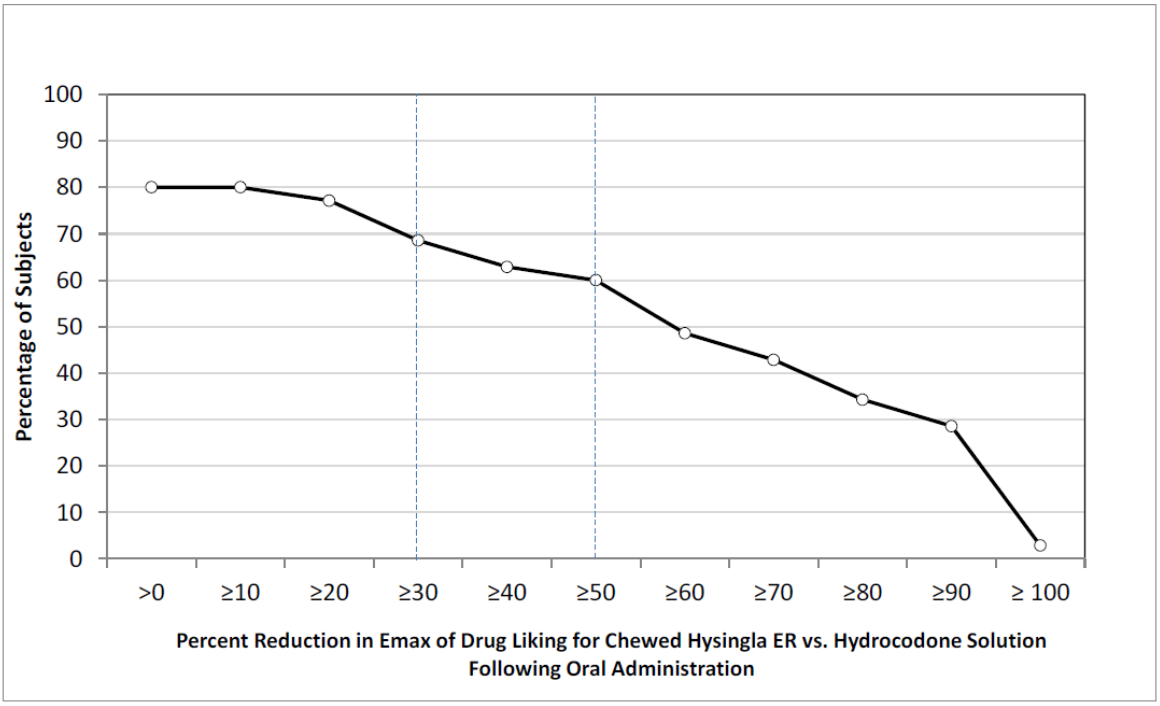
VAS Scale (100 point)	HYSINGLA ER		Hydrocodone
Oral (n=35)	Intact	Chewed	Solution
Drug Liking*			
Mean (SE)	63.3 (2.7)	69.0 (3.0)	94.0 (1.7)
Median (Range)	58 (50–100)	66 (50–100)	100 (51–100)
Take Drug Again**			
Mean (SE)	34.3 (6.1)	44.3 (6.9)	89.7 (3.6)
Median (Range)	24 (0-100)	55 (0-100)	100 (1-100)

*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’).

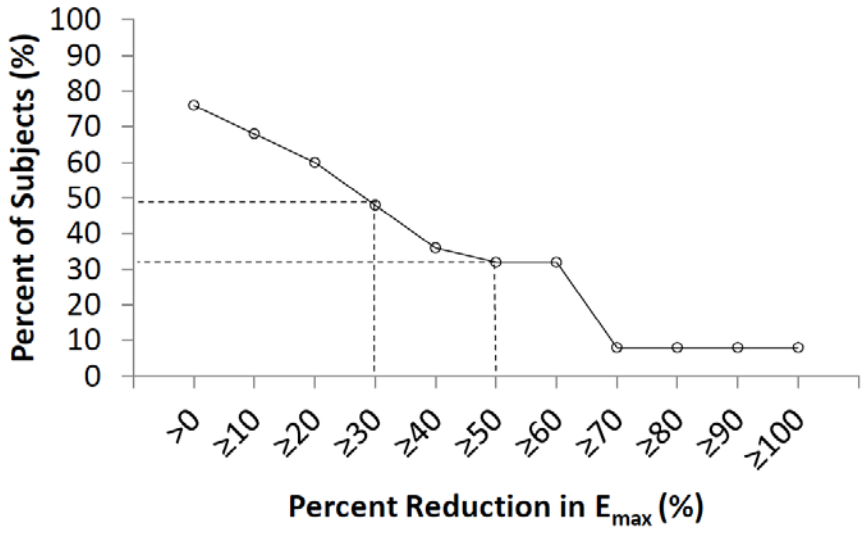
Intranasal administration of crushed MORPHABOND was associated with statistically significantly lower drug liking (E_{max}) scores ($P < 0.0001$), and significantly lower willingness to take the drug again (E_{max}) scores ($P = 0.034$), compared to crushed extended-release morphine (Table 2). Drug liking 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

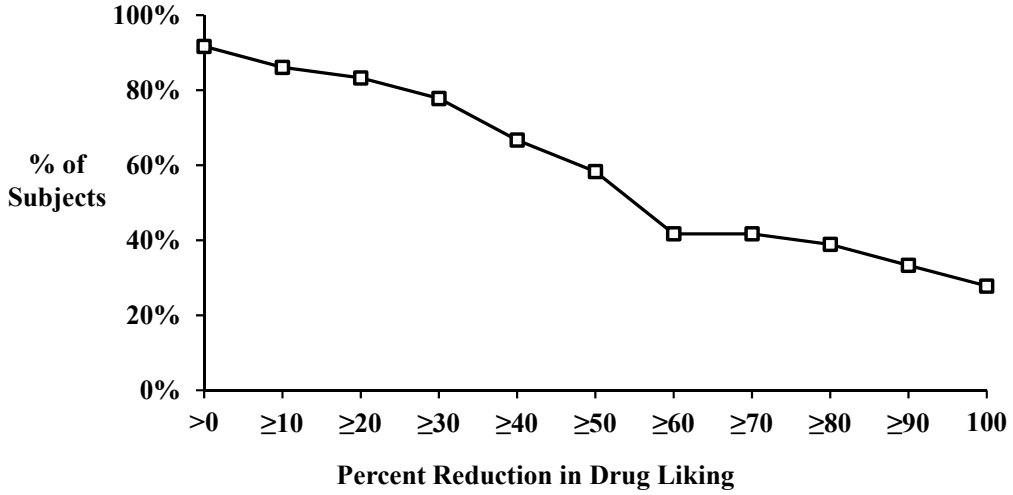
		XTAMPZA ER Intranasal	Crushed IR Oxycodone Intranasal	Placebo
Drug Liking* (E_{max})	Mean (SEM)	61.8 (2.6)	82.7 (1.8)	54.5 (2.0)
	Median (Range)	59.5 (16-94)	84 (60-100)	51 (28-93)
Take Drug Again* (E_{max})	Mean (SEM)	47.7 (4.6)	71.4 (3.9)	45.9 (2.9)
	Median (Range)	50 (0-100)	78.5 (18-100)	50 (0-97)

* 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 (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.

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.

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 (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 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)
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)**
	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.

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

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.

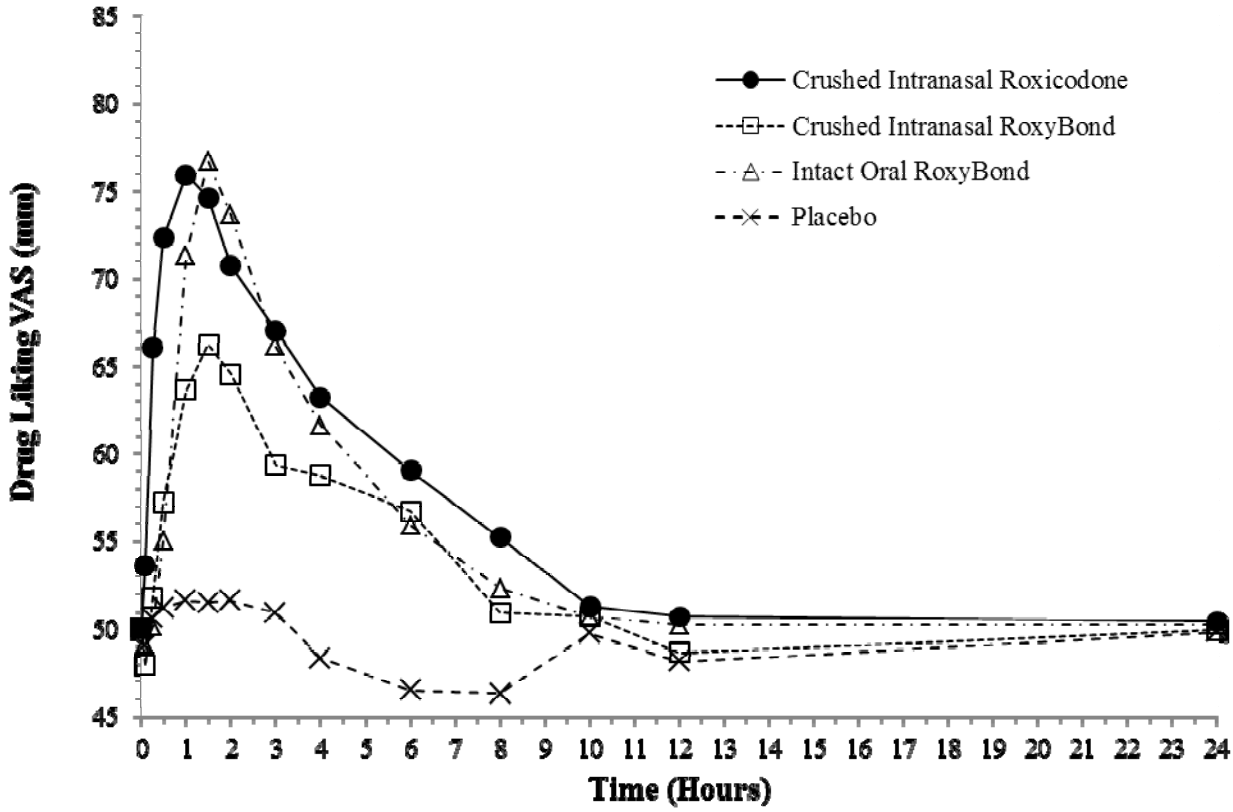
Compared to crushed intranasal oxycodone immediate-release tablets, intranasal administration of crushed ROXYBOND was associated with statistically significantly lower drug liking (E_{max}) and take drug again (E_{max}) scores, as summarized in Table 3. Similar reductions in drug liking and willingness 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	Mean	71.1	82.9	81.5	53.4

(E_{max})	(SD)	(12.01)	(11.55)	(11.49)	(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.

APADAZ (benzhydrocodone and acetaminophen) immediate-release tablets [NDA 208653]

Approval Date: February 23, 2018

Based on the guidance, "Abuse-Deterrent Opioids – Evaluation and Labeling Guidance for Industry", the primary pharmacodynamic endpoint of interest, Emax for drug liking VAS, and the secondary PD endpoints of interest, Emax for drug high VAS and take drug again VAS, Apadaz did not demonstrate abuse-deterrent properties. Section 9.2 of the label describes negative study results from in vitro testing and human abuse potential studies that do not support abuse-deterrent properties of Apadaz.

