

**FDA Briefing Document**

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

**June 8, 2016**

## **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 efficacy data, safety data, pharmacokinetic data, and results of studies evaluating the abuse of Troxyca ER (oxycodone hydrochloride/naltrexone hydrochloride) extended-release capsules 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 Life Support Drugs Advisory Committee and  
Drug Safety & Risk Management Advisory Committee*

**June 8, 2016**

### **Table of Contents- Open Session**

Background Materials	Page
1. Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) Director Memorandum (Dr. Hertz)	4
2. Regulatory History of Abuse-Deterrent Opioids	7
3. Guidance for Industry: Abuse-Deterrent Opioids-Evaluation and Labeling	10
4. Drug Utilization Review	39
5. Summary of Troxyca Efficacy and Safety Findings	49
6. Summary of Abuse-Deterrent Findings for Troxyca	
a. In vitro Studies	51
b. In vivo Studies	55
7. Overview of Risk Mitigation Strategies	
a. ERLA REMS	63
b. Postmarketing Requirements	65

## DIVISION DIRECTOR MEMO



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

---

### MEMORANDUM

---

**DATE:** May 3, 2016

**FROM:** Sharon Hertz, MD  
Director  
Division of Anesthesia, Analgesia, and Addiction Products  
Office of Drug Evaluation II, CDER, FDA

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

**RE:** Overview of the Open Session, June 8, 2016 AADPAC/DSaRM Meeting to  
Discuss NDA 207621

---

At this joint meeting of AADPAC and DSaRM, we will be discussing a new drug application from Pfizer, Inc. for an extended-release formulation of oxycodone hydrochloride and naltrexone. Troxyca ER was designed with properties intended to deter abuse based on the presence of naltrexone, which is sequestered within the formulation. 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 recently announced a comprehensive review of our approach to opioid medications. This multi-year action plan will focus 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 six approved extended-release/long-acting opioid analgesic products with labeling language describing studies conducted in support of abuse-deterrent properties; 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), and Xtampza ER (oxycodone extended-release capsules). There are currently no single-entity or combination (opioid/non-opioid) immediate-release opioid analgesics labeled with abuse-deterrent properties as described in the guidance.

Troxyca ER has been formulated with naltrexone, an opioid antagonist, sequestered within small pellets that are coated with oxycodone. The presence of naltrexone is intended to provide abuse-deterrent properties when the product is manipulated. With oral administration of intact capsules or pellets sprinkled on applesauce, the intention is that there is little or no exposure to the naltrexone. However, physical and/or chemical manipulation of the pellets is intended to release naltrexone, which will antagonize the effects of oxycodone and block its reinforcing effects by the oral, intranasal, and intravenous routes of administration.

The results of the Applicant’s in vitro physical and chemical manipulation studies and the in vivo clinical abuse potential studies will be presented during this meeting. 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 Troxyca ER 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. Are there sufficient data to support a finding that Troxyca ER has properties that can be expected to deter abuse by the oral, nasal, or intravenous routes of administration?
2. Should Troxyca ER be approved for the proposed indication?
3. Abuse-deterrent language for which route or routes of abuse should be included in the product label?

## 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, 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.

There are six approved ERLA opioid analgesic products with labeling language describing studies that evaluated their abuse-deterrent properties. 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 (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, an extended-release formulation of morphine sulfate, approved in 2015, is the second extended-release morphine product with abuse-deterrent labeling. Morphabond 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.

All Sponsors of ERLA opioid analgesics with approved AD language in the label are required to conduct postmarketing epidemiologic studies to determine whether the properties of their products result in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting. Additionally, all ERLA opioids, with or without approved AD language, are part of the ERLA Risk Evaluation and Mitigation Strategy (REMS) in order to mitigate the risks associated with this class of drugs.

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

*Additional copies are available from:*

*Office of Communications*

*Division of Drug Information, WO51, Room 2201*

*10903 New Hampshire Ave.*

*Silver Spring, MD 20993-0002*

*Phone: 301-796-3400; Fax: 301-847-8714*

*druginfo@fda.hhs.gov*

*<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>*

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

**Clinical Medical  
April 2015**

## TABLE OF CONTENTS

<b>I.</b>	<b>INTRODUCTION.....</b>	<b>1</b>
<b>II.</b>	<b>BACKGROUND .....</b>	<b>1</b>
<b>III.</b>	<b>ABUSE-DETERRENT PRODUCTS .....</b>	<b>3</b>
<b>IV.</b>	<b>PREMARKET STUDIES .....</b>	<b>4</b>
A.	<b>Laboratory Manipulation and Extraction Studies (Category 1).....</b>	<b>6</b>
B.	<b>Pharmacokinetic Studies (Category 2).....</b>	<b>8</b>
C.	<b>Clinical Abuse Potential Studies (Category 3) .....</b>	<b>9</b>
1.	<i>Blinding.....</i>	<i>10</i>
2.	<i>Pre-qualification Phase .....</i>	<i>10</i>
3.	<i>Assessment Phase .....</i>	<i>11</i>
4.	<i>Subjects .....</i>	<i>11</i>
5.	<i>Route of Administration, Dose Selection, Manipulation Mode, and Sample Preparation .....</i>	<i>12</i>
6.	<i>Outcome Measures and Data Interpretation .....</i>	<i>12</i>
7.	<i>Data Interpretation.....</i>	<i>13</i>
8.	<i>Statistical Analysis.....</i>	<i>14</i>
a.	<i>Background .....</i>	<i>14</i>
b.	<i>Primary analyses .....</i>	<i>15</i>
c.	<i>Secondary analyses .....</i>	<i>15</i>
d.	<i>Multiplicity.....</i>	<i>17</i>
<b>V.</b>	<b>POSTMARKET STUDIES (CATEGORY 4) .....</b>	<b>17</b>
A.	<b>Formal Studies .....</b>	<b>18</b>
1.	<i>General Characteristics.....</i>	<i>18</i>
2.	<i>Study Design Features.....</i>	<i>19</i>
B.	<b>Supportive Information.....</b>	<b>21</b>
<b>VI.</b>	<b>LABELING .....</b>	<b>22</b>
<b>VII.</b>	<b>ADDITIONAL RESEARCH NEEDS .....</b>	<b>25</b>

# **Abuse-Deterrent Opioids — Evaluation and Labeling Guidance for Industry<sup>1</sup>**

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

<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup>

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.

<sup>2</sup> 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.

<sup>3</sup> Ibid.

<sup>4</sup> 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.<sup>5</sup>

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

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

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

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

#### **IV. PREMARKET STUDIES**

First and foremost, any studies designed to evaluate the abuse-deterrent characteristics of an opioid formulation should be scientifically rigorous. Important general considerations for the design of these studies include the appropriateness of positive controls<sup>6</sup> 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

<sup>6</sup> 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.<sup>7</sup>

<sup>7</sup> 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.<sup>8</sup>

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

<sup>8</sup> 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.<sup>9</sup> 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.<sup>10</sup> 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

<sup>9</sup> 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.

