FDA Briefing Document

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

May 5, 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 results of studies evaluating the abuse of KP201 (benzhydrocodone/acetaminophen) tablets to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety & Risk Management Advisory Committee

May 5, 2016

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DIVISION DIRECTOR MEMO

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

M E M O R A N D U M

DATE: April 6, 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, May 5, 2016 AADPAC/DSaRM Meeting to Discuss NDA 208653

At this joint meeting of AADPAC and DSaRM, we will be discussing an application from KemPharm, Inc. for an immediate-release formulation of benzhydrocodone and acetaminophen with the proposed trade name Apadaz (also referred to as KP201 during development), designed with properties intended to deter abuse. The proposed indication for KP201 is the short-term (up to 14 days) management of acute pain.

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 currently no single-entity or combination (opioid/non-opioid) immediate-release opioid analgesics labelled with abuse-deterrent properties as described in the guidance. There are five 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), and Morphabond (morphine sulfate extended-release tablets).

Apadaz has been formulated with the intent to provide abuse-deterrent properties. According to the Applicant, benzhydrocodone is converted into hydrocodone by enzymes in the gastrointestinal (GI) tract. The Applicant states that this requirement for conversion in the GI tract can modify the pharmacokinetic profile and decrease the exposure to the active drug when taken by the nasal or intravenous routes of administration for the purposes of abuse. They also state that the nasal route of abuse is relevant for their product despite the known irritating effects of acetaminophen.

You will be asked to discuss whether the Applicant has demonstrated abuse-deterrent properties for their product that would support labeling. In addition, you will be asked to discuss whether the nasal route of abuse is relevant for products that contain hydrocodone and acetaminophen as active ingredients, as this pertains to the Applicant's claim for their product representing a benefit over hydrocodone/acetaminophen products. And finally, you will be asked whether the benefits of Apadaz outweigh its risks, and whether it should be approved.

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

Draft Points to Consider

1. Has the Applicant provided sufficient data to support that the nasal route of abuse is relevant for combination products such as theirs that contain hydrocodone and acetaminophen?

2. Has the Applicant demonstrated that KP201 has properties that can be expected to deter abuse?
    a. by the IV route of administration
    b. by the nasal route of administration

3. Is there sufficient data to support inclusion of language regarding abuse-deterrent properties in the product label?
    a. for the IV route of administration
    b. for the nasal route of administration

Regulatory History of Abuse-Deterrent Opioids

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 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 currently no approved immediate-release single-entity or combination opioid analgesics with abuse-deterrent labeling language as described in the Guidance for Industry: Abuse-Deterrent Opioids. There are five 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.

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 our 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:
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U.S. Department of Health and Human Services
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Abuse-Deterrent Opioids — Evaluation and Labeling
Guidance for Industry[1]

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

I. INTRODUCTION

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

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

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

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

II. BACKGROUND

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

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

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

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

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

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

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

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

[3] Ibid.

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

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

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

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

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

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

III. ABUSE-DETERRENT PRODUCTS

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

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

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

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

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

IV. PREMARKET STUDIES

First and foremost, any studies designed to evaluate the abuse-deterrent characteristics of an opioid formulation should be scientifically rigorous. Important general considerations for the design of these studies include the appropriateness of positive controls[6] and comparator drugs, outcome measures, data analyses to permit a meaningful statistical analysis, and selection of subjects for the study.

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

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

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

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

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

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

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

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

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

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

A. Laboratory Manipulation and Extraction Studies (Category 1)

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

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

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

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

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

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

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

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

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

- For a product with potential for abuse by the nasal route, the particle size distribution following attempted manipulation by various methods should be established, and the method that provides the smallest particle size should be used in subsequent studies.

- For a product with potential for abuse by smoking, the amount of drug produced by vaporization at temperatures encompassing the range from the melting point of the active ingredient to its degradation point should be determined. Appropriate controls, such as pure active ingredient, both in salt and free-base form should be included in these assessments.

- For a product with potential for abuse by injection, the amount of opioid that can be obtained in a syringe should be based on studies of intact and manipulated test product and comparator(s) using small volumes of water (5-10 mL) at room temperature and at 90° C – 95° C with and without agitation. Extraction times should range from 30 seconds to 30 minutes. The amount of opioid extracted, the volume of solution collected and the viscosity of the samples should be recorded. The ability to get the sample into a syringe and expel the sample using needles of various gauges should also be explored.

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

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

2. Quantity of the opioid extracted from the product following the various methods attempted that could be used for injection by intravenous or subcutaneous routes and a description of any barriers resulting from attempts at dissolution for drawing the drug into a syringe.

3. Quantity of opioid antagonist released from an agonist/antagonist combination when it is manipulated for administration by ingestion, nasal administration, or injection.

4. Quantity of opioid product following in vitro manipulation of the prodrug.

B. Pharmacokinetic Studies (Category 2)

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

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

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

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

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

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

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

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

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

C. Clinical Abuse Potential Studies (Category 3)

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

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

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

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

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

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

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

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

1. Blinding

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

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

2. Pre-qualification Phase

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

[11] Ibid.

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

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

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

3. Assessment Phase

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

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

4. Subjects

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

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

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

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

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

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

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

6. Outcome Measures and Data Interpretation

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

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

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

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

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

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

7. Data Interpretation

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

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

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

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

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

[16] See *Statistical Analysis* Section for further guidance.

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

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

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

8. Statistical Analysis

a. Background

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

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

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

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

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

b. Primary analyses

The primary analysis of abuse-deterrent effects should be based on the comparison of means[18] between crushed, chewed, or otherwise modified *T* and *C* with an abuse deterrence margin on drug liking VAS. That is, test

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

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

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

where $\delta_2 \ge 15$.

The significant level for both tests is 2.5%.

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

c. Secondary analyses

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

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

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

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

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

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

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

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

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

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

- Responder Analysis

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

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

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

- Analysis of the Median Percent Reduction

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

For assessing deterrent effects, we can test

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

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

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

d. Multiplicity

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

V. POSTMARKET STUDIES (CATEGORY 4)

Premarket studies focus on assessing the potentially abuse-deterrent properties of a product under controlled conditions. The goal of postmarket[20] studies, Category 4, is to determine whether the marketing of a product with abuse-deterrent properties results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting. As more abuse-deterrent products are approved, it is possible that the amount of reduction observed in an epidemiologic study may also change. Consequently, a reduction that is deemed meaningful at one time may not be meaningful at another. Given the changing landscape, a numerical threshold cannot define what would be considered a meaningful reduction.

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

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

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

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

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

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

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

A. Formal Studies

1. General Characteristics

Formal studies have the following characteristics:

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

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

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

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

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

2. Study Design Features

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

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

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

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

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

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

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

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

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

B. Supportive Information

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

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

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

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

VI. LABELING

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- Category 1

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

> *In vitro physical and chemical tablet manipulation studies were performed to evaluate the ability of different extraction methods to defeat the formulation. Results support that Tradename resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some extended-release properties despite manipulation.*
>
> *These in vitro data demonstrate that Tradename has physical and chemical properties that are expected to deter intravenous abuse. However, abuse of this product is still possible by the oral and nasal routes.*

- Category 1 and Category 2

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

> *In vitro physical and chemical tablet manipulation studies were performed to evaluate the ability of different extraction methods to defeat the formulation, and pharmacokinetic studies of the oral and intranasal routes were performed to determine the effect of manipulation on drug release. Results support that Tradename resists crushing, breaking, and dissolution using a variety of tools and solvents and retains its extended-release properties despite manipulation.*
>
> *The in vitro data demonstrate that Tradename has physical and chemical properties that are expected to deter oral, nasal and intravenous abuse. However, abuse of intact product is still possible by the oral route.*

- Category 2 and Category 3

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

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

> *The pharmacokinetic data demonstrate that crushing Tradename results in the simultaneous release and rapid absorption of opioid and antagonist. These data along with the results from oral and intranasal clinical abuse potential studies and a clinical abuse potential study of intravenous opioid and antagonist to simulate crushed Tradename indicate that Tradename has properties that are expected to deter abuse via the oral, intranasal, and intravenous routes. However, abuse of Tradename by these routes is still possible.*

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

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

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

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

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

VII. ADDITIONAL RESEARCH NEEDS

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

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

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

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

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

Drug Utilization Review

Date:	March 30, 2016
Reviewer(s):	LCDR Jennie Wong, Pharm.D., Division of Epidemiology II (DEPI II)
Team Leader	Rajdeep Gill, Pharm.D., Division of Epidemiology II (DEPI II)
Deputy Director For Drug Utilization:	LCDR Grace Chai, Pharm.D., Division of Epidemiology II (DEPI II)
Product Name(s):	KP201/APAP (Benzhydrocodone Hydrochloride/Acetaminophen), 6.67mg/325mg
Application Type/Number:	NDA 208653/Associated IND 108038
Applicant/sponsor:	Kempharm, Inc.
OSE RCM #:	2016-87

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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 advisory committee (DSaRM), scheduled on May 5, 2016, this review examined drug utilization patterns to assess the use of hydrocodone/acetaminophen and selected comparators during 2011 through 2015. This review will be used as background information to discuss a new drug application (NDA) 208653, benzhydrocodone/acetaminophen, immediate-release (IR) oral tablet, submitted by KemPharm, Inc., with the proposed indication of short-term (no more than 14 days) management of acute pain. The product has been formulated with the intent to provide abuse-deterrent properties. Because the majority of hydrocodone/acetaminophen products were sold to U.S. outpatient retail pharmacies, this review only focused on outpatient retail pharmacy settings.