Abuse Deterrent Studies
In vitro and human abuse potential studies comparing APADAZ to an immediate-release hydrocodone/acetaminophen tablet control were conducted to assess the potential abuse deterrent properties of APADAZ.

In Vitro Testing
In vitro physical and chemical manipulation studies were performed to evaluate the ability of different methods to extract and convert benzyhydrocodone to hydrocodone for the purpose of preparing APADAZ for abuse by the intravenous route or by smoking. The efficiency of extracting benzhydrocodone from APADAZ was similar compared to the efficiency of extracting hydrocodone from the non-abuse-deterrent hydrocodone/acetaminophen control. Further conversion (hydrolysis) of benzhydrocodone to hydrocodone in vitro is a difficult process. Overall, these studies showed no advantage for APADAZ over the hydrocodone/acetaminophen control.

Oral Clinical Abuse Potential Study
In an oral, single-center, randomized, double-blind, active-and placebo-controlled, 7-period, crossover, human abuse potential study, 71 recreational opioid users were randomized into the Treatment Phase; 62 subjects completed the study. Treatment arms included APADAZ (4, 8, and 12 tablets, each containing 6.12 mg benzhydrocodone and 325 mg acetaminophen), hydrocodone/acetaminophen (4, 8 and 12 tablets, each containing 4.54 mg hydrocodone and 325 mg acetaminophen), and placebo. The respective dosage strengths for APADAZ and hydrocodone/acetaminophen contained equimolar amounts of hydrocodone. The rate (Cmax) and extent (AUClast, AUCinf) of hydrocodone exposure following APADAZ administration was

comparable to that for hydrocodone/acetaminophen across all 3 dosage strengths. There were no statistically significant differences nor any clinically meaningful differences between APADAZ and the hydrocodone/acetaminophen control for the pre-specified primary endpoint of maximal score (Emax) for Drug Liking VAS or secondary endpoints of Emax for High VAS and Take Drug Again VAS. The results do not support a finding that APADAZ can be expected to deter abuse by the oral route of administration.

Intranasal Clinical Abuse Potential Study

In an intranasal single-center, randomized, double-blind, double-dummy, two-part human abuse potential study, 46 recreational opioid users were randomized into the Treatment Phase; 42 subjects completed the study. Five treatment arms included intranasal crushed and oral APADAZ (2 tablets, each containing 6.12 mg benzhydrocodone and 325 mg acetaminophen), intranasal crushed and oral hydrocodone/acetaminophen (2 tablets, each containing 4.54 mg hydrocodone and 325 mg acetaminophen), and intranasal placebo powder. The respective dosage strengths for APADAZ and hydrocodone/acetaminophen contained equimolar amounts of hydrocodone.

The pharmacokinetic data showed that overall (AUClast, AUCinf, and Cmax) hydrocodone exposure was comparable between intranasal crushed APADAZ and intranasal crushed hydrocodone/acetaminophen. These treatments were also comparable with cumulative hydrocodone exposure at the timepoints of 4, 8, and 24 hours (AUC0-4, AUC0-8, AUC0-24). Over the first 2 hours post-dosing (AUC0-0.5, AUC0-1, and AUC0-2), the cumulative hydrocodone exposure was lower following intranasal APADAZ compared to intranasal hydrocodone/acetaminophen.

There were numerically small but not statistically significant differences between APADAZ and the hydrocodone-acetaminophen control observed for the pre-specified primary endpoint, maximum effect on Drug Liking VAS (Emax), and the secondary endpoints of Emax for High VAS and Take Drug Again VAS.

Table 2: Summary Statistics of Maximum Scores (E_{max}) on Drug Liking, High and Take Drug Again, Following Intranasal Administration of Apadaz, Hydrocodone/APAP, and Placebo

VAS Scale (100 point) *intranasal (n=42)*	Apadaz Crushed	Hydrocodone/APAP Crushed	Placebo
Drug Liking *			
Mean (SE)	75.9 (2.3)	79.0 (2.7)	53.0 (1.2)
Median (Range)	74.0 (50-100)	80.0 (50-100)	51.0 (50-85)
High**			
Mean (SE)	61.8 (4.6)	59.1 (5.1)	8.8 (3.8)
Median (Range)	68.5 (0-100)	67.5 (0-100)	0.0 (0-100)
Take Drug Again*			
Mean (SE)	69.5 (3.9)	74.5 (3.9)	48.2 (2.2)
Median (Range)	68.0 (0-100)	81.5 (0-100)	50.0 (0-100)

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

Additional secondary analyses of Drug Liking based on area under the effect curve analyses (AUE) for the first half hour, hour, and 2 hours post-dosing, demonstrated numerically small differences between intranasal APADAZ and intranasal hydrocodone/acetaminophen. However, there were no differences between these two treatments with respect to the cumulative High experienced over the first 2 hours post-dosing using similar AUE analyses. There are no data to support that small differences in the early Drug Liking experience over the first 2 hours are clinically relevant findings consistent with possible abuse-deterrent effects, particularly in the setting of the Emax analyses for Drug Liking, Take Drug Again, and High that do not support a deterrent effect. Based on the overall results, APADAZ cannot be expected to deter abuse by the intranasal route of administration.

Summary
The in vitro studies that evaluated physical manipulation and extraction for the purpose of preparing APADAZ for abuse by the intravenous route or by smoking did not find an advantage for APADAZ over the hydrocodone/acetaminophen control.

The results of the oral and intranasal human abuse potential studies do not support a finding that APADAZ can be expected to deter abuse by the oral or nasal routes of administration.

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

Epidemiology Review

Date:	May 21, 2018
Reviewer(s):	Mallika Mundkur, MD, MPH *Division of Pharmacovigilance II* Sara Karami, PhD, MPH *Division of Epidemiology I* *Data Management and Analysis Team*
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Associate Office Director	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):	REMOXY®
Application Type/Number:	NDA #22324
Applicant/sponsor:	Pain Therapeutics
OSE RCM #:	2018-661

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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

CNS: Central Nervous System

CSA: Controlled Substances Act

DIM: Drug-Involved Mortality

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

ED: Emergency Department

FDA: U.S. Food and Drug Administration

FDC: Fixed Dose Combination

ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision

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: National Vital Statistics System

OTP: Opioid Treatment Program

PCC: Poison Control Center

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

RMPDC: Rocky Mountain Poison and Drug Center

SKIP: Survey of Key Informants' Patients

US: United States

EXECUTIVE SUMMARY

REMOXY is an extended-release (ER) formulation of oxycodone designed to deter abuse via non-oral routes through modified physical and chemical properties. REMOXY will be discussed at an Advisory Committee (AC) meeting on June 26, 2018. This review is intended to provide the committee members with an informed perspective regarding potential patterns of misuse and abuse for new oxycodone-containing products, based upon recent patterns of misuse and abuse for marketed products with similar characteristics. Given the nature of the product under consideration, we attempt to provide more detailed information, where possible, on abuse patterns for approved, ER/long-acting (ER/LA) formulations of oxycodone. Below, we outline key points from this review regarding the abuse profile of oxycodone and other opioid products in recent years. These points synthesize data drawn from distinct data sources, and relate to misuse/abuse in both the general US population, as well as in the subset of patients with more advanced opioid use disorder who are entering treatment.

- Scale of misuse and abuse of prescription opioid analgesics:
  In 2016, prescription opioids were the largest category of approved pharmaceutical products to be misused or abused by Americans, with 11.5 million individuals reporting misuse and 1.8 million individuals meeting DSM IV criteria for a substance use disorder involving a prescription opioid analgesic in a general population household survey. In comparison, an estimated 600,000 individuals in the US abused heroin the same year while 15 million individuals abused alcohol.

- Relative frequency of misuse and abuse of oxycodone and other selected opioids:
  During 2016, the most frequently misused opioid analgesics reported in a general population household survey were hydrocodone, oxycodone and codeine, estimated to have occurred in 6.9, 3.9 and 2.8 million individuals respectively. Among patients entering treatment for opioid use disorder, heroin abuse was most commonly reported (57%), followed by oxycodone (35%) and hydrocodone (28%). Such individuals endorsed abuse of both immediate-release (IR) (22%) and ER/LA (15%) formulations of oxycodone. Product availability appears to be an important factor driving abuse patterns, and adjustment for dispensed dosage units appears to increase the relative frequency of abuse of less widely prescribed opioids such as oxymorphone and hydromorphone compared with oxycodone and hydrocodone.

- Routes of abuse for oxycodone-containing products:
  In recent years, calls to poison control centers relating to single-substance exposures suggest that oxycodone-containing products are abused predominantly through the oral route (80% of intentional abuse exposures). Data from a surveillance system of individuals entering treatment for substance use disorder also suggest that oral abuse is the most common route of exposure for ER/LA oxycodone formulations (60%) with abuse-deterrent (AD) properties, though abuse of these products was also reported via the routes of inhalation/insufflation (20-30%), and intravenous injection (>30%). Paradoxically, crush-resistant tablets (CRT) appear to be abused significantly more frequently by alternative oral modes of administration (i.e., chewing, dissolving in mouth) than non-CRT.

- Morbidity and mortality for oxycodone and other specific opioid products:
  During 2016, an estimated 51,204 Emergency Department (ED) visits involved non-medical use of oxycodone, alone or in conjunction with other agents, leading to unresponsiveness, cardiac arrest or respiratory failure/distress in approximately 40% of such visits. Over the period 2010-2015, deaths involving oxycodone, as reported in the

literal text on US death certificates, remained high, with between five and six thousand deaths per year, and a total of 32,128 deaths occurring over this time frame. In comparison, deaths involving heroin have been rising in frequency, with a total of 46,603 deaths over the same time-period.

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 common in individuals entering treatment for substance use disorder. Public health benefits of abuse-deterrent opioid analgesics have been proposed, though no data demonstrating such benefit has been submitted and reviewed by FDA, and published studies evaluating such benefits have limitations. FDA is requiring sponsors of abuse-deterrent opioid products to conduct rigorous studies under a postmarket requirement (PMR) to assess potential benefits of AD products in the community.

1 INTRODUCTION

During 2016, opioids were associated with 42,000 deaths in the US, nearly half of which involved a prescription opioid.[1] Given the persistent contribution of prescription opioid analgesics to the burden of opioid-related morbidity and mortality in the United States, alongside historical considerations of risk and benefit at the level of the product's targeted patient population, FDA is now considering the broader impact of opioid drug approval on the public health at the time of approval.[2] Thus, while the Division of Anesthesia, Analgesia, and Addiction Products in the Office of New Drugs (OND) will present information on the risk-benefit profile of the intended use of this product in a targeted patient population, this review aims to provide a basis for considerations about risks and benefits to the community at-large.

Opioid analgesic formulations with abuse-deterrent (AD) properties have been proposed to promote several positive public health outcomes: reduction in product-specific abuse, transition to riskier routes of abuse, diversion of AD products, and deaths from overdose involving the AD product. Although these questions have been explored in a number of published epidemiologic studies, these studies are subject to significant limitations with regard to data quality, methods, and the ability to make clear causal inferences regarding the effect of the AD properties.[3-8, a] FDA is requiring sponsors of approved AD opioid analgesic products to conduct epidemiologic studies under a postmarketing requirement (PMR) to more directly assess the effects of abuse-deterrent 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 abuse-deterrent properties results in meaningful reductions in abuse, misuse and related adverse clinical outcomes, including addition, overdose, and death" in the community. [9]

[a] 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.

