

FDA Briefing Document

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

July 26, 2017

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 oxycodone extended-release oral tablets 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*

July 26, 2017

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DIVISION DIRECTOR MEMO



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

MEMORANDUM

DATE: June 22, 2017

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, July 26, 2017 AADPAC/DSaRM Meeting to
Discuss NDA 209653

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

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).

The results of the Applicant’s in vitro physical and chemical manipulation studies will be presented during this meeting. You will hear presentations from the Applicant regarding their findings. The Agency will present our approach to the development of abuse-deterrent opioid analgesic formulations based on the Guidance for Industry issued in 2015. You will also hear presentations regarding the safety of excipients as it relates to IV abuse of abuse-deterrent opioid analgesic formulations and the behavior of persons who abuse opioids in regards to deterrent properties of formulations. You will be asked to discuss whether the Applicant has demonstrated abuse-deterrent properties for their product that would support labeling, whether the benefits of the product at issue outweigh its risks, and whether it should be approved.

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 oxycodone extended-release tablets have properties that can be expected to deter abuse by the IV route of administration?
2. Are there sufficient data to support inclusion of language regarding abuse-deterrent properties in the product label for the IV route of administration?
3. Does the committee have concerns regarding the safety of exposure to the excipients in this product if administered by the IV route for the purpose of abuse.
4. Should oxycodone extended-release tablets be approved?



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

MEMORANDUM

DATE: June 22, 2017

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. **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.

All Sponsors of opioid analgesics with approved abuse-deterrent language in labeling are required to conduct postmarketing epidemiologic studies to determine whether the properties of their product results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting.

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

Abuse-Deterrent Opioids — Evaluation and Labeling

Guidance for Industry

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

**Clinical Medical
April 2015**

Abuse-Deterrent Opioids — Evaluation and Labeling

Guidance for Industry

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

**Clinical Medical
April 2015**

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Abuse-Deterrent Opioids — Evaluation and Labeling Guidance for Industry¹

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

I. INTRODUCTION

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

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

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

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

II. BACKGROUND

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

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

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

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

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

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

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

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

³ Ibid.

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

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

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

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

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

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

III. ABUSE-DETERRENT PRODUCTS

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

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

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

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

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

IV. PREMARKET STUDIES

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

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

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

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

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

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

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

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

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

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

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

A. Laboratory Manipulation and Extraction Studies (Category 1)

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

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

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

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

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

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

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

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

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

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

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

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

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

B. Pharmacokinetic Studies (Category 2)

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

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

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

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

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

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

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

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

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

C. Clinical Abuse Potential Studies (Category 3)

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

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

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

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

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

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

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

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

1. Blinding

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

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

2. Pre-qualification Phase

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

¹¹ Ibid.

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

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

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

3. Assessment Phase

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

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

4. Subjects

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

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

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

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

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

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

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

6. Outcome Measures and Data Interpretation

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

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

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

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

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

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

7. *Data Interpretation*

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

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

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

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

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

¹⁶ See Statistical Analysis Section for further guidance.

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

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

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

8. *Statistical Analysis*

a. *Background*

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

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

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

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

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

b. Primary analyses

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

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

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

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

where $\delta_2 \geq 15$.

The significant level for both tests is 2.5%.

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

c. Secondary analyses

In addition to the primary analysis, an analysis should be performed of the percent reduction for the potentially abuse-deterrant 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:

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

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

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

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

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

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

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

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

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

- Responder Analysis

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

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

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

- Analysis of the Median Percent Reduction

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

For assessing deterrent effects, we can test

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

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

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

d. Multiplicity

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

V. POSTMARKET STUDIES (CATEGORY 4)

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

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

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

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

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

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

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

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

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

A. Formal Studies

1. General Characteristics

Formal studies have the following characteristics:

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

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

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

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

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

2. Study Design Features

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

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

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

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

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

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

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

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

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

B. Supportive Information

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

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

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

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

VI. LABELING

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- Category 1

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

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

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

- Category 1 and Category 2

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

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

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

- Category 2 and Category 3

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

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

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

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

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

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

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

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

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

VII. ADDITIONAL RESEARCH NEEDS

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

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

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

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

**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: June 21, 2017

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Office of Surveillance and Epidemiology

Subject: Utilization Trends of Oxycodone ER and Other ER/LA
Opioid Analgesics

Drug Name(s): Oxycodone Extended-Release (ER) Tablets
(10mg, 15mg, 20mg, 30mg, 40mg, 60mg, and 80mg)

Application Type/Number: NDA 209653

Applicant/sponsor: Intellipharmaceutics Corp

OSE RCM #: 2017-518

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

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EXECUTIVE SUMMARY

On July 26, 2017, a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee Advisory Committee (DSaRM) will be held to discuss a New Drug Application (NDA 209653) for an extended-release oxycodone product with proposed abuse-deterring labeling. To provide context and background information, this review summarizes drug utilization analyses of oxycodone extended-release (ER) and other opioid analgesic products with formulations designed to deter abuse from 2012 through 2016 in the U.S. outpatient retail pharmacies.

In 2016, approximately 22 million prescriptions were dispensed for single-ingredient oxycodone products from U.S. outpatient retail pharmacies. Approximately 82% (18 million prescriptions) were for oxycodone IR products, while 18% (4.0 million prescriptions) were for oxycodone ER products. The total number of prescriptions dispensed for oxycodone ER products decreased by 23% from 2012 to 2016. Of the total ER/LA opioid market, oxycodone ER was the third top product among the ER/LA opioid analgesics utilized by patients, accounting for approximately 23% (837,000 patients) of the total patients who received a dispensed prescription for an ER/LA opioid analgesic in 2016. Morphine ER and transdermal (TD) fentanyl products, accounted for 34% (1.3 million patients) and 26% (1.0 million patients) of the total patients who received an ER/LA opioid analgesic prescriptions, respectively.

Of the top prescriber specialties, approximately one-quarter of the dispensed prescriptions for single-ingredient oxycodone ER products were written by general practice/family practice/internal medicine physicians in 2016. According to office-based physician survey data, the most common diagnoses reported in association with single-ingredient oxycodone ER use were for diseases of the musculoskeletal system and connective tissues.

Overall, although utilization of oxycodone ER appears to have decreased during the examined time, it was the third most used drug product out of the ER/LA opioid analgesic market in 2016. Oxycodone ER products also continue to account for the vast majority of the utilization of total opioid analgesic products with labeling for abuse-deterring formulation (ADF).

1 INTRODUCTION

In preparation for the upcoming joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee Advisory Committee (DSaRM) scheduled for July 26, 2017, this review summarizes the drug utilization analyses of oxycodone extended-release (ER) and other opioid analgesic products with labeling for formulations designed to deter abuse to provide context and background information.

The purpose of this Advisory Committee meeting is to discuss whether the data submitted by the Sponsor for a new drug application of an opioid extended-release formulation (oxycodone ER) is sufficient to support labeling as a product with properties expected to deter abuse. The proposed indication of this new drug application is for the management of chronic pain that may require around-the-clock, opioid treatment and for which alternative treatment options are inadequate.

1.1 BACKGROUND

NDA 209653 was submitted by the Sponsor for an extended-release formulation of oxycodone with proposed abuse-deterring properties. The proposed formulation is intended to prevent tampering when subjected to various forms of physical and chemical manipulation commonly used by abusers. Currently, there are ten opioid

analgesic products with FDA-approved labeling as products with abuse-deterrent properties¹. Of these products, two are single-ingredient oxycodone extended-release products, OxyContin and Xtampza. The proposed indication of 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.ⁱⁱ

2 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct this analysis to provide context to generate discussions at the upcoming Advisory Committee meeting. See Appendix 2 for detailed description and limitation of the databases.

2.1 DATA SOURCES

The QuintilesIMS, National Sales Perspectives™ (NSP) database was used to obtain the nationally estimated number of eaches (bottles/packages) sold for extended-release oxycodone from manufacturers to all U.S. channels of distribution in 2016. The sales distribution data do not reflect what is being sold to or administered to patients directly; but these data do provide a national estimate of units sold from the manufacturer into the various channels of distribution.

The QuintilesIMS, National Prescription Audit™ (NPA) database was used to obtain 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 2012 through 2016, annually. In addition, the top prescriber specialties for single-ingredient oxycodone ER products from U.S. outpatient retail pharmacies in 2016 were obtained from this database.

The QuintilesIMS, Total Patient Tracker™ (TPT) database was used to obtain the nationally estimated number of patients who received a dispensed prescription for extended-release/ long-acting opioid analgesics from U.S. outpatient retail pharmacies, from 2012 through 2016, annually.

inVentiv Health Research & Insights LLC., TreatmentAnswers™ with Pain Panel, a U.S. office-based physician survey database, was used to obtain top groups of diagnoses associated with the use of oxycodone ER in 2016. Diagnoses data by number of drug use mentions¹ were captured based on International Classification of Diseases (ICD-10-CM) codes and 95% confidence were applied to the estimates.

¹ A "drug use mention" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

2.2 MOLECULES INCLUDEDⁱⁱⁱ

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

Oral Single-ingredient (SE) Oxycodone Immediate-Release (IR) Molecules		
Active Ingredient	Brand Name	Initial U.S Approval
Oxycodone IR	Roxicodone	August 31, 2000
	Oxaydo	June 17, 2011
	(Roxybond)	April 20, 2017
Transdermal Extended-Release/Long-Acting Opioid 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 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	(Troxycia)	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-deterring properties.

3 RESULTS

3.1 SETTING OF CARE

The QuintilesIMS, National Sales Perspectives™ (NSP) database was used to determine the various settings of care where oxycodone ER was distributed by the manufacturer. Sales data in 2016 showed that approximately 76% of oxycodone ER bottles/packages were sold to U.S. outpatient retail settings, 22% to non-retail pharmacies, and less than 2% to mail-order/specialty.^{iv} As a result, only outpatient retail pharmacy utilization patterns were examined for oxycodone ER. Mail-order/specialty pharmacy and non-retail pharmacy settings data were not included in this analysis.

3.2 PRESCRIPTION DATA

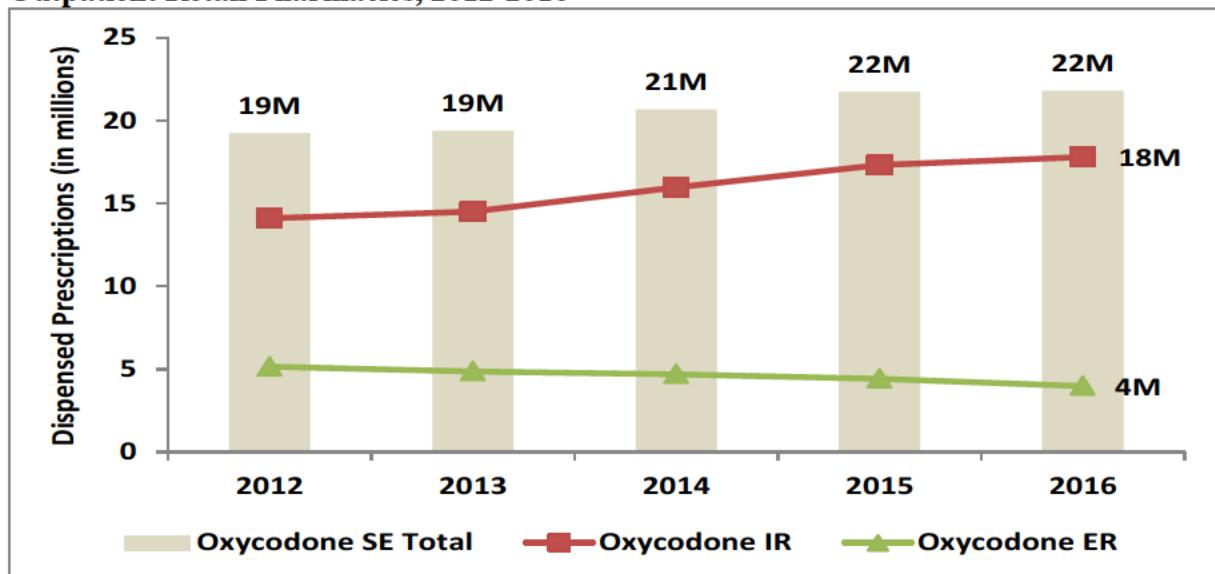
3.2.1 Single-ingredient Oxycodone Analgesics

Figure 3.2.1 and Table 3.2.1 in Appendix 1 provides the nationally estimated number of prescriptions dispensed for single-ingredient oxycodone from U.S. outpatient retail pharmacies, from 2012 through 2016, annually. Approximately 19-22 million prescriptions were dispensed for single-ingredient oxycodone annually from 2012 through 2016. Of the prescription dispensed for oxycodone IR there was a 26% increase from 14 million prescriptions in 2012 to 18 million prescriptions in 2016. Of the prescription dispensed for oxycodone ER there was a 23% decrease from 5.1 million prescriptions in 2012 to 4.0 million prescriptions in 2016.

In 2016, of the total number of prescriptions dispensed for single-ingredient oxycodone, the majority of the prescriptions were dispensed for the oxycodone IR product at approximately 82% (18 million prescriptions), while 18% (4.0 million prescriptions) were dispensed for the oxycodone ER product.

Figure 3.2.1

Nationally Estimated Number of Dispensed Prescriptions for Single-ingredient Oxycodone from U.S. Outpatient Retail Pharmacies, 2012-2016



Source: QuintilesIMS, National Prescription Audit (NPA). January 2012 - December 2016. Data extracted April 2017.

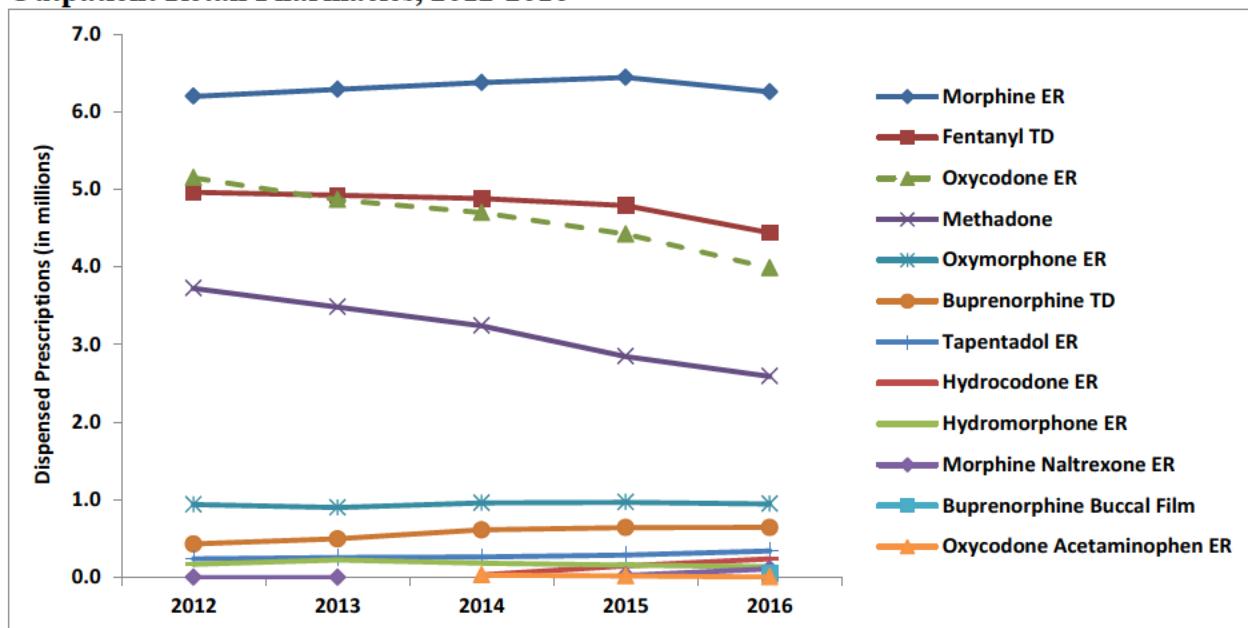
3.2.2 ER/LA Opioid Analgesics

Figure 3.2.2 below and Table 3.2.2 in Appendix 1 provide the nationally estimated number of prescriptions dispensed for ER/LA opioid analgesics from U.S. outpatient retail pharmacies from 2012 through 2016, annually. Approximately 20-22 million extended-release/long-acting opioid analgesic prescriptions were dispensed annually from 2012 through 2016.

In 2016, morphine ER accounted for approximately 32% (6.3 million prescriptions) of the total ER/LA opioid analgesic prescriptions. Fentanyl TD accounted for 23% (4.4 million prescriptions) of the total ER/LA prescriptions dispensed, with a relatively consistent number of prescriptions dispensed in the time period examined. Oxycodone ER accounted for 20% (4.0 million prescriptions), a 23% decrease from 2012 (5.1 million prescriptions). Methadone accounted for 13% (3.0 million prescriptions) of the total ER/LA prescriptions dispensed.