The utilization of hydrocodone/acetaminophen decreased from 46.5 million patients and 125 million prescriptions dispensed in 2011 to 40 million patients and 90 million prescriptions dispensed in 2015. The top prescriber specialties for hydrocodone/acetaminophen were general practice/family practice/doctor of osteopathy, followed by internal medicine, and dentistry. According to U.S. office-based physician surveys, hydrocodone/acetaminophen appears to be widely used for both acute and chronic conditions and are often associated with musculoskeletal pain and with pain related to injuries.

1 INTRODUCTION

In preparation for the upcoming joint meeting of the AADPAC and DSaRM scheduled on May 5, 2016, this review provides drug utilization data of combination hydrocodone/acetaminophen products and selected comparators as background information. This review will summarize the U.S. outpatient retail pharmacy utilization trends of selected immediate-release (IR) combination opioids such as, hydrocodone/acetaminophen, oxycodone/acetaminophen and IR single-entity (SE) opioids such as, oxycodone IR, oxymorphone IR, morphine IR, hydromorphone IR, tapentadol IR, as well as hydrocodone extended-release (ER) from year 2011 through year 2015.

1.1 BACKGROUND

Benzhydrocodone (KP201) is a prodrug for hydrocodone and is proposed to be available in a fixed dose combination with acetaminophen. There are currently no approved immediate-release (IR) hydrocodone formulations with abuse-deterrent properties on the market. The sponsor is requesting priority review of the new drug application (NDA) claiming KP201/acetaminophen has abuse deterrent properties; specifically resistance to intranasal abuse as well as physical and chemical tampering.

DAAAP will bring KP201/acetaminophen to an AC meeting to discuss whether the applicant has demonstrated abuse-deterrent properties for their product that would

support the proposed labeling and whether abuse via nasal administration is relevant for combination products made up of hydrocodone and acetaminophen. In preparation for the AC meeting, DAAAP has requested DEPI II to provide drug utilization data for combination hydrocodone/acetaminophen products to provide background information for the AC meeting.

1.2 PRODUCT INFORMATION

Benzhydrocodone Hydrochloride/acetaminophen (KP201/acetaminophen), 6.67mg/325mg, is a fixed dose, immediate-release formulation with a proposed indication for the short-term (no more than 14 days) management of acute pain.

1.3 MOLECULES INCLUDED AS COMPARATORS

Oral Immediate Release (IR) Combination molecules:

- Hydrocodone/acetaminophen
- Oxycodone/acetaminophen

Oral Immediate Release (IR) Single-Entity (SE) molecules:

- Oxycodone IR
- Oxymorphone IR
- Morphine IR
- Hydromorphone IR
- Tapentadol IR

Oral Extended Release (ER) molecule:

- Hydrocodone ER

2 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct this analysis. (See Appendix 2 for detailed descriptions of the databases).

2.1 DETERMINING SETTING OF CARE

The IMS Health, IMS National Sales Perspectives™ database was used to determine the settings of distribution for hydrocodone/acetaminophen, from 2011 through 2015. Sales data for hydrocodone/acetaminophen by eaches (bottles/packages) from the manufacturer to all U.S. channels of distribution showed that approximately 72% of hydrocodone/acetaminophen bottles/packages were distributed to outpatient retail pharmacies, 25% were to non-retail settings, and 3% were to mail-order/specialty pharmacies.[1] As a result, only outpatient retail pharmacy utilization patterns were examined for hydrocodone/acetaminophen. Mail-order/specialty pharmacy and non-retail pharmacy settings data were not included in this review.

[1] IMS Health, IMS National Sales Perspectives™, January 2011-December 2015. Extracted March 2016. Source file: NSP 2016-87 HCOD APAP by Superchannels, 3-4-2016.

2.2 DATA SOURCES USED

The IMS, Total Patient Tracker™ (TPT) database was used to obtain the nationally estimated number of patients who received a dispensed prescription for the selected opioid molecules (Refer to section 1.3) from U.S. outpatient retail pharmacies, from 2011 through 2015, yearly.

The IMS, National Prescription Audit™ (NPA) database was used to obtain nationally estimated number of prescriptions dispensed for selected molecules (Refer to section 1.3) from U.S. outpatient retail pharmacies, from 2011 through 2015, yearly.
In addition, this database was also utilized to obtain nationally estimated number of prescriptions dispensed for hydrocodone/acetaminophen from U.S. outpatient retail pharmacies, stratified by prescriber specialties, for years 2011 and 2015.

Encuity Research, LLC, Treatment Answers™, a U.S. office-based physician survey database was used to obtain top diagnoses associated with the use of hydrocodone/acetaminophen, stratified by acute versus chronic conditions for year 2015, cumulative. Diagnoses data by number of drug use mentions[2] were captured based on International Classification of Diseases (ICD-9-CM) codes.

3 RESULTS

3.1 UNIQUE PATIENTS

Table 3.1 below provides the nationally estimated number of patients who received a dispensed prescription for selected opioid molecules from U.S. outpatient retail pharmacies from 2011 through 2015. The total number of patients who received a dispensed prescription for hydrocodone/acetaminophen decreased from approximately 46.5 million patients in 2011 to 40 million patients in 2015. From 2011 through 2015, patients who received a dispensed prescription for hydrocodone/acetaminophen accounted for the majority of patients for the selected market with approximately 72% (40 million patients) of total patients in 2015. Patients who received a dispensed prescription for oxycodone/acetaminophen accounted for approximately 28% (15 million patients) of total patients in 2015. Patients who received a dispensed prescription for selected IR SE opioids and hydrocodone ER accounted for approximately 13% and less than 1% of total patients, respectively.

Among the selected IR SE opioids selected for this analysis, oxycodone IR represented approximately 78% of the patients, followed by hydromorphone IR at approximately 15%, morphine IR at approximately 10%, and tapentadol IR and oxymorphone IR at approximately 3% and <1%, respectively, in 2015.

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

Table 3.1

Nationally estimated number of patients who received a dispensed prescription for combination hydrocodone/acetaminophen and other selected* opioid analgesics from U.S. outpatient retail pharmacies, from 2011 – 2015, yearly

	2011		2012		2013		2014		2015	
	Patient	%	Patient	%	Patient	%	Patient	%	Patient	%
Grand Total	**59,224,788**	***100.0%***	**58,346,399**	***100.0%***	**57,979,009**	***100.0%***	**57,853,416**	***100.0%***	**55,243,215**	***100.0%***
Total R Hydrocodone/Acetaminophen	46,470,297	*78.5%*	45,458,329	*77.9%*	44,799,372	*77.3%*	43,852,743	*75.8%*	39,833,070	*72.1%*
Total R Oxycodone/Acetaminophen	15,048,828	*25.4%*	14,594,526	*25.0%*	14,394,820	*24.8%*	14,736,521	*25.5%*	15,294,607	*27.7%*
Total Selected^ IR SE Opioid Molecules	5,795,471	*9.8%*	6,066,949	*10.4%*	6,236,830	*10.8%*	6,787,932	*11.7%*	7,369,976	*13.3%*
Oxycodone	4,052,448	*69.9%*	4,388,037	*72.3%*	4,580,887	*73.4%*	5,143,814	*75.8%*	5,728,772	*77.7%*
Hydromorphone	1,007,901	*17.4%*	1,052,095	*17.3%*	1,075,744	*17.2%*	1,093,072	*16.1%*	1,098,101	*14.9%*
Morphine	546,269	*9.4%*	585,726	*9.7%*	646,690	*10.4%*	675,385	*9.9%*	698,513	*9.5%*
Tapentadol	447,189	*7.7%*	355,515	*5.9%*	238,712	*3.8%*	198,041	*2.9%*	180,728	*2.5%*
Oxymorphone	61,764	*1.1%*	54,154	*0.9%*	51,977	*0.8%*	53,882	*0.8%*	52,511	*0.7%*
Total ER Hydrocodone**	0	*0.0%*	0	*0.0%*	0	*0.0%*	20,215	*0.0%*	60,367	*0.1%*
Hysingla ER	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	*0.0%*	40,073	*66.4%*
Zohydro ER	0	*0.0%*	0	*0.0%*	0	*0.0%*	20,215	*100.0%*	22,078	*36.6%*

Source: IMS Health, Total Patient Tracker (TPT). Data Extracted February and March 2016.
* For selected opioid molecules refer to section 1.3
** Hydrocodone ER products: Zohydro ER approved in 10/2013 and Hysingla approved in 11/2014, therefore no data for years 2011, 2012, and 2013.
^Selected Immediate-Release (IR) Single-Entity (SE) Opioid Molecules include: Oxycodone IR, Hydromorphone IR, Morphine IR, Tapentadol IR, and Oxymorphone IR
***Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Therefore, summing across time is not advisable and may result in overestimates of patient counts.