For the purposes of this review, we focus on the landscape of abuse and related morbidity and mortality for oxycodone and comparator opioid analgesic products to give the committees an idea of the potential abuse-related harms and potential for prevention of route-specific abuse of the product under discussion.

1.1 REGULATORY HISTORY

REMOXY® ER is a gel-formulation of extended-release (ER) oxycodone, intended to impede tampering via non-oral routes.

1.2 APPROVED ABUSE-DETERRENT LABELING FOR RELATED PRODUCTS

In the United States, there are two currently marketed ER, single-ingredient, formulations of oxycodone, OxyContin and Xtampza, with abuse-deterrent labeling based on premarket studies. Of note, FDA approved a reformulated version of OxyContin in April 2010. The reformulated version has properties intended to deter abuse. On August 5, 2010, the sponsor stopped shipping original OxyContin tablets to pharmacies and began shipping only reformulated OxyContin. AD labeling was approved in April 2013, and at that time, FDA determined that original OxyContin was withdrawn for "reasons of safety or effectiveness."[10] Other AD ER formulations of oxycodone-products have been approved as multi-ingredient formulations such as Targiniq (oxycodone-naloxone ER), and Troxyca (oxycodone-naltrexone ER). However, the multi-ingredient products have not been marketed, and the NDA for Troxyca was withdrawn on May 2, 2018.[11]

There are four categories of studies that contribute to the final approved labeling in the section on Drug Abuse and Dependence (9.2).[9] The first three categories are conducted in the premarket setting and the fourth is conducted in the postmarket setting. Briefly, pre-market studies assess:

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

Postmarket studies (Category 4) assess whether introduction of the abuse-deterrent formulation reduces actual abuse, misuse, and related adverse clinical outcomes including addiction, overdose, and death in the postmarket setting. While there are ten opioid analgesic products with section 9.2 labeling that describes expected abuse-deterrent properties based on premarket testing (Category 1-3 studies), no products have category 4 labeling, to date. Each AD opioid product with labeling based on category 1-3 studies was assigned the postmarket Category 4 studies under postmarketing requirements (PMRs), upon approval; such 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 reviewed several data sources to describe the misuse/abuse of oxycodone and related morbidity and mortality in recent years. We selected data sources that could provide insight into patterns of misuse/abuse and overdose death in the general population, as well as the subset of individuals with more advanced substance use disorder (SUD). The framework used to summarize findings from these data sources is outlined in **Table 1**, with a more detailed

description of our use of each data source in the sections below. Standard regulatory definitions of misuse/abuse were applied throughout this review, unless otherwise indicated.[12,13]

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. Framework Used to Assess Current Landscape of Prescription Opioid Misuse/Abuse

Characteristic assessed	Data sources used	Use of data source(s)	Major limitations
Scale of misuse/abuse	General population National Survey on Drug Use and Health (NSDUH), 2015-2016; National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES, 2016)	• Estimate number of individuals in the general US population reporting misuse/abuse of prescription opioid analgesics (NSDUH) • Estimate number of Emergency Department (ED) visits resulting from non-medical use of prescription opioid analgesics (NEISS-CADES)	• Most recent complete year of data from 2016 (NSDUH, NEISS-CADES)
Specific products, relative frequency of misuse/abuse	General population NSDUH, 2015-2016; National Poison Data System (NPDS) exposure calls to Poison Control Centers (PCCs), 2012-2016 Population with opioid or substance use disorders RADARS® Treatment Center Program, 2016 (TCP); Literature (Cassidy, et al) /National Addictions Vigilance Intervention and Prevention Program, 2016 (NAVIPPRO™)	• Misuse of specific opioid analgesic products in general population (NSDUH) • Calls to PCCs, by product (NPDS) • Proportion of patients with opioid or substance use disorder (OUD/SUD) reporting past thirty-day abuse of specific products (RADARS® TCP, NAVIPPRO™)	• Earliest NSDUH data on opioid analgesic subtype in 2015, inability to assess long-term trends • Product information may not be available in all exposure calls to PCCs (NPDS) • Findings from people entering treatment for OUD/SUD may not be broadly generalizable

Characteristic assessed	Data sources used	Use of data source(s)	Major limitations
Routes of abuse	General population NPDS Population with OUD or SUD Literature (Cassidy, et al; Butler et al)/NAVIPPRO™	• Assess routes of abuse for single-substance exposure calls (NPDS) • Assess product-specific routes of abuse among people entering or being assessed for SUD (Literature/ NAVIPPRO™)	• Findings regarding route from NPDS exposure calls may not generalize to the entire US population • Findings from patients entering treatment for SUD may not be broadly generalizable
Morbidity and mortality	General population Drug-involved Mortality (DIM) data for overdose deaths, 2010-2015 NEISS-CADES, 2016	• Assess outcomes such as need for healthcare intervention, or death occurring in association with specific opioid analgesic active ingredients	• Under-capture of serious outcomes • Limited ability in attributing events to specific products • NEISS-CADES did not begin capture of ED visits for non-medical pharmaceutical use until 2016 • The most current data available for DIM is for 2015

2.2 NATIONAL SURVEY OF DRUG USE AND HEALTH (NSDUH)

Data Source
NSDUH is an annual, federally-funded survey sponsored by the Substance Abuse and Mental Health Services Administration *(*SAMHSA) designed to provide nationally representative estimates of illicit as well as prescription drug misuse/abuse in the general US population. Strengths of this data source include an in-person survey, and predominantly stable survey design with the ability to assess temporal changes in drug misuse/abuse in the general US population.

NSDUH uses a multistage probability sample design to provide representative state and country-level estimates for non-institutionalized residents of the United States who are aged 12 years and above. Population subgroups not covered by the survey include individuals residing within institutional facilities (e.g., jails, nursing homes), as well as those without a permanent address (e.g., homeless individuals). The survey is conducted in a face-to-face manner, and during the year 2016, the interview response rate of 53% included 67, 942 completed interviews. For the years 2015 and 2016, 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 DSM IV criteria, combining both for the purpose of reporting into the broad category of "substance use disorder."[14,15]

Search Strategy and Analysis
We extracted data from the most recent survey (i.e., 2016) 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 2015, where possible. We reported past-year weighted estimates of abuse/dependence of heroin and prescription opioids, relative to other commonly used substances in the United States in 2016. 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. Statistically significant changes in percentages were demarcated.

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 regarding exposures to prescription drugs, over-the-counter medications as well as unapproved products.[18] NPDS provides more detailed product-specific information compared with other data sources, such as information on reported routes of exposure and associated medical outcomes in the general US population.

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 unknown intent. Additional detail regarding the definition of these variables is provided in Appendix A.

Search Strategy and Analysis
In our review of NPDS, we assessed calls for oxycodone and comparators 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 comparators, 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 the most recent five year period for which all cases had been closed (i.e., no unverified or "open" cases).

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	4/2018
Date range for query	1/1/2012- 12/31/2016
Call type	Exposure
Case status	Closed
Species	Human
Exposure Reason	Intentional
Minimum Age	12 (years)

Analysis of NPDS consisted of two components: evaluation of trends and characteristics in exposure calls. Analyses were performed independently by two analysts to optimize accuracy of results, with any discrepancy resolved by detailed review of processes.

For exposure trends, we stratified intentional exposure calls by year and exposure reasons (i.e., all intentional, misuse and/or abuse) to portray global patterns in trends of calls for misuse/abuse for oxycodone vs. comparators through this data source. Trends were adjusted for population changes using Census Bureau estimates of population size, and annual rates of exposure calls were reported as calls per million population.[19] In describing exposure characteristics, we aggregated data for the 5-year period, and evaluated reasons for exposure, for both oxycodone and comparators, stratifying the former by formulation (i.e., ER/LA vs. IR). In addition, we evaluated routes of abuse for oxycodone and comparators. Of note, for drugs involved in multi-substance exposures, NPDS does not currently provide information on route of exposure information for individual drugs, therefore analyses of route were restricted to single-substance exposures (personal communication, Elisa Aguenza, AAPCC).

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

Data Source

The RADARS® System Substance Abuse Treatment Program surveys individuals entering treatment in private and public opioid dependence treatment programs with a total of 194 participating sites from 48 states during the year 2016. This data source provides information on 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.[20]

RADARS® TCP includes data from two distinct programs: the RADARS® System Opioid Treatment Program, and the RADARS® System Survey of Key Informants' Patients Program (SKIP). The Opioid Treatment Program surveys a convenience voluntarily recruited sample of patients enrolling in public medication-assisted treatment programs from 65 sites in 31 states, while SKIP surveys patients seeking treatment at a private treatment facility and covers 129 sites in 45 states. Surveys in both settings are self-administered, and include questions about prescription or illicit drugs used in the past month for the purpose of "getting high" (i.e., abuse). Surveys also include questions relating to the primary source of the drug and route of abuse.

Search Strategy and Analysis
FDA obtains analytic reports from RADARS® TCP every six months through an ongoing contract with the Rocky Mountain Poison and Drug Center (RMPDC). This report contains both quarterly and cumulative (i.e., annual) rates of abuse for specific opioid products, in which numerators represent the total number of endorsements and denominators represent the total number of respondents for that time-period. The analytic report also includes rates that adjust for the total estimated number of dosage units dispensed in a given coverage area, using zip-code-based projections from IQVIA (previously QuintilesIMS™). For the purpose of this review, we first assessed cumulative and dosage unit-adjusted rates of abuse at the level of active pharmaceutical ingredient. Subsequently, we assessed analogous data for IR and ER/LA formulations, allowing for more robust comparison of abuse at the level of specific products. Future reports will include information on route of abuse, though this information is not currently available from the bi-annual report provided to FDA from RADARS® TCP.

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

Data Source
The National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™) is a surveillance system that includes a number of data streams relating 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 at a participating facility, with variable adoption by state and locality— during the year 2016, NAVIPPRO included a total of 445 treatment sites in 38 states.[22]

Search Strategy and Analysis
For this review, we cite data from this system using the most recently published data containing descriptive information of interest. We selected only recently published articles that utilized the NAVIPPRO™ system to assess relative frequency and routes of abuse of various prescription opioids, including but not limited to oxycodone. These articles were identified searching PubMed for the following search terms: (route[tiab] OR routes[tiab]) AND opioid[tiab] AND abuse[tiab] AND NAVIPPRO[tiab], restricting to publications within the past two years, and human studies only. The date of the search was May 12, 2018.

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

Cases and national estimates of the number of emergency department (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 United States 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.[23-26] 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). Each NEISS-CADES case is assigned a sample weight derived from the inverse probability of selection, adjusted for nonresponse and post-stratified to adjust for the number of annual hospital ED visits.

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 abuse, self-harm, drugs used for unknown intent, and assault, in addition to therapeutic adverse drug events.

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

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

National data on drug-involved mortality were made available to the Agency by the National Center for Health Statistics. Drug-involved mortality (DIM) data combine the cause-of-death, demographic, and geographic information from the National Vital Statistics System (NVSS) – Mortality files, with information extracted from the death certificate literal text, which allow for a more granular analysis of specific drugs involved in deaths. The method used to extract information on DIM has been described previously[21] 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 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. Additional information on these variables is provided in Appendix B.

In NVSS-M, cause of death is captured by ICD-10 codes, where no information on specific drug involvement is available. Our review of DIM data was performed on January 29, 2018 and included all overdose deaths, 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), of U.S. residents, ages 12 years and older, from January 1, 2010 through December 31, 2015 (the most recent data year available) where oxycodone, hydrocodone, morphine and heroin were mentioned in the literal text as contributing to the death. For overdose deaths involving these substances, we evaluated trends and patterns of overdose deaths by year.