Figure 3.2.2

Nationally Estimated Number of Dispensed Prescriptions for ER/LA Opioid Analgesics from U.S. Outpatient Retail Pharmacies, 2012-2016



Source: QuintilesIMS, National Prescription Audit (NPA). January 2012 - December 2016. Data Extracted April 2017. File: NPA 2017-58 TRx for oxycodone ER and comparator ER by 2012_2016, 4-10-2017.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

3.2.3 Opioid Analgesics with Abuse-Deterrent Formulation

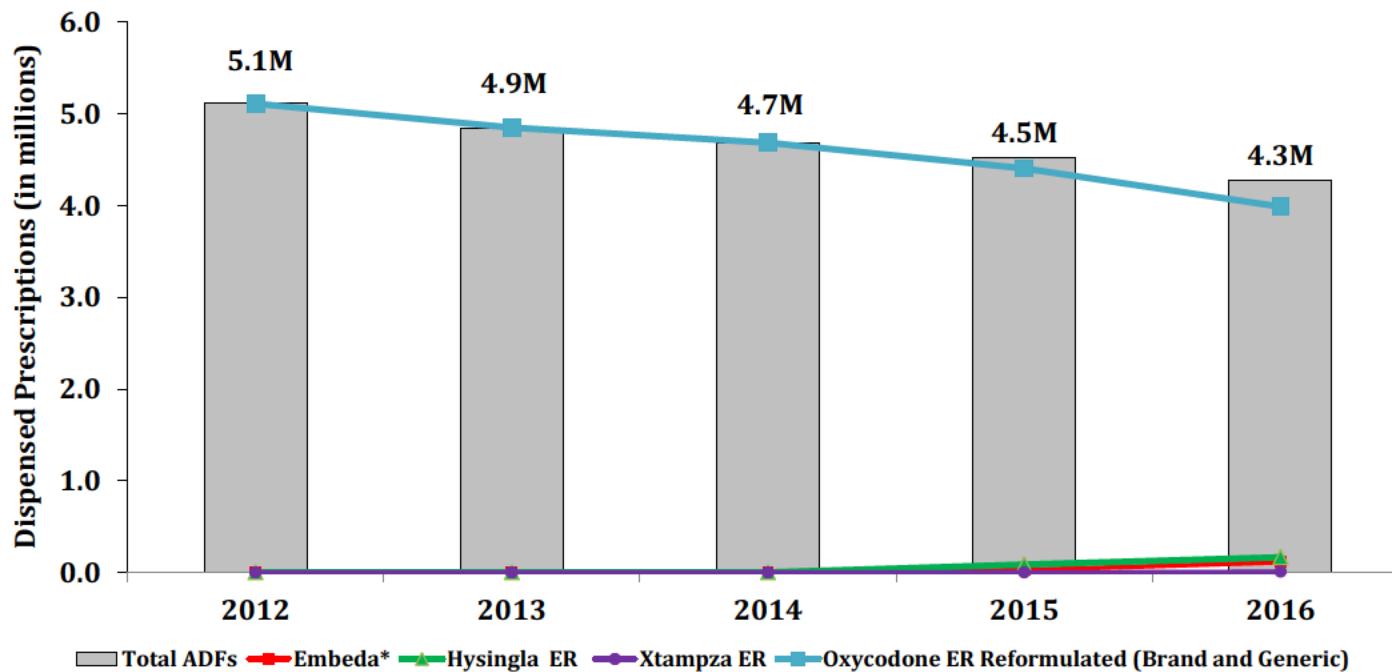
Figure 3.2.3 below and Table 3.2.3 in Appendix 1 provides the nationally estimated number of prescription dispensed for abuse-deterrent formulation (ADF) opioid analgesic products from U.S. outpatient pharmacies from 2012 through 2016, annually. Approximately 4-5 million prescriptions were dispensed for ADF products

from 2012 through 2016. The total number of prescriptions dispensed for ADF products decreased approximately from 5.1 million prescriptions in 2012 to approximately 4.3 million prescriptions in 2016.

Of total ADF prescriptions, the vast majority of prescriptions dispensed were for reformulated oxycodone ER at approximately 4.0 million prescriptions in 2016. Similar utilization trends were noted for the previous examined years.

Figure 3.2.3

Nationally Estimated Number of Prescriptions Dispensed for Abuse-Deterrent Formulation (ADF) Opioid Analgesic Products from U.S. Outpatient Retail Pharmacies, 2012-2016



Source: National Prescription Audit (NPA). January 2012- December 2016. Data extracted March 2017.

Note: Morphabond, Targiniq, and Troxyca are not shown in this analysis because products were not marketed in the U.S. during the study time period. Armyo, Roxybond, and Vantrela were approved after the study time period; thus were not included in this analysis

3.3 PATIENT DATA

3.3.1 Single-ingredient Oxycodone Analgesics

Table 3.3.1 in Appendix 1 provide the nationally estimated number of patients who received a dispensed prescription for single-ingredient oxycodone, from U.S. outpatient retail pharmacies, from January 2012 through December 2016, annually. Approximately 5-6 million patients received a dispensed prescription for a single-ingredient oxycodone annually from 2012 through 2016. Of the patients who received a dispensed prescription for oxycodone IR there was a 36% increase from 4.4 million patients in 2012 to 5.9 million patients in 2016. Of the patients who received a dispensed prescription for oxycodone ER there was a 22% decrease from 1.1 million patients in 2012 to 837,000 patients in 2016.

In 2016, of the total number of patients who received a dispensed prescription for single-ingredient oxycodone, the majority received oxycodone IR product at approximately 94% (5.9 million patients), while only 13% received oxycodone ER product. Patient utilization trends were similar to prescription trends across time.

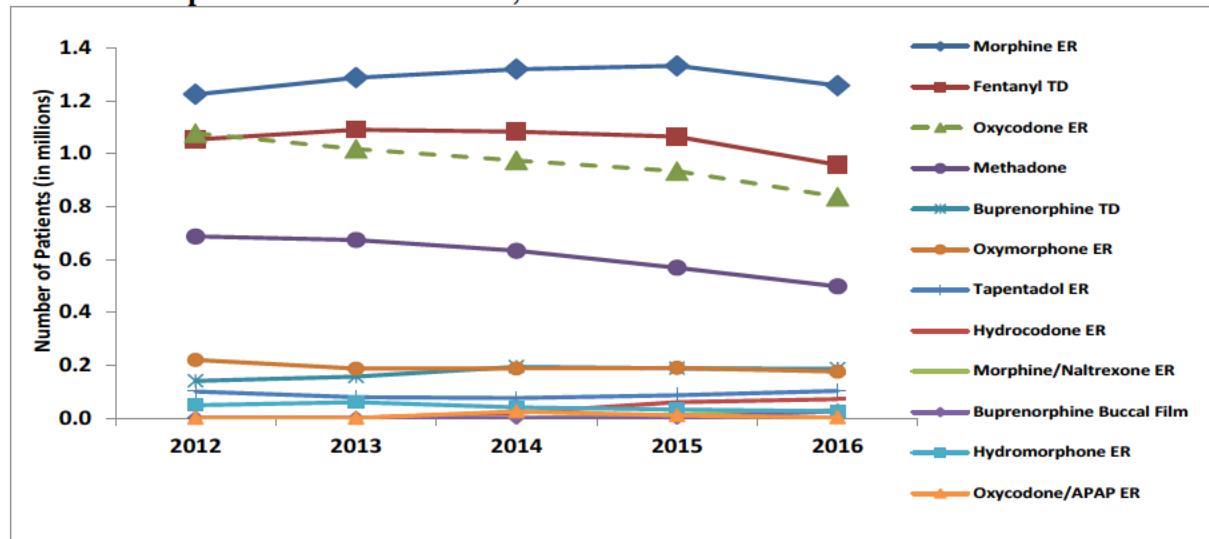
3.3.2 ER/LA Opioid Analgesics

Figure 3.3.2 below and Table 3.3.2 in Appendix 1 provide the nationally estimated number of unique patients who received prescriptions for ER/LA opioid analgesics from U.S. outpatient retail pharmacies, from January 2012 through December 2016, annually. Approximately 4.0 million patients received a dispensed prescription for an extended-release or long-acting opioid analgesic annually from 2012 through 2016.

In 2016, of the total number of patients who received a prescription for an ER/LA product approximately 34% of the patients (1.3 million patients) had morphine ER. Fentanyl TD accounted for 26% (1.0 million patients) of the total patients who received an ER/LA prescription, with a relatively consistent number of patients who received the product during the time examined. Oxycodone ER accounted for 23% (837,000 patients) of the total patients, a 22% decrease from 2012 (1.1 million patients). Methadone accounted for 14% (498,000 patients) of the total patients, a 28% decrease from 2012 (687,000 patients). Overall, the number of patients receiving a prescription for oxycodone ER declined steadily in the time examined. Of note, unique patients may have switched or received multiple products during the examined time.

Figure 3.3.2

Nationally Estimated Number of Patients* who Received a Dispensed Prescriptions for ER/LA Opioid Analgesics from U.S. Outpatient Retail Pharmacies, 2012-2016



Source: QuintilesIMS, Total Patient Tracker (TPT). January 2012 - December 2016. Data Extracted April 2017. File: TPT 2017-518 All ER Products 2012_2016_4-10-2017.xls

*Unique patient counts may not be added across time periods or across products due to the possibility of double counting those patients who are receiving treatment for multiple products or over multiple periods in the study.

3.4 PRESCRIBER SPECIALTY DATA

Table 3.4.1 provides the nationally estimated number of prescriptions dispensed for oxycodone ER from U.S. outpatient retail pharmacies by the top prescribing specialties in 2016. General practice, family practice, and internal medicine were the top prescribers of oxycodone ER (26% of total prescriptions), followed by nurse

practitioners and physician assistant (23%). Anesthesiologists and osteopathic medicine doctors both prescribed similar number of prescriptions (11% of total prescriptions) each.

Table 3.4.1

Nationally Estimated Number of Dispensed Prescriptions for Single-Ingredient Oxycodone ER from U.S. Outpatient Retail Pharmacies, Stratified by Top 10 Prescriber Specialties, 2016

	Year 2016	
	TRxs	%
Single-Ingredient Oxycodone ER	3,987,452	100.0%
Family Practice/General Practice/Internal Medicine	1,027,645	25.8%
Nurse Practitioner/Physician Assistant	915,782	23.0%
Anesthesiology	451,759	11.3%
Osteopathic Medicine	440,569	11.1%
Physical Medicine & Rehab	325,801	8.2%
Pain Medicine	226,979	5.7%
Oncology	126,310	3.2%
Orthopedic Surgery	104,858	2.6%
Neurology	69,388	1.7%
Rheumatology	45,727	1.2%
All Others	252,634	6.3%

Source: IMS Health, National Prescription Audit (NPA). January 2016 - December 2016. Data Extracted June 2017. File: NPA 2017-518 Oxycodone ER TRx by specialties in 2016, 6-14-2017.xlsx

3.5 DIAGNOSIS DATA

Table 3.5.1 in Appendix 1 provides the diagnosis (ICD-10) in terms of drug use mentions associated with the utilization of single-ingredient oxycodone ER products as reported by U.S. office-based physician surveys. In 2016, diagnoses associated with diseases of the musculoskeletal system and connective tissue were the top diagnosis (59% of total drug use mentions), followed by diseases of the nervous system and neoplasms (16% and 8% of total drug use mentions), respectively.

4 DISCUSSION

This review provides drug utilization data for extended-release oxycodone and other opioid analgesic products with labeling for formulations designed to deter abuse in the U.S. market. The data provided will serve as context and background information to generate discussions at the advisory committee for a new drug application for an extended-release formulation of oxycodone that will deter abuse.

Our analyses showed that the outpatient utilization of single-ingredient oxycodone ER products decreased from 2012 to 2016. The steady decline in the overall utilization of oxycodone ER may be attributed to multiple factors such as 1) introduction of reformulated OxyContin in 2010, 2) inception of the ER/LA opioid analgesic REMS in 2012, and 3) regulatory actions from the federal, state, and local levels in response to the continuing

opioid epidemic in the nation. However, our study did not assess the reasons behind the trends in utilization. It is important to note the only oxycodone ER products available in the market have abuse-deterrent formulations approved by the Agency.

The prescription data showed that primary care providers such as general practice/family practice/internal medicine were the top prescribers for oxycodone ER in 2016. According to the office-based physician survey data in 2016, reported drug use mentions of single-ingredient oxycodone ER products were primarily associated with the diseases of the musculoskeletal system and connective tissue such as back pain. Although survey data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, survey data are best used to identify the typical uses for the products from an office-based physician setting and thus does not represent other settings where oxycodone ER may be prescribed such as oncology clinics, pain clinics, and hospitals.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that oxycodone products are distributed primarily to the outpatient retail pharmacy setting based on the IMS Health, IMS National Sales Perspectives™ in 2016. As a result, we focused our analysis on only the outpatient retail pharmacy settings; thus these estimates may not apply to other settings of care in which these products are used (i.e., mail-order pharmacies, clinics, non-federal hospitals, etc.)

5 CONCLUSIONS

In preparation for the upcoming Advisory Committee for an extended-release formulation of oxycodone, this review provides the current drug utilization patterns of oxycodone ER and other opioid analgesic products with formulations designed to deter abuse in the market to provide context to generate discussions. In 2016, of the ER/LA opioid analgesic products, oxycodone ER accounted for the third most utilized in the market with approximately 837,000 patients receiving a dispensed prescription and 4.0 million prescriptions dispensed. In addition, oxycodone ER products continue to account for the vast majority of the utilization of total opioid analgesic products with labeling for abuse-deterrent formulation.

6 APPENDICES

6.1 APPENDIX 1: TABLES AND FIGURES

Table 3.2.1

Nationally Estimated Number of Dispensed Prescriptions for Single-Ingredient Oxycodone from U.S. Outpatient Retail Pharmacies, 2012-2016

	2012		2013		2014		2015		2016	
	TRx	%								
Grand Total Single-Ingredient Oxycodone	19,256,761	100.0%	19,378,727	100.0%	20,671,709	100.0%	21,740,503	100.0%	21,789,172	100.0%
Oxycodone IR	14,108,130	73.3%	14,513,238	74.9%	15,972,555	77.3%	17,317,048	79.7%	17,801,720	81.7%
Oxycodone ER	5,148,631	26.7%	4,865,489	25.1%	4,699,154	22.7%	4,423,455	20.3%	3,987,452	18.3%

Source: QuintilesIMS, National Prescription Audit (NPA). January 2012 - December 2016. Data Extracted April 2017.

Table 3.2.2

Nationally Estimated Number of Dispensed Prescriptions for ER/LA Opioid Analgesics from U.S. Outpatient Retail Pharmacies, 2012-2016

	2012		2013		2014		2015		2016	
	TRx	%								
Grand Total ER/LA Opioid Analgesic Products	21,817,818	100.0%	21,446,004	100.0%	21,287,835	100.0%	20,761,985	100.0%	19,757,860	100.0%
Morphine ER	6,198,303	28.4%	6,288,088	29.3%	6,375,570	29.9%	6,441,121	31.0%	6,256,262	31.7%
Fentanyl Transdermal	4,961,133	22.7%	4,923,139	23.0%	4,881,447	22.9%	4,791,686	23.1%	4,439,684	22.5%
Oxycodone ER	5,148,631	23.6%	4,865,489	22.7%	4,699,154	22.1%	4,423,455	21.3%	3,987,452	20.2%
Methadone	3,725,332	17.1%	3,484,537	16.2%	3,242,281	15.2%	2,846,882	13.7%	2,591,013	13.1%
Oxymorphone ER	939,908	4.3%	901,307	4.2%	960,933	4.5%	968,029	4.7%	947,081	4.8%
Buprenorphine Transdermal	431,793	2.0%	497,697	2.3%	613,086	2.9%	643,634	3.1%	645,450	3.3%
Tapentadol ER	242,059	1.1%	259,294	1.2%	264,048	1.2%	289,459	1.4%	343,610	1.7%
Hydrocodone ER ¹	-	-	-	-	35,093	0.2%	149,957	0.7%	240,748	1.2%
Hydromorphone ER	170,654	0.8%	226,452	1.1%	185,035	0.9%	160,632	0.8%	138,126	0.7%
Morphine Naltrexone ER ²	5	0.0%	1	0.0%	-	-	27,775	0.1%	110,865	0.6%
Buprenorphine Buccal Film ³	-	-	-	-	-	-	-	-	50,575	0.3%
Oxycodone Acetaminophen ER ⁴	-	-	-	-	31,188	0.1%	19,355	0.1%	6,994	0.0%

Source: QuintilesIMS, National Prescription Audit (NPA). January 2012 - December 2016. Data Extracted April 2017.

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 3.2.3
Nationally Estimated Number of Prescriptions Dispensed for Abuse-Deterrent Formulation (ADF) Opioid Analgesic Products from U.S. Outpatient Retail Pharmacies, 2012-2016

	2012		2013		2014		2015		2016	
	TRx	%								
Total ADF Prescriptions	5,148,636	100.0%	4,865,490	100.0%	4,699,154	100.0%	4,537,164	100.0%	4,272,465	100.0%
Oxycodone ER (Brand and Generic)	5,148,631	100.0%	4,865,489	100.0%	4,699,154	100.0%	4,423,455	97.5%	3,987,452	93.3%
Hysingla ER	—	—	—	—	—	—	85,934	1.9%	166,243	3.9%
Embeda*	5	0.0%	1	0.0%	—	—	27,775	0.6%	110,890	2.6%
Xtampza ER	—	—	—	—	—	—	—	—	7,880	0.2%

Source: National Prescription Audit (NPA). January 2012- December 2016. Data extracted March 2017.

*Embeda 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.

Note: Morphabond, Targiniq, and Troxyca are not included in this analysis because products were not marketed in the U.S. during the study time period. Armo, Roxybond, and Vantrela were approved after the study time period; thus were not included in this analysis.

Table 3.3.1
Nationally Estimated Number of Patients* who Received a Dispensed Prescriptions for Single-Ingredient Oxycodone from U.S. Outpatient Retail Pharmacies, 2012-2016

	2012		2013		2014		2015		2016	
	Patients N	Share %								
Grand Total Single-Ingredient Oxycodone	4,926,354	100.0%	5,071,146	100.0%	5,588,342	100.0%	6,140,761	100.0%	6,317,106	100.0%
Oxycodone IR	4,388,037	89.1%	4,580,887	90.3%	5,143,814	92.0%	5,728,772	93.3%	5,944,398	94.1%
Oxycodone ER	1,077,965	21.9%	1,018,434	20.1%	975,021	17.4%	934,080	15.2%	837,445	13.3%

Source: QuintilesIMS, Total Patient Tracker (TPT). January 2012 - December 2016. Data Extracted April 2017. File: TPT 2017-518 All ER Products 2012_2016_4-10-2017.xls

*Unique patient counts may not be added across time periods or across products due to the possibility of double counting those patients who are receiving treatment for multiple products or over multiple periods in the study.