3.2 PRESCRIPTIONS

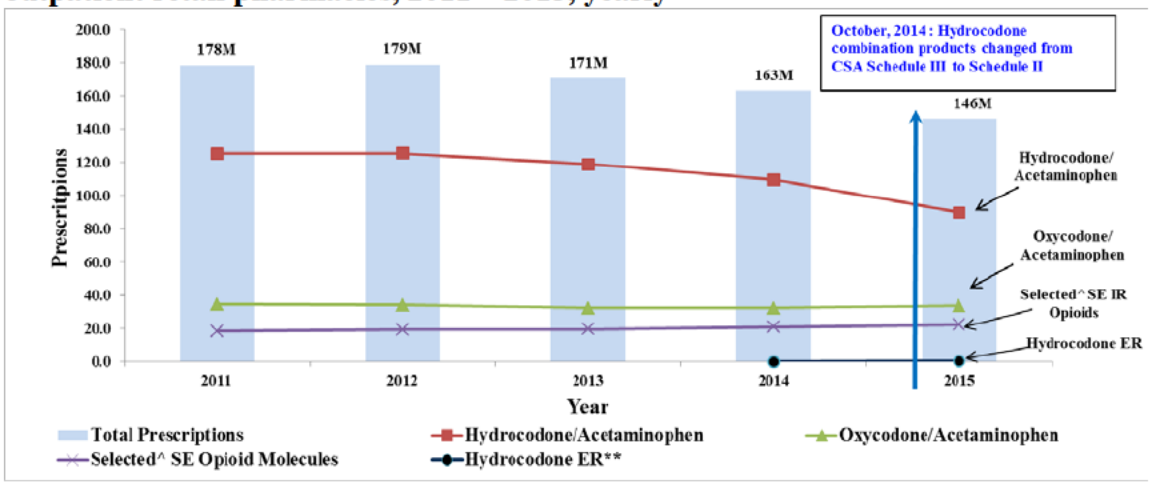
Figure 3.2 below and Table 1 in Appendix 1 provide the nationally estimated number of prescriptions dispensed for selected opioid molecules (Refer to section 1.3) from U.S. outpatient retail pharmacies, from 2011 through 2015. The total number of prescriptions dispensed for hydrocodone/acetaminophen decreased from approximately 125 million prescriptions in 2011 to 90 million prescriptions in 2015.

In year 2015, of the total number of dispensed prescriptions for selected opioids, hydrocodone/acetaminophen IR represented the majority of the prescriptions dispensed at 62% (approximately 90 million prescriptions), followed by oxycodone/acetaminophen IR at 23% (approximately 34 million prescriptions), then selected IR SE opioid molecules at 15% (approximately 22 million prescriptions), and hydrocodone ER at less than 1% (approximately 149,000 prescriptions).

Among the selected IR SE opioids for this analysis, oxycodone IR accounted for 75% of prescriptions, followed by hydromorphone IR, morphine IR, tapentadol IR, and oxymorphone IR with approximately 13%, 8%, 2%, and 1% of IR SE opioid prescriptions dispensed, respectively.

Figure 3.2

Nationally estimated number of prescriptions dispensed for combination hydrocodone/acetaminophen and other selected* opioid analgesics from U.S. outpatient retail pharmacies, 2011 – 2015, yearly



*For selected opioid molecules refer to section 1.3

** Hydrocodone ER products: Zohydro ER approved in 10/2013 and Hysingla ER approved in 11/2014, therefore no data for years 2011, 2012, and 2013.

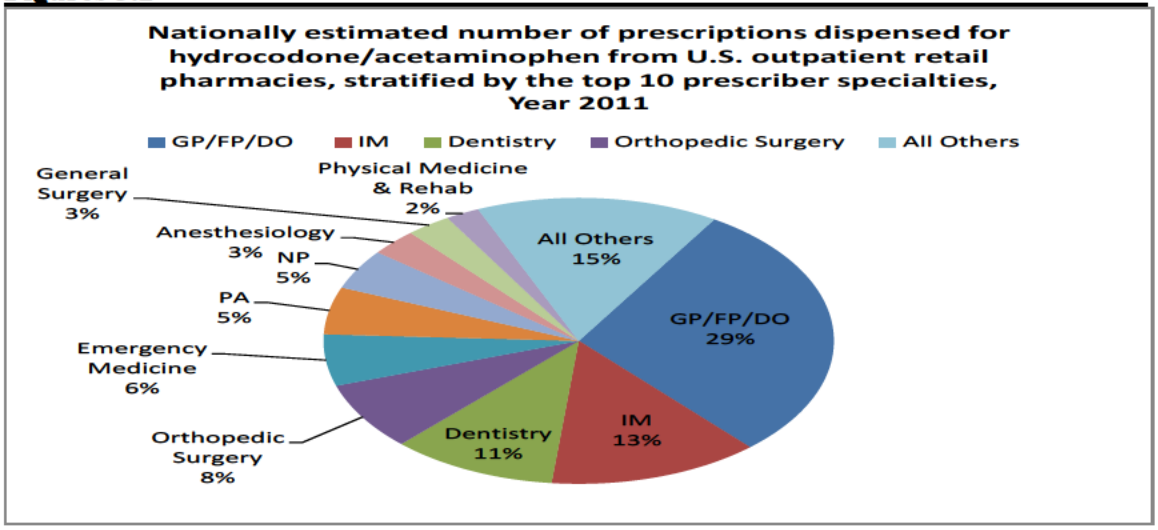
^Selected Immediate-Release (IR) Single-Entity (SE) Opioid Molecules include: Oxycodone IR, Hydromorphone IR, Morphine IR, Tapentadol IR, and Oxymorphone IR

Source: IMS, National Prescription Audit™ (NPA). Data Extracted February 2016.

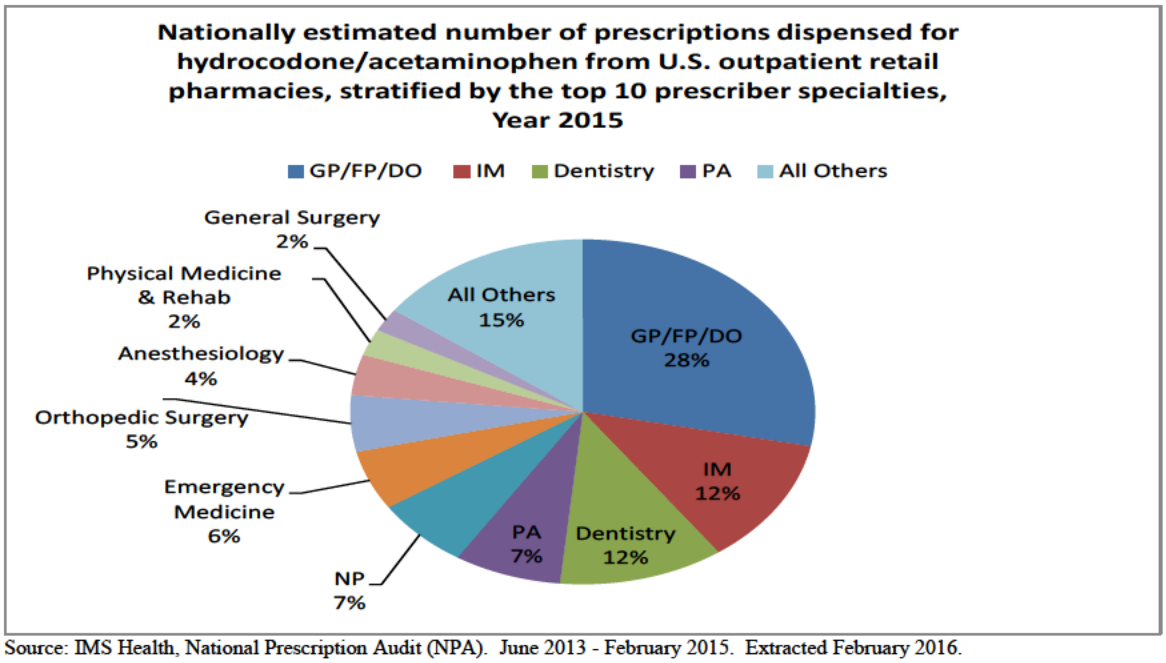
3.3 PRESCRIBER SPECIALTY

Figures 3.2 below and Table 2 in Appendix 1 below provides the total number of prescriptions dispensed for combination hydrocodone/acetaminophen from U.S. outpatient retail pharmacies by the top prescribing specialties for 2011 and 2015. General practice/family practice/doctor of osteopathy were the top prescriber specialties (28-29% of total prescriptions), followed by internal medicine with approximately 12-13% and dentistry with approximately 10-11% of the total hydrocodone/acetaminophen prescriptions dispensed from U.S. outpatient retail pharmacies.

Figures 3.2



Source: IMS Health, National Prescription Audit (NPA). June 2013 - February 2015. Extracted February 2016.



Source: IMS Health, National Prescription Audit (NPA). June 2013 - February 2015. Extracted February 2016.

3.4 DIAGNOSES ASSOCIATED WITH THE USE (GROUPED BY ICD-9 CODES) FOR HYDROCODONE/ACETAMINOPHEN

Table 3 in Appendix 1 provides the most common diagnoses associated with the use of hydrocodone/acetaminophen for year 2015, stratified by acute versus chronic diagnoses, as reported by U.S. office-based physician surveys.

Acute diagnoses accounted for approximately 51% of the drug use mentions while chronic diagnoses accounted for approximately 44% of the drug use mentions.

Among acute diagnoses, "Injury and Poisoning" (ICD-9 codes 800-999) accounted for the majority of drug use mentions at approximately 42%, followed by "Diseases of the musculoskeletal system and connective tissue" (ICD-9 codes 710-739) which accounted for approximately 17% of use mentions.

Among chronic diagnoses, "Diseases of the musculoskeletal system and connective tissue" (ICD-9 codes 710-739) accounted for the majority of drug use mentions at approximately 54%, followed by "Follow Up Visits" (ICD-9 codes V01-V91) accounted for approximately 14% of use mentions.