3 RESULTS

NSDUH

During 2016, over 90 million individuals in the general US population were estimated to have

used prescription opioid analgesics during the previous year. Nearly 12 million, or 4.3% of the total US population, were estimated to have misused them— "misuse" being defined in NSDUH 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." In the subgroup of individuals reporting any past-year use of a prescription opioid analgesic, the most frequently misused products were buprenorphine, oxymorphone and methadone, respectively misused in 31.6%, 27.6% and 25.5% of individuals who reported past-year use of each opioid (**Table 3**.)

Table 3. National Survey on Drug Use and Health, 2016: Reported past year use or misuse of prescription pain relievers, by active ingredient, individuals aged 12 and older

Prescription Pain Reliever (Active Pharmaceutical Ingredient)	Past-Year Any Use (Numbers in Thousands)	Past-Year Misuse (Numbers in Thousands)	Misuse in Total Population % (SD)	Misuse in Past-Year Any Users % (SD)
Any	91,846	11,517	4.3 (0.11)*	12.5 (0.30)
Hydrocodone	54,807	6,924	2.6 (0.08)	12.6 (0.39)
Oxycodone	**27,622**	**3,905**	**1.4 (0.06)**	**14.1 (0.57)**
Tramadol	18,931	1,591	0.6 (0.04)	8.4 (0.55)
Codeine**	26,544	2,767	1.0 (0.05)	10.4 (0.52)
Morphine	6,828	536	0.2 (0.02)	7.9 (0.83)
Fentanyl***	1,837	228	0.1 (0.01)	12.4 (1.96)
Buprenorphine	2,253	712	0.3 (0.02)	31.6 (2.48)
Oxymorphone	1,094	302	0.1 (0.01)	27.6 (3.36)
Demerol®	1,387	95	0.0 (0.01)	6.9 (2.74)
Hydromorphone	2,118	239	0.1 (0.02)	11.3 (1.97)
Methadone	1,357	346	0.1 (0.02)*	25.5 (3.30)
Other	23,253	793	0.3 (0.03)	2.4 (0.33)

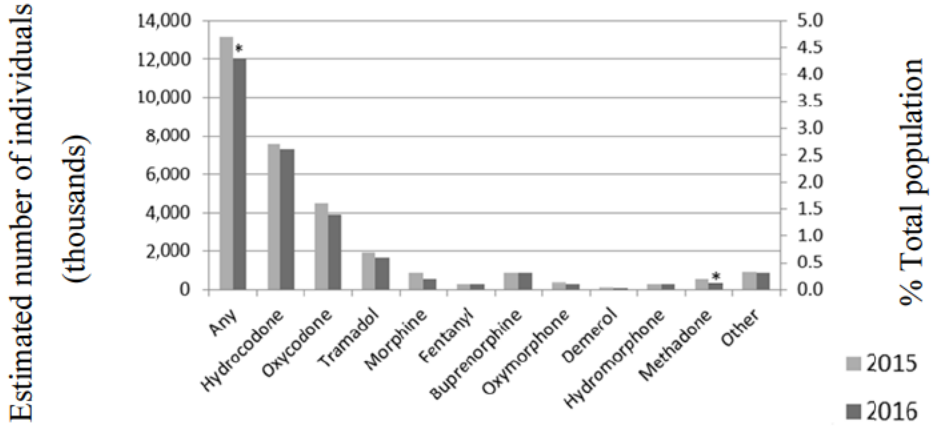
*represent statistically significant changes relative to 2015
**product-specific information first available in 2016
***estimate does not include illicit fentanyl

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. Accessed on 4/20/2018. 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."

The top three most frequently misused opioid analgesic products in the general population were hydrocodone, oxycodone and codeine, with estimated misuse in 6.9 million, 3.9 million and 2.8 million individuals, respectively (**Figure 1**).

Within the subgroup of individuals misusing prescription opioid analgesics, an estimated 2 million or 0.7% of the total population appeared to meet criteria for abuse or dependence (i.e., substance use disorder), second only to marijuana and alcohol 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 2015 to 2016 (**Figure 2**).

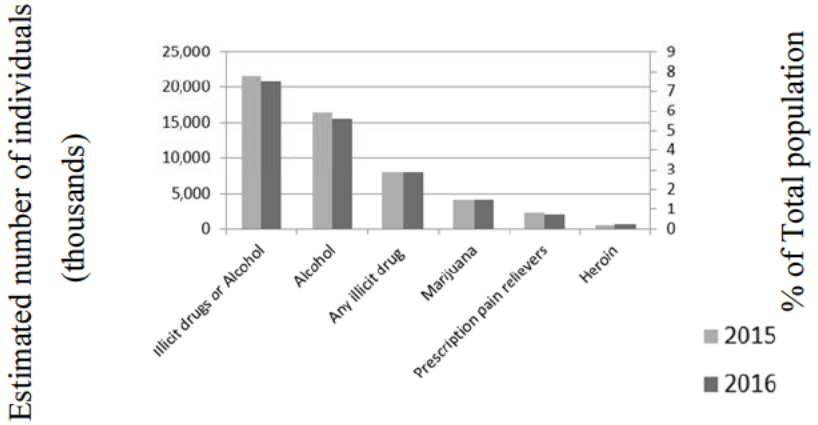
Figure 1. NSDUH 2015-2016*:
Past-year misuse of prescription opioid analgesics, individuals ≥12 years



NSDUH, National Survey of Drug Use and Health
*Asterisks denote changes that are statistically significant

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.
Accessed on 4/20/2018. 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."

Figure 2. NSDUH 2015-2016*:
Past-year abuse/dependence (substance use disorder), illicit drugs or alcohol, individuals ≥12 years



NSDUH, National Survey of Drug Use and Health
*No values in 2016 were statistically different from those in 2015

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. Accessed on 4/20/2018.

AAPCC/NPDS

Over the period 2012-2016, a total of 51,836 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, a total of 75,939 hydrocodone, 9,466 morphine, and 24,275 heroin exposure calls were received by U.S. PCCs. Population-adjusted rates of calls for drug products varied depending upon the type of exposure. Across all intentional exposure calls, hydrocodone and oxycodone-involved exposure call rates were highest (56.3 and 38.4 calls per million, respectively). Among intentional abuse exposure calls, exposure call rates were highest for heroin and oxycodone (12.7 and 6.8 calls per million, respectively). For misuse/abuse exposure calls combined, adjusted rates of exposure calls involving heroin, hydrocodone and oxycodone appeared similar (14.2, 14.1 and 12.0 calls per million, respectively). Across exposure types, rates of exposure calls involving IR oxycodone products were several-fold higher than rates of exposure calls involving ER oxycodone (**Table 4**).

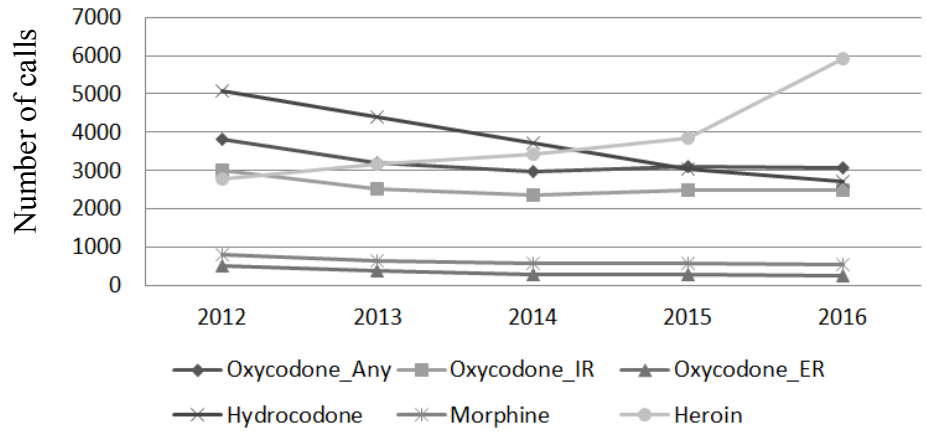
Table 4. AAPCC/NPDS 2012-2016: Number of intentional exposure calls by exposure type, individuals 12 years and older (Population-adjusted rate*)

Exposure Type	Specific product formulations		Active Pharmaceutical Ingredient			
	Oxycodone ER	Oxycodone IR	Oxycodone All	Hydrocodone	Morphine	Heroin
All**	4,564 (3.4)	41,978 (31.1)	51,836 (38.4)	75,939 (56.3)	9,466 (7.0)	24,275 (18.0)
Abuse	1,115 (0.8)	7,178 (5.3)	9,224 (6.8)	8,440 (6.3)	1,993 (1.5)	17,087 (12.7)
Misuse	605 (0.4)	5,704 (4.2)	6,942 (5.1)	10,534 (7.8)	1,218 (0.9)	2,089 (1.5)
Misuse/Abuse	1,720 (1.3)	12,882 (9.5)	16,166 (12.0)	18,974 (14.1)	3,211 (2.4)	19,176 (14.2)

AAPCC, American Association of Poison Control Centers; ER, extended-release; IR, immediate-release; NPDS, National Poison Data System
*Average call rate per 1 million census population for those 12 years and older
**Includes suicide attempt, other, misuse/abuse

Trends in PCC misuse/abuse exposure calls are depicted in **Figure 3**, showing stable levels of exposure calls involving oxycodone (both ER and IR formulations) and morphine, a decline in exposure calls for hydrocodone, and a rise in heroin exposure calls, with a pronounced rise in exposure calls for the latter since 2015.

Figure 3. AAPCC/NPDS 2012-2016:
Intentional misuse/abuse exposure calls for oxycodone vs. other opioid products, individuals 12 and older



AAPCC, American Association of Poison Control Centers; IR, Immediate Release; ER, Extended Release; NPDS, National Poison Data System

AAPCC/NPDS (continued)

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 exposures, the majority of abuse exposures for oxycodone occurred via ingestion (i.e., an oral route) **(Table 5, Figure 4).** A nontrivial percentage of single-substance abuse exposures indicated injection of oxycodone ER (N=62, 13%), though this was substantially lower than the percentage of such exposures indicating injection of morphine products (N=184, 23%) or heroin (N=5772, 58%). Of note, 16% of single-substance heroin abuse exposures occurred via ingestion, while 13% occurred via snorting/inhalation.