<sup>10</sup> 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,<sup>11</sup> 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.<sup>12</sup> In general,

<sup>11</sup> Ibid.

<sup>12</sup> 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.<sup>13</sup> 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.

<sup>13</sup> 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.<sup>14</sup>

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  $E_{max}$ <sup>15</sup> 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.<sup>16</sup> What

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

<sup>15</sup> 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.

<sup>16</sup> 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,<sup>17</sup> 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 means<sup>18</sup> 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  $\delta_2$ . 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  $\delta_1$  is related to  $\mu_C$ , hence, it may vary according to abuse potential measures and the route of drug administration. The  $\delta^*$  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.

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

<sup>18</sup> 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

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

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

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

d. Multiplicity

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

## V. POSTMARKET STUDIES (CATEGORY 4)

Premarket studies focus on assessing the potentially abuse-deterrent properties of a product under controlled conditions. The goal of postmarket<sup>20</sup> 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

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

<sup>20</sup> 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<sup>21,22</sup> 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

<sup>21</sup> 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>.

<sup>22</sup> International Society for Pharmacoepidemiology and Risk Management, Guidelines for Good Practices and Pharmacoepidemiologic Studies, available at [http://www.pharmacoepi.org/resources/guidelines\\_08027.cfm](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.<sup>23</sup>
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).

<sup>23</sup> 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.<sup>24</sup> 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.

<sup>24</sup> 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.<sup>25</sup> 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

<sup>25</sup> 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: May 2, 2016

Reviewer: Joann H. Lee, Pharm.D.  
Drug Utilization Data Analyst  
Division of Epidemiology II (DEPI II)

Team Leader Rajdeep Gill, Pharm.D.  
Drug Utilization Data Analysis Team Leader  
DEPI II

Division Director LCDR Grace Chai, Pharm.D.  
For Drug Utilization DEPI II

Drug Name(s): Troxyca (oxycodone/naltrexone) Extended-Release (ER)  
Application Type/Number: NDA 207621  
Applicant/sponsor: Pfizer, Inc.  
OSE RCM #: 2016-574

## CONTENTS

EXECUTIVE SUMMARY .....	2
1 INTRODUCTION .....	3
1.1 Background .....	3
1.2 Product Information.....	3
2 METHODS and MATERIALS.....	4
2.1 Determining Setting of Care.....	4
2.2 Data Sources Used.....	5
3 RESULTS .....	5
3.1 Prescription Data .....	5
3.2 Prescriber Specialty for Oxycodone ER .....	6
4 DISCUSSION .....	6
5 CONCLUSION.....	7
6 APPENDICES .....	8
6.1 APPENDIX A: TABLES .....	8
6.2 APPENDIX B: DRUG USE DATABASE DESCRIPTIONS .....	9

## **EXECUTIVE SUMMARY**

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 (DSaRM) scheduled for June 8, 2016, this review summarizes the drug utilization analyses of oxycodone ER and other extended-release/long-acting (ER/LA) opioid analgesics 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 combination extended-release formulation (oxycodone/naltrexone ER) are 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.

This drug utilization review focused on the U.S. outpatient retail prescription utilization trends of oxycodone ER and all other ER/LA opioid analgesics from 2011 through 2015. During the examined time period, a decrease in utilization was observed in the number of prescriptions dispensed for oxycodone ER. The total number of prescriptions dispensed decreased by approximately 24% from 5.8 million prescriptions in 2011 to 4.4 million prescriptions in 2015. In contrast, some of the other ER/LA opioid analgesics (buprenorphine TD, tapentadol ER, hydrocodone ER, hydromorphone ER, and morphine ER) showed an overall uptake in utilization from 2011 through 2015 as most of these products were approved around or after 2010.

Our overall findings suggest that utilization of oxycodone ER declined from 2011 through 2015 and it was the third most frequently dispensed drug in the ER/LA opioid analgesic market during 2015, after morphine ER and fentanyl transdermal patch. The top physician specialties prescribing oxycodone ER was family practice/general practice/osteopathy in 2015.

## **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 (DSaRM) scheduled for June 8, 2016, this review summarizes the drug utilization patterns of oxycodone ER and other extended-release/long-acting (ER/LA) opioid analgesics 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 combination product (oxycodone/naltrexone) are sufficient to support labeling as a product that may have abuse deterrent properties. The proposed indication 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<sup>1,2</sup>**

NDA 207621 was submitted by the Sponsor as the first extended-release combination product that contains *oxycodone hydrochloride and naltrexone hydrochloride* (Troxyc ER). Currently, there are two extended-release, analgesic combination drug product containing an opioid agonist and an opioid antagonist in the U.S. market, Embeda (morphine/naltrexone) and Targiniq (oxycodone/naloxone). The proposed indication of Troxyc ER under consideration is for the management of chronic pain that may require daily, around-the-clock, opioid treatment and for which alternative treatment options are inadequate.<sup>3</sup>

This drug utilization review is provided as context for the discussions to be held at the upcoming Advisory Committee Meeting on June 8, 2016.

### **1.2 PRODUCT INFORMATION**

Table 1 provides the list of all brand and generic drug products covered under the ER/LA opioid analgesic REMS program included in this review:

<sup>1</sup> Oxycontin ER Prescribing Information accessed March-2016 at:  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/022272s027lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022272s027lbl.pdf)

<sup>2</sup> Naltrexone hydrochloride Prescribing Information accessed March-2016 at:  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2000/75-434\\_Naltrexone%20Hydrochloride\\_prntlbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/75-434_Naltrexone%20Hydrochloride_prntlbl.pdf)

<sup>3</sup> PF-06412527 (ALO-02) Extended-Release Capsules/NDA 207621/Common Technical Document (CTD)  
Introduction:  
<http://darrts.fda.gov:9602/darrts/changeAppViewAppHistory.do?applicationId=207798&submissionHistoryFlag=0>  
Accessed April-2016

**Table 1. Oxycodone ER and all other opioid ER/LA opioid analgesic products<sup>4</sup>**

Active Ingredient	Trade Name	Approval Date
Methadone tablets or liquid	Dolophine	March 14, 1973
<b>Extended-release, Oral-dosage Forms Containing Active Ingredient</b>		
Morphine ER	MS Contin	May 29, 1987
	Kadian	July 3, 1996
	Avinza	Feb 20, 2002
	Embeda (morphine/naltrexone)*	Aug 13, 2009
	Morphabond**	October 2, 2015
Oxycodone ER	Oxycontin	December 12, 1995
	Targiniq (oxycodone/naloxone) <sup>†</sup>	July 23, 2014
Hydromorphone ER	Exalgo	March 1, 2010
Oxymorphone ER	Opana ER	June 22, 2006
Tapentadol ER	Nucynta ER	August 25, 2011
Hydrocodone ER	Zohydro ER	October 25, 2013
	Hysingla ER	November 20, 2014
<b>Transdermal Delivery Systems</b>		
Fentanyl Transdermal	Duragesic	August 7, 1990
Buprenorphine Transdermal	Butrans	June 30, 2010

\*Embeda ER (morphine/naltrexone) was withdrawn from the market in March 2011 because of stability issues. It was approved with a manufacturing supplement in November 2013.