Table 3.3.2

Nationally Estimated Number of Patients* who Received a Dispensed Prescriptions for Extended-Release/Long-Acting (ER/LA) Opioid Analgesics from U.S. Outpatient Retail Pharmacies, 2012-2016

	2012		2013		2014		2015		2016	
	Patients N	Share %								
Grand Total of ER/LA Opioid Analgesic Products	3,978,434	100.0%	4,032,057	100.0%	4,052,985	100.0%	3,965,110	100.0%	3,684,471	100.0%
Morphine ER	1,224,934	30.8%	1,288,415	32.0%	1,320,256	32.6%	1,333,103	33.6%	1,258,226	34.1%
Fentanyl Transdermal	1,054,023	26.5%	1,091,541	27.1%	1,084,149	26.7%	1,064,525	26.8%	958,125	26.0%
Oxycodone ER	1,077,965	27.1%	1,018,434	25.3%	975,021	24.1%	934,080	23.6%	837,445	22.7%
Methadone	687,428	17.3%	673,984	16.7%	633,255	15.6%	568,969	14.3%	498,444	13.5%
Buprenorphine Transdermal	140,283	3.5%	156,793	3.9%	194,047	4.8%	187,750	4.7%	186,277	5.1%
Oxymorphone ER	219,764	5.5%	186,945	4.6%	187,888	4.6%	189,940	4.8%	175,361	4.8%
Tapentadol ER	100,344	2.5%	79,232	2.0%	75,211	1.9%	86,304	2.2%	102,271	2.8%
Hydrocodone ER ¹	-	-	-	-	20,215	0.5%	60,367	1.5%	71,897	2.0%
Morphine/Naltrexone ER ²	-	-	-	-	-	-	12,293	0.3%	29,289	0.8%
Buprenorphine Buccal Film ³	-	-	-	-	-	-	-	-	26,439	0.7%
Hydromorphone ER	48,621	1.2%	59,829	1.5%	40,582	1.0%	32,236	0.8%	25,697	0.7%
Oxycodone/Acetaminophen ER ⁴	-	-	-	-	24,593	0.6%	9,833	0.2%	1,855	0.1%

Source: QuintilesIMS, Total Patient Tracker (TPT). January 2012 - December 2016. Data Extracted April 2017. File: TPT 2017-518 All ER Products 2012_2016_4-10-2017.xls

*Unique patient counts may not be added across time periods or across products due to the possibility of double counting those patients who are receiving treatment for multiple products or over multiple periods in the study.

¹ Zohydro Approved October 2013; Hysingla Approved 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 3.5.1

Diagnoses (ICD-10) in terms of drug use mentions* associated with the use of single-ingredient oxycodone extended-release analgesics as reported by office-based physician surveys, 2016

		2016		
		Uses	%	95% CI
Single-Entity Oxycodone ER		1,139,000	100.0%	951,000 – 1,327,000
Diseases of the musculoskeletal system and connective tissue (M00-M99)		669,000	58.7%	525,000 – 813,000
Diseases of the nervous system (G00-G99)		180,000	15.8%	105,000 – 255,000
Neoplasms (C00-D49)		94,000	8.3%	40,000 – 149,000
Factors influencing health status and contact with health services (Z00-Z99)		60,000	5.2%	17,000 – 103,000
Injury, poisoning and certain other consequences of external causes (S00-T88)		39,000	3.4%	4,000 – 73,000
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)		28,000	2.5%	<0.5 – 58,000
Diseases of the genitourinary system (N00-N99)		27,000	2.4%	<0.5 – 57,000
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)		17,000	1.5%	<0.5 – 40,000
Diseases of the digestive system (K00-K95)		8,000	0.7%	<0.5 – 24,000
Endocrine, nutritional and metabolic diseases (E00-E89)		7,000	0.6%	<0.5 – 22,000
External causes of morbidity (V00-Y99)		7,000	0.6%	<0.5 – 21,000
Diseases of the circulatory system (I00-I99)		3,000	0.2%	<0.5 – 11,000

Source: inVentiv Health Research and Insights LLC., TreatmentAnswers™ with Pain Panel. 2016. Data extracted May 2017.

*The term "drug uses" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

6.2 APPENDIX 2: DRUG USE DATABASE DESCRIPTIONS

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

The QuintilesIMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

QuintilesIMS National Prescription Audit™

The National Prescription Audit (NPA™) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over 3.5 billion prescription claims per year, captured from a sample of the universe of approximately 59,400 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 88% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 45 – 75% (varies by class and geography) of mail service pharmacies and approximately 70 – 85% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

QuintilesIMS, Total Patient Tracker™ (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

inVentiv Health Research & Insights LLC., TreatmentAnswers™

inVentiv Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

6.3 REFERENCES

ⁱ Office of the Commissioner. “Fact Sheets - FDA Facts: Abuse-Deterrent Opioid Medications.” US Food and Drug Administration Home Page. Date Accessed May 09, 2017, from website: <https://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm514939.htm>

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

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

^{iv} IMS Health, IMS National Sales Perspectives™. Year 2016. Data extracted April 2017.

^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

DATE: June 22, 2017

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 ($\pm SD$) 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 (\pm 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)

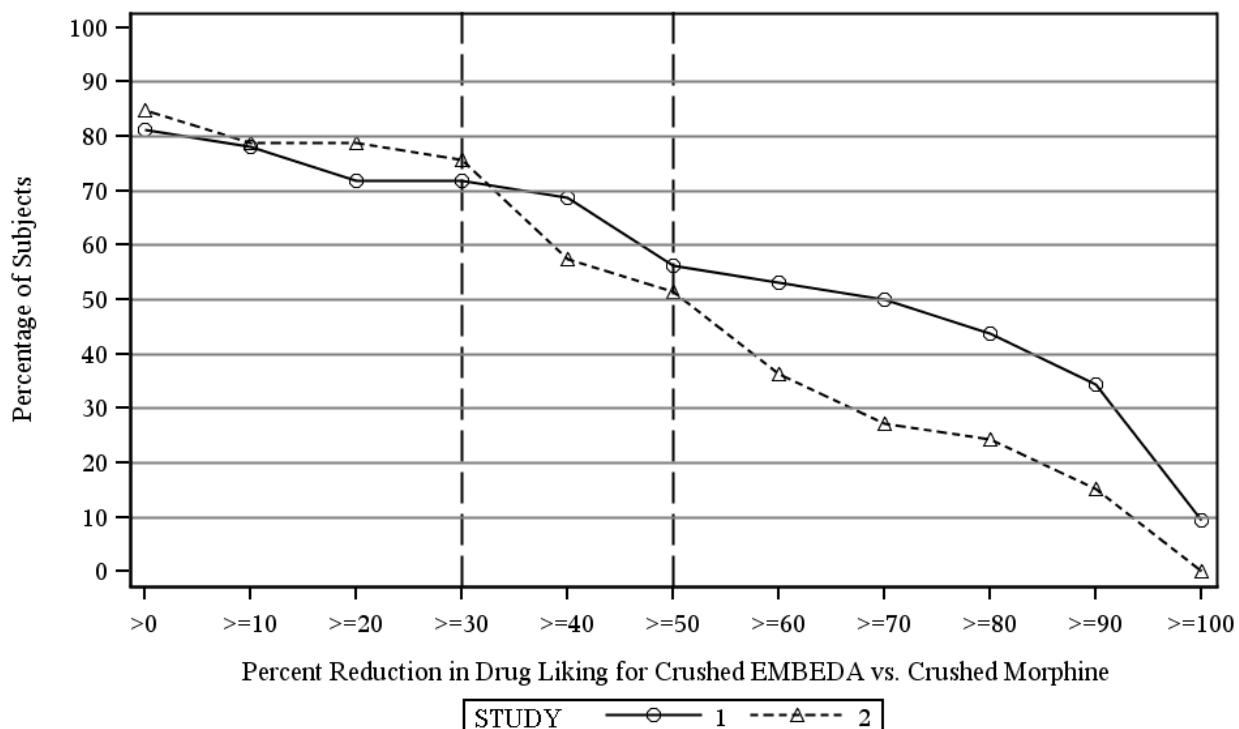
VAS Scale (100 point)		E_{max}	
		Crushed EMBEDA (120 mg/4.8 mg)	Crushed Morphine (120 mg)
Study 1		Immediate Release	
Drug Liking*	Mean (SE)	68.1 (3.1)	89.5 (2.2)
	Median (range)	62 (50-100)	93 (57-100)
Drug High**	Mean (SE)	54.7 (6.1)	90.2 (2.1)
	Median (range)	64 (0-100)	97 (61-100)
Study 2		Extended 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 (\pm 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)

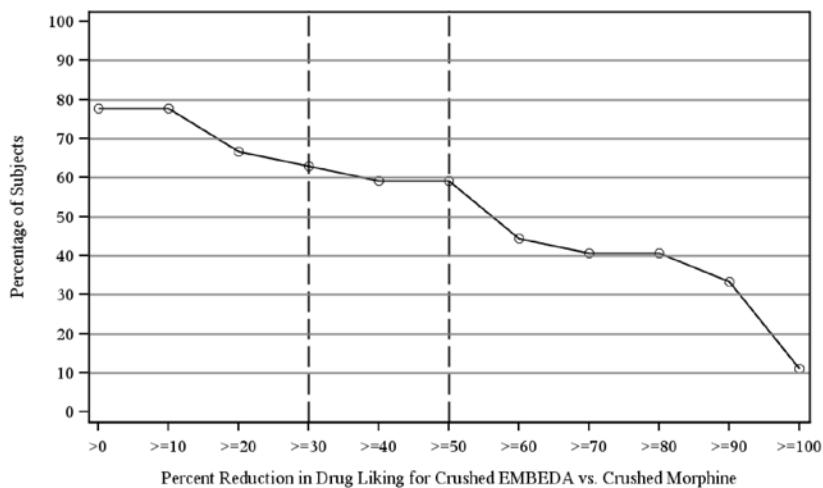
VAS Scale (100 point)		E_{max}	
		Crushed EMBEDA (30 mg/1.2 mg)	Crushed ER Morphine (30 mg)
Drug Liking*	Mean (SE)	69.0 (3.5)	88.4 (3.2)
	Median (range)	66 (50-100)	100 (51-100)
Drug High**	Mean (SE)	48.6 (7.8)	84.4 (3.8)
	Median (range)	51 (-39-100)	100 (42-100)
Take Drug Again*	Mean (SE)	59.1 (5.4)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

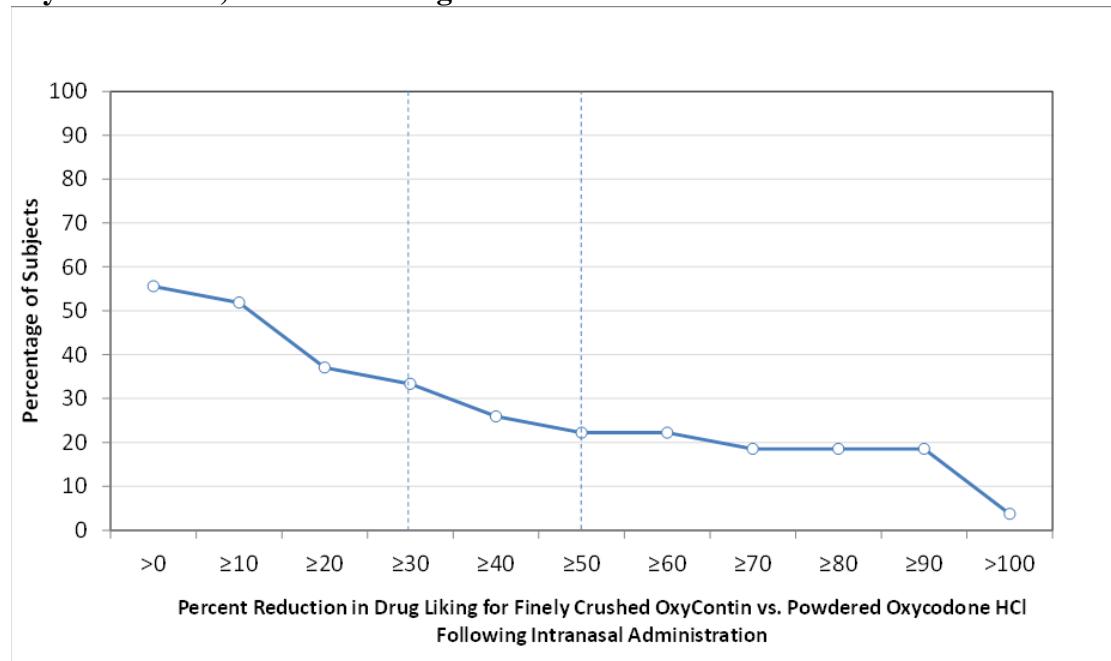
Table 4: Summary of Maximum Drug Liking (E_{max}) Data Following Intranasal Administration

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

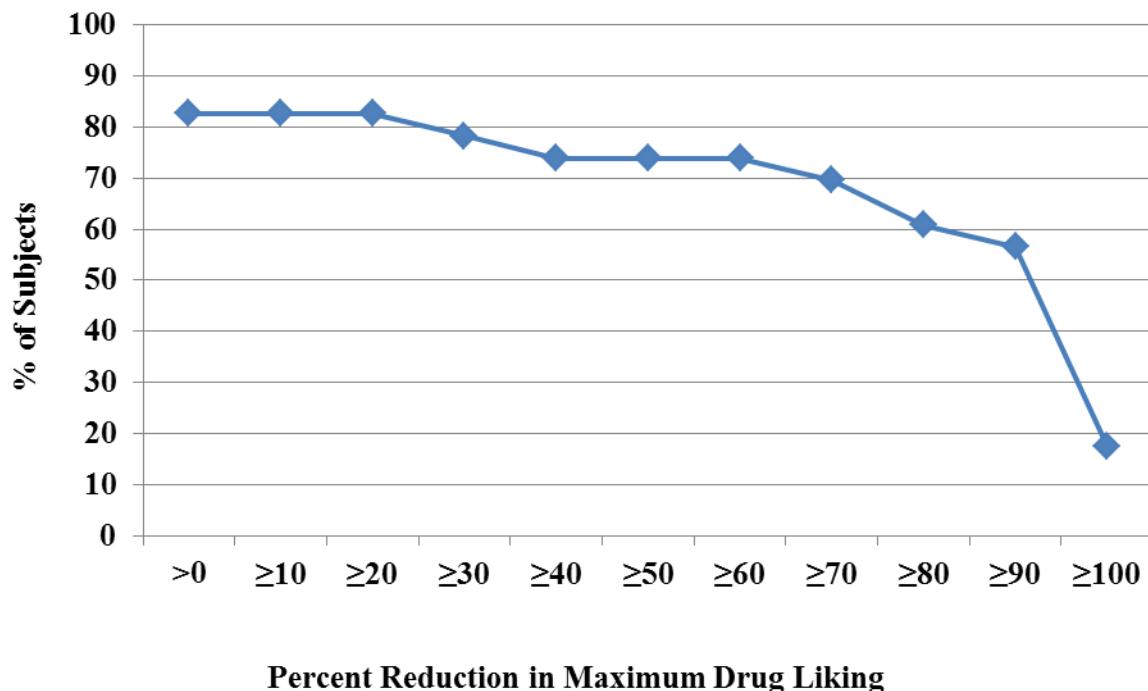
SE: standard error

* 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)
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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

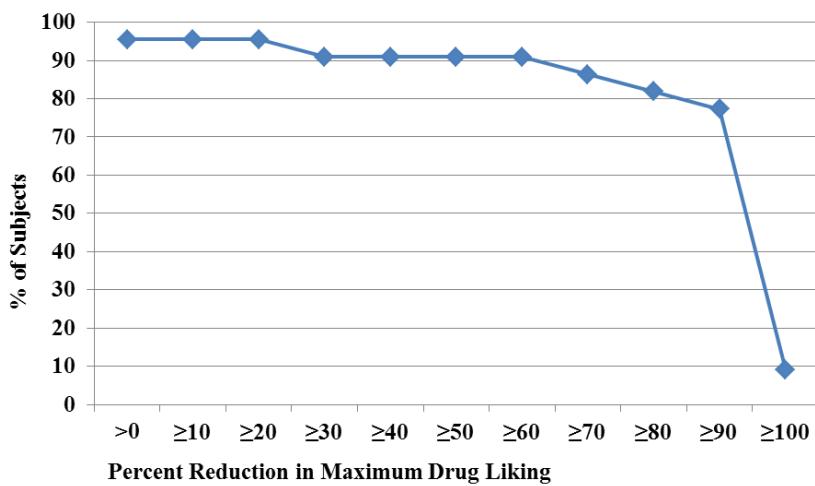
SE: standard error

* 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

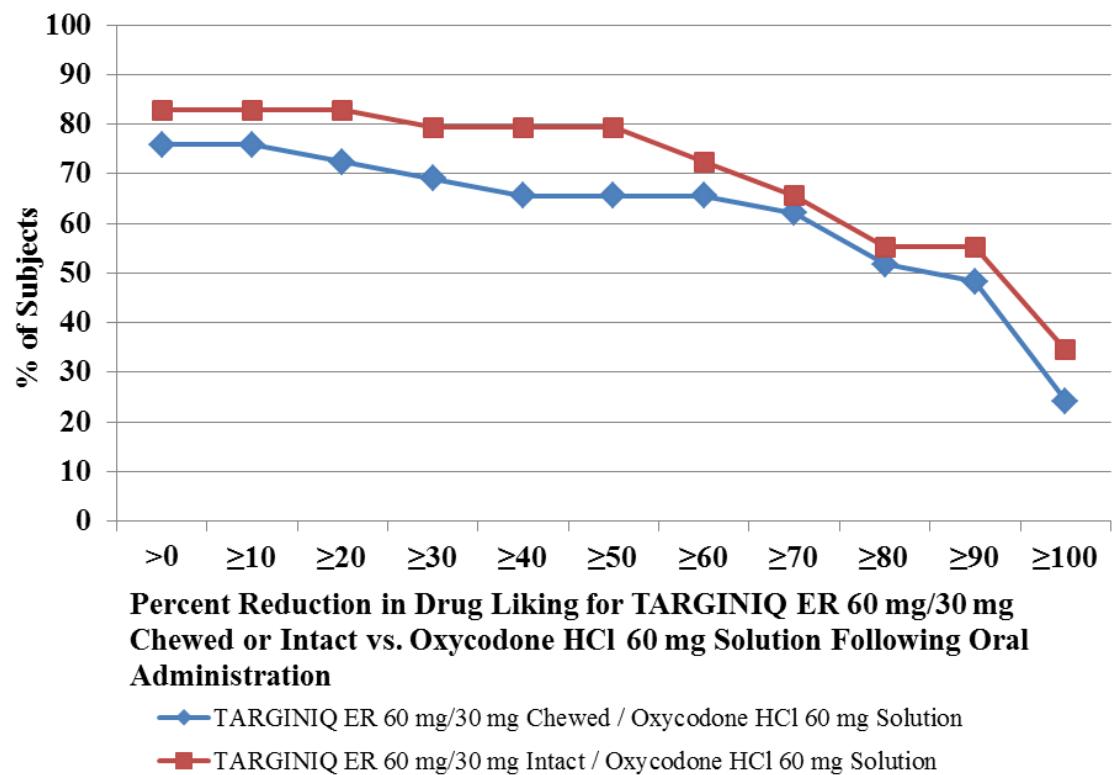
* Drug Liking Question text: “At this moment, my liking for this drug is”; scale: 0 = maximum disliking, 50 = neither liking nor disliking (neutral response), 100 = maximum liking.