4 DISCUSSION

The focus of this drug utilization analysis is to provide drug utilization data on hydrocodone/acetaminophen and other selected opioids for the upcoming advisory committee meeting to discuss a new drug application for combination benzhydrocodone/acetaminophen.

Decreasing trends were seen in both the patient and prescription data for combination hydrocodone/acetaminophen over the examined time. The total number of patients decreased by approximately 14% from 46.5 million patients in 2011 to 40 million patients in 2015. Similarly, the total number of prescriptions dispensed decreased by 28%

from 125 million prescriptions in 2011 to 90 million prescriptions in 2015. The decline in utilization may be possibly attributed to the rescheduling of hydrocodone combination products that occurred in October 2014.[3]

Using U.S. office-based physician surveys data, drug use mentions for acute and chronic diagnoses associated with hydrocodone/acetaminophen were obtained; designation of diagnosis as "acute" vs. "chronic" were attributed by the prescriber on survey responses. We further grouped the ICD-9 codes captured under the categories of acute and chronic diagnoses into diagnostic categories. The results of the acute diagnoses data showed that the majority of hydrocodone/acetaminophen use in 2015 were associated with "Injury and Poisoning" (ICD-9 codes 800-999) which include injuries related to sprains, fractures, dislocation of joint, wound, contusion. For the chronic diagnoses data, the results showed that the majority of hydrocodone/acetaminophen use in 2015 were associated with "Diseases of the musculoskeletal system and connective tissue" (ICD-9 codes 710-739), which include arthritic conditions and back pain.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We focused our analysis on only the outpatient retail pharmacy settings where the majority of sales of the direct comparator, hydrocodone/acetaminophen, were distributed to; 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.

5 CONCLUSIONS

Drug utilization analyses show that despite the decrease in the utilization of hydrocodone/acetaminophen from 2011 through 2015, substantial utilization still remains with approximately 90 million prescriptions dispensed and 40 million patients in 2015.

The top specialties prescribing hydrocodone/acetaminophen were general practice/family practice/doctor of osteopathy, followed by internal medicine, and dentistry. Hydrocodone/acetaminophen appears to be used widely for acute and chronic conditions that are often associated with musculoskeletal pain and pain related to injuries.

[3] Jones, C, Lurie, P, Throckmorton, D. Effect of US Drug Enforcement Administration's Rescheduling of Hydrocodone Combination Analgesic Products on Opioid Analgesic Prescribing. Journal of American Medical Association (JAMA) Internal Medicine. March 2016; 176(3):399-402.Accessed on 2/22/2016 at http://archinte.jamanetwork.com/

6 APPENDICES

6.1 APPENDIX 1: TABLES AND FIGURES

6.1.1 Table 1

Nationally estimated number of prescriptions dispensed for selected opioid molecules from U.S. outpatient retail pharmacies, January 2011 - December 2015

	2011		2012		2013		2014		2015	
	Rx	%	Rx	%	Rx	%	Rx	%	Rx	%
Total Prescriptions	**178,266,285**	***100.0%***	**178,879,991**	***100.0%***	**170,770,922**	***100.0%***	**162,882,011**	***100.0%***	**145,961,982**	***100.0%***
Total IR Hydrocodone/Acetaminophen	125,185,313	*70.2%*	125,424,574	*70.1%*	118,901,119	*69.6%*	109,591,521	*67.3%*	89,811,458	*61.5%*
Total IR Oxycodone/Acetaminophen	34,672,460	*19.4%*	34,182,548	*19.1%*	32,352,014	*18.9%*	32,277,674	*19.8%*	33,702,684	*23.1%*
Total Selected IR SE Opioid Molecules	18,408,512	*10.3%*	19,272,869	*10.8%*	19,517,789	*11.4%*	20,978,068	*12.9%*	22,298,810	*15.3%*
Oxycodone IR	12,769,384	*69.4%*	13,565,218	*70.4%*	13,972,391	*71.6%*	15,445,943	*73.6%*	16,800,731	*75.3%*
Hydromorphone IR	2,764,753	*15.0%*	2,971,802	*15.4%*	2,942,455	*15.1%*	2,949,105	*14.1%*	2,942,662	*13.2%*
Morphine IR	1,730,515	*9.4%*	1,798,141	*9.3%*	1,826,126	*9.4%*	1,858,680	*8.9%*	1,858,568	*8.3%*
Tapentadol IR	908,812	*4.9%*	776,153	*4.0%*	592,050	*3.0%*	513,783	*2.4%*	485,771	*2.2%*
Oxymorphone IR	235,048	*1.3%*	161,555	*0.8%*	184,767	*0.9%*	210,557	*1.0%*	211,078	*0.9%*
Total ER Hydrocodone	0	*0.0%*	0	*0.0%*	0	*0.0%*	34,748	*0.0%*	149,030	*0.1%*
Hysingla ER	0	*0.0%*	0	*0.0%*	0	*0.0%*	0	0.0%	85,285	57.2%
Zohydro ER	0	*0.0%*	0	*0.0%*	0	*0.0%*	34,748	100.0%	63,745	42.8%

Source: IMS Health, National Prescription Audit™. Extracted February 2016.

6.1.2 Table 2

Nationally estimated number of prescriptions dispensed for *hydrocodone/ acetaminophen* from U.S. outpatient retail pharmacies, stratified by the top 10 prescriber specialties for years 2011 and 2015

	Year 2011		Year 2015	
	TRxs N	*Share %*	TRxs N	*Share %*
Total Prescriptions	**125,185,313**	***100.0%***	**89,811,458**	***100.0%***
General Practice/Family Practice/Doctor Of Osteopathic	36,847,704	*29.4%*	25,327,319	*28.2%*
Internal Medicine	16,749,844	*13.4%*	10,682,748	*11.9%*
Dentistry	13,155,729	*10.5%*	10,313,577	*11.5%*
Physician Assistant	6,696,928	*5.3%*	6,715,455	*7.5%*
Nurse Practitioner	5,666,090	*4.5%*	5,962,868	*6.6%*
Emergency Medicine	7,267,727	*5.8%*	5,007,816	*5.6%*
Orthopedic Surgery	9,662,555	*7.7%*	4,748,194	*5.3%*
Anesthesiology	3,730,248	*3.0%*	3,432,518	*3.8%*
Physical Medicine & Rehab	2,659,293	*2.1%*	2,213,769	*2.5%*
General Surgery	3,547,614	*2.8%*	1,955,988	*2.2%*
All Others	19,201,581	*15.3%*	13,451,206	*15.0%*

Source: IMS Health, National Prescription Audit (NPA). June 2013-February 2015. Extracted February 2016. File: NPA 2016-87 IR Hydrococodone APAP by specialties, 2-17-2016

6.1.3 Table 3

Diagnoses associated with the use of *hydrocodone/acetaminophen* as reported by U.S. office-based physician surveys, stratified by acute and chronic conditions and grouped ICD-9 codes, for Year 2015, cumulative

	2015	
	Uses N	Share %
Total Market	31,529,000	100.0%
Acute	**16,073,000**	**51.0%**
Injury and Poisoning (800-999)	6,771,000	42.1%
Disease of the Musculoskeletal System and Connective Tissue (710-739)	2,734,000	17.0%
Follow Up Visits (V01-V91)****	1,738,000	10.8%
Diseases of the Digestive System (520-579)	1,052,000	6.5%
Symptoms, Signs, and Ill-Defined Conditions (780-799)	786,000	4.9%
Diseases of the Genitourinary System (580-629)	612,000	3.8%
Neoplasms (140-239)	593,000	3.7%
Diseases of the Skin and Subcutaneous Tissue (680-709)	508,000	3.2%
Diseases of the Nervous System and Sense Organs (320-389)	445,000	2.8%
Infectious and Parasitic Diseases (001-139)	357,000	2.2%
Endocrine, Nutritional and Metabolic Diseases, and Immunity Disorders (240-279)	184,000	1.1%
Diseases of the Respiratroy System (460-519)	160,000	1.0%
All Others***	137,000	1.0%
Chronic	**14,002,000**	**44.4%**
Disease of the Musculoskeletal System and Connective Tissue (710-739)	7,537,000	53.8%
Follow Up Visits (V01-V91)****	1,979,000	14.1%
Diseases of the Nervous System and Sense Organs (320-389)	885,000	6.3%
Diseases of the Genitourinary System (580-629)	758,000	5.4%
Neoplasms (140-239)	692,000	4.9%
Diseases of the Skin and Subcutaneous Tissue (680-709)	474,000	3.4%
Diseases of the Digestive System (520-579)	442,000	3.2%
Injury and Poisoning (800-999)	428,000	3.1%
Symptoms, Signs, and Ill-Defined Conditions (780-799)	273,000	1.9%
Congenital Anomalies (740-759)	142,000	1.0%
Endocrine, Nutritional and Metabolic Diseases, and Immunity Disorders (240-279)	139,000	1.0%
All Others^	134,000	1.0%
Diseases of the Circulatory System (390-459)	116,000	0.8%
Unspecified	**1,455,000**	**4.6%**

Source: Encuity Research Treatment Answers™ Audit LLC. Extracted Oct 2015.
*Diagnoses (coded to ICD-9) are linked to drug product mentioned during a patient encounter, and then grouped into diagnostic categories (collapsed to 3-digit ICD-9 codes).
** Diagnostic categories were grouped based on the groupings found in the 2015 ICD-9-CM Diagnoses Codes under ICD9Data.com
***Acute, All others include the following: Diseases of the Blood and Blood-Forming Organs (280-289), Mental Disorders (290-319), Diseases of the Circulatory System (390-459), , Complications of Pregnancy, Childbirth, and the Puerperium (630-679), Congenital Anomalies (740-759)
^Chronic, All others include the following: Infectious and Parasitic Diseases (001-139), Diseases of the Blood and Blood-Forming Organs (280-289), Mental Disorders (290-319), Diseases of the Respiratory System (460-519), Complications of Pregnancy, Childbirth, and the Puerperium (630-679)
****Follow Up Visits include Supplementary Classification of Factors Influencing Health Status and Contact with Health Services (V01-V91)

6.2 APPENDIX 2: 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, Total Patient Tracker (TPT)

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

IMS, National Prescription Audit

The National Prescription Audit (NPA™) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.NPA™ receives over 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.