\*\*Morphabond approved in October 2015, drug utilization data not available for this review.

<sup>†</sup>Targiniq ER (oxycodone/naloxone) is currently not marketed in the United States.

## 2 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct the analyses in this review. (see Appendix B for full database description).

### 2.1 DETERMINING SETTING OF CARE

The IMS Health, *IMS National Sales Perspectives*<sup>TM</sup> was used to determine various retail and non-retail channels of distribution for the ER/LA opioid analgesics. The sales data for 2015 shows that

<sup>4</sup> Drugs at FDA: Approved Risk Evaluation and Mitigation Strategies (REMS) at <http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=17>. Accessed March-2016.

approximately 75% of oxycodone ER bottles or packages were distributed to outpatient retail pharmacies (including chain, independent, and food stores). The sales data for all other ER/LA opioids (Table 1, Section 1.2) also show that majority of sales were towards retail pharmacies (including chain, independent, and food stores). Therefore, outpatient retail pharmacy utilization patterns were examined in this review for the opioid ER/LA analgesic products. Mail-order specialty and non-retail settings were not included in this review.

## 2.2 DATA SOURCES USED

*The IMS, National Prescription Audit™ (NPA) database* was used to obtain nationally estimated number of prescriptions dispensed for oxycodone ER and all other ER/LA opioid analgesics (Table 1, Section 1.2) from U.S. outpatient retail pharmacies, from 2011 through 2015, annually.

NPA database was also used to obtain the nationally estimated number of prescriptions dispensed for oxycodone ER from U.S. outpatient retail pharmacies, stratified by top prescriber specialties for 2015.

# 3 RESULTS

## 3.1 PRESCRIPTION DATA

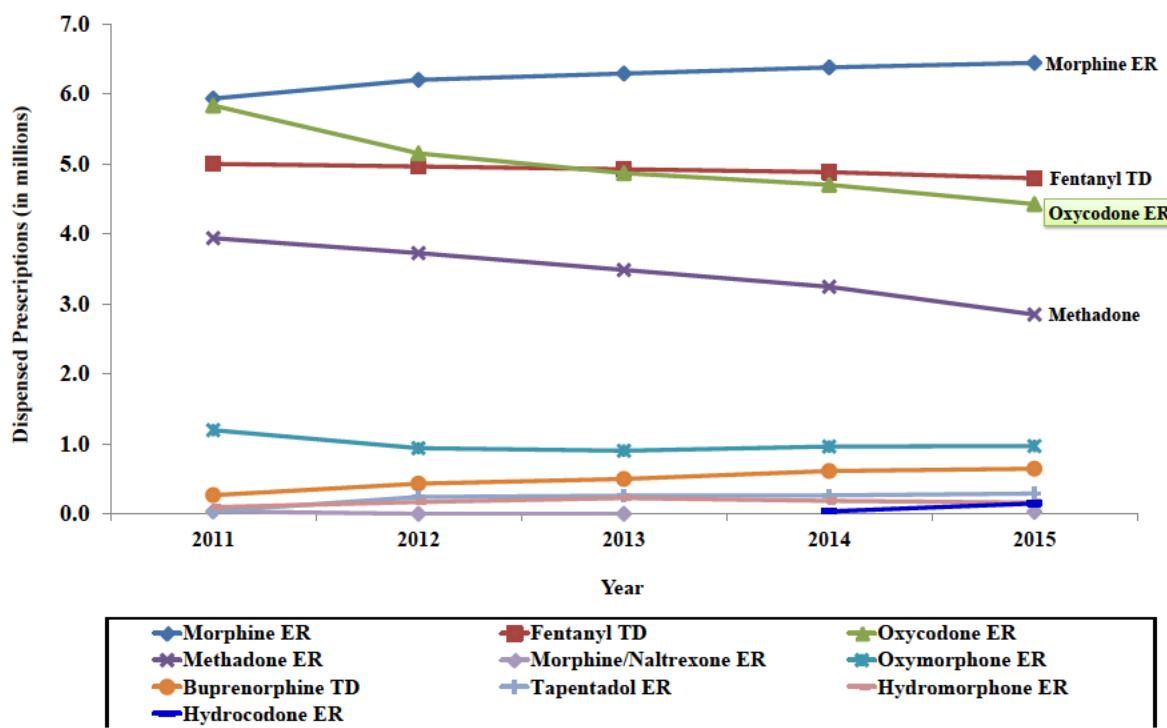
**Figure 1 below and Table 2 in Appendix A** show the nationally estimated number of ER/LA opioid analgesic prescriptions dispensed from U.S. outpatient retail pharmacies from 2011 through 2015.

Approximately 21-22 million ER/LA opioid analgesic prescriptions were dispensed annually from 2011 through 2015. In 2015, morphine ER accounted for 31% (6.4 million prescriptions) of the total ER/LA prescriptions dispensed, followed by fentanyl TD (23%, 4.8 million prescriptions), and oxycodone ER (21%, 4.4 million prescriptions). Methadone prescriptions accounted for 14% (2.8 million prescriptions) of the total ER/LA prescriptions dispensed.

Looking at the yearly trends, oxycodone ER prescriptions dispensed decreased by 24% from 2011 through 2015. Morphine ER prescriptions dispensed increased by approximately 9% and fentanyl TD remained steady while prescriptions for methadone decreased by 28% from 2011 through 2015.

## **FIGURE 1**

**Nationally estimated number of prescriptions dispensed for ER/LA opioid analgesics from U.S. outpatient retail pharmacies from 2011 - 2015**



Source: IMS, National Prescription Audits (NPA) Data extracted March 2015. File: NPA 2016-574 Rx Troxyca ERLA AC 04-04-16.xlsx

\*\*No data for years 2011, 2012, and 2013 for hydrocodone products: Zohydro ER approved in 10/2013 and Hysingla ER approved 11/2014

### **3.2 PRESCRIBER SPECIALTY FOR OXYCODONE ER**

**Table 3 in Appendix A** provides the total number of prescriptions dispensed for oxycodone ER from U.S. outpatient retail pharmacies by the top prescribing specialties for year 2015. Family practice/general practice/osteopathy was the top prescriber specialty (26% of total prescriptions) followed by internal medicine (12%), nurse practitioner (11%) and anesthesiology (11%) in 2015.

## **4 DISCUSSION**

This review provides drug utilization data for oxycodone ER and other ER/LA opioid analgesics as context and background information in support of discussions for a new drug application for an extended-release formulation of an opioid combination product (oxycodone/naltrexone ER). During the examined time period, a decrease in utilization was observed in the number of prescriptions dispensed for oxycodone ER. The steady decline in the overall utilization of oxycodone ER may be attributed to multiple factors such as the introduction of reformulated OxyContin (oxycodone ER) to the market in August 2010, approval of other ER/LA opioid analgesics since year 2010, the ER/LA opioid analgesic REMS, federal and state level regulations in addition to other initiatives and actions by various organizations.