**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)	HYSINGLA ER Manipulated	Hydrocodone Powder
<i>Intranasal (n=25)</i>		
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)

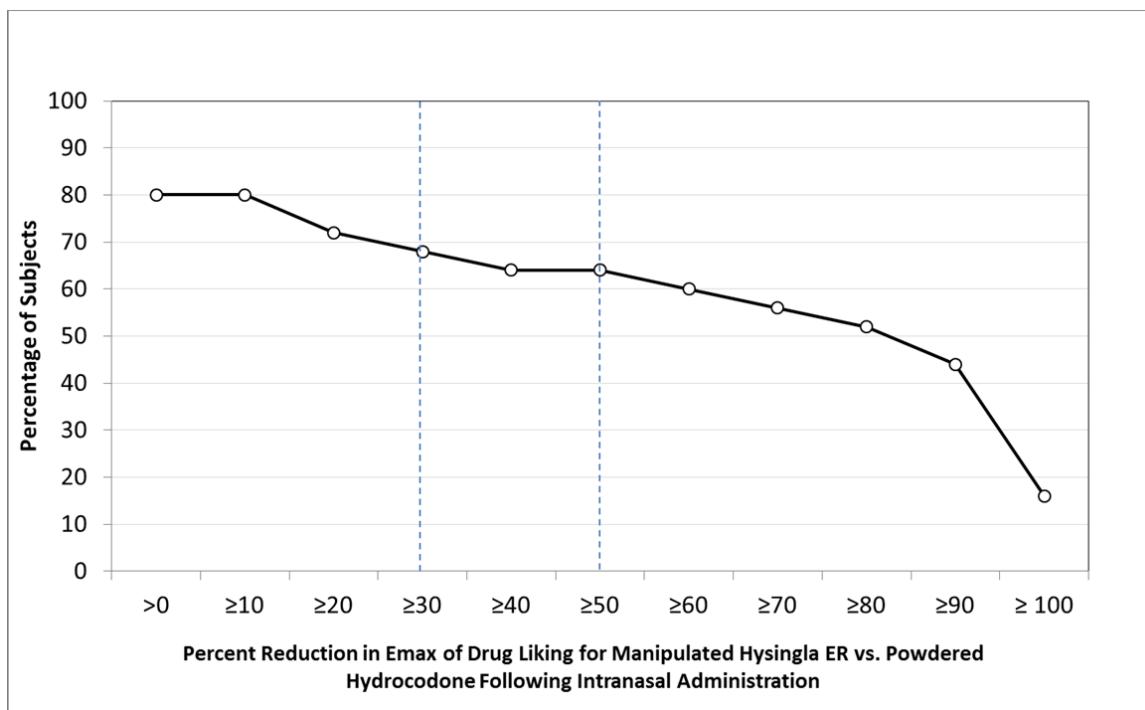
*Bipolar scale (0=maximum negative response, 50=neutral response, 100=maximum positive response)

** 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) Oral (n=35)	HYSINGLA ER Intact	Chewed	Hydrocodone 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)

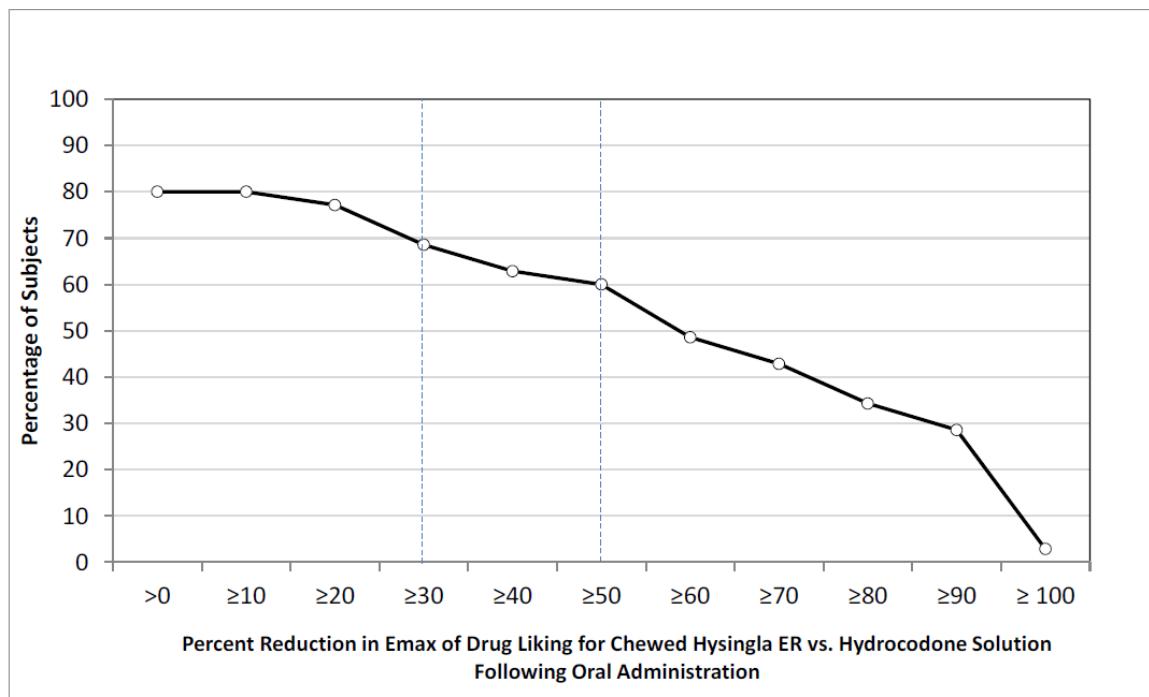
*Bipolar scale (0=maximum negative response, 50=neutral response, 100=maximum positive response)

** 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').

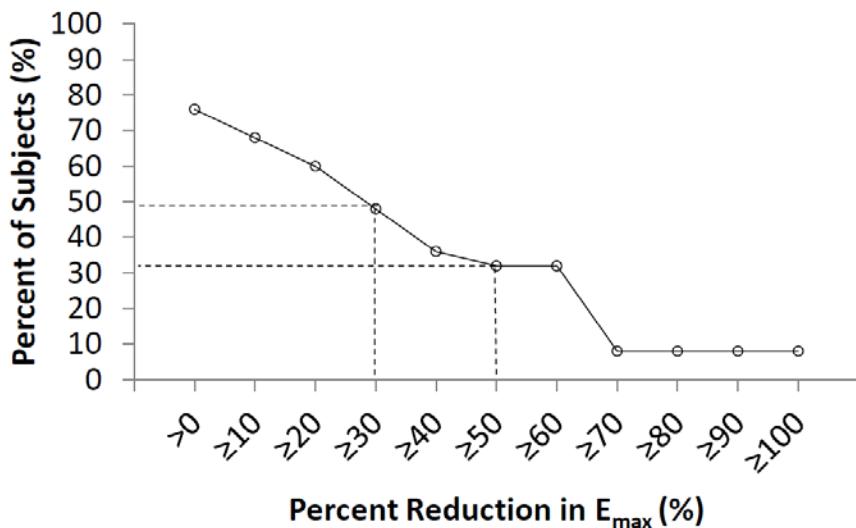
Intranasal administration of crushed MORPHABOND was associated with statistically significantly lower drug liking (E_{max}) scores ($P < 0.0001$), and significantly lower willingness to take the drug again (E_{max}) scores ($P = 0.034$), compared to crushed extended-release morphine (Table 2). Drug liking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

		XTAMPZ A ER Intact (Fasted)	XTAMPZ A 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

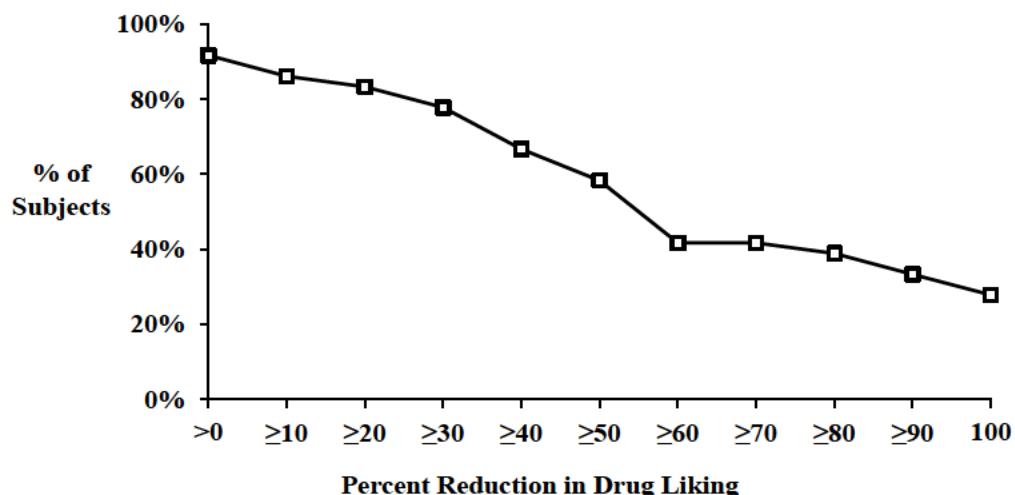
		XTAMPZA ER Intranasal	Crushed IR Oxycodone Intranasal	Placebo
Drug Liking* (E_{max})	Mean (SEM)	61.8 (2.6)	82.7 (1.8)	54.5 (2.0)
	Median (Range)	59.5 (16-94)	84 (60-100)	51 (28-93)
Take Drug Again* (E_{max})	Mean (SEM)	47.7 (4.6)	71.4 (3.9)	45.9 (2.9)
	Median (Range)	50 (0-100)	78.5 (18-100)	50 (0-97)

* 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 [*see Warnings and Precautions (5.1), Drug Abuse and Dependence (9.1)*].

ARYMO ER (morphine sulfate) extended-release tablets [NDA 208603]

Approval Date: January 9, 2017

Abuse Deterrence Studies

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

To evaluate the ability of ARYMO ER to reduce the potential for misuse and abuse, a series of abuse-deterring 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)	
<i>C</i> 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)
<i>T</i> max (h)			
Median (Range)	2.1 (0.9, 4.2)	4.1 (1.6, 6.1)	0.9 (0.6, 4.1)
<i>AUC</i> 0-∞ (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-∞ = 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 VAS¹ 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 (C_{max}) but not the total exposure (AUC_{0-inf}) relative to dosing the intact product. Relative to immediate-release hydrocodone, the C_{max} for all VANTRELA ER treatments was significantly lower and the T_{max} 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-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-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 (C_{max}) and shorter time to peak concentration (T_{max}) than taking VANTRELA ER orally and lower C_{max} and longer T_{max} than 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-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-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 [see *Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1)*].

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

Approval Date: April x, 2017

Abuse Deterrence Studies

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

In Vitro Testing

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

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

Clinical Abuse Potential Studies

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

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

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

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

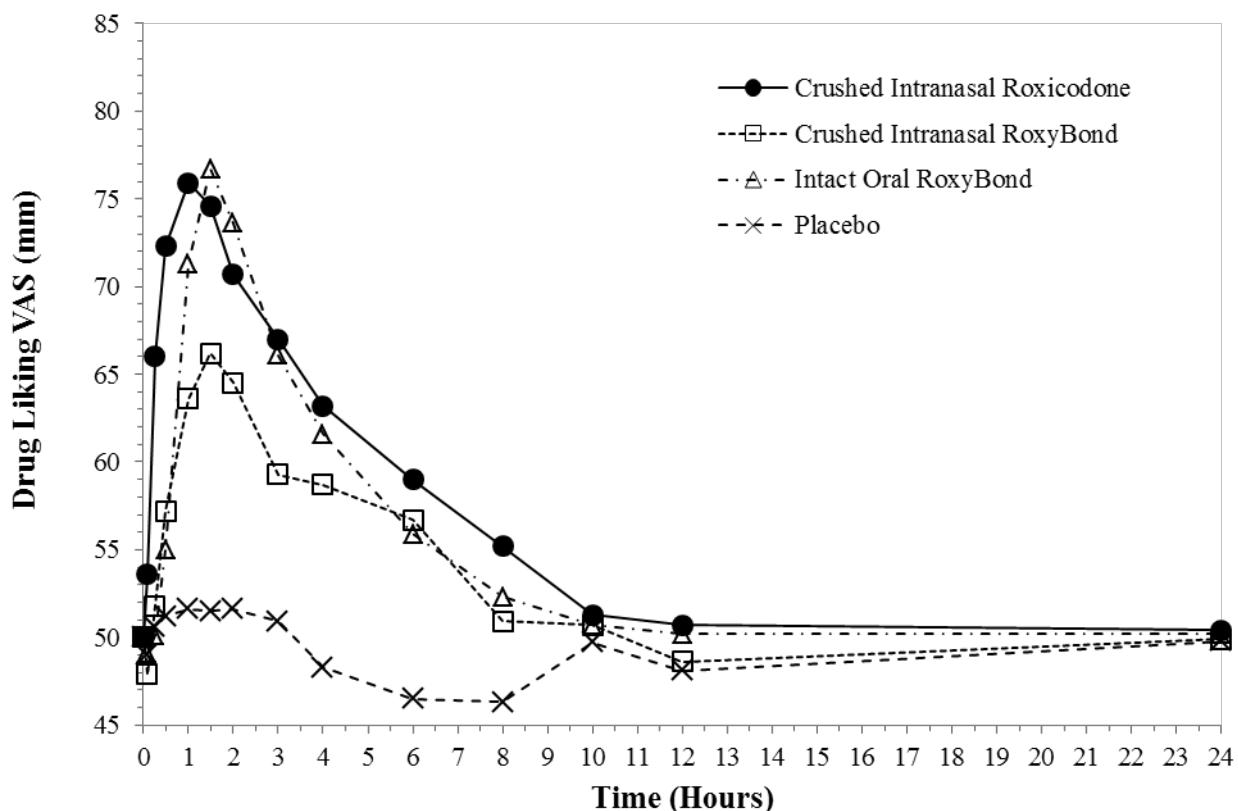
AUC_{0-t} = Area under the plasma concentration vs time curve from 0 to last measurable concentration.

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

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



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M E M O R A N D U M

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RE: Summary of Clinical Data for Oxycodone Extended Release Tablets

Summary of Clinical Data for Oxycodone Extended-Release Tablets

The proposed indication for oxycodone extended-release (ER) tablets is for the management of moderate-to-severe pain when a continuous, around-the-clock analgesic is needed for an

extended period of time. The safety and efficacy of oxycodone ER tablets is based on the demonstration of bioequivalence to the listed drug, OxyContin (NDA 22272) for this 505(b)(2) New Drug Application. The clinical program for oxycodone ER tablets consisted of seven Phase 1 pharmacokinetic (PK) studies using the final to-be-marketed formulation. Efficacy studies were not required for this NDA application if bioequivalence with OxyContin was established. The safety information collected in the pharmacokinetic studies was of limited value due to the fact that these were generally single-dose studies (except one multiple dose study) conducted in healthy volunteers who were naltrexone-blocked. There were no human abuse liability studies submitted with the NDA. No new safety signals were identified during the review of the oxycodone ER tablets application beyond what is already known for oxycodone products.

The clinical pharmacology review focused on seven Phase 1 studies (1878, 1879, 656-15-80, 655-15-80, OXY-80-186, OXY-80-184 and OXY-10-80-185) using the to-be-marketed commercial formulation. All studies were randomized, open-label, crossover studies conducted in healthy volunteers under naltrexone blockade. Studies 1878 and 1879 assessed the comparative bioavailability of lowest proposed strength, oxycodone ER 10 mg tablets and OxyContin 10 mg tablets under fasting condition and fed conditions, respectively. Studies 656-15-80 and 655-15-80 assessed the comparative bioavailability of highest proposed strength, oxycodone ER 80 mg tablets and OxyContin 80 mg tablets under fasting condition and fed conditions, respectively. These single dose comparative bioavailability studies under fasted and fed conditions for the highest and lowest proposed strengths between oxycodone ER tablets and OxyContin tablets are considered to be the pivotal PK studies. Final determination regarding the results from these studies are pending acceptable inspection results of the clinical and bioanalytical study sites. Studies OXY-80-186, OXY-80-184 and OXY-10-80-185 assessed food effect, dose-proportionality using all strengths and multiple-dose PK of oxycodone ER tablets, respectively. PK results of comparative bioavailability, food effect, multiple dose and dose proportionality obtained from these studies are summarized as follows:

Comparative bioavailability between oxycodone ER tablets and OxyContin tablets:

Oxycodone ER tablets (1 x 10 mg and 1x 80 mg) showed equivalent AU_{Ct}, AU_{Cinf} and C_{max} values, and similar median T_{max} values in comparison to corresponding strengths of OxyContin tablets (1 x 10 mg and 1x 80 mg) both under fasted and fed conditions. The oxycodone PK parameters for oxycodone ER 10 mg tablets and OxyContin 10 mg tablets under fasted and fed conditions and oxycodone ER 80 mg tablets and OxyContin 80 mg tablets under fasted and fed conditions are listed below in Table 1 and Table 2, respectively.