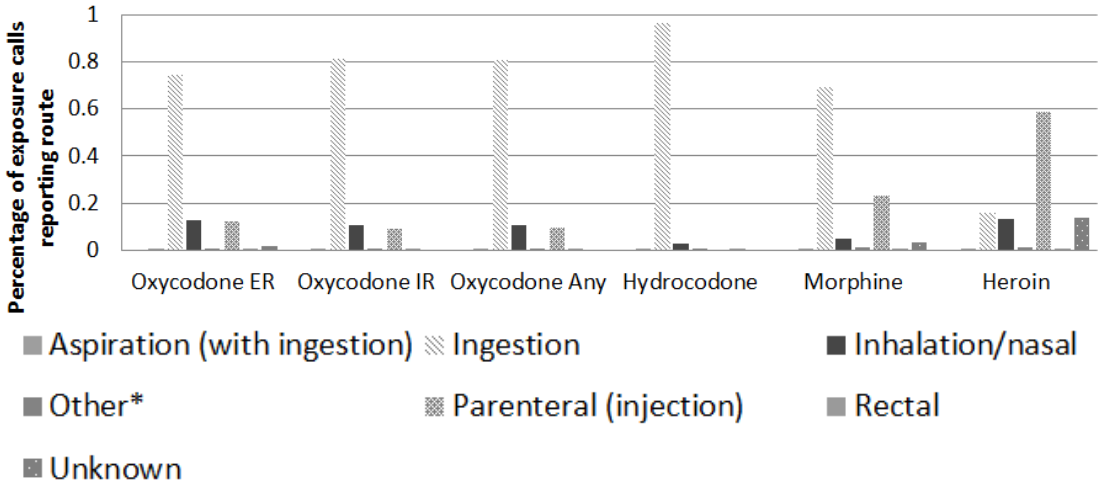
Table 5. AAPCC/NPDS, 2012-2016:
Percentage (%) of single-substance abuse exposure calls reporting specific exposure routes, oxycodone and selected other opioids^, among individuals 12 years and older

Route	Specific products		Active Pharmaceutical Ingredient			
	Oxycodone ER (N=497)	Oxycodone IR (N=2,600)	Oxycodone Any (N=3,444)	Hydrocodone (N=3,203)	Morphine (N=815)	Heroin (N=10,122)
Aspiration (with ingestion)	0.4	0.04	0.1	0.03	0.3	0.1
Ingestion	74.3	81.0	80.6	96.4	69.4	15.8
Inhalation/nasal	12.7	10.6	10.6	2.9	5.2	13.0
Other*	0.6	0.5	0.4	0.2	1.1	1.1
Parenteral	12.3	9.2	9.4	1.0	23.2	58.4

(injection)						
Rectal	0.2	0.1	0.1	0.1	0.4	0.2
Unknown	1.4	0.7	0.8	0.3	3.1	13.9

AAPCC, American Association of Poison Control Centers; ER, extended-release; IR, immediate-release; NPDS, National Poison Data System
^Routes are represented as percentage of exposure calls reporting a specific route. 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
* "Other" includes exposure routes categorized as dermal, vaginal, and/or other

Figure 4. AAPCC/NPDS, 2012-2016:
Percentage (%) of single-substance abuse exposure calls reporting specific exposure routes, oxycodone and selected other opioids^, among individuals 12 years and older



AAPCC, American Association of Poison Control Centers; ER, Extended-Release; IR, Immediate-Release; NPDS, National Poison Data System
^Routes are represented as percentage of exposure calls reporting a specific route. 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
* "Other" includes exposure routes categorized as dermal, vaginal, and/or other

RADARS® TCP

In 2016, assessment of individuals with opioid use disorder (OUD) entering private and public treatment programs participating in the RADARS® surveillance program indicated that, at the level of active pharmaceutical ingredient (API) or drug substance, past-month abuse of heroin was most prevalent, followed by oxycodone, and hydrocodone—with 57%, 35% and 28% of respondents reporting past-month abuse of these products, respectively. For both IR and ER products, past-month abuse of oxycodone was significantly more common than abuse of hydrocodone (**Table 6, Figure 5A-C**).

Adjusting for the number of dispensed dosage-units, the estimated relative frequency of abuse by product differed from unadjusted frequencies, with relatively higher abuse of fentanyl at the level of API, oxymorphone among IR products, and hydrocodone and hydromorphone among ER products (**Table 6, Figure 5D-F**). However, survey design may lead to misclassification of certain products, and may complicate interpretation of these results.[b]

Table 6. RADARS® Substance Abuse Treatment Program, 2016: Past-Month Abuse (% of respondents), or Rate of Past-Month Abuse per 100,000 Dispensed Dosage-Units

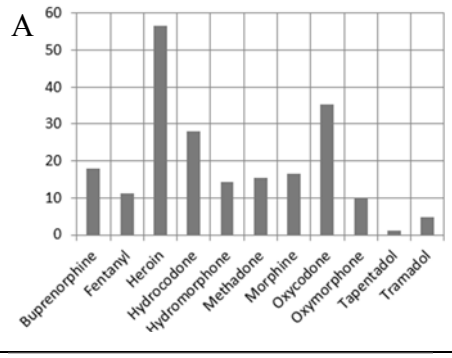
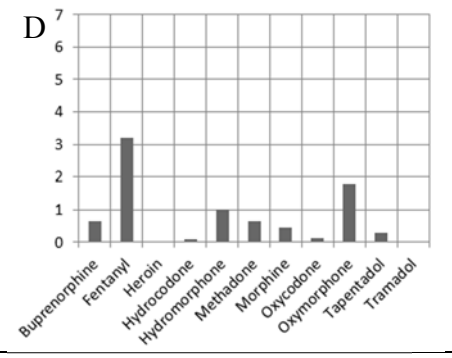
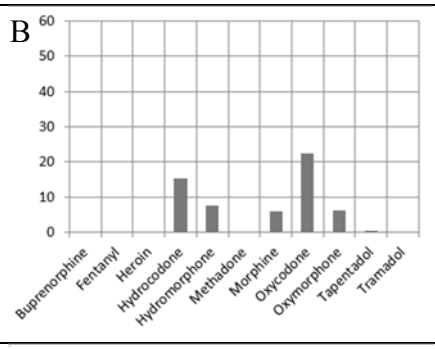
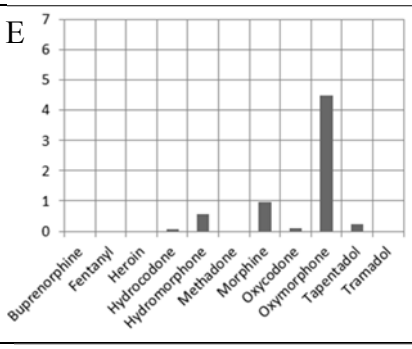
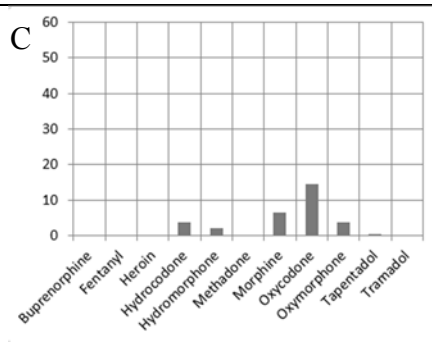
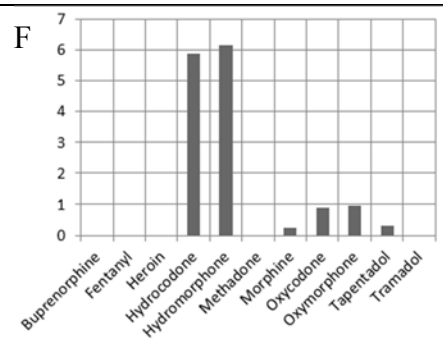
	Past-Month Abuse, Unadjusted (% Respondents, (95% CI))			Past-Month Abuse per 100,000 Dosage-Units (Rate, (95% CI))		
	API	IR	ER	API	IR	ER
Buprenorphine	17.8 (17.0- 18.6)	NR	NR	0.64 (0.61-0.67)	NR	NR
Fentanyl	11.2 (10.6-11.9)	NR	NR	3.19 (3.00-3.39)	NR	NR
Heroin	56.7 (55.6-57.7)	NR	NR	NR	NR	NR
Hydrocodone	27.9 (27.0-28.8)	15.5 (14.8-	3.7 (3.3-4.1)	0.08 (0.08 -	0.05 (0.05-0.06)	5.88 (5.27-6.53)

[b] Of note, the finding of high oxymorphone IR abuse rates relative to oxymorphone ER has not been observed in other data sources. For further discussion of potential misclassification issues in RADARS® treatment center data, please refer to the following resource:

FDA briefing document [Internet]. "Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) Meeting: Postmarketing safety issues related to reformulated Opana ER®, Addendum" [cited 2018 May 25.] Available from: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM545761.pdf

Table 6. RADARS® Substance Abuse Treatment Program, 2016: Past-Month Abuse (% of respondents), or Rate of Past-Month Abuse per 100,000 Dispensed Dosage-Units						
	Past-Month Abuse, Unadjusted (% Respondents, (95% CI))			Past-Month Abuse per 100,000 Dosage-Units (Rate, (95% CI))		
	API	IR	ER	API	IR	ER
		16.3)		0.09)		
Hydromorphone	14.4 (13.7-15.1)	7.7 (7.2-8.3)	2.2 (1.9-2.5)	1 (0.95-1.06)	0.57 (0.53-0.61)	6.15 (5.33-7.07)
Methadone	15.5 (14.8-16.2)	NR	NR	0.66 (0.62-0.69)	NR	NR
Morphine	16.6 (15.8-17.4)	6.1 (5.6-6.6)	6.6 (6.0-7.0)	0.47 (0.44-0.49)	0.97 (0.89-1.05)	0.24 (0.22-0.26)
Oxycodone	**35.2 (34.2-36.2)**	**22.3 (21.4-23.2)**	**14.6 (13.9-15.3)**	**0.13 (0.13-0.14)**	**0.09 (0.09-0.09)**	**0.89 (0.84-0.94)**
Oxymorphone	9.7 (9.1-10.3)	6.2 (5.7-6.7)	3.9 (3.5-4.3)	1.78 (1.66-1.90)	4.50 (4.14-4.89)	0.96 (0.86-1.06)
Tapentadol	1.1 (0.9-1.3)	0.6 (0.4-0.8)	0.4 (0.3-0.6)	0.28 (0.23-0.34)	0.24 (0.18-0.31)	0.32 (0.23-0.44)
Tramadol	4.9 (4.4-5.3)	NR	NR	0.03 (0.03-0.04)	NR	NR
API, Active Pharmaceutical Ingredient; IR, Immediate-Release Formulation; ER, Extended-Release Formulation; NR, Not Reported						

Figure 5. RADARS® Substance Abuse Treatment Program, 2016: Past-Month Abuse (% of Respondents) or Rate of Past-Month Abuse (per 100,000 Dispensed Dosage-Units)*

	% of Respondents Reporting Past-Month Abuse	Rate of Past-Month Abuse per 100,000 Dispensed Dosage-Units
API		
IR		
ER		

* Scales on y-axes may differ

API, Active Pharmaceutical Ingredient; IR, Immediate-Release opioid analgesic Formulation; ER, Extended-Release opioid analgesic Formulation

IR/ER data do not include data on buprenorphine, fentanyl, heroin, tramadol, methadone

PUBLISHED LITERATURE: NAVIPPRO™

Using the search strategy described in Section 3 to identify studies reporting data from NAVIPPRO™, two articles were identified.[27,28]

Butler, 2017

The first study, by Butler and colleagues, used NAVIPPRO™ to examine the relative abuse of crush-resistant tablets (CRT) via intended (i.e., swallowing) versus alternative oral routes (i.e., chewing, dissolving).[27] This study covered assessments completed over the period January 1, 2009- March 31, 2015 and included data from adult assessments only (i.e, individuals 18 years and older) collected through the ASM IV® data stream. For patients with multiple assessments, only the first was included for analysis. Furthermore, only individuals endorsing abuse of specific target products of interest were included for analysis: crush-resistant tablets (a composite category including OxyContin reformulated, OxyNeo, Opana ER reformulated and Nucynta ER), non-crush-resistant versions of those products (e.g., Non-CRT oxycodone ER, oxymorphone ER), and finally other comparators of interest (e.g., morphine ER, oxycodone IR single-entity). Logistic regression was used to generate the abuse prevalence for specific products, with a focus on the oral route, including the intended oral mode of administration (i.e., swallowing) as well as "alternative" modes of oral administration (i.e., chewing, dissolving in mouth, dissolving in liquid/drinking).