Encuity Research, LLC., TreatmentAnswers™

Encuity Research, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients,

drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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: March 30, 2016

FROM: Jacqueline Spaulding, M.D., Medical Officer, DAAAP
Pamela Horn, M.D., Clinical Team Leader, DAAAP

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

RE: Open Session Background Document: Clinical Development Program, May 5, 2016 AADPAC/DSaRM Meeting to Discuss NDA 208653

APADAZ CLINICAL DEVELOPMENT PROGRAM

The new drug application for APADAZ (benzhydrocodone hydrochloride and acetaminophen) tablets was submitted according to Section 505(b)(2). The applicant has relied on the Agency's previous findings of safety and effectiveness for hydrocodone and acetaminophen using relative bioavailability studies with the listed drugs Vicoprofen (hydrocodone and ibuprofen) and Ultracet (tramadol and acetaminophen), in addition to comparison to Norco (hydrocodone and acetaminophen). No additional efficacy studies were required.

The primary development goal for APADAZ was to reduce the intranasal (IN) and oral abuse potential of immediate-release (IR) hydrocodone/acetaminophen products. The product was formulated with a benzyl group attached to the hydrocodone molecule by an ester bond, creating a hydrocodone prodrug (benzhydrocodone, called KP201 during development), which is hydrolyzed to release hydrocodone in the presence of esterases in the gastrointestinal system or blood.

The clinical development program for APADAZ tablets was comprised of ten clinical pharmacology studies designed to describe the pharmacokinetic properties of the formulation, the presence of a food effect, the relative bioavailability to the listed drugs and Norco, and to assess APADAZ's abuse-deterrent properties. These studies are listed in Table 1.

Table 1 Clinical Development Program

Study	Study Population	N	KP201 Dosage/Formula	Study Design
KP201.101	Healthy adult subjects; fasting	24	Single oral dose: 5 mg KP201 capsule (5 and 10 mg administered	Open-label, single-dose, 3-treatment, 3-period, 6-sequence, randomized, crossover, Phase 1 bioavailability study.
KP201.102	Healthy adult subjects; fasting	30	Single oral dose: 6.67 mg KP201/325 mg APAP Tablet	Open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence, crossover bioequivalence study
KP201.104	Healthy adult subjects; fed	42	Single oral dose: 6.67 mg KP201/325 mg APAP Tablet	Single-dose, 3-period, 3-treatment, 6-sequence study of the effect of food on the bioavailability and of PK hydrocodone and APAP from KP201/APAP
KP201.103	Healthy adult subjects; fasting	26	Single and repeat oral doses: 6.67 mg KP201/325 mg APAP Tablet	Open-label, single-period, single- and multiple-dose study
KP201.105	Healthy adult subjects; fasting	30	Single oral dose: 6.67 mg KP201/325 mg APAP Tablet	Open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence crossover relative bioequivalence study
KP201.106	Healthy adult subjects; fasting	30	Single oral dose: 6.67 mg KP201/325 mg APAP Tablet	Open-label, single-dose, randomized, 2-treatment, 2-period, 2-sequence crossover relative bioequivalence study
KP201.A01	Healthy adult subjects; opioid-experienced; nondependent	151	Single oral dose of 6.67 mg KP201/325 mg APAP Tablet (12, 8, or 4 tablets)	Randomized, double-blind, placebo-controlled, single-dose, 7-way crossover study
KP201.A02	Healthy adult subjects; opioid-experienced; nondependent	Part A 110 Part B 80	Part A: Escalating intranasal doses (1 to 4 tablets, crushed); Part B: intranasal dose (2 tablets, crushed) and oral dose (2 tablets), 6.67 mg KP201/325 mg APAP Tablet	Randomized, double-blind, double-dummy, placebo-controlled, single-dose, 2-part, 5-way crossover study
KP201.A03	Healthy adult subjects; opioid-experienced; nondependent	66	Single intranasal dose: 13.34 mg KP201 API	Randomized, double-blind, single-dose, 2-way crossover study
KP201.S01	Healthy adult subjects	50	Oral dose of 6.67mg KP201/325 mg APAP Tablet (1 tablet every 4 hours for 72 hours)	Randomized, 2-way, crossover study to assess the gastrointestinal effect of KP201/APAP compared with Norco

N= Number of subjects enrolled

Overview of Safety

The assessment of the safety of APADAZ relies on the clinical data provided from the Applicant's studies and the Agency's prior findings of safety for the listed drugs, Vicoprofen and Ultracet. No additional data was required to assess the safety of the benzhydrocodone because there was no detectable systemic exposure, indicating that hydrolysis to hydrocodone was rapid and complete. The safety profile of APADAZ was assessed in 418 healthy subjects who received at least one dose of KP201/APAP and 245 healthy subjects who received multiple doses of KP201/APAP across ten clinical studies.

There were no serious adverse events or deaths reported during clinical development of APADAZ.

For subjects in the APADAZ treatment groups, three subjects were discontinued from studies because they met the vital sign criteria for withdrawal and experienced clinically significant adverse events of hypotension, two subjects were discontinued due to nausea and vomiting, and one subject was discontinued because of presyncope and hypotension. One subject was discontinued due to supraventricular extrasystoles and ventricular extrasystoles, but, as systemic exposure to KP201 is minimal, and these are not adverse events known to occur with hydrocodone or acetaminophen, they are unlikely to be related to study participation.

The majority of adverse events were reported as mild in severity, and reflect typical opioid-associated adverse reactions.

In the intranasal human abuse liability studies, there were more subjects who reported nasal discomfort, rhinorrhea, and throat irritation after insufflation of crushed KP201/APAP compared to insufflation of crushed hydrocodone/APAP.

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: March 31, 2016

FROM: Suresh Naraharisetti, Ph.D.
Yun Xu, 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: Clinical Pharmacology Summary, May 5, 2016 AADPAC/DSaRM Meeting to Discuss NDA 208653

Clinical Pharmacology Summary

Pharmacokinetics

Metabolism and Pharmacokinetics of KP201, the prodrug

Chemically, benzhydrocodone (KP201) is an inactive prodrug of hydrocodone and is converted rapidly to hydrocodone by enzymes in the intestinal tract. In the in vitro metabolic stability study (KP201-VSTA-025), upon incubating KP201 with human intestinal fluid, there was a quick depletion of KP201 over time. The percent of KP201 remaining at 5, 10 and 15 minutes was 5.3%, 0.3% and 0.1%, respectively. In the negative control incubations, intestinal fluid without pancreatin and the PBS buffer, KP201 was stable. This study suggests that after oral administration, KP201 is hydrolyzed rapidly and completely, and it does not survive long enough to have significant interactions with any transporters and CYP enzymes.

In all human pharmacokinetic (PK) studies following oral administration of the drug product formulated as KP201 and acetaminophen (APAP), plasma concentrations of KP201 were below the limit of quantitation of 25 pg/mL. KP201 is measureable in plasma following intranasal (IN)

administration of the crushed product in human abuse liability studies. Mean Cmax and AUC values for KP201 increased with an increase in dose. The mean Cmax and AUCinf for KP201 ranged from 9.4 ± 2.8 ng/mL and 7.6 ± 2.4 h·ng/mL (KP201/APAP 6.67/325 mg, crushed) to 27.0 ± 25.7 ng/mL and 26.1± 20.6 h·ng/mL (KP201/APAP 26.68/1300 mg, crushed). The median Tmax range of KP201 was 0.46 to 0.73 hours post-dose. The half-life of KP201 was short, ranging from 1 to 1.48 hours.

Pharmacokinetics of KP201/APAP Compared to Vicoprofen and Ultracet

The proposed product, KP201/APAP tablet, contains 6.67 mg benzhydrocodone (KP201) and 325 mg acetaminophen. KemPharm is relying on the FDA's findings of efficacy and safety of two listed drugs, Vicoprofen (7.5 mg hydrocodone bitartrate/ 200 mg ibuprofen oral tablet; NDA 020716), and Ultracet (37.5 mg tramadol hydrochloride/325 mg APAP oral tablet; NDA 021123). To establish the scientific bridge with each listed drug, two bioequivalence studies were conducted in the fasted state comparing KP201/APAP with Vicoprofen for hydrocodone (study KP201.105, n=28) and Ultracet for APAP (study KP201.106, n=27). The proposed KP201/APAP product met the bioequivalence criteria for AUC and Cmax for hydrocodone compared to Vicoprofen; and for APAP compared to Ultracet. The mean concentration-time profiles for hydrocodone (Figure 1) and APAP (Figure 2) and statistical comparison of pharmacokinetic parameters for hydrocodone (Table 1) and APAP (Table 2) are shown.