The prescription data showed that primary care providers such as family practice/internal medicine/osteopathy were the top prescriber specialties for oxycodone ER in 2015.

Findings from this review should be interpreted in the context of the known limitations of the databases used. Based on the IMS Health, IMS National Sales Perspectives™, sales data for 2015 showed that a vast majority of various ER/LA opioid bottles or packages were distributed to outpatient retail pharmacies. We focused our analysis on only the outpatient retail pharmacy settings; therefore, these estimates may not apply to other settings of care in which these products are used (e.g. mail-order setting, clinics, non-federal hospitals, etc.). The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products. All changes over time or between products should be considered approximate and may be due to random error.

## **5 CONCLUSION**

Our overall findings suggest that utilization of oxycodone ER declined from 2011 through 2015 and was the third most frequently dispensed drug (4.4. million prescriptions dispensed) in the ER/LA opioid analgesic market during 2015, after morphine ER and fentanyl transdermal patch. Approximately one-quarter of oxycodone ER prescriptions were written by family practice/general practice/osteopathy in 2015.

## 6 APPENDICES

### 6.1 APPENDIX A: TABLES

**TABLE 2.**

Nationally estimated number of prescriptions dispensed for ER/LA opioid analgesics from U.S. outpatient retail pharmacies, 2011-2015

	2011		2012		2013		2014		2015	
	Prescriptions (N)	Share (%)								
<b>Grand Total</b>	<b>22,330,862</b>	<b>100.0%</b>	<b>21,817,818</b>	<b>100.0%</b>	<b>21,446,002</b>	<b>100.0%</b>	<b>21,256,647</b>	<b>100.0%</b>	<b>20,742,630</b>	<b>100.0%</b>
Morphine ER	5,931,628	26.6%	6,198,303	28.4%	6,288,088	29.3%	6,375,570	30.0%	6,441,121	31.1%
Fentanyl TD	4,997,384	22.4%	4,961,133	22.7%	4,923,139	23.0%	4,881,447	23.0%	4,791,686	23.1%
Oxycodone ER	<b>5,831,523</b>	<b>26.1%</b>	<b>5,148,631</b>	<b>23.6%</b>	<b>4,865,489</b>	<b>22.7%</b>	<b>4,699,154</b>	<b>22.1%</b>	<b>4,423,455</b>	<b>21.3%</b>
Methadone	3,938,607	17.6%	3,725,332	17.1%	3,484,537	16.2%	3,242,281	15.3%	2,846,882	13.7%
Oxymorphone ER	1,196,953	5.4%	939,908	4.3%	901,305	4.2%	960,933	4.5%	968,029	4.7%
Buprenorphine TD	266,332	1.2%	431,793	2.0%	497,697	2.3%	613,086	2.9%	643,634	3.1%
Tapentadol ER	37,531	0.2%	242,059	1.1%	259,294	1.2%	264,048	1.2%	289,459	1.4%
Hydromorphone ER	95,823	0.4%	170,654	0.8%	226,452	1.1%	185,035	0.9%	160,632	0.8%
Hydrocodone ER	—	—	—	—	—	—	35,093	0.2%	149,957	0.7%
Morphine/Naltrexone ER	35,081	<1%	5	<0.1%	1	<0.1%	—	—	27,775	<1%

Source: IMS, National Prescription Audit (NPA). Extracted April 2016. File: NPA 2016-574 Rx Troxyca ERLA AC 04-22-16.xlsx

**TABLE 3.**

Nationally estimated number of prescriptions dispensed for oxycodone ER from U.S. outpatient retail pharmacies, stratified by top 10 prescriber specialties, 2015

PRESCRIBER SPECIALTY	Prescriptions (N)	Share (%)
<b>Oxycodone ER Total Prescriptions</b>	<b>4,423,455</b>	<b>100.0%</b>
Family Practice/General Practice/Osteopathy	1,161,703	26.3%
Internal Medicine	533,490	12.1%
Nurse Practitioner	506,116	11.4%
Anesthesiology	499,795	11.3%
Physician Assistant	425,805	9.6%
Physical, Medicine & Rehabilitation	360,153	8.1%
Pain Medicine	216,042	4.9%
Oncology	141,366	3.2%
Orthopedic Surgery	135,106	3.1%
Neurology	81,408	1.8%
All Other Specialties	362,471	8.2%

Source: IMS, National Prescription Audit (NPA). Year 2015. Extracted April-2016. File: NPA 2016-572-specialty oxycodone ERLA AC.xlsx

## **6.2 APPENDIX B: DRUG USE DATABASE DESCRIPTIONS**

### **IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail**

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

### **IMS, National Prescription Audit**

The National Prescription Audit (NPATM) 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. NPATM receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 86% 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 40 - 70% (varies by class and geography) of mail service pharmacies and approximately 45-55% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

## **Clinical Summary**

**NDA 207621**

### **Troxyca ER (oxycodone/naltrexone) Extended-Release Capsules**

The Applicant submitted a 505(b)(2) application for Troxyca ER (oxycodone hydrochloride and naltrexone hydrochloride) capsules, an extended-release formulation of oxycodone with properties intended to deter abuse by the oral, intranasal, and intravenous routes of administration, 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 Applicant relied on the Agency's prior findings of efficacy and safety for Roxicodone (NDA 021011) and Revia (NDA 018932) and cross-referenced another one of their products with a similar formulation, Embeda (NDA 022321, morphine sulfate with sequestered naltrexone hydrochloride). The intent of the addition of naltrexone in both Troxyca ER and Embeda is to provide abuse-deterring properties.

The naltrexone in Troxyca ER is sequestered within the formulation. With oral administration of intact capsules or with sprinkling the contents on food, there is little to no exposure to naltrexone in the blood. However, crushing of the capsule, or crushing or dissolution of its contents is intended to result in release of the naltrexone, which antagonizes the effects of the oxycodone and blocks the extent of euphoria experienced by an abuser, whether by oral, intranasal, or intravenous routes of administration.

Support for clinical efficacy and safety of the oxycodone component of Troxyca ER was based, in part, on reliance on the Agency's previous findings for the listed drug, Roxicodone, using relative bioavailability data as the scientific bridge for doing so, and, in part, on a clinical efficacy study conducted by the Applicant in patients with chronic, moderate-to-severe, low back pain. One adequate and well-controlled efficacy study was required for several reasons. First, bioequivalence cannot be established between an extended-release oxycodone product for twice daily administration and an immediate-release product dosed every 4 to 6 hours. Next, the indications for Roxicodone and Troxyca ER are different, and the clinical study was conducted in the intended population. In addition, because there were measurable naltrexone levels in some patients following oral administration of Troxyca ER, it was necessary to ensure that the naltrexone exposure was not sufficient to interfere with the efficacy of the oxycodone or cause opioid withdrawal symptoms in patients. The safety and efficacy of naltrexone is based on reliance on the Agency's prior findings for the listed drug, Revia, and published literature. Additionally, the Applicant conducted in vitro and in vivo studies to evaluate the abuse-deterring properties of the formulation.