Table 1: Oxycodone PK parameters for oxycodone ER 10 mg tablet versus OxyContin 10 mg tablet under fasted and fed conditions

PK parameter ^a	Study 1878, Fasted (n=31)		Study 1879, Fed (n=29)	
	Oxycodone ER tablet 10 mg	OxyContin tablet 10 mg	Oxycodone ER tablet 10 mg	OxyContin tablet 10 mg
Cmax (ng/mL)	10.0 (30)	11.0 (27)	14.0 (23)	16.0 (27)
AUC0-t (h×ng/mL)	116 (33)	108 (28)	144 (28)	152 (30)
AUCinf (h×ng/mL)	122 (31)	113 (27)	148 (28)	158 (30)
Tmax (h) ^b	5.5 (1.0, 10.0)	5.0 (2.0, 6.0)	5.5 (1.5, 10.0)	5.0 (3.0, 10.0)
t _{1/2} (h)	5.2 (27)	4.6 (23)	4.0 (16)	4.2 (16)

^a values are arithmetic mean (% CV)

^b values are median (minimum, maximum)

Table 2: Oxycodone PK Parameters for oxycodone ER 80 mg tablet versus OxyContin 80 mg tablet under fasted and fed conditions

PK parameter ^a	Study 656-15-80, Fasted (n=30)		Study 655-15-80, Fed (n=29)	
	Oxycodone ER tablet 80 mg	OxyContin tablet 80 mg	Oxycodone ER tablet 80 mg	OxyContin tablet 80 mg
Cmax (ng/mL)	73 (33)	86 (35)	106 (25)	120 (28)
AUC0-t (h×ng/mL)	852 (33)	922 (32)	1053 (30)	1034 (31)
AUCinf (h×ng/mL)	870 (34)	933 (32)	1068 (30)	1045 (31)
Tmax (h) ^b	4.8 (1.0, 10.0)	4.9 (2.0, 6.0)	5.0 (1.0, 12.0)	5.5 (1.5, 10.0)
t _{1/2} (h)	4.9 (26)	4.7 (17)	4.2 (19)	4.1 (17)

^a values are arithmetic mean (% CV)

^b values are median (minimum, maximum)

The total exposures of oxycodone (AUCt, AUCinf and Cmax) for oxycodone ER tablets and OxyContin tablets met bioequivalence (BE) criteria both under fasted and fed conditions. The point estimate of the geometric mean ratio (oxycodone ER tablets / OxyContin tablets) and the corresponding 90% confidence intervals (CIs) for oxycodone AUCt, AUCinf and Cmax fell within the 80 - 125% BE limit. The analysis of bioequivalence for oxycodone PK parameters comparing oxycodone ER tablets versus OxyContin tablets under fasted and fed conditions are shown below in Table 3.

Table 3: Analysis of bioequivalence comparing oxycodone ER tablets versus OxyContin tablets under fasted and fed conditions

Strength, Condition	Geometric mean ratio (90%CI)		
	(Oxycodone ER tablets Vs OxyContin tablets)	AUC0-t	AUCinf
10 mg, fasted	106.10 (99.28 - 113.39)	107.33 (100.29 - 114.86)	93.00 (88.50 - 97.73)
10 mg, fed	95.30 (90.87 - 99.95)	95.12 (90.72 - 99.74)	88.03 (83.10 - 93.27)
80 mg, fasted	93.0 (85.63 - 100.94)	93.7 (86.31 - 101.70)	86.0 (80.17 - 92.34)
80 mg, fed	101.6 (94.88 - 108.70)	101.9 (95.32 - 108.86)	89.0 (81.94 - 96.75)

The median Tmax for oxycodone ER tablets 10 mg or 80 mg under fasted or fed conditions was 4.8 to 5.5 h, and is similar to that of OxyContin of 4.9 to 5.5 h. When range of individual Tmax (min, max) were compared, the Tmax range of oxycodone ER tablets under fasted state is 1.0 to 10 h compared to 2.0 to 6.0 h for OxyContin. Under fed state, Tmax range is 1.0 to 12 h for oxycodone ER tablets; and 1.5 to 10 h for OxyContin. Being an ER formulation taken to achieve steady state concentrations for the management of moderate-to-severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time, the impact of Tmax on clinical efficacy of oxycodone ER tablets is not expected. There was no difference in mean half-life (range) between oxycodone ER tablets 10 mg or 80 mg (4.0 to 5.2 h) and OxyContin 10 mg or 80 mg (4.0 to 4.7 h) under fasted or fed conditions.

Food Effect:

The fed bioequivalence of oxycodone ER 10 and 80 mg tablets is established to reference drug OxyContin 10 and 80 mg tablets in the studies 1879 and 655-15-80, respectively as shown above. In addition, food effect (fed versus fasted) on oxycodone ER 80 mg tablets was assessed in the study OXY-80-186. Oxycodone PK parameters for oxycodone ER tablet (1x 80 mg) under fasting and fed conditions are listed below in Table 4.

Table 4: Oxycodone PK parameters for 80 mg oxycodone ER tablet fed versus 80 mg oxycodone ER tablet fasted.

PK Parameter ^a	Oxycodone ER tablet	Oxycodone ER tablet
	80 mg, fasted (n=25)	80 mg, fed (n=25)
Cmax (ng/mL)	82 (30)	91 (21)
AUC0-t (h×ng/mL)	972 (24)	972 (24)
AUCinf (h×ng/mL)	996 (25)	1002 (24)
Tmax (h) ^b	5 (2, 7)	5 (2, 10)
t _{1/2} (h)	5.8 (31)	5.3 (16) ^c

^a values are arithmetic mean (% CV)

^b values are median (minimum, maximum)

^c N=24

Oxycodone ER tablet showed comparable overall exposure (AUC_t, and AUC_{inf}) and Cmax value following the administration of a single dose of 80 mg tablet between fed and fasted state.

In addition, oxycodone ER tablets showed bioequivalence to OxyContin tablets under the fed state and OxyContin labeling does not recommend a food restriction. Therefore, oxycodone ER tablet may also be taken without regard to food intake.

Dose Proportionality:

Following a single dose administration of oxycodone ER 10 mg, 15 mg, 20mg, 30 mg, 40 mg, 60 mg, and 80 mg tablets to healthy volunteers under naltrexone block and fasted conditions, oxycodone Cmax and AUC values was dose proportional based on the analyses on log transformed parameters using a power model. The slopes of log-transformed Cmax, AUCl, and AUCl_{inf} values for oxycodone were 0.88669, 0.97271 and 0.95310, respectively, and they fell within the range of 0.80 to 1.25. Therefore, dose proportionality is demonstrated over the range of 10 mg to 80 mg oxycodone ER tablets. As described in its label, dose proportionality was also demonstrated for OxyContin tablets.

Multiple Dose Pharmacokinetics

Multiple-dose PK of oxycodone ER 80 mg tablets and its comparison to OxyContin 80 mg tablets was evaluated in healthy volunteers under naltrexone blockade. A total of 6 multiple doses of oxycodone ER tablets or OxyContin tablets, one tablet every 12 hours (BID x 3 days) were administered in two treatment periods. With BID dosing, the steady state is achieved within one day for oxycodone ER tablets or OxyContin tablets. The multiple dose PK parameters, steady state AUC (AUCl_{0-tau,ss}), steady state maximum concentrations (Cmax,ss), average concentrations over the dosing interval (Cavg) and Tmax after multiple dosing are comparable between oxycodone ER tablets and OxyContin tablets (Table 5).

Table 5: Oxycodone PK parameters after multiple dosing of oxycodone ER 80 mg tablets versus OxyContin 80 mg tablets

PK Parameter ^a	Oxycodone ER tablets	OxyContin tablets
	80 mg (n=24)	80 mg (n=24)
C max(ss) (ng /mL) ^b	84 (38)	79 (22)
C min (ss) (ng /mL)	31(40)	30 (37)
AUC0-tau (ng*hr/mL)	678 (30)	638 (24)
Cavg (ng /mL) ^c	57 (30)	53 (24)
*T max after last multiple dose (h) ^d	2.3 (1.5 , 7.0)	3.0 (1, 10.0)

^a values are arithmetic mean (% CV)

^b Cmax,ss: Cmax after last multiple dose

^c Cav: average concentration over the dosing interval, AUCl_{0-tau} /12 h

^d Tmax, values are median (minimum, maximum)



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

MEMORANDUM

DATE: June 22, 2017

FROM: Xiaobin Shen, Ph.D., Review Chemist
Julia Pinto, Ph.D., Branch Chief

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

RE: Open Session Study Results Document: In Vitro Studies of Proposed Abuse-Deterrence Properties, July 26th, 2017 AADPAC/DSaRM Meeting to Discuss NDA 209-653

Nomenclature

Rexista, Oxycodone Extended-Release Tablets, Oxycodone HCl ER

- All refer to the drug product under review. The various names have been used throughout the NDA and may show up in the contents below as some are directly reproduced from the Applicant's NDA submission. Note that Rexista is a firm internal name and is not approved by the Agency.

OxyContin, OxyContin 80 mg

- All refer to the commercial comparator drug product OxyContin 80 mg.

1. Overview of the Proposed Product Abuse Deterrent Formulation (ADF) Features

The drug product is an oral extended-release (ER) tablet formulation containing 10, 15, 20, 30, 40, 60 and 80 mg oxycodone hydrochloride.

The tablet contains blue dye. The Applicant believes that the dye causes stigmatization to the potential abuser and imparts abuse-deterrent characteristics to the product. The tablet also has a component that is a nasal irritant to deter abuse via insufflation.

All tablet strengths share an identical product design. The lowest 10 mg and the highest 80 mg product strengths were selected to conduct most of the in vitro abuse- deterrent studies. The comparator product was OxyContin 80 mg.

The coding for specific in vitro conditions discussed below is included as an appendix in the closed session briefing document.

2. In Vitro Abuse Deterrence Study Results

Among the in vitro abuse-deterrent studies conducted to assess the relative difficulty and effectiveness of various potential manipulation methods to defeat the drug product's abuse-deterrent properties, only the methodologies and results that reflect the most probable abuse approaches and that pose the most challenges to the drug product under evaluation are summarized below.

A. Physical Manipulation (Size Reduction) Study Results (Study Report: IPC-R-OXY CAT1.STUDY-01)

The oxycodone extended-release tablets are relatively easier to reduce into fine particles than OxyContin tablets. Note that resistance to particle size reduction is not one of the product's mechanisms for abuse deterrence.

For the 10 common household tools tested, 7 tools (Tools 1, 3, 5, 6, 7, 8, 9 and 10) can be used to reduce the oxycodone extended-release tablets into fine particles; while only 5 tools (Tools 5, 6, 7, 8, 9 and 10) can be used to reduce the OxyContin tablets into fine particles. Further, when the most efficient, Tool 10, was used to manipulate the tablets, the oxycodone extended-release tablets can be reduced into much finer particles than the OxyContin tablets, as shown in the results summarized below (Table 1).

Product	Time	D10 (um)	D50 (um)	D90 (um)
Rexista 10 mg	1 min	17.7	84.1	298.3
	3 min	13.4	59.8	254.4
	5 min	13.1	56.1	252.7
Rexista 80 mg	1 min	10.6	84.9	302.8
	3 min	9.7	63.3	262.8
	5 min	7.6	50.8	232.8
OxyContin 80 mg	1 min			
	3 min	6.9	227.9	481.3
	5 min	4	194.6	502.9

Table 1. Particle size distributions of the oxycodone extended-release tablets and the comparator product OxyContin 80 mg after being particle size reduced using Tool 10 for different durations.

As the oxycodone extended-release tablets were already found easier in terms of particle size reduction, further pretreatment and then particle size reduction was not performed.

The optimal particle size reduction approach was identified as manipulating the tablets using Tool 10 for an optimal number of tablets and optimal time duration. This method was used to prepare the powder samples used in subsequent in vitro studies.

B. Large Volume Extraction Using Various Solvents Study Results (Study Report: IPC-R-OXY-CAT1.STUDY-05)

Extraction in Model Solvents

This part of the study tested all oxycodone extended-release tablet strengths. The results provide an overall extraction profile.

Solvent 1

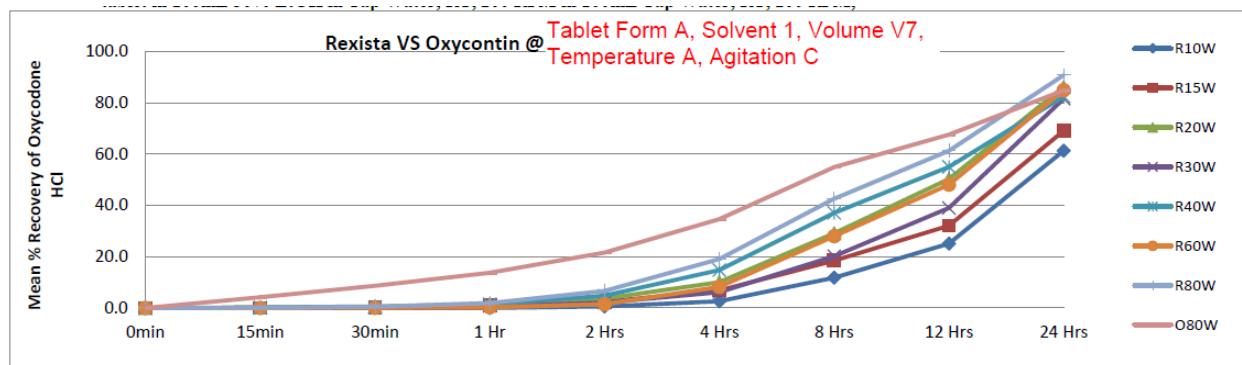


Figure 1. Extraction recoveries of oxycodone extended-release tablets (all product strengths) and the comparator OxyContin 80 mg. The study variables are specified in the figure legend.

Reference the codes to the coding appendix
in the Closed Session document for actual variable meanings.

The comparator OxyContin tablet showed clearly higher recoveries than all oxycodone extended-release tablet strengths at all time points except at 24 hours (Figure 1).

Similar recovery profiles were observed when Volume V8 of Solvent 1 was used to repeat the testing with all other conditions unchanged. There was no apparent difference in extraction in the first hour when compared to the Volume V7 test results. Thereafter, as sampling time increased, slightly higher extractions were observed at the corresponding sampling times.

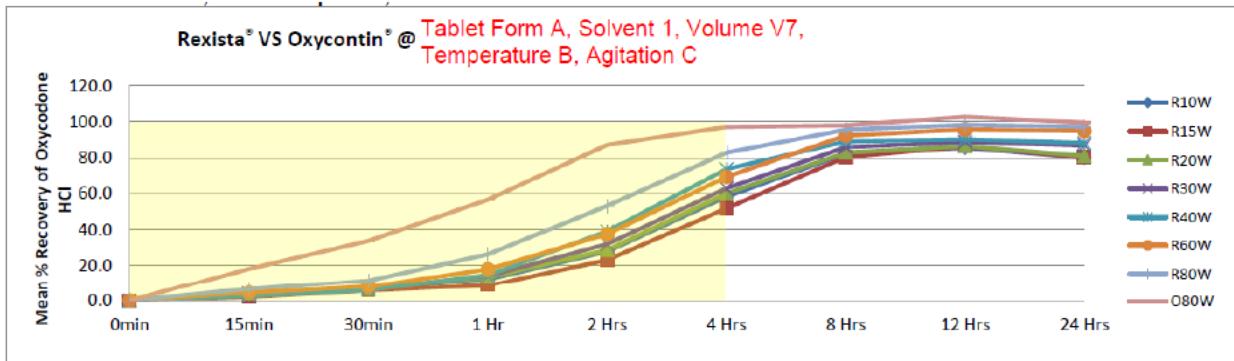


Figure 2. Extraction recoveries of oxycodone extended-release tablets (all product strengths) compared to the comparator OxyContin 80 mg.

As shown in Figure 2, when tested at Volume V7 but at Temperature B, the extraction profile approximated complete extraction by plateauing at 4 - 8 hrs. OxyContin showed clearly higher extractions than all oxycodone extended-release tablets in the earlier sampling times.

When solvent volume changed to Volume V8, the extraction profiles showed no apparent change.

Solvent 14

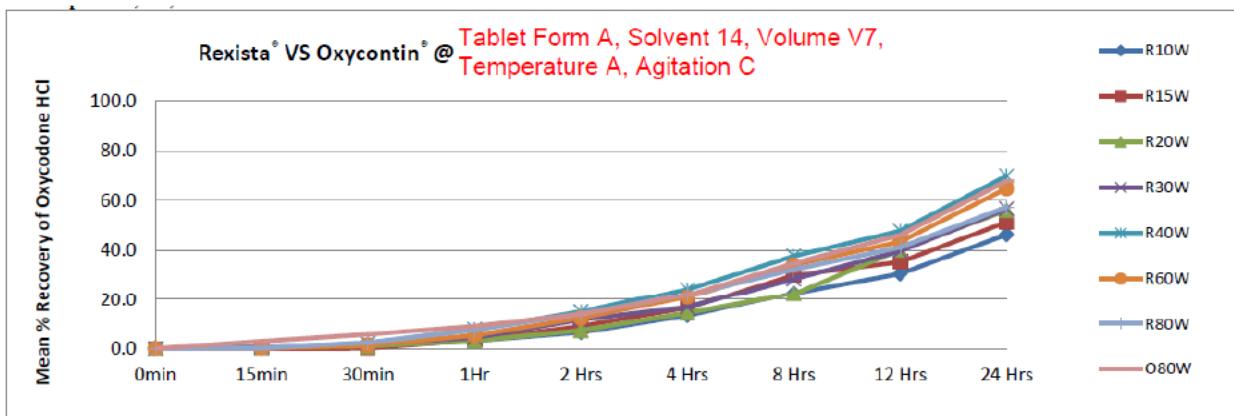


Figure 3. Extraction recoveries of oxycodone extended-release tablets (all product strengths) compared to the comparator OxyContin 80 mg.

As shown in Figure 3, Solvent 14 apparently is not as efficient as Solvent 1 for oxycodone extraction. Despite of the compressed chart scale, OxyContin had clearly higher recoveries (verified by the % recovery numbers in the corresponding tables provided) than all oxycodone extended-release tablet strengths in the first hour. Then as sampling time increased, the 40 mg oxycodone extended-release tablets started to extract faster than OxyContin. However, when all oxycodone extended-release tablet strengths are considered along with analytical variation, there was no meaningful difference in

extraction efficiency between OxyContin and oxycodone extended-release tablets for the sampling points between 2 and 24 hours.

Similar recovery profiles were observed when Volume V8 of Solvent 14 was used to repeat the testing with all other conditions unchanged. This change showed no clear extraction difference between the oxycodone extended-release tablets and OxyContin tablets.

Note that Solvent 14 was not conducive to be tested at Temperature B.

Extraction in Twenty Various Solvents

This part of the study tested oxycodone extended-release 10 mg and 80 mg tablets in comparison to the OxyContin 80 mg tablets. The other oxycodone extended-release tablet strengths are considered bracketed.

High level summaries are provided below to highlight the critical outcomes and aspects of the study results.

Tablet Form A / Solvent 1

The test using Solvent 1, Volume V7, at Temperature A and Agitation A represents a starting point of the overall study. The extraction profile showed clearly higher extraction recoveries of OxyContin® 80 mg tablets across all tested time points, as shown below in Figure 4.