Results from this study included assessments from 364,329 unique individuals aged 18 years and older, across 1,008 treatment centers and other settings in which individuals were assessed for substance use disorders in the US. From this population, 76,108 reported past-month abuse of any prescription opioid analgesic, 19,698 reported abuse of at least one of the target opioid analgesic products of interest, and 18,135, or 92% reported oral abuse of the products of interest. In this study, the authors noted that swallowing products whole was the most common oral mode of administration (MOA), followed by chewing, dissolving and finally dissolving in a liquid/drinking—for CRT products, abuse prevalence via these MOA were 48.96, 22.65, 7.66, and 2.58, respectively. Further, the study found that among abusers of the product via any route, past-month abuse prevalence via alternative oral MOA (i.e., not swallowed whole) was significantly higher for CRT than Non-CRT products. For instance, the reported abuse prevalence for CRT by an alternative oral route was 26.25 endorsements per 100 assessments, while for non-CRT oxycodone ER, abuse prevalence via an alternative oral route was only 20.63 ($p < 0.0001$). CRT products were reported to be abused more frequently via chewing and dissolving in the mouth relative to Non-CRT ($p<0.0001$), with no significant differences in the abuse-prevalence of swallowing whole ($p=0.27$) or dissolving in liquid ($p=0.87$) for CRT and Non-CRT products. This study demonstrated first, that oral abuse of products is reported for a large proportion of this study population, and second, that reformulation to include crush-resistant properties may paradoxically increase reported attempts at abusing via alternative oral MOAs, without affecting abuse prevalence via intended MOAs. **Figure 6**, extracted from this study, highlights some of these differences in graphical form.

Figure 6. NAVIPPRO™, January 1, 2009- March 31, 2015:
Abuse Prevalence of CRT and Non-CRT Products via Specific Oral Modes of Administration

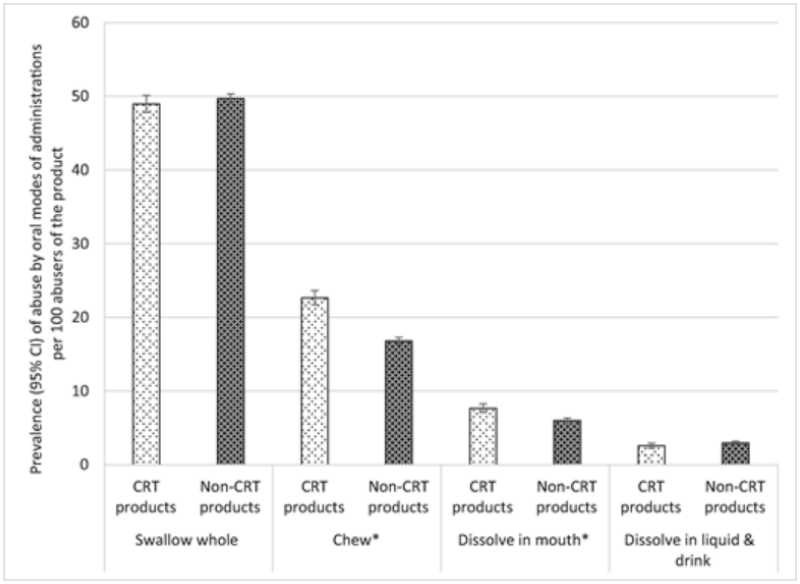


Figure Source: Butler, et al.; Pain Medicine, 2017

CRT, Crush Resistant Tablets (OxyContin reformulated, OxyNeo Reformulated, Opana ER reformulated, Nucynta ER reformulated);
Non-CRT, Non-Crush Resistant Tablets (Original or generic oxycodone, Original or generic oxymorphone ER, Nucynta IR)

Cassidy, 2017

The second study, by Cassidy et al., examined patterns of abuse and routes of administration for various opioid products, with a focus on hydrocodone IR, though also examining patterns of abuse for other prescription opioid analgesics such as oxycodone.[28]

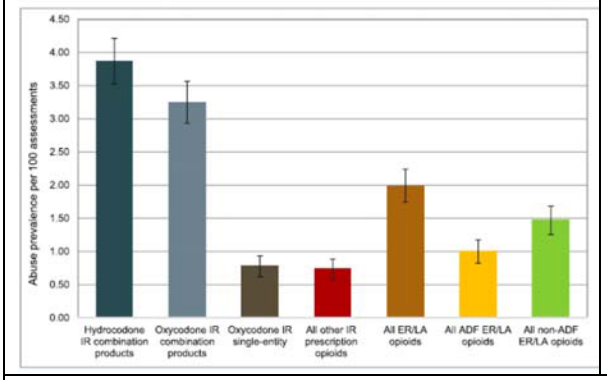
This study included NAVIPPRO™ ASM IV® assessments of adults 18 years and older, as with the Butler study, and also incorporated assessments from adolescents (primarily aged 13-18), derived from the Comprehensive Health Assessment for Teens (CHAT®). The time-period covered by this study was January 1, 2012 through June 30, 2015. In this study, the primary measure of abuse prevalence was measured by number of past 30-day abuse endorsements per 100 assessments. Additional measures of abuse prevalence were number of endorsements adjusted for number of prescriptions dispensed (per 100,000 prescriptions). Routes of administration were assessed based the number and proportion of individuals reporting specific routes of abuse for specific products of interest.

Results from this study included 226,357 adult assessments from 831 sites in the US, and 12,906 adolescent assessments from 180 sites in 26 states in the US. The study reported that past thirty-day abuse prevalence for IR hydrocodone and IR oxycodone products was significantly higher than for other prescription opioid products. The primary findings from this study were that among both adults and adolescents past thirty-day abuse-prevalence of hydrocodone and oxycodone IR products were significantly greater than for other products, although when adjusting for number of prescriptions dispensed, the relative frequency of abuse appeared to be significantly higher for ER/LA products, including both AD and non-AD formulations (**Figure 7**).

The study also reported routes of administration by product, reporting that oral routes of administration were generally more common for all products, with the exception of oxycodone IR single-entity for which intranasal abuse was more common and IR opioid products other than oxycodone or hydrocodone for which injection was more frequent than oral abuse **(Figure 8).** For adults reporting abuse of AD ER/LA products specifically, oral routes of administration were reported in 60% of assessments, while non-oral routes were also reported in a substantial proportion of assessments—with between 20-30% endorsing snorting, and approximately 30% reporting injection.

Figure 7. NAVIPPRO™/ASM IV®, January 1, 2012- June 30, 2015: Past thirty-day abuse-prevalence of prescription opioid analgesics*

Abuse prevalence (Number of endorsements per 100 assessments)	Adjusted abuse prevalence (per 100,000 prescriptions)



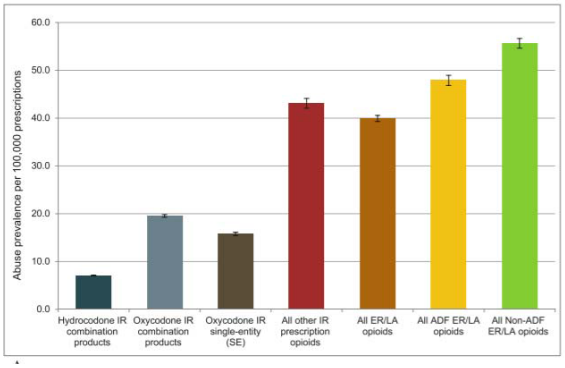
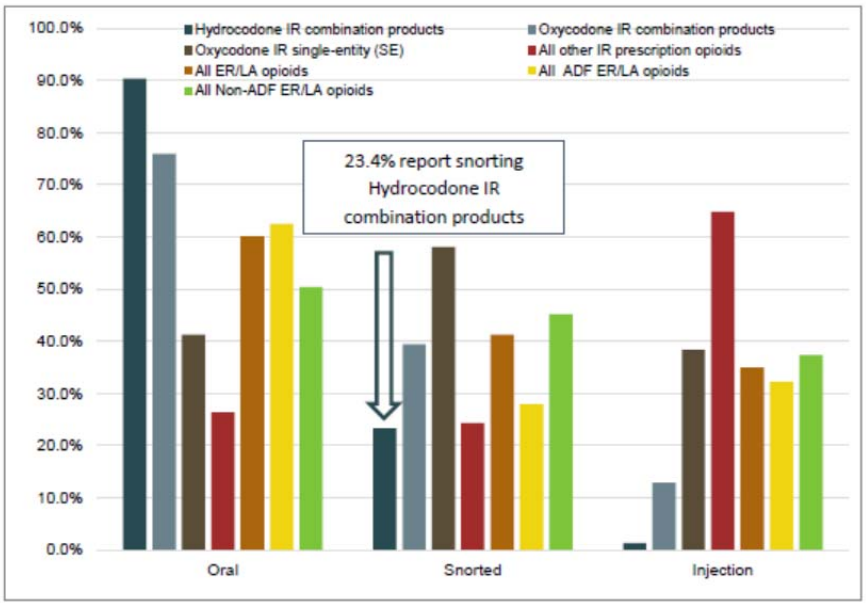


Figure Source: Cassidy, et al.; PDS, 2017

*Results depicted include adult assessments only
ADF, abuse-deterrent formulation; ER/LA, extended-release/long-acting; IR, immediate-release; SE, single-entity

Figure 8. NAVIPPRO™®, January 1, 2012- June 30, 2015: Reported Route of Abuse, by Product*



Percent* of route of administration for hydrocodone IR combination products and other opioids among adult past 30-day abusers within substance abuse treatment. *Note: respondents selected multiple routes so that percentages do not add to 100%

Figure Source: Cassidy, et al.; PDS, 2017, Supplemental Table 1A

*route of administration calculated by % of assessments endorsing abuse of specific product by specific route; percentages may total 100 if individuals report multiple routes of abuse, data depicted
ADF, abuse-deterrent formulation; ER/LA, extended-release/long-acting; IR, immediate-release

In summary, the two recently published studies we identified that utilized the NAVIPPRO™ surveillance system highlight the prevalence of oral abuse of prescription opioid products (>90% of assessments) as the most frequent route of administration reported among patients entering treatment (Butler, et al.). The incorporation of tamper-resistant features, such as resistance to chewing, may not deter individuals from chewing tablets, and may paradoxically increase attempts at manipulation via alternative oral routes (Butler, et al.). Finally, while oral abuse remains the most common route of administration for the majority of prescription opioid products, even for AD formulations alternative routes of administration such as snorting and injection are reported among 20-30% of individuals endorsing abuse of such products (Cassidy, et al.).

NEISS-CADES

During 2016, there were an estimated 274,940 ED visits for harms attributed to use of a prescription opioid product, of which nearly half (105,771) involved oxycodone-containing products specifically. Among ED visits associated with non-medical use of an opioid product, 40% (N=51,204) involved an oxycodone product **(Table 7).** For nonmedical use visits involving oxycodone, an estimated 43% led to an admission, transfer or observation in the emergency room.