The Applicant provided an adequate assessment of the pharmacokinetic properties of Troxyca ER, in comparison to Roxicodone, to create the scientific bridge needed to rely on the Agency's prior finding of clinical safety and effectiveness for Roxicodone and provided an adequate

justification in lieu of a clinical pharmacology study to support a scientific bridge to the Agency's prior finding of clinical safety and effectiveness for Revia. There are adequate data from the clinical efficacy trial to confirm that the systemic exposure to naltrexone does not interfere with the efficacy of the oxycodone from Troxyca ER or cause significant withdrawal symptoms in patients, and there are adequate clinical data to support the safety of the formulation and support the proposed dosing instructions. The adverse events in the clinical studies were consistent with an opioid analgesic, and there were no unexpected findings.



**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: April 30, 2016

FROM: Benjamin Stevens, Ph.D., M.P.H.  
Julia Pinto, Ph.D.

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

RE: Open Session Background Document: In Vitro Studies of Proposed Abuse-Deterrent Properties, NDA 207621 Troxyca® ER Tablets

---

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

The drug product is an extended release composition comprising oxycodone hydrochloride and naltrexone hydrochloride. The capsules are available in 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2mg, and 80 mg/9.6 mg strengths of oxycodone/naltrexone. The abuse deterrence mechanism relies on the incorporation of naltrexone, a  $\mu$ -opioid receptor antagonist, into the drug product pellets. The naltrexone antagonist is sequestered from the oxycodone agonist by a membrane comprising the excipient mixture A. This membrane acts as a barrier for naltrexone release in aqueous solutions, but may be disrupted by certain organic solvents or physical manipulations. Therefore, such manipulations ideally result in an inseparable mixture of the two drug substances in sufficient concentrations to effectively limit the euphoric and analgesic effects of the agonist.

A schematic of the drug product pellet is shown below. These pellets are housed within a capsule. The formulation technology does not limit the tampering of the outer capsule.

Note that codes for specific in vitro conditions are provided in the closed session document. These codes may differ from those used by the applicant.

## 1. Summary of In Vitro Studies

Extensive in vitro abuse-deterrent studies were conducted to assess the relative difficulty and effectiveness of various potential manipulation methods to defeat the drug product's abuse-deterrent properties. Only the methodologies that reflect the most probable abuse approaches and that pose the most challenges to the drug product under evaluation are summarized below. When used, the comparator was an IR oxycodone 30mg tablet.

### A. Physical Manipulation (Size Reduction)

Particle size reduction is a common first step abusers employ to increase the release rate of a product. Several simulated common techniques that are used by abusers to manipulate the drug product through crushing and grinding were studied. Similar particle size was thoroughly characterized via laser diffraction for all methods of manipulation.

### B. Extraction Studies

These studies were designed to determine the extraction potential of oxycodone and naltrexone when extracted from the pellet formulations with Common Solvents A to P, under both stress and non-stress conditions. Studies used both intact and crushed pellets. The formulation was defeated in the following solvents, when extracted for 12 hours or longer using intact pellets (Common Solvents A, J, O, and L). When Common Solvent L was used, 90% of oxycodone was extracted in 3 hours or more, and when Common

Solvents M and N were used, about 60% of the oxycodone could be extracted within 15 minutes or less.

When crushed pellets were used for the extraction study, no oxycodone could be extracted in common solvents A or J. When common solvents I were used, about 40% to 50% of oxycodone, in 30 minutes or less was isolated.

Under stress conditions, 80% to 90% of the oxycodone was isolated within 1 to 4 hours of extraction time using intact pellets. With crushed pellets no oxycodone was isolated.

The overall results indicate that ALO-02 intact pellets are readily defeated using common solvents A (nearly completely selective extraction) at varying pH although extraction times under non-stress conditions are long (12+ hours). Stress conditions increase the effective rate of selective extractions (~2-4 hours). Common solvents L to N are particularly effective at selectively extracting oxycodone from intact pellets. Alternatively, common solvents A and L to N, are generally unable to extract oxycodone from naltrexone selectively in crushed pellets. One unique exception appears to be the use of Solvents F, G, H and O on crushed pellets, which selectively extracts naltrexone from oxycodone. Of the common solvents I and P, solvent P selectively extracts the oxycodone in a manner that appears dependent on the intrinsic solubility of the two APIs, not on the delayed release of naltrexone by the sequestering membrane. This is further supported by the ability of solvent P to selectively extract oxycodone even in crushed tablets. Solvents I appear to extract oxycodone selectively from crushed tablets

#### C. Small Volume Extractability with Intact Pellets

Sufficient data was obtained to indicate that moderate levels of naltrexone could be extracted in low volumes of solvent A (~5-10 ml) in relatively short periods under stress conditions. Low concentration of solvents O, B and C were also evaluated, but showed no advantage over Solvent A.

#### D. Volatilization Studies Using Intact and Crushed Pellets

Samples of oxycodone HCl drug substance, naltrexone HCl drug substance, intact and crushed ALO-02 pellets, and crushed oxycodone IR tablets were heated and the resulting vapor was condensed and analyzed by HPLC at 3, 5, and 10 min time points. Observed levels of oxycodone were negligible for either form of ALO-02 and while levels were higher for the IR oxycodone tablets, these levels were still low overall (less than 5%). Therefore, while these studies suggest that oxycodone is not readily vaporized from ALO-02 at high temperatures, similar results were observed for the control IR oxycodone tablet implying that no significant advantage may exist for the abuse deterrent technology against this mode of abuse.

In conclusion, oxycodone is selectively extracted from intact ALO-02 pellets by a number of straightforward techniques. Common Solvents F, G and H appear to be capable of removing naltrexone selectively from crushed ALO-02. Solvent A under stress conditions, considerably increases the rate of oxycodone extraction with only minor increases in naltrexone content. Thermal volatilization studies indicate that negligible oxycodone is afforded from heated ALO-02 vapor while control IR oxycodone tablets produce only very low (<5%) concentrations of oxycodone.



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

**Date:** April 26, 2016

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

**Through:** Michael Klein, Ph.D., Director *Michael Klein 4/26/16*  
Controlled Substance Staff

**From:** James M. Tolliver, Ph.D., Pharmacologist *SMT 4/26/16*  
Controlled Substance Staff

**Subject:** OPEN SESSION BACKGROUND DOCUMENT on Oral Human Abuse Potential Study B4531008, Intranasal Human Abuse Potential Study B4531009 and simulated Intravenous Human Abuse Potential Study B4981002 submitted Under NDA 207-621. Prepared for the FDA Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety & Risk Management Advisory Committee Meeting June 8, 2016.  
Sponsor: Pfizer, Inc.

### **Background Document**

Oral human abuse potential study B4531008, intranasal human abuse potential study B4531009, and simulated intravenous human abuse potential study B4981002 were submitted by Pfizer Inc. under NDA 207-621 in support of Troxyca ER Capsules (Oxycodone HCl-Naltrexone HCl ER Capsules, an intended abuse-deterrant formulation. This type of study is thought to be predictive of the likelihood that the new formulation with abuse deterrent properties will deter or reduce the abuse of the product when taken through selected routes of abuse. Brief descriptions of these studies and the results obtained are provided below.