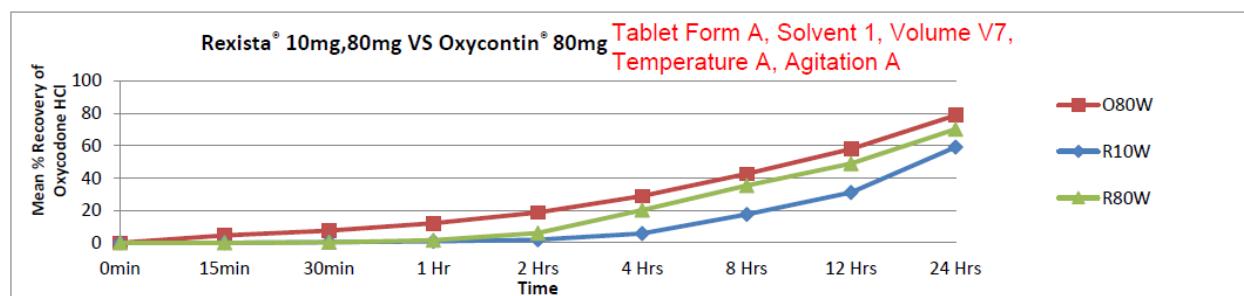


Figure 4. Extraction recoveries of oxycodone extended-release tablets (10 mg and 80 mg strengths) and the comparator OxyContin 80 mg – Baseline study for Tablet Form A.

Testing using Volume V8, with all other variables unchanged, only marginally increased the extraction recoveries for all tested tablets over all tested time points, the overall extraction profile remained similar.

Testing at Agitation C, with all other variables unchanged, clearly increased the extraction recoveries for all tested tablets over all tested time points, the overall extraction profile remained similar.

Testing at Temperature B, with all other variables unchanged, significantly increased the extraction recoveries for all tested tablets over earlier tested time points, thus the overall extraction profile changed, as illustrated below in Figure 5.

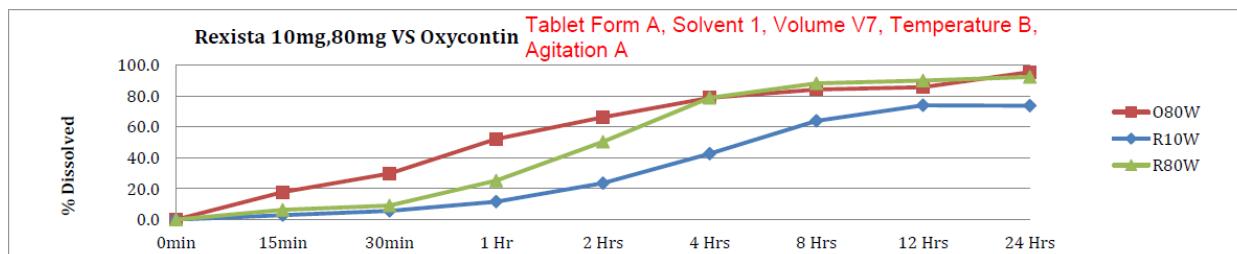


Figure 5. Extraction recoveries of oxycodone extended-release tablets (10 mg and 80 mg strengths) and the comparator OxyContin 80 mg – Effect of Temperature.

Figure 6 below shows the extraction profiles with the most effective extractions under the given conditions.

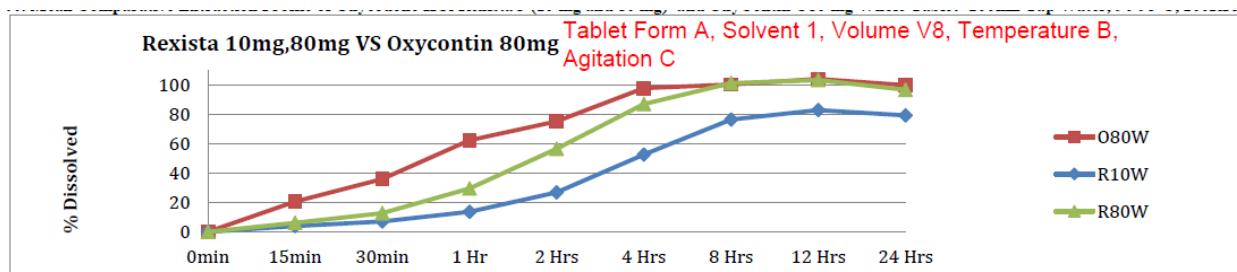


Figure 6. Extraction recoveries of oxycodone extended-release tablets (10 mg and 80 mg strengths) and the comparator OxyContin 80 mg – Most efficiency extractions for Tablet Form A and Solvent 1.

In all cases, OxyContin® had higher extractions at earlier time points.

Tablet Form A / Other Solvents

Solvent 2, Solvent 4 – 8, and Solvent 12, showed higher extraction recoveries than Solvent 1 at the corresponding test conditions and time points. This is illustrated by the extraction profiles for Solvent 7, which approximately shows the best extraction recoveries at the most effective conditions among all solvents listed in this sub-section (Figure 7).

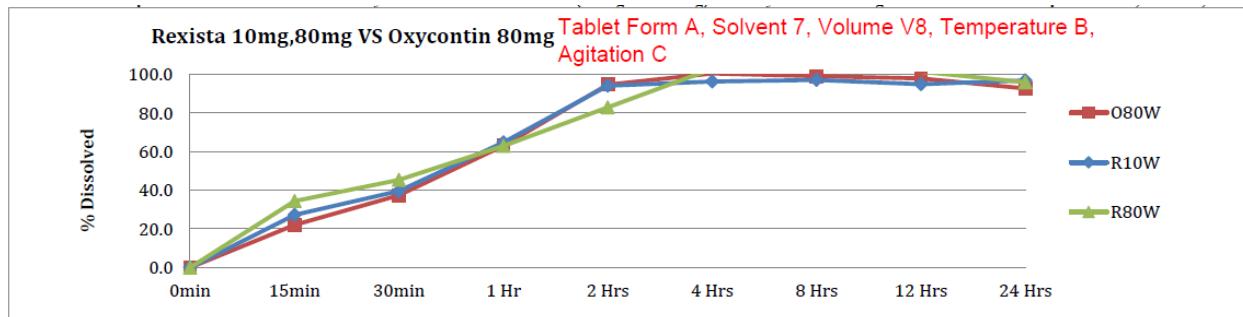


Figure 7. Extraction recoveries of oxycodone extended-release tablets (10 mg and 80 mg strengths) and the comparator OxyContin 80 mg – Most efficiency extractions for Tablet Form A and Solvent 7.

Despite of the different extraction recoveries, when analytical variations are considered, OxyContin either had clearly higher recoveries or had no meaningful difference in extraction recoveries from the oxycodone extended-release tablets dependent on the sampling points between 15 min and 24 hours. In other words, the oxycodone extended-release tablets had similar or lower extraction efficiency than OxyContin tablets.

It is important to note that Solvent 3 was found to be very unique. Although its extraction efficiency was not the least among all solvents tested at Temperature A, as shown in Figure 8, changing from Temperature A to Temperature B allows it to become the most effective solvent to extract oxycodone from the oxycodone extended-release tablets. Meanwhile, it still had poor extraction efficiency for OxyContin tablets.

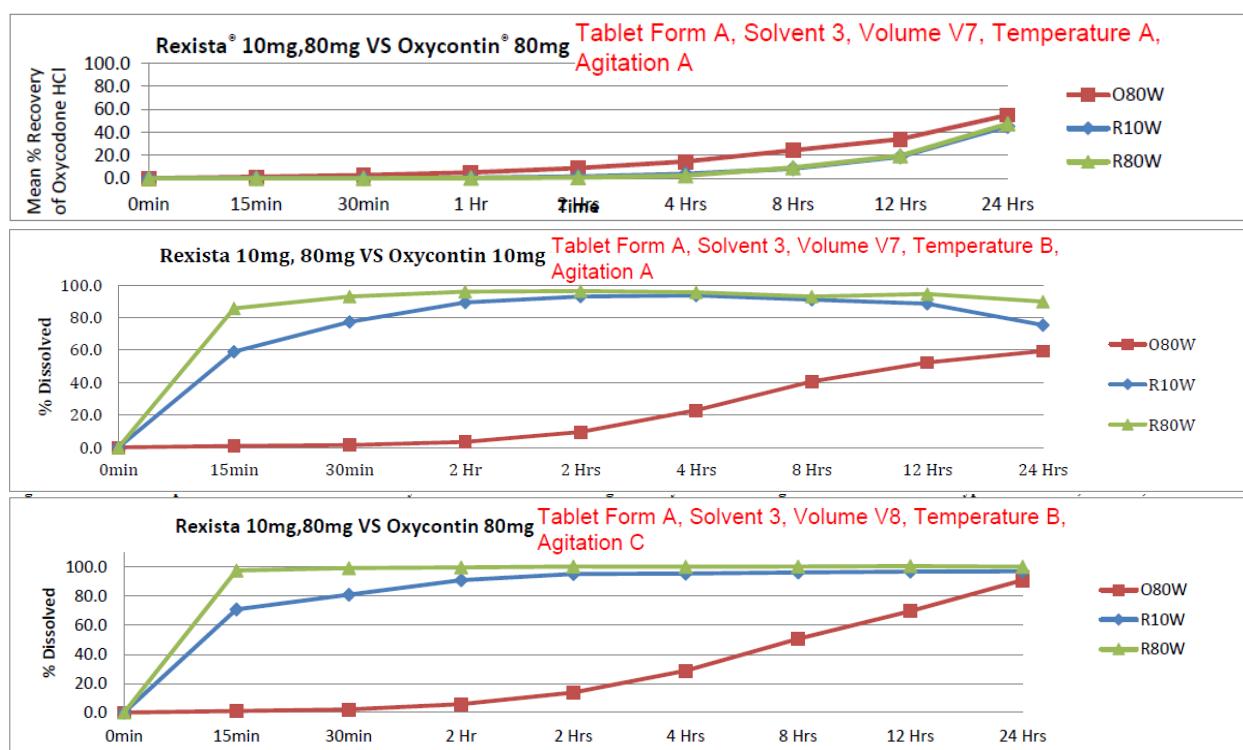


Figure 8. Extraction recoveries of oxycodone extended-release tablets (10 mg and 80 mg strengths) and the comparator OxyContin 80 mg – A comparison of temperature effect on extraction efficiency for Tablet Form A and Solvent 3.

All other solvents had poorer extraction efficiency than Solvent 1 in general.

Tablet Form B / Solvent 1

The test using Solvent 1, Volume V7, at Temperature A and Agitation A represents a starting point of the study for Tablet Form B. The extraction profile, across all tested time points, showed no clear difference in extraction recoveries of OxyContin 80 mg tablets from the oxycodone extended-release 80 mg tablets although oxycodone extended-release 10 mg tablets clearly had lower extraction efficiencies (Figure 9). The overall higher recoveries indicate that Tablet Form B is significantly easier to be extracted.

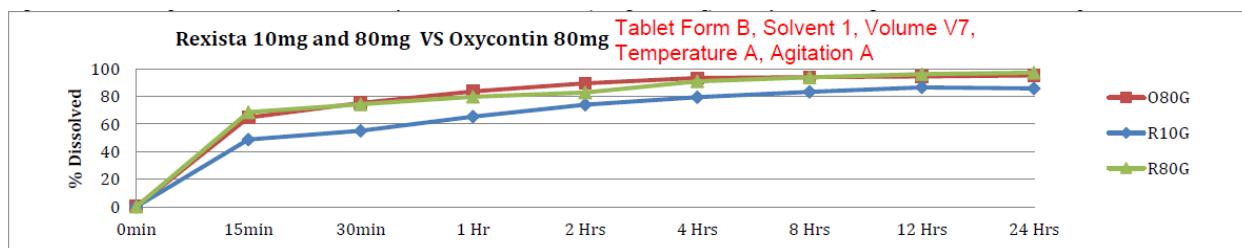


Figure 9. Extraction recoveries of oxycodone extended-release tablets (10 mg and 80 mg strengths) and the comparator OxyContin 80 mg – Baseline study for Tablet Form B.

As expected, while keeping other factors unchanged, changing from Temperature A to Temperature B, and from Agitation A to Agitation C, each change increased the oxycodone extraction efficiency for all products and shifted the profile plateau region to earlier sampling times. Collectively these changes make the extraction profiles reaching their plateaus in 15 minutes and possibly sooner (Figure 10). However, there is no apparent difference between OxyContin and the oxycodone extended-release tablets when analytical variations are considered.

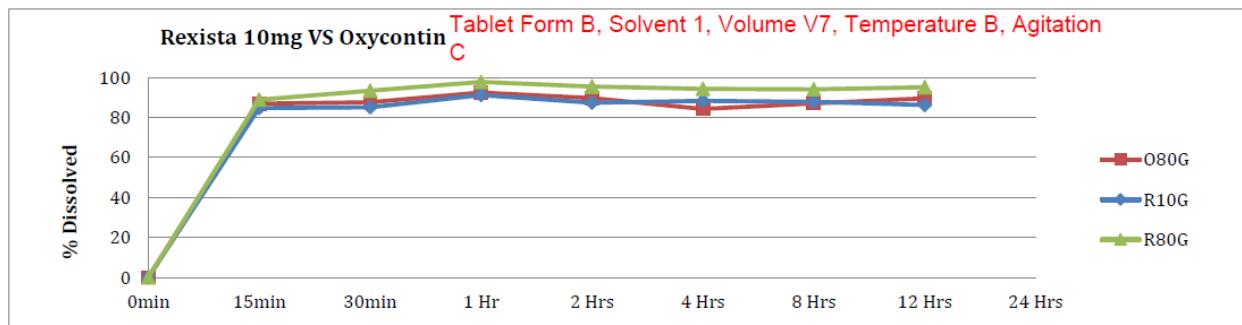


Figure 10. Extraction recoveries of oxycodone extended-release tablets (10 mg and 80 mg strengths) and the comparator OxyContin 80 mg – Changing temperature and agitation increased extraction efficiency.

Further change in solvent volume from Volume V7 to Volume V8, with other factors kept the same, had no apparent effect to oxycodone extraction because it has been approximately complete already (profiles not reproduced).

Tablet Form B / Other Solvents

Except Solvent 20, which had relatively low oxycodone extraction recoveries as shown below in Figure 11, all other tested solvents were very efficient in extraction and had 60% to 100% of recoveries for all tablet products by 15 minutes. Apparently Tablet Form B and Agitation C are the most important factors in determining oxycodone extractions.

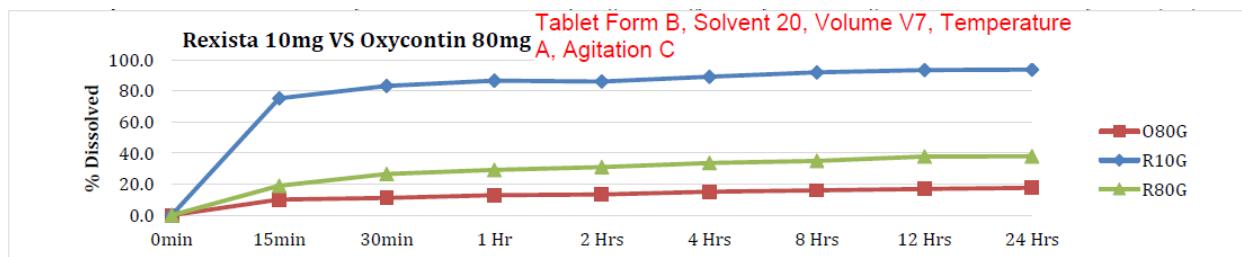


Figure 11. Extraction recoveries of oxycodone extended-release tablets (10 mg and 80 mg strengths) and the comparator OxyContin 80 mg – Solvent 20 has apparently different extraction characteristics based on tablet strength.

The extraction profiles across all tested time points, except in Solvent 20 as shown above, had no clear difference in extraction recoveries of OxyContin® 80 mg tablets from the oxycodone extended-release tablets. Solvent 20, however, showed selectively high extraction recoveries for oxycodone extended-release 10 mg tablets.

Solvent 21 showed practically no oxycodone extraction from either product.

C. Syringeability / Injectability Study Results (Study Report: IPC-R-OXY-CAT1.STUDY-06)

Study conditions that are not syringeable are briefly summarized. The conditions that had syringeable content will be summarized in more detail.

The Applicant's definition of syringeable is for a sample to be withdrawn, within 2 minutes, into the syringe at 20% or more of the test solvent volume used in each test. This was a subjective but reasonable criterion for the applicant to filter out meaningless studies.

Tablet Form B with Pre-treatment A – Prepared in Solvent 1

This part of the study was conducted on oxycodone extended-release 10 mg, 80 mg and OxyContin 80 mg tablets.

When varying volumes of Solvent 1 were used to prepare the sample for syringing, due to high viscosity, the samples were not syringeable with a single dose of oxycodone extended-release tablet or OxyContin tablet (Comparator) at Temperature A or at Temperature B using a D gauge needle, regardless of Agitation type or the sampling time tested.

The syringeability pictures of oxycodone extended-release 80 mg sampled at 30 min for the two extreme volumes (V1) and (V6) and the two extreme temperatures (A and B) as shown in Figure 12 below are typical of all samples.

			
Volume V1 mL	Volume V6 mL	Volume V1 mL	Volume V6 mL
Temperature A	Temperature A	Temperature B	Temperature B

Figure 12. Samples with Pre-treatment A cannot be syringed when prepared in Volume V6 mL or smaller volume of Solvent 1.

			
Rexista 80 mg	OxyContin 80 mg	Rexista 80 mg	OxyContin 80 mg
Temperature A	Temperature A	Temperature B	Temperature B

Figure 13. Visual presentation showing that the sample is viscous at 30 minutes after preparation – Tablet Form B with Pre-treatment A prepared in Volume V6 mL Solvent 1.

Other needle sizes were deemed not necessary to be tested.

Tablet Form B with Pre-treatment A – Prepared in Solvent 1 (Extended Time)

This study is also called by the Applicant as the Gel-Blob Syringeability study. It was conducted using Tablet Form B of the oxycodone extended-release 80 mg and OxyContin

80 mg tablets, Volume V2 mL of Solvent 1 at Temperature A, Temperature B and Agitation A, a D Ga needle, for durations of 4 and 24 hours.

At Temperature A, the samples were not syringeable at either 4 or 24 hours.

At Temperature B, the solution was syringeable at 4 hours but not at 24 hours. The syringed liquid had an average of 27.0% of oxycodone recovery from oxycodone extended-release 80 mg tablet sample, and 46.1% from the OxyContin 80 mg sample. This demonstrated that oxycodone extended-release tablets are not more syringeable than OxyContin tablets.