Figure 1: The mean ± SD plasma hydrocodone concentration-time profile (0-24 h) following administration of KP201/APAP tablet (6.67 mg/325 mg) and Vicoprofen tablet (7.5 mg/200 mg) to healthy subjects under fasted conditions (Study KP201.105)

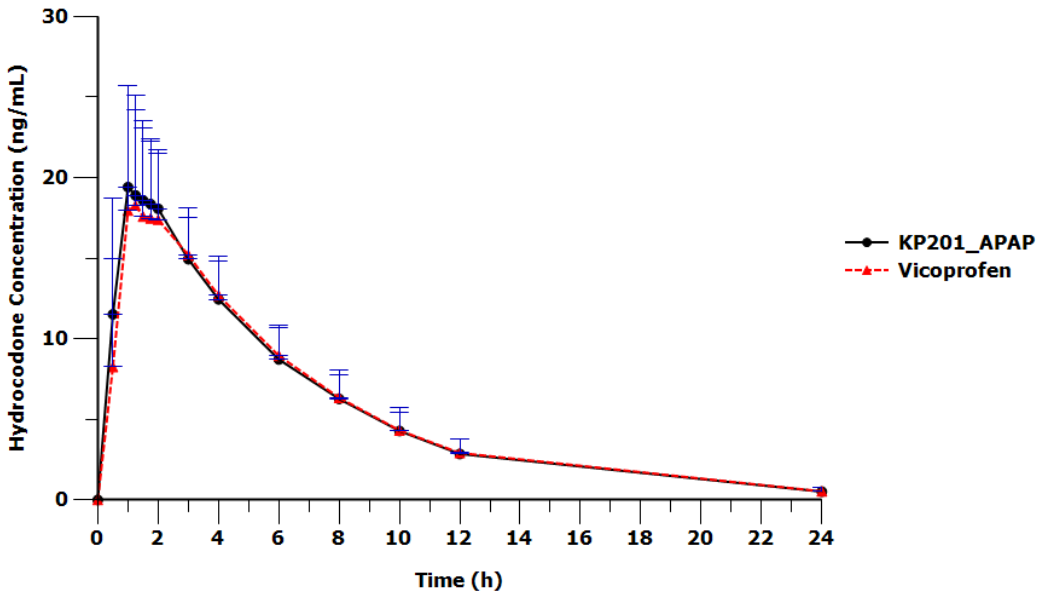


Table 1: Statistical comparison of pharmacokinetic parameters for hydrocodone after oral administration of single doses of KP201/APAP (test) and Vicoprofen (reference) to healthy subjects under fasted conditions (Study KP201.105)

Parameter	Geometric Mean [a]		Geometric Mean Ratio [%]	
	Test	Reference	Estimate	90% Confidence Interval (Lower, Upper)
KP201/APAP, 6.67 mg/325 mg vs. Vicoprofen, 7.5 mg/200 mg				
Cmax	20.58	20.46	100.55	94.50 , 106.99
AUC0-t	128.40	128.90	99.61	95.39 , 104.03
AUCinf	132.37	132.61	99.82	95.62 , 104.20

[a] Least squares geometric means, based on the analysis of natural log-transformed data.

Figure 2: The mean ± SD plasma APAP concentration-time profile (0-24 h) following administration of KP201/APAP tablet (6.67 mg/325 mg) and Ultracet tablet (37.5 mg/325 mg) to healthy subjects under fasted conditions (Study KP201.106)

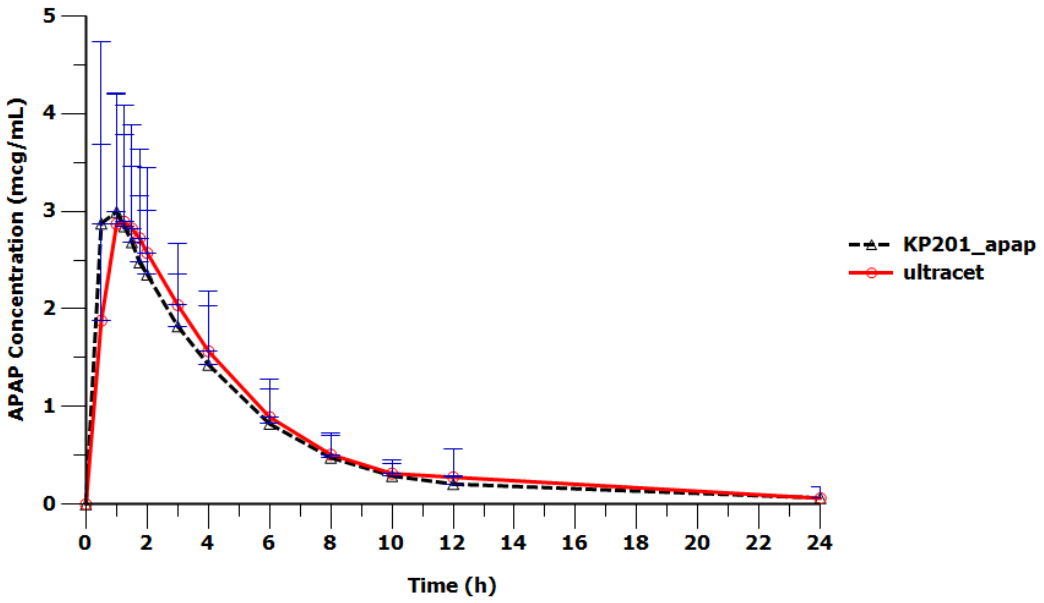


Table 2: Statistical comparison of pharmacokinetic parameters for APAP after oral administration of single doses of KP201/APAP (test) and Ultracet (reference) to healthy subjects under fasted conditions (Study KP201.106)

Parameter	Geometric Mean [a]		Geometric Mean Ratio [%]	
	Test	Reference	Estimate	90% Confidence Interval (Lower, Upper)
KP201/APAP, 6.67 mg/325 mg vs. Ultracet, 37.5 mg/325 mg				
Cmax	3.60	3.60	99.99	91.73 , 108.98
AUC0-t	14.78	15.42	95.86	88.71 , 103.59
AUCinf	14.94	15.36	97.28	93.32 , 101.39

[a] Least squares geometric means, based on the analysis of natural log-transformed data.

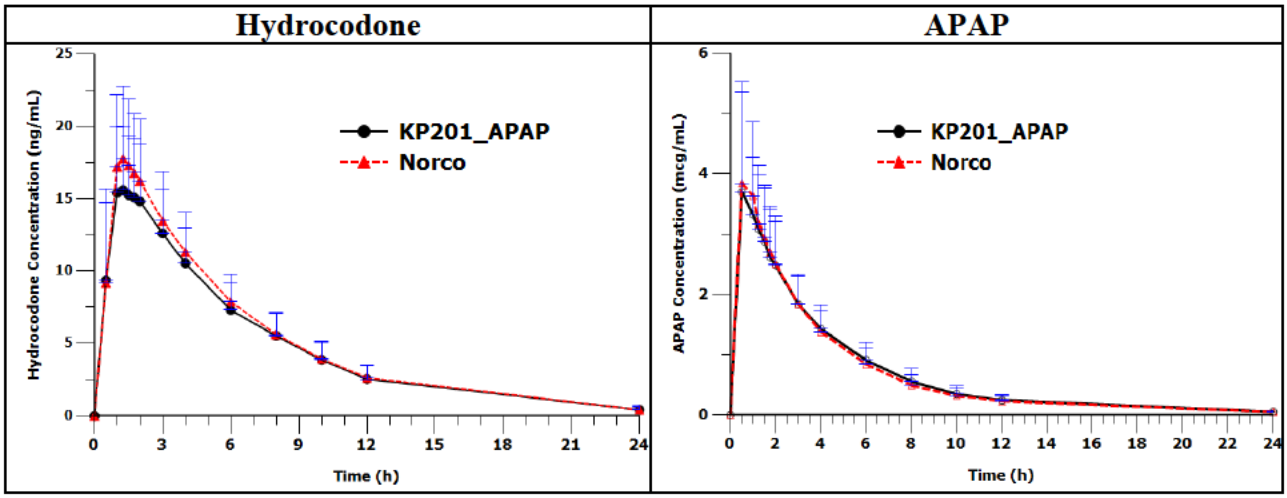
Pharmacokinetics of KP201/APAP Compared to Norco

KP201/APAP was also compared to Norco (7.5 mg hydrocodone bitartrate/325 mg APAP oral tablet; ANDA 040148) in the fasted state (study KP201.102) and the fed state (study KP201.105) to support that KP201/APAP does not represent a novel combination. The effect of food on the bioavailability (BA) and pharmacokinetics of KP201/APAP and the relative BA of KP201/APAP to Norco under fed conditions was compared in the study KP201.105.

Study KP201.102 – KP201/APAP Compared to Norco -Fasted Conditions

Study KP201.102 compared the rate and extent of absorption of hydrocodone and APAP from a single dose of KP201/APAP relative to a single dose of Norco when administered orally under fasted conditions in 23 subjects. The mean ± SD hydrocodone and APAP plasma concentrations vs time profiles by treatment are presented in Figure 3 below.

Figure 3: Mean ± SD plasma hydrocodone and APAP concentration-time profile (0-24 h) following administration of single doses of KP201/APAP and Norco to healthy subjects under fasted conditions (Study KP201.102)



A statistical comparison of pharmacokinetic parameters for hydrocodone after administration of KP201/APAP or Norco under fasted condition is presented in Table 3. Geometric means ratios for hydrocodone Cmax, AUC0-t, and AUCinf were 86.79%, 94.17%, and 94.05%, respectively. The associated 90% confidence intervals (CI) for all 3 parameters were contained within 80% to 125%, meeting bioequivalence criteria with respect to hydrocodone.