**Oral Human Abuse Potential Study B4531008 entitled “A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Single-Dose, 6-Way Crossover Study to Determine the Relative Abuse Potential of ALO-02 (Oxycodone Hydrochloride and Naltrexone Hydrochloride Extended-Release Capsules) Compared to Oxycodone Immediate-Release and Placebo When Administered Orally to Non-Dependent, Recreational Opioid Users.”**

## Description of Study B4531008

Study B4531008 was a randomized, double-blind, double-dummy, placebo, and active-controlled, 6-way crossover study in 31 (completer population) healthy, non-dependent, recreational opioid users. Study included a Screening Phase, Naloxone Challenge, Drug Discrimination Phase, Treatment Phase, and End-of-Study Visit.

Primary objectives include:

- To determine the relative abuse potential of intact and crushed ALO-02 60 mg/7.2 mg compared to crushed oxycodone HCl Immediate Release (IR) 60 mg and placebo administered orally to non-dependent, recreational opioid users.
- To determine the relative abuse potential of crushed ALO-02 40 mg/4.8 mg compared to crushed oxycodone HCl IR 40 mg and placebo when administered orally to non-dependent, recreational opioid users.

During the Drug Discrimination Phase, subjects randomly received 1 of the 2 treatments listed below, 1 treatment per day, over 2 consecutive days (Days 1 and 2), in a fasted state and double-blind fashion:

- Oxycodone IR 40 mg (2 x 20 mg oxycodone IR tablets crushed in solution) administered orally.
- Placebo solution administered orally.

Pharmacodynamic and safety assessments conducted during the Drug Discrimination Phase were conducted at pre-dose and up to 5 hours post-dose. In order to advance to the Treatment Phase, subjects were required to:

- Distinguish oxycodone IR from placebo on select subjective drug measures (i.e.,  $\geq 15$  points peak increase for Drug Liking and Take Drug Again, and  $\geq 30$  points peak increase for High within 2 hours following dosing with oxycodone relative to placebo). A peak score of  $\geq 65$  must have been indicated on bipolar measures of Drug Liking within 2 hours post-dose and Take Drug Again at 5 hours post-dose in response to oxycodone IR.
- Display an acceptable placebo response, defined as a VAS response between 0 to 10 inclusive for High or 40 to 60 inclusive for Drug Liking and Take Drug Again.
- Tolerate study treatments safely (i.e., no episodes of vomiting within the first 4 hours post-dose).
- Demonstrate general behavior suggestive that the subject could successfully complete the study, as judged by the study center staff.

Treatment Phase consisted of 6 treatment periods each with a 2-night confined stay, where each dosing was separated by a washout period of a minimum of 5 days and did not exceed 14 days. Treatments were randomized according to a Williams Square design. During each Treatment Period, subjects received a single dose of the treatments listed in Table 3 in a randomized, double-blind, double-dummy crossover manner:

- Placebo (microcrystalline cellulose)
- Troxyca ER 60 mg/7.2 mg Intact
- Troxyca ER 60 mg/7.2 mg Crushed
- Oxycodone IR 60 mg Crushed

- Troxyca ER 40 mg/4.8 mg Crushed
- Oxycodone IR 40 mg Crushed

Troxyca ER capsule contents (1 x 40 mg/4.8 mg capsule and 1 x 60 mg/7.2 mg capsule) and oxycodone IR tablets (2 x 20 mg tablets and 3 x 20 mg tablets) were mixed in an artificially sweetened, non-carbonated, flavored, room temperature solution. Subjects were instructed to swallow intact study medication whole, not to open the capsules, and not chew medication prior to swallowing.

Blood samples for pharmacokinetic (PK) measures were taken pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 14, 24, and 36 hours post-dose. Pharmacokinetic endpoints determined for oxycodone and naltrexone included, but was not limited to:

- Cmax = maximum plasma concentration achieved
- Tmax = time to reach Cmax
- AUC0-2hrs = area under the plasma concentration-time curve from time 0 to 2 hour post-dose
- AUCinf = area under the plasma concentration-time curve from time 0 extrapolated to infinity.

The two primary measures included:

- The 0-100 mm bipolar Drug Liking VAS. For assessing Drug Liking, subjects were required to respond to the statement “At this moment, my liking of this drug is” The response was scored using a 0-100 mm bipolar VAS anchored on the left with “strong disliking” (score of 0); “neither like nor dislike” (score of 50) in the middle; and anchored on the right with “strong liking” (score of 100).
- The 0-100 mm Unipolar High VAS in which subjects were required to respond to the statement “I am feeling high.” The response was scored using a unipolar 0-100 mm VAS anchored on the left by “Not at all” (score of 0) and on the right by “extremely” (score of 100).

Various secondary subjective measures were conducted including the Take Drug Again VAS. To assess Take Drug Again VAS, subjects were required to respond to the statement “I would take this drug again.” The response was scored using a 0-100 mm VAS anchored on the left (score of 0 mm) by “Definitely not” and on the right (score of 100 mm) by “Definitely so.”

Drug Liking VAS and High VAS were administered at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 14, 24, and 36 hours post-dose. Take Drug Again VAS was given at 12, 24, and 36 hours post-dose.

Various specific parameters of the subjective measures were conducted by the Sponsor, including but not limited to:

- Emax: Maximum observed effect
- TEmax: Time to achieve maximum observed effect
- AUE0-2hrs: Area under the effect versus time curve over the first two hours of treatment.

### Findings Regarding Study B4531008

- Maximum Drug Liking (Emax) produced by oral administration of crushed Troxyca ER pellets at doses of 40 mg/4.8 mg (Emax = 70.1 mm) and 60 mg/7.2 mg (Emax = 74.4 mm) was significantly greater than that produced by placebo (Emax = 51.6 mm), but significantly lower than that produced by either crushed oxycodone IR 40 mg (Emax = 85.5 mm) or crushed oxycodone IR 60 mg (Emax = 89.7 mm).
- Likewise, with respect to maximum High, oral administration of crushed Troxyca ER pellets at doses of 40 mg/4.8 mg (Emax = 47.3 mm) and 60 mg/7.2 mg (Emax = 53.4 mm) was significantly greater than that produced by placebo (Emax = 10.9 mm), but significantly lower than that produced by either crushed oxycodone IR 40 mg (Emax = 77.9 mm) or crushed oxycodone IR 60 mg (Emax = 84.7 mm).
- The lower scores for Emax of Drug Liking and High associated with crushed Troxyca ER compared to crushed oxycodone IR treatments, at similar doses, was not due to differences in bioavailability of oxycodone since corresponding treatments resulted in similar maximum oxycodone plasma levels (Cmax), median times to reach Cmax (Tmax), and areas under the oxycodone plasma concentration curve from 0 to 2 hours (AUC0-2hrs).
- These data suggest that orally administered crushed Troxyca ER Capsules is associated with some abuse potential that is significantly lower than that associated with orally administered crushed oxycodone IR tablets. The reduced abuse potential of crushed Troxyca ER Capsules is not due to reduced bioavailability of oxycodone but, instead is related to the opioid antagonism by naltrexone released in response to crushing.