An oxycodone product was the only implicated pharmaceutical in over half of ED visits involving nonmedical use of oxycodone (53%); a benzodiazepine was also implicated in 32% of these visits. Approximately one-fifth of ED visits for nonmedical use of oxycodone products involved concurrent use of alcohol (21%) or marijuana (18%) **(Table 8).**

In 38% of nonmedical use visits involving oxycodone products, the patient experienced cardiac arrest, was unresponsive, or had respiratory failure/distress, and in an additional 33% of visits, the patient experienced altered mental status **(Table 9).**

Table 7. National Estimates of ED Visits for Harms from Use of Oxycodone-containing and Comparator Products, by Intent of Drug Use, 2016a

Opioid Analgesic Product	Cases	Annual Estimate		
	No.	No.	%	95% CI
Non-medical Use[b] (Total Estimate = 129,862 ED Visits)				
Oxycodone-containing Product	**751**	**51,204**	**39.4**	**(32.8 - 46.0)**
Hydrocodone-containing Product	194	16,745	12.9	(7.2 - 18.6)
Morphine-containing Product	108	7,532	5.8	(4.0 - 7.6)
Therapeutic Use[c] (Total Estimate = 106,066 ED Visits)				
Oxycodone-containing Product	**532**	**38,396**	**36.2**	**(27.1 - 45.3)**
Hydrocodone-containing Product	260	24,250	22.9	(14.9 - 30.8)
Morphine-containing Product	116	8,863	8.4	(6.2 - 10.5)
Self-harm Attempt (Total Estimate = 39,012 ED Visits)				
Oxycodone-containing Product	**210**	**16,171**	**41.5**	**(31.9 - 51.0)**
Hydrocodone-containing Product	127	9,268	23.8	(16.7 - 30.8)
Morphine-containing Product	23	1,889	4.8	(2.7 - 7.0)

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, and undetermined intent of use.

[c]Includes adverse events from therapeutic use (e.g., adverse effects, allergic reactions, medication errors, and unsupervised ingestions by children aged <11 years).

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

Table 8. National Estimates of ED Visits for Nonmedical Use of Oxycodone-containing Products, by Case Characteristics, 2016[a]				
Patient and Case Characteristics	**Cases**	**Annual Estimate**		
	No.	**No.**	**%**	**95% CI**
Patient Age (Years)				
<10	0	--	--	--
10-24	116	7,537	14.7	(11.7 - 17.7)
25-34	203	13,339	26.1	(22.7 - 29.4)
35-44	123	8,830	17.2	(13.8 - 20.7)
45-54	132	9,706	19.0	(15.6 - 22.4)
55-64	130	8,630	16.9	(13.5 - 20.2)
65-74	43	2,950	5.8	(3.5 - 8.0)
>74	4	--	--	--
Patient Sex				
Female	273	20,680	40.4	(34.6 - 46.1)
Male	478	30,525	59.6	(53.9 - 65.4)
Disposition				
Admitted, Transferred, or Held for Observation	304	22,208	43.4	(32.6 - 54.2)
Treated/Released or Left Against Medical Advice	447	28,997	56.6	(45.8 - 67.4)
Number of Implicated Pharmaceuticals				
1	387	26,876	52.5	(45.4 - 59.6)
2	247	16,194	31.6	(26.8 - 36.5)
3	86	6,055	11.8	(8.2 - 15.4)
4	31	2,079	4.1	(2.1 - 6.0)
Implicated Oxycodone Product				
Single-ingredient Oxycodone	425	28,529	55.7	(46.8 - 64.6)
Oxycodone in Combination with Acetaminophen	334	22,970	44.9	(35.7 - 54.0)
Oxycodone in Combination with Aspirin	1	--	--	--
Co-implicated Pharmaceuticals				
>1 Rx Opioid	116	7,538	14.7	(9.9 - 19.6)
Benzodiazepine	248	16,241	31.7	(26.3 - 37.2)
Illicit Drugs/Alcohol				
≥1 Illicit Drug	287	18,198	35.5	(30.4 - 40.7)
Alcohol	167	10,859	21.2	(16.8 - 25.6)
Illicit Drug(s) or Alcohol	388	24,725	48.3	(44.1 - 52.5)
Cocaine	101	5,656	11.0	(7.1 - 15.0)
Fentanyl	8	--	--	--
Heroin	68	4,021	7.9	(4.7 - 11.0)
Marijuana	141	9,591	18.7	(14.3 - 23.1)
Methamphetamine	36	2,246*	4.4*	(0.9 - 7.8)
Other/Unknown Illicit Drug	24	--	--	--
Total	**751**	**51,204**	**100.0**	

Table 8. National Estimates of ED Visits for Nonmedical Use of Oxycodone-containing Products, by Case Characteristics, 2016[a]

Patient and Case Characteristics	Cases	Annual Estimate		
	No.	No.	%	95% CI

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, and undetermined intent of use. Estimates based on <20 cases or total estimates <1,200 are considered statistically unreliable 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).

*Coefficient of variation >30%.

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

Table 9. National Estimates of ED Visits for Nonmedical Use of Oxycodone-containing Products, by Adverse Event Manifestation, 2016[a]

Adverse Event Manifestation[b]	Oxycodone-containing Product			
	Cases	Annual Estimate		
	No.	No.	%	95% CI
Cardiac Arrest/Unresponsive/Respiratory Failure/Distress	253	19,638	38.4	(28.4 - 48.3)
Severe Allergic Reaction	0	--	--	--
Altered Mental Status	271	16,902	33.0	(26.4 - 39.7)
Injection-related Infection/Reaction	15	--	--	--
Fall/Injury	21	1,868	3.6	(1.7 - 5.6)
Presyncope/Syncope/Dyspnea	15	--	--	--
Psychiatric or Other Central Nervous System Effect	27	1,540*	3.0*	(0.2 - 5.8)
Cardiovascular Effect	17	--	--	--
Mild-to-Moderate Allergic Reaction	0	--	--	--
Gastrointestinal Effect	15	--	--	--
Other/Unspecified Effect	117	6,715	13.1	(8.9 - 17.3)
Total	751	51,204	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, and undetermined intent of use. Estimates based on <20 cases or total estimates <1,200 are considered statistically unreliable 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).
*Coefficient of variation >30%.

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

NSVSS-M and DIM

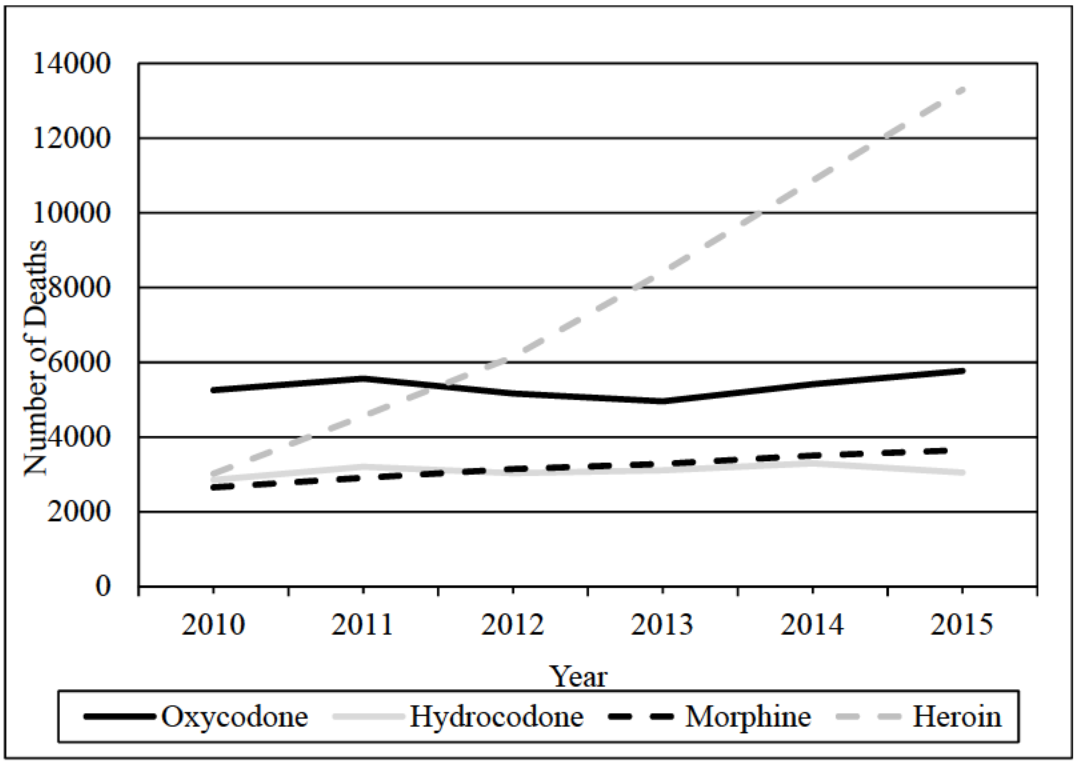
Analysis of the NVSS-M and DIM linked databases found that in the six-year period from 2010-2015, there were a total of 32,128 oxycodone, 18,551 hydrocodone, 19,149 morphine, and 46,303 heroin-involved overdose deaths in the U.S. in individuals aged 12 years and older (**Table 10**). Oxycodone-involved overdose deaths rose slightly from 5,257 in 2010 to 5,566 in 2011, then decreased gradually to 4,956 deaths in 2013, and subsequently increased to 5,711 deaths in 2015 **(Figure 9).** A gradual increase in the number of overdose deaths involving morphine (from 2,655 to 3,651) was observed from 2010-2015. A similar pattern was observed for hydrocodone-involved overdose deaths from 2010-2014 (from 2,854 to 3,298), though a small decrease was noted in 2015 (N=3,050). A sharp increasing trend was observed for heroin-involved overdose deaths from 2010 to 2016, where the number of deaths rose from 3,020 to 13,296.

Table 10. Select Opioid Involved Drug Overdose Deaths among Individuals 12+ Years of Age by Year, 2010-2015

	2010	2011	2012	2013	2014	2015	Total
Drug	N	N	N	N	N	N	N
Oxycodone	5257	5566	5165	4956	5413	5771	32128
Hydrocodone	2854	3204	3033	3112	3298	3050	18551
Morphine	2655	2909	3144	3283	3507	3651	19149
Heroin	3020	4562	6149	8410	10866	13296	46303

Underlying cause of death ICD-10: X40-X44, X60-X64, X85 or Y10-Y14

Figure 9. Number of Opioid Involved Drug Overdose Deaths among Individuals 12+ Years of Age by Year, 2010-2015



4 DISCUSSION

4.1 SUMMARY OF THE DATA AND DISCUSSION

Scale of misuse/abuse
Although national discourse on the opioid epidemic is now dominated by discussion of deaths arising from ultra-potent illicit opioids such as fentanyl,[29,30] 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 2016, an estimated 90 million individuals in the general US population had used prescription opioid analgesics the previous year, 12 million had misused them, and 2 million individuals met the criteria for abuse or dependence involving prescription opioid analgesics. The same year, approximately 275,000 estimated ED visits in the United States were for harms from use of a prescription opioid analgesic, of which, nearly 130,000 visits were for non-medical opioid use, and over 50,000 involved non-medical use of oxycodone products specifically.

Specific products, relative frequency of misuse/abuse
Data from NSDUH suggest that the most frequently misused opioid analgesics in the general population during 2016 were hydrocodone, oxycodone and codeine, with misuse occurring among 6.9 million, 3.9 million and 2.8 million individuals respectively. Over the period 2012-2016, calls to poison control centers in NPDS reporting intentional abuse were highest for heroin and oxycodone, respectively at 12.7 and 6.8 calls per million individuals; trends in exposure calls over this time demonstrate a plateau in calls for oxycodone, with a rise in calls for heroin since 2015.