Since it was syringeable using a D Ga needle, a C Ga needle was used to test again. This time the syringed liquid had an average of 25.3% of oxycodone recovery from oxycodone extended-release 80 mg tablet sample, and 59.2% from the OxyContin 80 mg sample. This demonstrated that oxycodone extended-release tablets are not more syringeable than OxyContin tablets.

Further testing with a B Ga needle showed that neither sample was syringeable.

Tablet Form B with Pre-treatment D – Prepared in Solvent 1

Solvent Volume – V1 mL

This part of the study was conducted on Tablet Form B of oxycodone extended-release 80 mg tablets and OxyContin 80 mg tablets, using Volume V1 mL of Solvent 1 over sampling times of 0.5 min, 3 min and 5 min.

Solvent Temperature A –

Both samples were syringeable with a D Ga needle at 0.5 min. The oxycodone extended-release tablet samples had negligible oxycodone recoveries at an average of 1.5% and 2.9% at 0.5 min and 3 min respectively. The OxyContin samples had significantly higher oxycodone recoveries, reaching an average of 72.9% at 0.5 min.

Further testing with an A Ga needle also demonstrated syringeability of both samples. Again, the oxycodone extended-release tablet sample had a low average of 2.0% recovery at 0.5 min. The OxyContin sample had an average of 40.2% oxycodone recovery at 0.5 min. This also indicates that the samples are also syringeable using B Ga and C Ga needles.

Solvent Temperature B –

Both samples were syringeable with a D Ga needle at 0.5 min. The oxycodone extended-release tablet samples had relatively low oxycodone recoveries at an average of 16.5%. The OxyContin samples had significantly higher oxycodone recoveries, reaching an average of 38.7% at 0.5 min. Note that the results were very variable among the three replicates.

Similarly, further testing with an A Ga needle also demonstrated syringeability of both samples. The oxycodone extended-release tablet samples had an average oxycodone recovery of 7.0% and 0.90%, at 0.5 min and 3 min respectively. The OxyContin sample had an average of 64.9% oxycodone recovery at 0.5 min. Hence oxycodone extended-release tablet is relatively less syringeable than OxyContin. These results indicate that the samples are also syringeable using B Ga and C Ga needles.

Solvent Volume – V2 mL

This part of the study was conducted on Tablet Form B of oxycodone extended-release 80 mg tablets and OxyContin 80 mg tablets, using Volume V2 mL of Solvent 1 over sampling times of 0.5 min, 3 min and 5 min.

Solvent Temperature A –

Both samples were syringeable with a D Ga needle at 0.5 min. The oxycodone extended-release tablet samples had oxycodone recoveries at an average of 20.0%, 14.3% and 15.9% at 0.5 min, 3 min and 5 min respectively. The OxyContin samples had oxycodone recoveries at an average of 85.0% at 0.5 min already.

When tested with an A Ga needle, the oxycodone extended-release tablet samples had oxycodone recoveries at an average of 19.1% and 22.1% at 0.5 min and 5 min respectively. The OxyContin samples had oxycodone recoveries at an average of 34.5% and 19.8% at 0.5 min and 3 min respectively. These results indicate that the samples are also syringeable using B Ga and C Ga needles.

Solvent Temperature B –

Both samples were syringeable with a D Ga needle at 0.5 min and 3 min. The oxycodone extended-release tablet samples had oxycodone recoveries at an average of 51.8% and 18.7% at 0.5 min and 3 min respectively. The OxyContin samples had oxycodone recoveries at an average of 47.8% and 14.3% at 0.5 min and 3 min respectively.

When tested with an A Ga needle, the oxycodone extended-release tablet samples had oxycodone recoveries at an average of 22.8% and 24.9% at 0.5 min and 5 min respectively. The OxyContin samples had oxycodone recoveries at an average of 44.2% and 9.9% at 0.5 min and 3 min respectively. These results indicate that the samples are also syringeable using B Ga and C Ga needles.

Solvent Volume – V3 mL

This part of the study was conducted on Tablet Form B of oxycodone extended-release 80 mg tablets and OxyContin 80 mg tablets, using Volume V3 mL of Solvent 1 over sampling times of 0.5 min, 3 min and 5 min.

Solvent Temperature A –

Both samples were syringeable with a D Ga needle at 0.5 min. The oxycodone extended-release tablet samples had oxycodone recoveries at an average of 33.7%, 35.3% and 22.4% at 0.5 min, 3 min and 5 min respectively. The OxyContin samples had oxycodone recoveries at an average of 43.1% and 40.78% at 0.5 min and 3 min respectively.

When tested with an A Ga needle, the oxycodone extended-release tablet samples had oxycodone recoveries at an average of 28.3% and 18.5% at 0.5 min and 3 min respectively. The OxyContin samples had oxycodone recoveries at an average of 36.0% and 29.8% at 0.5 min and 3 min respectively. These results indicate that the samples are also syringeable using B Ga and C Ga needles.

Solvent Temperature B –

Both samples were syringeable with a D Ga needle at 0.5 min, 3 min and 5 min. The oxycodone extended-release tablet samples had oxycodone recoveries at an average of 18.5%, 24.9% and 16.5% at 0.5 min, 3 min and 5 min respectively. The OxyContin samples had oxycodone recoveries at an average of 25.6%, 25.9% and 16.2% at 0.5 min, 3 min and 5 min respectively.

When tested with an A Ga needle, the oxycodone extended-release tablet samples had oxycodone recoveries at an average of 24.3%, 21.0% and 17.3% at 0.5 min, 3 min and 5 min respectively. The OxyContin samples had oxycodone recoveries at an average of 28.1%, 28.5% and 26.6% at 0.5 min, 3 min and 5 min respectively. These results indicate that the samples are also syringeable using B Ga and C Ga needles.

Tablet Form B with Pre-treatment A – Prepared in Solvent 2

This part of the study was conducted on Tablet Form B of oxycodone extended-release 10 mg tablet, 80 mg tablets and OxyContin 80 mg tablets.

All volumes of Solvent 2 tested were not syringeable with single dose of oxycodone extended-release tablet sample or OxyContin (Comparator) tablet sample at Temperature A or Temperature B using a D gauge needle, regardless of shaking speed or the sampling time tested.

At solvent volumes of V4 mL and V6 mL, Solvent 2 appeared to allow discernibly more liquid to be syringed than Solvent 1, despite of the still low volume.

Although defined as not syringeable when the syringed content is less than 20% in the volume of solvent used, in some Volume V6 mL samples, up to 2.8 g and 7 g of the solvent was withdrawn into the syringe for the oxycodone extended-release tablet samples and OxyContin tablet samples respectively. Note that the applicant's goal is to compare to the OxyContin and demonstrate their oxycodone extended-release tablet's non-inferiority.

Similarly, other needle sizes were deemed not necessary to be tested.

Tablet Form B with Pre-treatment A – Prepared in Solvent 22

This part of the study was conducted on Tablet Form B of oxycodone extended-release 80 mg tablets and OxyContin 80 mg tablets using Volume V2 mL of Solvent 22 over 0.5 min, 3 min and 5 min.

Neither oxycodone extended-release 80 mg tablet sample nor OxyContin 80 mg tablet sample was syringeable through a D Ga needle under the studied conditions at Temperature A or Temperature B.

Tablet Form A with Pre-treatment A – Prepared in Solvent 2

This part of the study was conducted on Tablet Form A of oxycodone extended-release 80 mg tablet and OxyContin 80 mg tablets.

Apparently due to the observation that Solvent 2 renders better syringeability than Solvent 1, the study was only conducted using Solvent 2 and at Volume V6 mL over 5 min, 10 min and 30 min sampling points.

For both oxycodone extended-release 80 mg tablets and OxyContin 80 tablets, the liquid volume syringed using a D Ga needle ranged between 7 and 11 g, regardless of the sampling time, solvent temperature or agitation speed. Despite of reaching approximately the 20% syringeability definition criterion, chemical analysis showed that the oxycodone active recovered from the syringed liquid was low, mostly at 0% but at up to 7.3% for oxycodone extended-release tablet and 12.26% for OxyContin. The oxycodone extended-release 80 mg tablet is comparatively less syringeable than OxyContin 80 mg tablet in Solvent 2.

Multiple Dose Tablet in Tablet Form B with Pre-treatment A – Prepared in Solvent 1

This part of the study was conducted on a three dose equivalent of oxycodone extended-release 80 mg tablets and OxyContin 80 mg tablets, prepared in Tablet Form B. The syringeability test solvent volumes used were Volume V3 mL and V4 mL. The testing was conducted at Temperature A and Temperature B, with Agitation A and Agitation C, for extraction duration of 10 minutes.

The samples were not syringeable using a D Ga needle, no additional testing was needed.

Multiple Dose Tablet in Tablet Form B with Pre-treatment D – Prepared in Solvent 1

This part of the study was conducted on a three dose equivalent of oxycodone extended-release 80 mg tablets and OxyContin 80 mg tablets, prepared in Tablet Form B and after application of Pre-treatment D. The syringeability test solvent volumes used were Volume V3 mL and V4 mL. The testing was conducted at Temperature A and Temperature B, with Agitation A and Agitation C, for extraction duration of 10 minutes. The results are reported below based on study condition combinations.

Solvent Volume – V3 mL / Temperature A / Agitation C

Oxycodone extended-release tablet sample was not syringeable using a D Ga needle. OxyContin sample was syringeable with an A Ga needle, recovering an average of 56% oxycodone from the syringed contents.

Solvent Volume – V3 mL / Temperature B / Agitation C

Oxycodone extended-release tablet sample was not syringeable using a D Ga needle. OxyContin sample was syringeable with an A Ga needle, recovering an average of 63.2% oxycodone from the syringed contents.

Solvent Volume – V4 mL / Temperature A / Agitation C

Oxycodone extended-release tablet sample was not syringeable using an A Ga needle. OxyContin sample was syringeable, recovering an average of 26.4% oxycodone from the syringed contents.

Solvent Volume – V4 mL / Temperature B / Agitation C

Both samples were syringeable with an A Ga needle. The Oxycodone extended-release tablet sample had an average oxycodone recovery of 29.6%. The OxyContin sample had an average oxycodone recovery of 60.28%.

D. Dye and Nasal Irritant Elimination Study Results (Study Report: IPC-P-OXY-CAT1.STUDY-04)

Dye Elimination by Extraction with Various Solvents

The extraction results for the filtrate and residue are summarized in Table 2 below.

Solvent Type	Color		Sample Type	% Oxycodone HCl Recovered			% Average Recovery	% RSD
	Initial	24 hr		1	2	3		
Solvent 11	Blue	Blue	Filtrate	80	87.2	101.7	89.6	12.3
	-	Light Blue	Residue	8.5	10	7.9	8.8	12.3
Solvent 23	Blue	Blue	Filtrate	45.3	44	45.2	44.8	1.6
	-	Light Blue	Residue	38.5	44.1	47.2	43.3	10.2
Solvent 13	Blue	Blue	Filtrate	95.3	97.8	97.2	96.7	1.3
	-	Deep Blue	Residue	0.19	0.27	0.18	0.2	24.0
Solvent 18	Blue	Blue	Filtrate	96.2	97.8	97.8	97.3	0.9
	-	Deep Blue	Residue	0.89	0.08	0.73	0.6	75.1
Solvent 20	Blue	Colorless	Filtrate	37.5	38.6	37.9	38.0	1.4
	-	Deep Blue	Residue	52.67	51.59	52.65	52.3	1.2
Solvent 24	Blue	Colorless	Filtrate	0	0	0	0.0	N/A
	-	Deep Blue	Residue	67.3	81.88	81.16	76.8	11.7

Table 2. Extraction results of the oxycodone extended-release 80 mg tablet using a variety of solvents to separate the blue dye from the oxycodone active.

Only Solvent 20 and Solvent 24 allowed elimination of the blue dye, but the oxycodone recovery was low and the solvents are not suitable for direct ingestion or injection.

Dye Elimination by Selective Degradation

Pre-treatment B resulted in no discernable color change to the ground oxycodone extended-release tablet powder. Pre-treatment E caused the oxycodone extended-release tablet powder color to darken from light blue.

There was no color elimination with Solvent 25 treatment in either the not pre-treated samples or Pre-treatment B and Pre-treatment E treated samples. The oxycodone recoveries in the filtrates from all control and pretreated samples ranged between 47.7% and 51.3%.

When treated using Solvent 26, the solution color was a function of time. All control and pretreated samples remained in light blue color at 30 minutes of treatment. By 24 hours, the blue colored solutions were filtered, the filtrates were milky white and the residues were visually white. However, the oxycodone recoveries in the filtrates from all control and pretreated samples ranged only between 15.5% and 19.2%.

There was no color elimination with Solvent 27 treatment in either the not pre-treated samples or Pre-treatment B and Pre-treatment E treated samples. The oxycodone recoveries in the filtrates from all control and pretreated samples ranged between 5.1% and 5.2%.

Overall, the blue dye cannot be easily separated or selectively degraded.

Selective Separation of Oxycodone from Nasal irritant

The extraction results for the filtrate and residue are summarized in Table 3 below.

Sample #	1	2	3	Mean	% RSD
Net wt. (mg)	486.71	487.33	487.27	487.10	
Theoretical amount of Oxycodone (mg)	79.92	79.65	79.93	79.83	
Extracted amount (Salt, mg)	79.48	77.83	77.36	78.22	1.4
Assay, mg	66.13	66.72	63.86	65.57	2.3
% Recovery of Oxycodone salt	82.78	83.41	79.85	82.0	2.3
% Purity of Oxycodone Salt	82.95	85.47	82.30	83.6	2.0

Table 3. Recovery of oxycodone base separated from Nasal Irritant in the oxycodone extended-release 80 mg tablet.

Despite that the oxycodone base was separated with good recoveries and purity, the Applicant noted that “this process is not commonly known to all abusers as the procedure involved requires sufficient knowledge of the chemistry behind the processes”. The process used is akin to the final purification step typically employed in drug substance

manufacturing. Therefore it is reasonable to state that technical know-how is needed to achieve the separation.

E. Complex Extraction and Isolation Study Results (Study Report: IPC-R-OXY-CAT1. STUDY-09)

Free-Base Extraction Study

Oxycodone base extracted with Solvent 24 from oxycodone extended-release tablet produced colorless crystals. It is 96.4% pure but with 33.8% yield. Similar results were obtained with OxyContin with a mean purity of 92.0% and 58.6% yield.

Oxycodone base extracted with Solvent 20 from oxycodone extended-release tablet produced a blue colored crystal material, 85.1% pure at 81.4% recovery. After further extraction with Solvent 24, separation and evaporation, it produced colorless crystals but further purity and yield were not reported. When OxyContin was similarly extracted, it has 93.4% purity at 82.5% recovery.

Oxycodone base extracted with Solvent 19 from oxycodone extended-release tablet produced a blue colored crystal material, 82.5% pure at 47.6% recovery. After further extraction with Solvent 24, separation and evaporation, it produced colorless crystals but further purity and yield were not reported. When OxyContin was similarly extracted, it has 85.3% purity at 74.2% recovery.

The key parameters of above results are also summarized in Table 4 for quick comparison.

Extraction Solvent	Tablet	Extract Appearance	Extract Purity (%)	Yield (%)
Solvent 24	Rexista 80 mg	Colorless crystals	96.4	33.8
	OxyContin 80 mg	Colorless crystals	92.0	58.6
Solvent 20	Rexista 80 mg	Colorless crystals ¹	85.1	81.4
	OxyContin 80 mg	Colorless crystals	93.4	82.5
Solvent 19	Rexista 80 mg	Colorless crystals ¹	82.5	47.6
	OxyContin 80 mg	Colorless crystals	85.3	74.2

¹. The first round of extract was a blue colored crystal. Further extraction, separation and evaporation were needed to produce colorless crystals.

Table 4. Yield and purity of different solvent extracts from the oxycodone extended-release 80 mg tablet and the OxyContin 80 mg tablet.

Free-Base Precipitation Study

46.1% oxycodone base was precipitated from oxycodone extended-release tablet with a purity of 51.4%.

55.1% oxycodone base was precipitated from OxyContin tablet with a purity of 91.4%.

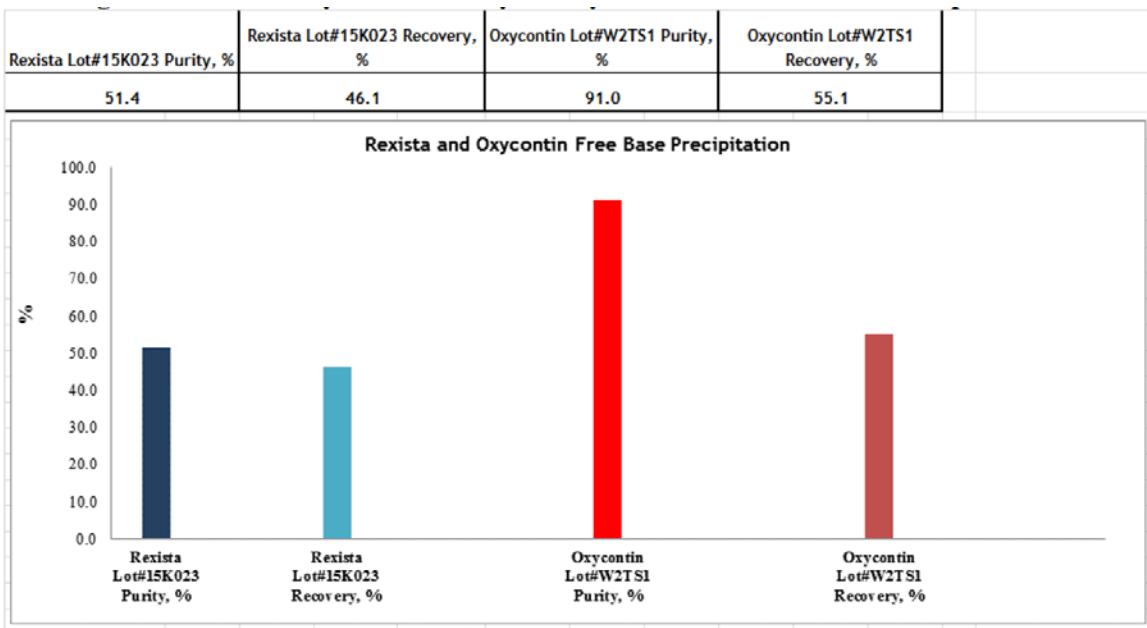


Figure 14. Purity and recovery of oxycodone obtained in the free base precipitation study.
F. Effect of In Vitro Manipulation on Dissolution Study Methods (Study Report: IPC-R-OXY-CAT1.STUDY-08)

Effect of Various Physical Manipulations on Dissolution

The results (Figure 15 and Figure 16) show progressive increase in drug release, from the oxycodone extended-release tablets samples as the tablets were progressively manipulated. Even under the greatest extent of manipulation tested, the release profile still demonstrated extended release characteristics. The dissolution profiles and trends obtained from both types of dissolution media are similar.