### **Intranasal Abuse Potential Study B4531009 entitled “A Randomized, Double-Blind, Placebo-Controlled, Single-Dose, 4-Way Crossover Study to Determine the Relative Abuse Potential of ALO-02 (Oxycodone Hydrochloride and Naltrexone Hydrochloride Extended-Release Capsules) Compared to Oxycodone Immediate-Release, and Placebo When Administered Intranasally to Non-Dependent, Recreational Opioid Users.”**

#### Description of Study B4531009

Study B4531009 Study was a single center, randomized, double-blind, placebo and active-controlled, 4-way crossover study in 28 (completer population) healthy, non-dependent, recreational opioid users with experience in the insufflation of opioids. Study includes a Screening Phase, Naloxone Challenge, Drug Discrimination Phase, Treatment Phase, and End-of-Study Visit.

Primary objective was to determine the relative abuse potential of crushed Troxyca ER compared to crushed oxycodone HCl IR and placebo administered intranasally (IN) in non-dependent, recreational opioid users.

During the Drug Discrimination Phase, subjects randomly received 1 of the 2 treatments, 1 treatment per day, over 2 consecutive days (Days 1 and 2), in a fasted state and double-blind fashion:

- Intranasal Oxycodone HCl Immediate Release (IR) 30 mg (3 x 10 mg oxycodone IR tablets crushed)
- Intranasal Placebo (crushed lactose tablet, weight matched to oxycodone IR tablet).

In order to advance to the Treatment Phase, subjects were required to satisfy the same Drug Discrimination criteria as noted under oral study B4531008 (See page 2) with the exception that subjects were required not to have any episodes of vomiting within the first 2 hours post-dose.

During the Treatment Phase intranasal single doses were administered to subjects in a randomized (Williams Square), double-blind, 4-way crossover design on Day 1 of each Treatment Period following a fast of at least 8 hours. Treatments included:

- Placebo (sugar squares) crushed, weight match Troxyca ER capsule fill weight
- Troxyca ER 30 mg/3.6 mg capsule crushed
- Placebo (lactose tablets) crushed, weight matched to oxycodone IR (3 x 10 mg)
- Oxycodone IR 30 mg (3 x 10 mg tablets crushed)

Insufflation was conducted double-blind with subjects given 5 minutes to complete. For each subject, the amount insufflated was documented, expressed as the percentage of dose insufflated.

Blood samples for pharmacokinetic (PK) measures were taken pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours post-dose. Pharmacokinetic endpoints determined for oxycodone and naltrexone included, but not limited to: Cmax, Tmax, and AUCinf. For definitions of these parameters see page 3.

Primary subjective measures included Drug Liking VAS and High VAS which are described on page 3 of this document. Both measures were administered 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 hours post-dose.

Other measures (secondary) were conducted by Sponsor including Take Drug Again VAS, also described on page 2 of this document. Take Drug Again VAS was assessed at 12 and 24 hours, post-dose. To assess Take Drug Again VAS, subjects were required to respond to the statement "I would take this drug again." The response was scored using a 0-100 mm VAS anchored on the left (score of 0 mm) by "Definitely not" and on the right (score of 100 mm) by "Definitely so."

Among the parameters determined were Emax, TEmax, and AUE0-2hrs. See page 3 for definitions for these terms.

The Subject-Rated Scale for Nasal Effects was used to assess burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal congestion using a 6-point scale (0 = not present/no problem; 1 = very mild problem; 2 = mild/ slight problem; 3 = moderate problem; 4 = severe problem; 5 = problem "as bad as can be").

## Findings Regarding Study B4531009

- The positive comparator, oxycodone IR 30 mg IN, produced Emax of Drug Liking and High (92.8 mm for Drug Liking, 85.8 mm for High) that was statistically significantly higher than then the Emax from placebo (50.9 mm for Drug Liking and 2.2 mm for High), thereby validating the study with respect to these measures.
- Crushed Troxyca ER 30 mg IN produced Emax values for Drug Liking (60.5 mm) and High (26.6 mm) were significantly lower than that produced by oxycodone IR 30 mg IN (92.8 mm for Drug Liking, 85.8 mm for High) but statistically similar to that of placebo (50.9 mm for Drug Liking and 2.2 mm for High), thereby indicating little subjective reinforcing effects when crushed and insufflated.
- Intranasal administration of crushed Troxyca ER 30 mg/3.6 mg was associated with an approximately 30% reduction in oxycodone plasma Cmax compared to intranasal treatment with crushed oxycodone IR 30 mg (geometric means of 56.37 ng/mL and 80.38 ng/mL, respectively). Tmax was longer following crushed Troxyca ER 30 mg/3.6 mg (median Tmax of 1.6 hours) compared with crushed oxycodone IR 30 mg (median Tmax of 0.5 hours). Oxycodone systemic plasma exposure based on geometric mean AUCinf was about 20% lower for crushed Troxyca ER 30 mg/3.6 mg compared with crushed oxycodone IR 30 mg.
- The mean and median scores for all the domains of the Subject-Rated Scale for Nasal Effects were low. For Burning, Need to Blow Nose, Facial Pain/Pressure the oxycodone IR group had slightly higher mean Emax than the Troxyca ER 30 mg/3.6 mg and the placebo treatments. Overall, there was trend towards oxycodone IR resulting in more nasal effects relative to the other treatments; however this effect was minor and not indicative of any clinically significant or severe nasal adverse reactions.
- The data support a possible deterrent effect of Troxyca ER Capsules to intranasal abuse.

## **Simulated Intravenous Human Abuse Potential Study Study B4981002 entitled “A Randomized, Single-Dose, Placebo-Controlled, Double-Blind, 3-Way Crossover Study to Determine the Relative Abuse Potential of Intravenous Oxycodone Hydrochloride Alone or in Combination with Intravenous Naltrexone Hydrochloride in Opioid Experienced Non-Dependent Subjects.”**

### Description of Study B4981002

Study B4981002 is a single-center, randomized, double-blind, placebo-controlled, 3-way crossover study in 29 (completer population) non-dependent, recreational, and otherwise healthy opioid users. Study included a Screening Phase, Naloxone Challenge, Drug Discrimination Phase, Treatment Phase, and End-of-Study Visit.

Primary objective was to determine the relative abuse potential of IV oxycodone HCl when combined with IV naltrexone HCl (i.e., simulated IV administration of Troxyca ER) compared with an equivalent IV dose of oxycodone HCl alone and with IV placebo, when administered to non-dependent, recreational opioid users.

During the Drug Discrimination Phase, subjects randomly received 1 of the 2 treatments, 1 treatment per day, over 2 consecutive days (Days 1 and 2), in a fasted state and double-blind fashion:

- Oxycodone HCl 20 mg IV push over 4 minutes ( $\pm$ 15 seconds)
- Placebo (administered as 0.9% sodium chloride) IV push over 4 minutes ( $\pm$ 15 seconds).