Table 3: Statistical comparison of pharmacokinetic parameters for hydrocodone after oral administration of single doses of KP201/APAP (test) and Norco (reference) to healthy subjects under fasted conditions (Study KP201.102)

Parameter	Geometric Mean [a]		Geometric Mean Ratio [%]	
	Test	Reference	Estimate	90% Confidence Interval (Lower, Upper)
KP201/APAP, 6.67 mg/325 mg vs. Norco, 7.5 mg/325 mg				
Cmax	16.27	18.75	86.79	81.38 , 92.56
AUC0-t	108.01	114.70	94.17	89.99 , 98.54
AUCinf	111.76	118.83	94.05	90.32 , 97.94

[a] Least squares geometric means, based on the analysis of natural log-transformed data.

A statistical comparison of pharmacokinetic parameters for APAP after administration of KP201/APAP or Norco is presented in Table 4. Geometric means ratios for APAP Cmax, AUC0-t, and AUCinf were 90.76%, 101.15%, and 100.76%, respectively. The associated 90% CIs for both AUCs were contained within 80% to 125%. For Cmax, the lower limit of the 90% CI was 79.81%, slightly under the 80% limit. This slight difference is unlikely to have clinical impact on the efficacy or safety of KP201/APAP.

Table 4: Statistical comparison of pharmacokinetic parameters for APAP after oral administration of single doses of KP201/APAP (test) and Norco (reference) to healthy subjects under fasted conditions (Study KP201.102)

Parameter	Geometric Mean [a]		Geometric Mean Ratio [%]	
	Test	Reference	Estimate	90% Confidence Interval (Lower, Upper)
KP201/APAP, 6.67 mg/325 mg vs. Norco, 7.5 mg/325 mg				
Cmax	3.79	4.18	90.76	79.81 , 103.20
AUC0-t	15.82	15.64	101.15	98.08 , 104.32
AUCinf	16.76	16.63	100.76	97.66 , 103.96

[a] Least squares geometric means, based on the analysis of natural log-transformed data.

Study KP201.104 – KP201/APAP Compared to Norco under Fed Conditions and Food effect on KP201/APAP

This study evaluated the effect of food on the bioavailability and pharmacokinetics of hydrocodone and APAP from KP201/APAP, and the relative bioavailability of KP201/APAP and Norco under fed conditions in healthy volunteers. Eligible subjects received the following 3 treatments:

Treatment A:	KP201/APAP, 1 x 6.67 mg/325 mg tablet with 240 mL of water under fed conditions*
Treatment B:	KP201/APAP, 1 x 6.67 mg/325 mg tablet with 240 mL of water under fasted conditions [$].
Treatment C:	Norco Tablets, 1 x 7.5 mg/325 mg tablet under fed conditions*

*Treatments A and C were administered after subjects had completed an overnight fast for at least 10 hours, followed by an FDA standard high-calorie, high-fat breakfast meal. The FDA standard high-calorie, high-fat breakfast meal was to be consumed in its entirety within 30 minutes of being served. Treatments A and C were administered within 5 minutes of completing the standard high-calorie, high-fat breakfast meal

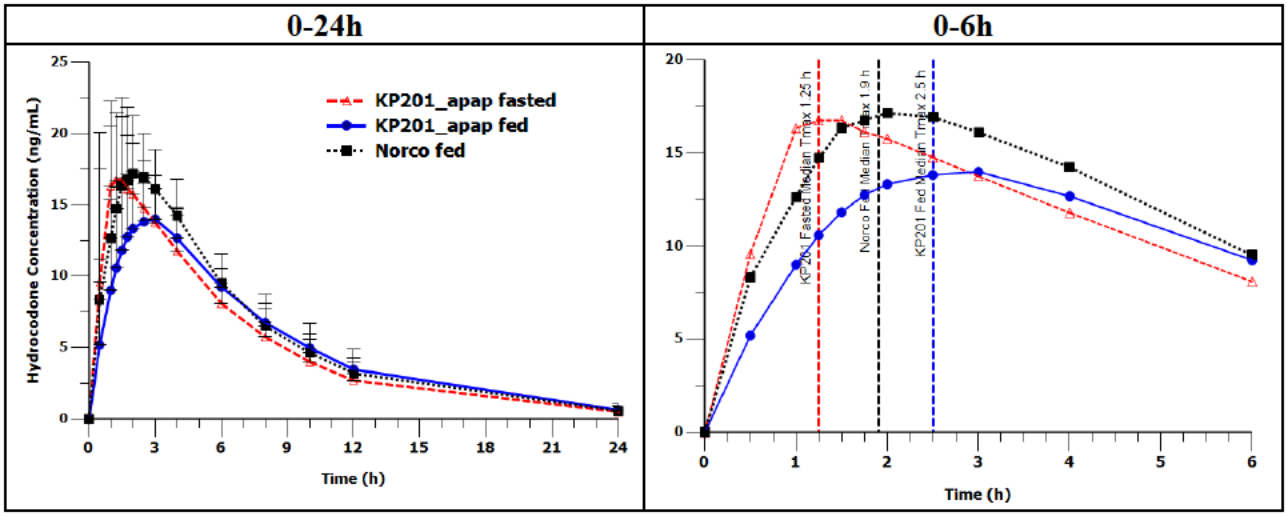
[$]Fasted doses were administered after a standard overnight fast (approximately 10 hours)

A total of 42 subjects were enrolled. Thirty-eight subjects completed all 3 periods. The PK analysis population was comprised of 40 subjects for Treatment A (39 for APAP), 38 subjects for Treatment B, and 40 subjects for Treatment C.

Hydrocodone:

The proposed dosing regimen for KP201/APAP is 4-6 h as needed for pain, which is the same as the approved dosing regimen for Norco, every 4 to 6 hours as needed for pain. The mean ± SD plasma hydrocodone concentration-time profile for 0-24h and mean plasma hydrocodone concentration-time profile over the typical dosing regimen (every 6 h), with median Tmax for KP201/APAP or Norco is presented in Figure 4.

Figure 4: Mean ± SD plasma hydrocodone concentration-time profile for 0-24h (left) and mean concentration-time profile 0-6h (right) following administration of single doses of KP201/APAP under fasted and fed conditions and Norco under fed conditions to healthy subjects (Study KP201.104)



The pharmacokinetic parameters for hydrocodone after administration of KP201/APAP or Norco are summarized in Table 5.

Table 5: Summary of pharmacokinetic parameters for hydrocodone after oral administration of single doses of KP201/APAP under fed and fasted conditions and Norco under fed conditions to healthy subjects (Study KP201.104)

Parameter [a]	**KP201/APAP, 6.67 mg/325 mg**		**Norco, 7.5 mg/325 mg**
	Fed	**Fasted**	**Fed**
Cmax (ng/mL)	16.04 ± 3.60 (40)	19.18 ± 4.84 (38)	20.95 ± 7.65 (40)
Tmax (h)	2.50 (40) [0.50–4.00]	1.25 (38) [0.50–3.00]	1.90 (40) [0.50–4.00]
AUC0-t (h×ng/mL)	125.80 ± 26.90 (40)	121.40 ± 35.18 (38)	135.37 ± 30.30 (40)
AUCinf (h×ng/mL)	130.91 ± 29.45 (40)	125.73 ± 36.78 (38)	140.17 ± 31.66 (40)
t½ (h)	4.53 ± 0.70 (40)	4.33 ± 0.67 (38)	4.36 ± 0.68 (40)

[a] Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

A statistical comparison of pharmacokinetic parameters for hydrocodone is presented in Table 6.

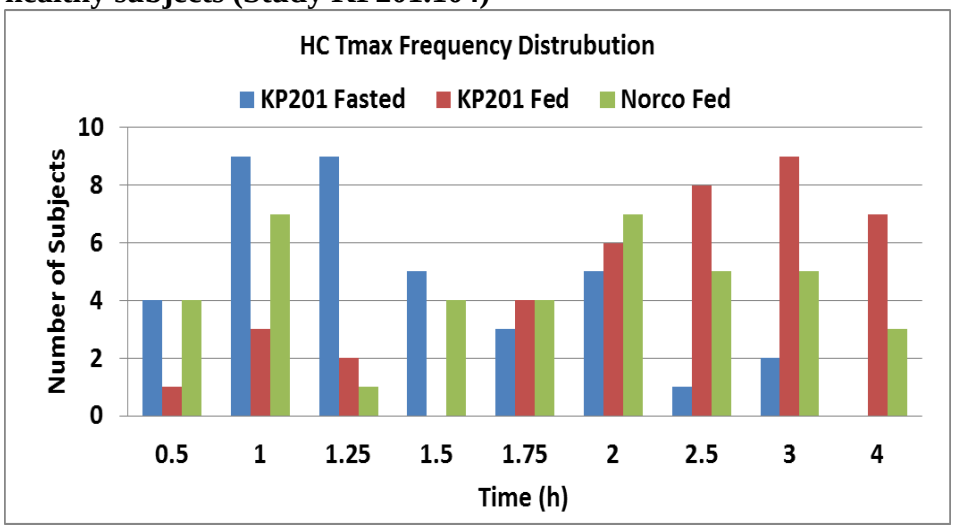
Table 6: Statistical comparison of pharmacokinetic parameters for hydrocodone after oral administration of single doses of KP201/APAP under fed and fasted conditions and Norco under fed conditions to healthy subjects (Study KP201.104)

Parameter	**Geometric Mean** [a]		**Geometric Mean Ratio [%]**	
	Test	**Reference**	**Estimate**	**90% Confidence Interval (Lower, Upper)**
KP201/APAP, 6.67 mg/325 mg, Fed (test) vs. Fasted (reference)				
Cmax	15.70	18.40	85.31	79.40, 91.65
AUC0-t	122.85	115.80	106.09	101.00 , 111.42
AUCinf	127.66	120.00	106.39	101.62 , 111.38
KP201/APAP, 6.67 mg/325 mg, Fed (test) vs. Norco, 7.5 mg/325 mg, Fed (reference)				
Cmax	15.70	20.03	78.36	73.04 , 84.06
AUC0-t	122.85	132.14	92.97	88.60 , 97.56
AUCinf	127.66	136.88	93.27	89.16 , 97.56

[a] Least squares geometric means, based on the analysis of natural log-transformed data.