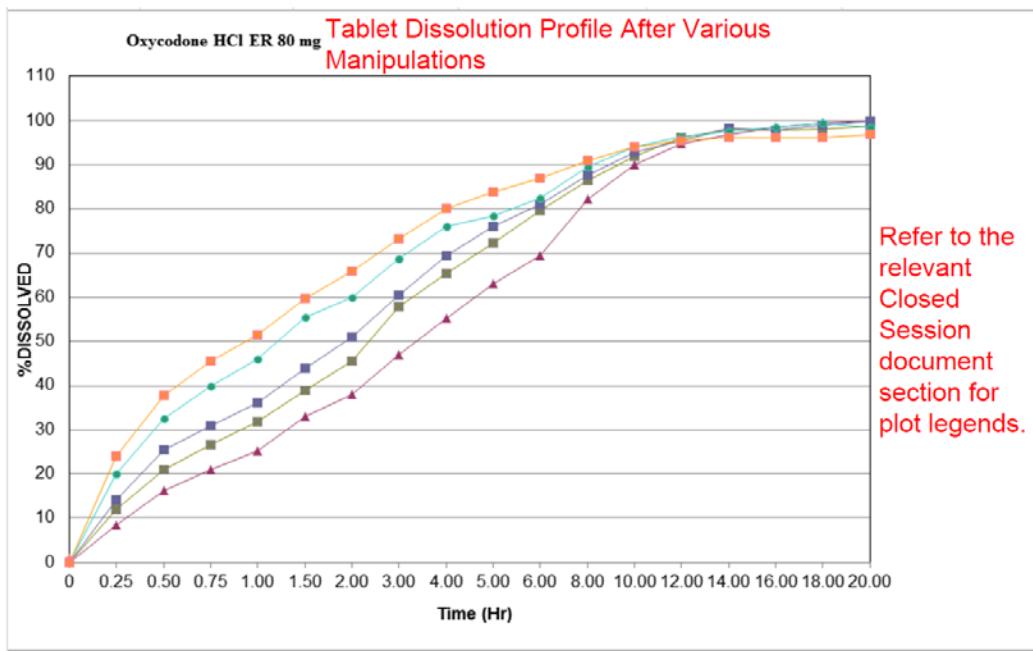


Figure 15. Effect of various physical manipulations on oxycodone dissolution rate in simulated gastric fluid.

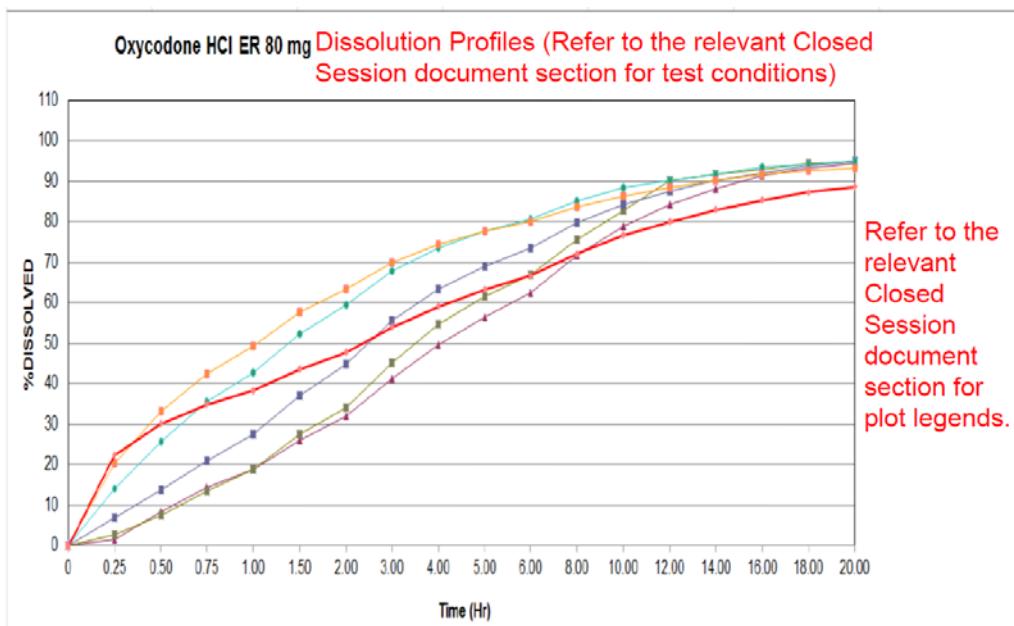


Figure 16. Effect of various physical manipulations on oxycodone dissolution rate in simulated intestinal fluid.

Figure 17 shows the dissolution results for two extreme manipulation scenarios for the oxycodone extended-release tablets.

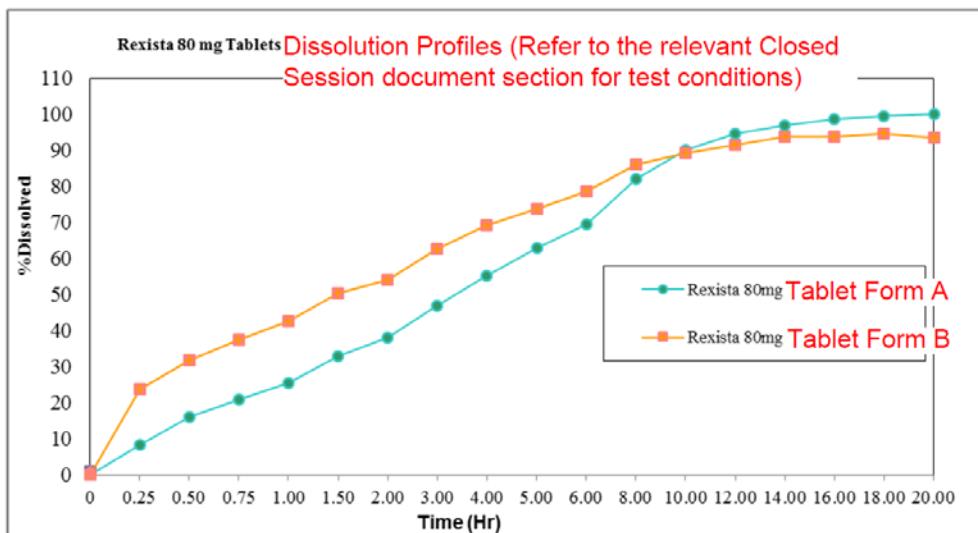


Figure 17. Effect of extreme physical manipulations on oxycodone extended-release tablet dissolution rate in simulated gastric fluid.

Comparison of Manipulated OxyContin and Oxycodone Extended-Release Tablet Dissolution

For the comparator product OxyContin tablets, the dissolution results for the two corresponding extreme manipulation scenarios showed higher dissolution at earlier time points (Figure 18).

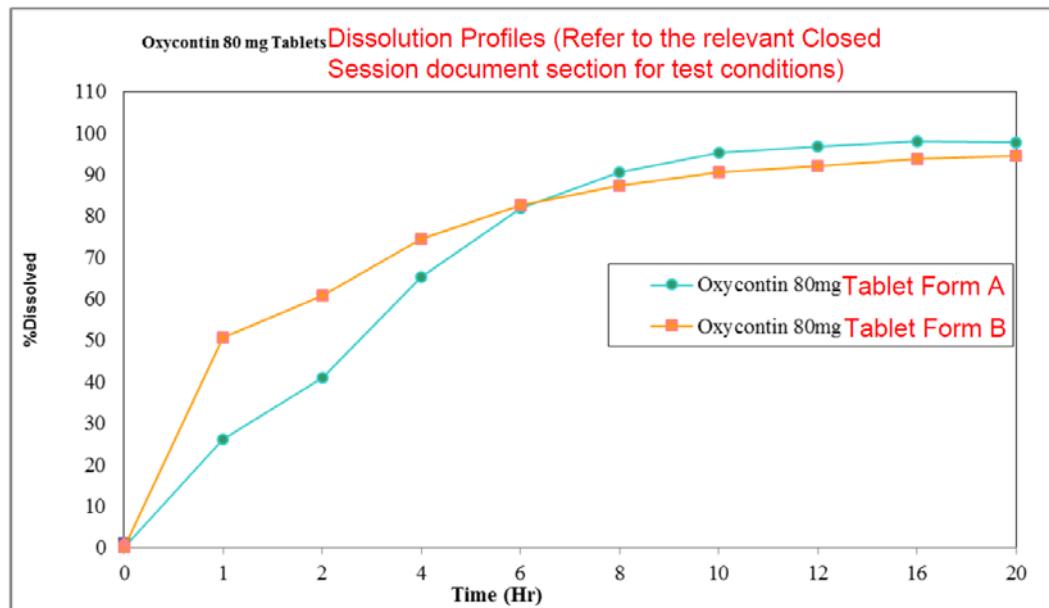


Figure 18. Effect of extreme physical manipulations on OxyContin tablet dissolution rate in simulated gastric fluid.

Pretreatment Effect on Dissolution

As shown in Figure 19, the two different pre-treatments can cause some difference in the dissolution of both products. However, there is significant difference between the oxycodone extended-release tablets and the OxyContin tablets.

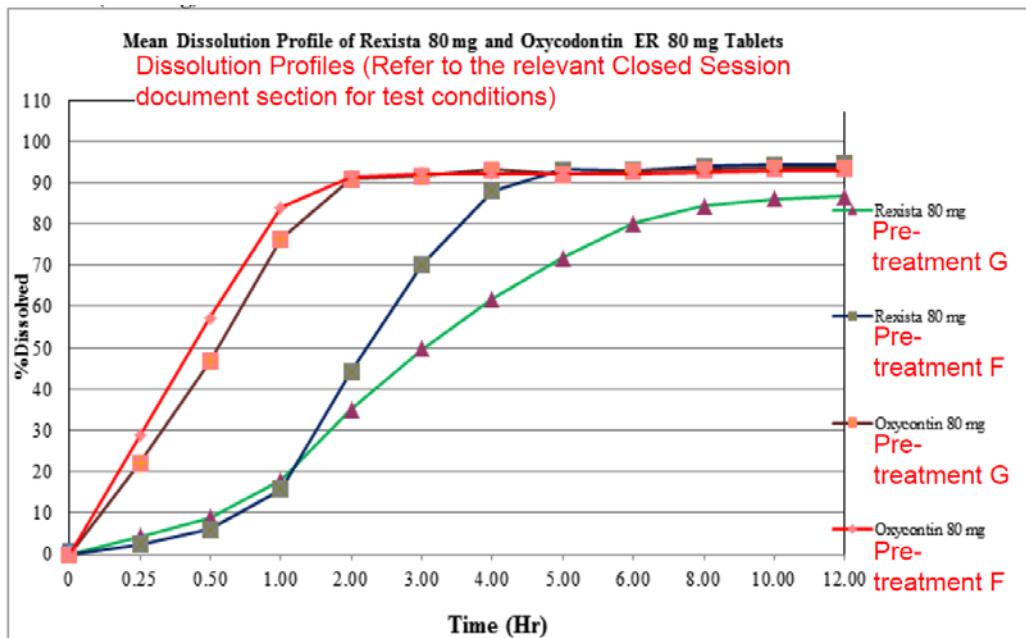


Figure 19. Effect of Pre-treatment F & G on oxycodone extended-release 80 mg tablet and OxyContin tablet dissolution rate.

G. Vaporization (Smoking) Study Results (Study Report: IPC-R-OXY-CAT1.STUDY-10)

Vaporization studies of oxycodone (base and salt) showed that under the same heating conditions, oxycodone base vaporizes more easily than oxycodone hydrochloride salt.

Oxycodone extended-release tablets and Oxycontin tablets contain Oxycodone HCl as the active ingredient. At the selected optimal heating temperature and duration, the following vaporization results were obtained.

Time (min)	% Rexista @ X °C	% Vapor_Rexista @ X °C	% Oxycontin @ X °C	% Vapor_Oxycontin @ X °C
0	100	0	100	0
10	5.5	5.9	14.1	6.9

Table 5. Residue and vaporized oxycodone recovered after heating for 10 minutes in the vaporization study.

As expected and supported by the study results, vaporization is not efficient for OxyContin and it appears slightly less efficient for the oxycodone extended-release tablets.

3. In Vitro Abuse Deterrence Study Results Summary

- A. The oxycodone extended-release tablets are relatively easier to reduce into fine particles than OxyContin tablets. Tool 10 was found as the most efficient tool to grind the tablets.
- B. When extracted using various solvents with large volumes (V7 and V8) –
 - Extraction recoveries can be affected by multiple factors. Tablet Form B, Temperature B and Agitation C are the top factors that significantly affect extraction recoveries.
 - Extraction recoveries generally increase with extraction time, until the testing stopped at 24 hours or until the recoveries plateaued.
 - Under given test conditions, Solvent 2, Solvent 4 – 8, and Solvent 12, showed higher extraction recoveries than Solvent 1 at the corresponding time points.
 - When analytical variations are considered, except Solvent 3, all other twenty tested solvents had similar or lower extraction recoveries from oxycodone extended-release tablets than from OxyContin tablets.
 - Extraction with Solvent 3 is unique. When tested at the correct combination of conditions, it can reach approximately 60 – 85% of extraction recoveries in 15 minutes for oxycodone extended-release tablets (Figure 8).
 - Tablet Form B, Temperature B and Agitation C in combination allow the most efficient extraction from both oxycodone extended-release and OxyContin tablets.
- C. When tested for syringeability –
 - Tablet Form B and Pretreatment D are the most important factors that affect syringeability.
 - Without Pretreatment D, neither oxycodone extended-release tablet samples nor OxyContin tablet samples were syringeable.
 - At the correct combination of testing conditions, the oxycodone extended-release tablet samples were similar or less syringeable than OxyContin tablet samples.
- D. When efforts were made to separate the blue dye and nasal irritant, neither was easy to separate or eliminate without using extensive chemistry knowledge.
- E. When tested using complex extraction and isolation procedures, oxycodone base can be achieved with similar or lower purity and yield from oxycodone extended-release tablet samples than from OxyContin tablet samples.
- F. Varying extent of physical manipulations progressively increase the oxycodone dissolution rate from both oxycodone extended-release and OxyContin tablet samples. Even with the largest extent of manipulation, the oxycodone extended-release tablet samples still retained some extended-release characteristics.
- G. The oxycodone extended-release tablet samples are less efficient to vaporize than the OxyContin tablet samples.



**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: June 21, 2017

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 Opioid Analgesics Labeled with Abuse-Deterrent Properties

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

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

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

AND

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

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

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

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

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

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

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

M E M O R A N D U M

DATE: June 21, 2017

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

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

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

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

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

psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships.

The following timetable is the schedule for this study:

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

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

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

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

The following timetable is the schedule for this study:

Final Protocol Submission:	11/2014
Study Completion:	04/2019
Final Report Submission:	09/2019

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

The following timetable is the schedule for this study:

Final Protocol Submission: 04/2015
Study Completion: 10/2015
Final Report Submission: 01/2016

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

The following timetable is the schedule for this study:

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

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

The following timetable is the schedule for this study:

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

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

The following timetable is the schedule for this study:

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

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

The following timetable is the schedule for this study:

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

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

The following timetable is the schedule for this study:

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

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

The following timetable is the schedule for this study:

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

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

The following timetable is the schedule for this study:

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

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

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

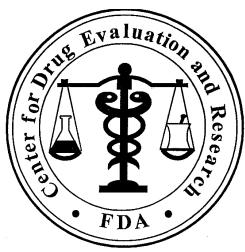
The following timetable is the schedule for this trial:

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

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

1. In order to provide the baseline data to support the hypothesis-testing studies required under 2 (below), conduct a descriptive study that analyzes data on the following:
 - 1) utilization of TRADENAME and selected comparators. Reports should include nationally-projected quarterly retail dispensing, 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.
2. Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of TRADENAME actually result in a meaningful decrease in

misuse and abuse, and their consequences, addiction overdose, and death, in post-approval settings. The studies should allow FDA to assess the impact, if any, attributable to the abuse-deterrent properties of TRADENAME and should incorporate recommendations contained in Abuse-Derterrent 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.



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

Date: June 5, 2017

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: Oxycodone hydrochloride extended-release tablets (209653)

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

If approved, Oxycodone hydrochloride extended-release tablets (NDA 209653) will be required to become a member of the extended-release/long-acting (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 Analgesic 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 Analgesic REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

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

physicians, nurse practitioners, physician assistants). Under the REMS, application holders¹ of ER/LA opioid analgesics are required to make education programs available to healthcare providers (HCPs) who are prescribers of ER/LA opioid analgesics. The application holders are meeting this requirement by providing educational grants to accredited continuing education (CE) providers who offer training to prescribers at no or nominal cost. To be considered compliant with the ER/LA Opioid Analgesic REMS, the CE courses are required to include the content and messages of a “blueprint” developed by FDA for this purpose. The FDA Blueprint includes general and product-specific information about the ER/LA opioid analgesics; information on proper patient selection for use of these drugs; guidance for safely initiating therapy, modifying dosing, and discontinuing use of ER/LA opioid analgesics; guidance for monitoring patients; and information for counseling patients and caregivers about the safe use of these drugs.² Additionally, prescribers are provided information for how to recognize evidence of and potential for opioid misuse, abuse, and addiction. The ER/LA Opioid Analgesics REMS also includes a patient counseling document for prescribers to assist them in properly counseling patients on their responsibilities for using these medicines safely and to provide patients with additional written instructions as needed. The labeling for ER/LA opioid analgesics includes a product-specific one-page Medication Guide to be given to patients each time they receive a prescription of their ER/LA opioid analgesic medicine. The Medication Guide contains consumer-friendly information on the safe use and disposal of ER/LA opioid analgesics and instructions for patients to consult their health care professional before changing doses, signs of potential overdose and emergency contact instructions, and advice on safe storage to prevent accidental exposure to family members.

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

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