While national estimates for the number of individuals abusing specific opioid analgesic products in the general population could not be identified through NSDUH due to current survey design, data on the relative frequency of abuse of such products in patients entering treatment for substance use disorder was inferred from the RADARS® and NAVIPPRO™ surveillance systems. In RADARS®, we found that heroin was the most frequently abused opioid followed by oxycodone, with past-month abuse endorsed among 57% and 35% of respondents, respectively; 15% of respondents endorsed abuse of ER oxycodone, specifically. The Cassidy study based upon data from NAVIPPRO™ revealed a slightly different though not entirely inconsistent pattern, with the highest abuse prevalence reported for hydrocodone followed by oxycodone.[28]

In both RADARS® data as well as the Cassidy study, differences between the utilization-adjusted and unadjusted rates of abuse were observed. However, in the Cassidy paper, adjustment for number of prescriptions led to an apparent increase in the relative frequency of abuse of oxycodone ER/LA ADs, a shift not observed in the RADARS® data. Differences between utilization-adjusted and unadjusted rates of abuse occurred because the unadjusted rates can be driven largely by product availability while differences in utilization-adjusted rates may be more attributable to properties of the active moiety or characteristics of the formulation like the dosage strength, the bio-availability of the drugs via different routes, the relative likability of the active moiety, and other factors.

Differences in the patterns of abuse-prevalence of opioid products in the RADARS® and NAVIPPRO™ surveillance systems may be explained by several factors, including differences in the underlying populations as well as in survey format and methods. For example, RADARS®

TCP represents a population of patients specifically entering treatment for OUD, while the NAVIPPRO™ treatment centers include patients entering or being assessed for treatment for any SUD. As such, the represented populations are distinct, and care should be taken to acknowledge these population differences prior to generalizing results, or comparing results between populations. Differences in format and order of survey questions relating to specific opioid products, as well as the inherent potential for product misclassification, may also contribute to discrepancies between the two surveillance systems in relative abuse rates.

Route of misuse/abuse
AAPCC/NPDS and the NAVIPPRO™ studies,[27, 28] depicted somewhat different pictures regarding routes of abuse, underscoring differences in population characteristics, the former being a population of patients with single-substance abuse exposures resulting in a call to a PCC; the latter, a population of patients with presumably more advanced substance use disorders. Although oral abuse was generally the most common route of abuse for prescription opioids in both populations, specific products were abused by alternate routes in each population to a differing extent.

The NAVIPPRO™ studies revealed that oral abuse was the most common route of abuse for prescription opioids; for AD ER/LAs, in particular, oral abuse was reported among 60% of respondents, followed by snorting (20-30%) and injection (30%). In NPDS, though not directly comparable, for oxycodone ER/LAs, oral abuse was reported among 74% of exposure calls, followed by snorting (13%) and injection (12%). The Butler study based upon NAVIPPRO™ also determined that CRT are significantly more often abused via alternative oral modes of administration (i.e., chewing, dissolving in mouth) than intended modes (i.e., swallowing whole).

Morbidity and mortality
A high frequency of adverse outcomes continues to be reported in association with misuse/abuse of prescription opioid analgesics. Data from NEISS-CADES indicated that an estimated 51,204 ED visits in 2016 involved non-medical use of oxycodone products, either alone or in conjunction with other agents such as a benzodiazepine or marijuana; concurrent use of alcohol or illicit drugs was also frequently documented. Over 40% of such visits required observation, admission or transfer to another hospital; and an estimated 19,600 visits involved patients with cardiac arrest, respiratory failure/distress or non-responsiveness. Mortality data from NVSS-M/DIM for the period 2010-2015 identified a total of 32,128 deaths involving oxycodone, 18,551 deaths from hydrocodone and 19,149 deaths involving morphine. Although deaths involving heroin increased dramatically over time, with a total of 46,303 deaths over the period 2010-2015, the trends in deaths involving prescription opioids have not declined. For instance, with oxycodone, rates have plateaued fluctuating from between five to six thousand deaths per year during a six-year period.

4.2 LIMITATIONS OF DATA AND REVIEWED STUDIES

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, and in general it is not sufficiently detailed to examine specific branded products and formulations. Information on route of administration is very limited. Individuals with advanced substance use disorders may be underrepresented, particularly if they become homeless, incarcerated, or enter a residential treatment facility.

NPDS

PCC call data should not be interpreted as representing the complete incidence of national exposures or cases of misuse/abuse related to any substance. These data only capture abuse events if the exposure resulted in a call to a PCC. PCC data rely on information electively shared by patients and healthcare personnel, and most substance classification is based on history alone and does not involve any biologic confirmation. Drug exposures resulting in unattended or out-of-hospital death are unlikely to generate a call to a PCC, and therefore, 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 rates in part reflect changes in public and professional awareness of the risks associated with specific drugs, and awareness of the abuse potential of a drug among call center personnel could also increase the likelihood of an exposure being coded as intentional abuse. Call rates may also be influenced by general changes in use of PCCs over time.

RADARS® TCP and NAVIPPRO™/ ASI-MV® data

An important limitation of data collected from people entering or being assessed for substance use disorder treatment is the potential for misclassification, including in the identification of the specific product(s) being abused. Another limitation is that these are convenience samples, and because they are enriched with individuals with advanced substance use disorders who have sought or been referred for treatment or assessment, patterns observed in these study populations may not reflect those that exist in a broader population of individuals who abuse drugs. Numerous factors—for example, judicial referral policies and availability and funding of substance use disorder treatment—can 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 disorder treatment in the U.S.

NEISS-CADES

NEISS-CADES data can be used to calculate national estimates of ED visits for harms from pharmaceutical use, but NEISS-CADES does not include cases that do not result in an ED visit or that result in death before or during ED evaluation. NEISS-CADES also does not include inadequate therapy, drug withdrawal, detoxification treatment, medical clearance, occupational exposures, or adverse events from ED treatment. The quality of these surveillance data depend on the completeness and accuracy of medical record documentation by the healthcare provider and, to be included in the database, cases require documentation by the healthcare provider that a drug or drug class (e.g., “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 additional drugs were involved and not recorded. It is also possible that some medications recorded as “oxycodone” may have been oxycodone-combination products.

NVSS-M and DIM linked data

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. Therefore, findings may describe the minimum number of opioid-involved deaths. Moreover, there may have been changes in the probability of reporting or testing for specific drug-involvement in the literal text over the course of the study period.

5 CONCLUSIONS

As new opioid analgesic products with proposed abuse-deterrent properties are considered for approval, risks to both patients and the broader community must be weighed against potential benefits. This review focuses on considerations relevant to public health. Misuse and abuse of prescription opioid analgesics is a persistent problem in the US, and commonly observed for individuals in both the general population and those more specifically with SUD. Both IR and ER/LA formulations of oxycodone are abused, including products with AD labeling based on premarket testing. While oral abuse remains the most common route of abuse for ER/LA oxycodone formulations, all of which have AD labeling based on premarket studies, successful manipulation of such products has been reported in a sizeable fraction of individuals, with chewing, insufflation, and intravenous injection all being reported routes of abuse. Prescription opioid analgesics such as oxycodone continue to contribute to a large burden of morbidity and mortality in the United States, and approval of new products should be considered with respect to both the patient and public health risk/benefit balance.

6 APPENDICES

6.1 APPENDIX A. NPDS—DEFINITIONS OF EXPOSURE REASONS

NPDS Definitions for Intentional Exposure Reason Categories	
Intentional Exposure Reasons	**NPDS Definition[c]**
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.

6.2 APPENDIX B: 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

[c] American Association of Poison Control Centers. National Poison Data System (NPDS) Data Dictionary. Version 2016.07.11. July 11, 2016

literal text. The analytical dataset was constructed for analysis on October 6, 2016. The method used to extract information on drug-involved mortality has been described previously[21] 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.[21] 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 percent of drug overdose deaths with at least one mention of a specific drug has improved from 67% in 2010 to 78% in 2014.[31] Undercounting of deaths with involvement of specific drugs is likely with the drug-involved mortality data.

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

Date: May 21, 2018

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)

NDA: Remoxy (oxycodone HCL) extended-release capsules (22324)

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

If approved, Remoxy (oxycodone HCL) extended-release capsules (NDA 22324) will be required to become a member of the Extended-release (ER) and Long-acting (LA) (ER/LA) Opioid Analgesics 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 ER/LA Opioid Analgesics REMS is a shared system that was initially approved in July 2012 and is part of a multi-agency Federal effort to address the growing problem of prescription drug abuse and misuse.

ER/LA opioid analgesics are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The goal of the ER/LA Opioid Analgesics REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

The ER/LA Opioid Analgesics REMS is intended to reduce risks and improve safe use of ER/LA opioid analgesics while continuing to provide access to these medications for patients in pain. The central component of the ER/LA Opioid Analgesics REMS is an education program for prescribers (e.g., physicians, nurse practitioners, physician assistants). Under the ER/LA REMS,

application holders[1] of ER/LA opioid analgesics are required to make education programs available to healthcare providers (HCPs) who are prescribers of ER/LA opioid analgesics. The application holders are meeting this requirement by providing educational grants to accredited continuing education (CE) providers who offer training to prescribers at no or nominal cost.

To be considered compliant with the ER/LA Opioid Analgesic REMS, the CE courses are required to include the content and messages of a "blueprint" developed by FDA for this purpose. The currently approved FDA Blueprint includes general and product-specific information about the ER/LA opioid analgesics; information on proper patient selection for use of these drugs; guidance for safely initiating therapy, modifying dosing, and discontinuing use of ER/LA opioid analgesics; guidance for monitoring patients; and information for counseling patients and caregivers about the safe use of these drugs.[2] Additionally, prescribers are provided information for how to recognize evidence of and potential for opioid misuse, abuse, and addiction.

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

On September 28, 2017, FDA notified all application holders of immediate-release (IR) opioid analgesics, that are expected to be used in the outpatient setting and that are not already covered by another REMS program, that those products are subject to the same REMS requirements as the ER/LA opioid analgesics to ensure the benefits outweigh the risks of these products. FDA also notified the application holders of the ER/LA opioid analgesics that the REMS must be modified to expand the content of the training and to make the training available to health care professionals who are involved in the management of patients with pain, including nurses and pharmacists, which is in addition to prescribers of opioid analgesics. The letters further informed the application holders that in the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs for drugs with similar serious risks, FDA determined that all application holders should work together, using the existing infrastructure of the ER/LA Opioid Analgesics REMS, to develop a shared system Opioid Analgesics REMS. The Agency is currently reviewing the proposed major modification of ER/LA Opioid Analgesics REMS to develop the Opioid Analgesics REMS.

In January 2018, following consideration of public input, the Agency published a draft revised FDA Blueprint, "Opioid Analgesic REMS Education Blueprint for Health Care Providers

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

[2] FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. The FDA Blueprint contains core messages intended for use by continuing education (CE) providers to develop educational materials to train prescribers of ER/LA opioid analgesics under the REMS.

Involved in the Treatment and Monitoring of Patients with Pain", and made it available, in advance of the approval of the Opioid Analgesic REMS. The draft revised FDA Blueprint 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 revised draft also 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. Accredited CE providers will develop CE materials and activities based on the revised blueprint. The draft revised FDA Blueprint is available at the following link: https://www.regulations.gov/contentStreamer?documentId=FDA-2017-D-2497-0683&attachmentNumber=1&contentType=pdf. Once the Opioid Analgesic REMS is approved, a list of the REMS-compliant CE activities will be made available.

If approved, Remoxy (oxycodone HCL) extended-release capsules (NDA 22324) will be required to join the Opioid Analgesic REMS when that modification is approved.

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: May 21, 2018

FROM: Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, 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 and for Opioid Analgesics Labeled with Abuse-Deterrent Properties

The following PMRs are required for all approved ER/LA 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 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 retail dispensing data, overall and by age group and census region; AND

2) 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.

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 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*.

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.