In order to advance to the Treatment Phase, subjects were required to satisfy the same Drug Discrimination criteria as noted under oral study B4531008 (See page 2) with the exception that subjects were required not to have any episodes of vomiting within the first 2 hours post-dose.

The Treatment Phase consisted of 3 Treatment Periods, where each dosing was separated by a washout period of a minimum of 5 days. During each Treatment Period, subjects received under fasted conditions a single dose of the treatment, randomized using a Williams Square design. The intravenous treatments are listed below.

- Placebo – 0.9% sodium chloride i.v. push over 4 minutes  $\pm$  15 seconds
- Simulated i.v. Troxyca ER 20 mg/2.5 mg – Oxycodone HCl 20 mg i.v. + naltrexone HCl 2.4 mg simultaneously i.v. push over 4 minutes  $\pm$  15 seconds.
- Oxycodone HCl 20 mg – Oxycodone HCl 20 mg i.v. push over 4 minutes + 15 seconds.

Study was conducted as a parenteral simulation of a Troxyca ER formulation using solution preparations of oxycodone 20 mg and naltrexone 2.4 mg that are suitable for i.v. administration. The doses selected represent the exact amount of oxycodone HCl and naltrexone HCl contained in a Troxyca ER 20 mg/2.4 mg capsule and is the maximum amount of oxycodone/naltrexone that would be liberated if a Troxyca ER 20 mg/2.4 mg capsule were crushed and the contents solubilized in aqueous solution. Such tampering efforts are required by drug users who attempt to prepare such formulations for injection. In this study, naltrexone and oxycodone were given simultaneously to mimic as closely as possible the injection of a solution derived from tampering with Troxyca ER.

Blood samples for pharmacokinetic determination were taken pre-dose and at 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. Pharmacokinetic endpoints determined of oxycodone and naltrexone and examined in this review include

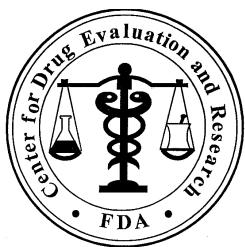
- C<sub>5min</sub> = concentration observed at 5 minutes after the start of infusion
- AUC<sub>0-1hr</sub> = area under the plasma concentration-time curve from time 0 to 1 hour post-dose
- AUC<sub>0-2hrs</sub> = area under the plasma concentration-time curve from time 0 to 2 hour post-dose
- AUC<sub>0-8hrs</sub> = area under the plasma concentration-time cure from time 0 to 8 hours post-dose
- AUC<sub>inf</sub> = area under the plasma concentration-time curve from time 0 extrapolated to infinity.

Primary measures included Drug Liking VAS and High VAS which are described on page 3 of this document. Endpoints included Emax and AUE<sub>0-2hrs</sub> (see page 3). Drug Liking VAS and High VAS were administered at 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose.

Statistical analysis of the subjective measures including Drug Liking VAS and High VAS were conducted by the FDA CDER Office of Biostatistics.

### Findings Regarding B4981002

- Intravenous injection of the positive comparator, oxycodone HCl 20 mg, produced levels of Drug Liking and High significantly greater than that produced by placebo, thereby validating the study with respect to Drug Liking VAS and High VAS. Intravenous placebo responses were also deemed appropriate for both Drug Liking VAS and High VAS.
- 2.4 mg Naltrexone HCl 2.4 mg i.v. blocked the Drug Liking response and most of the High response produced by intravenous 20 mg oxycodone HCl. Simulated Troxyca ER 20 mg/2.4 mg injected intravenously produced Emax for Drug Liking and High of 58.2 mm and 17.4 mm, respectively, which were similar to that produced by intravenous placebo (52.3 mm for Drug Liking and 3.7 mm for High).
- Intravenous injection of oxycodone HCl 20 mg produced an Emax of Drug Liking (92.4 mm) and High 93.1 mm that was statistically significantly greater than that produced by intravenous simulated Troxyca ER 20 mg/2.4 mg.
- For both active treatments, the concentration of oxycodone in plasma at 5 minutes post-dosing (C5min) and the various partial areas under the oxycodone concentration curve versus time curve (partial AUC) were similar; therefore, the differences in Drug Liking and High were not due to differences in oxycodone exposure.
- Troxyca ER capsules may have a deterrent effect to intravenous abuse when the capsule contents are crushed and all of the naltrexone is released, resulting in the blockade of the effects of the concomitantly released oxycodone.
- Study B4981002 does not establish the degree of blocking oxycodone HCl induced Drug Liking and High when the ratio of oxycodone HCl to naltrexone HCl is increased. This is significant considering that results from in vitro studies (Category 1) indicate that under some conditions, oxycodone HCl may be preferentially extracted at higher levels compared to the extraction of naltrexone HCl as determined from percentage of label claim extracted. Naltrexone acts via competitive opioid receptor blockade to attenuate Drug Liking and High produced by oxycodone HCl administered IV. It is possible that with higher levels of oxycodone HCl compared to levels of naltrexone HCl, the competitive blockade would be partially overcome thereby allowing greater expression of Drug Liking and High following oxycodone HCl administration i.v.



**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:** April 29, 2016

**To:** Sharon Hertz, M.D., Director  
Division of Anesthesia, Analgesia, and Addiction Products  
Office of Drug Evaluation II  
*Office of New Drugs*

**From:** Cynthia LaCivita, Pharm.D., Director  
Division of Risk Management (DRISK)  
Office of Medication Error Prevention and Risk Management  
*Office of Surveillance and Epidemiology (OSE)*

**Drug Name (s):** Troxyca ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules

**Application Number:** NDA 207621

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

If approved, Troxyca ER (oxycodone hydrochloride and naltrexone hydrochloride) extended-release capsules 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 holders<sup>1</sup> 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.<sup>2</sup> 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.

<sup>1</sup> 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.

<sup>2</sup> 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.

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

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

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

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

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

The following timetable is the schedule for this study:

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

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

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

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

The following timetable is the schedule for this study:

Final Protocol Submission: 11/2014

Study Completion: 04/2019

Final Report Submission: 09/2019

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

The following timetable is the schedule for this study:

Final Protocol Submission: 04/2015

Study Completion: 10/2015

Final Report Submission: 01/2016

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

The following timetable is the schedule for this study:

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

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

The following timetable is the schedule for this study:

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

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

The following timetable is the schedule for this study:

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

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

The following timetable is the schedule for this study:

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

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

The following timetable is the schedule for this study:

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

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

The following timetable is the schedule for this study:

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

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

The following timetable is the schedule for this study:

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

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

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

The following timetable is the schedule for this trial:

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

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-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry (April 2015). Assessing the impact of the abuse-deterrent formulation on the incidence of clinical outcomes, including overdose and death, is critical to fulfilling this PMR. Any studies using electronic healthcare data should use validated outcomes and adhere to guidelines outlined in FDA's Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.