The frequency histogram for the Tmax of hydrocodone for KP201/APAP and Norco is presented in Figure 6.

Figure 6: Frequency histogram for hydrocodone Tmax following administration of single doses of KP201/APAP under fasted and fed conditions and Norco under fed conditions to healthy subjects (Study KP201.104)



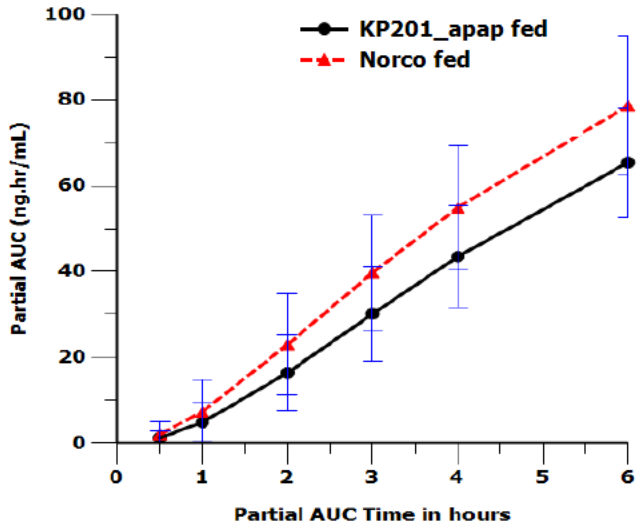
KP201/APAP Fed vs Fasted (hydrocodone):

When KP201/APAP was administered under fed conditions compared to fasted conditions, geometric means ratios for hydrocodone Cmax, AUC0-t, and AUCinf were 85.31%, 106.09% and 106.39%, respectively. The associated 90% CI for Cmax was 79.40% to 91.65%. The 90% CIs for AUC0-t, and AUCinf were contained within 80% to 125% range. Although the median Tmax is slightly delayed from 1.25 h to 2.5 under fed condition, it is still shorter than the 4-6 h dosing interval. In addition, the Tmax range under fed condition is within the minimum recommended dosing interval of 4 hours.

KP201/APAP Fed vs Norco Fed (hydrocodone):

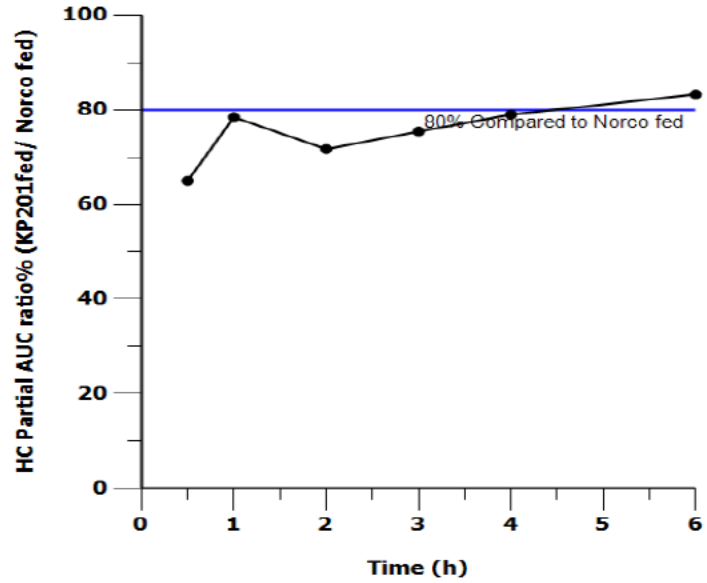
Dosing KP201/APAP and Norco in the fed state led to median hydrocodone Tmax values of 2.5 and 1.9 hours, respectively. The Tmax ranges were identical and within the minimum recommended dosing interval of 4 hours (0.5 to 4 hours for both products). While the hydrocodone Cmax for KP201/APAP under fed condition is 78% compared to Norco, the overall exposure to hydrocodone (AUClast and AUCinf) was within the 80% to 125% range. When hydrocodone partial AUCs in a typical dosing interval (4 to 6 hours) were compared for KP201/APAP fed and Norco fed, the data demonstrated a slight decrease in hydrocodone partial exposure for KP201/APAP compared to Norco. However, numerically it is not much lower and the standard deviations in hydrocodone partial AUCs overlapped between the two treatments. The data are shown in Figure 7.

Figure 7: Hydrocodone partial AUC (SD) for KP201/APAP Vs. Norco under fed conditions at different time points.



The partial AUC ratios of KP201/APAP under fed conditions range from 65 to 83% compared to Norco fed at different time points (0.5 h to 6 h) in a typical dosing interval (6 hours), which is shown in Figure 8.

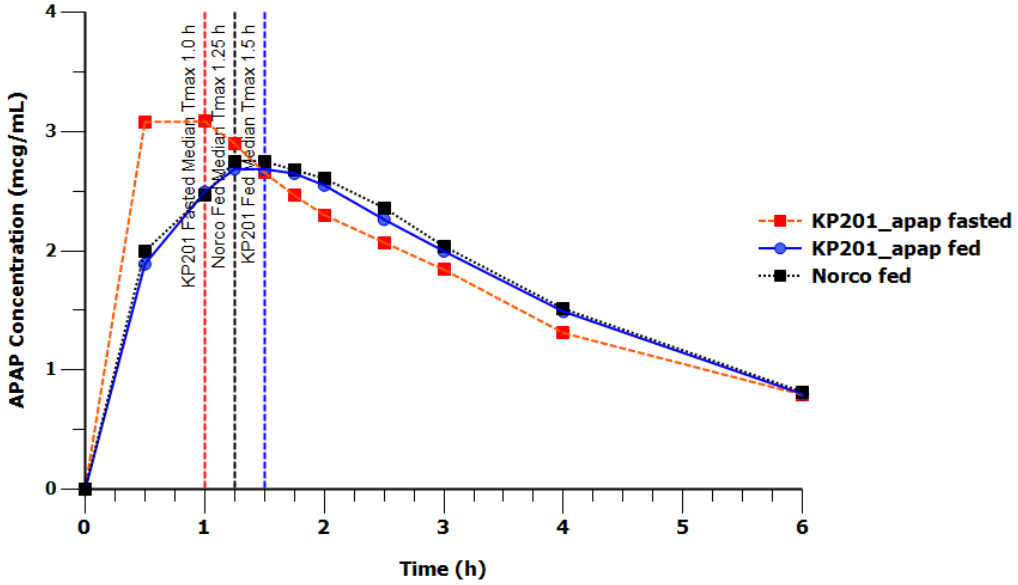
Figure 8: Hydrocodone partial AUC ratios (KP201/APAP fed/ Norco fed) at different time points (0.5 h to 6 h) in a typical dosing interval (6 hours).



APAP

The mean plasma APAP concentration-time profile over the typical dosing regimen, (every 6 hours) with median Tmax representation for KP201/APAP under fasted and fed conditions and Norco under fed conditions is presented in Figure 9.

Figure 9: Mean plasma APAP concentration-time profile (0-6h) following administration of single dose of KP201/APAP under fasted and fed conditions and Norco under fed conditions to healthy subjects (Study KP201.104)



The pharmacokinetic parameters for APAP after administration of KP201/APAP or Norco are summarized in Table 7.

Table 7: Summary of pharmacokinetic parameters for APAP after oral administration of single dose of KP201/APAP under fed and fasted conditions and Norco under fed conditions to healthy subjects (Study KP201.104)

Parameter [a]	**KP201/APAP, 6.67 mg/325 mg**		**Norco, 7.5 mg/325 mg**
	Fed	**Fasted**	**Fed**
Cmax (µg/mL)	3.34 ± 1.01 (39)	4.05 ± 1.30 (38)	3.52 ± 1.20 (40)
Tmax (h)	1.50 (39) [0.50–4.00]	1.00 (38) [0.50–3.00]	1.25 (40) [0.50–3.00]
AUC0-t (h×µg/mL)	14.5 ± 3.41 (39)	14.6 ± 4.42 (38)	14.8 ± 3.34 (40)
AUCinf (h×µg/mL)	15.0 ± 3.53 (36)	14.7 ± 3.87 (36)	15.3 ± 3.45 (40)
t½ (h)	5.64 ± 1.58 (30)	4.78 ± 1.30 (36)	5.54 ± 1.47 (40)

[a] Arithmetic mean ± standard deviation (N) except Tmax for which the median (N) [Range] is reported.

A statistical comparison of pharmacokinetic parameters for hydrocodone after administration of KP201/APAP under fed or fasted conditions or Norco under fed condition is presented in Table 8.

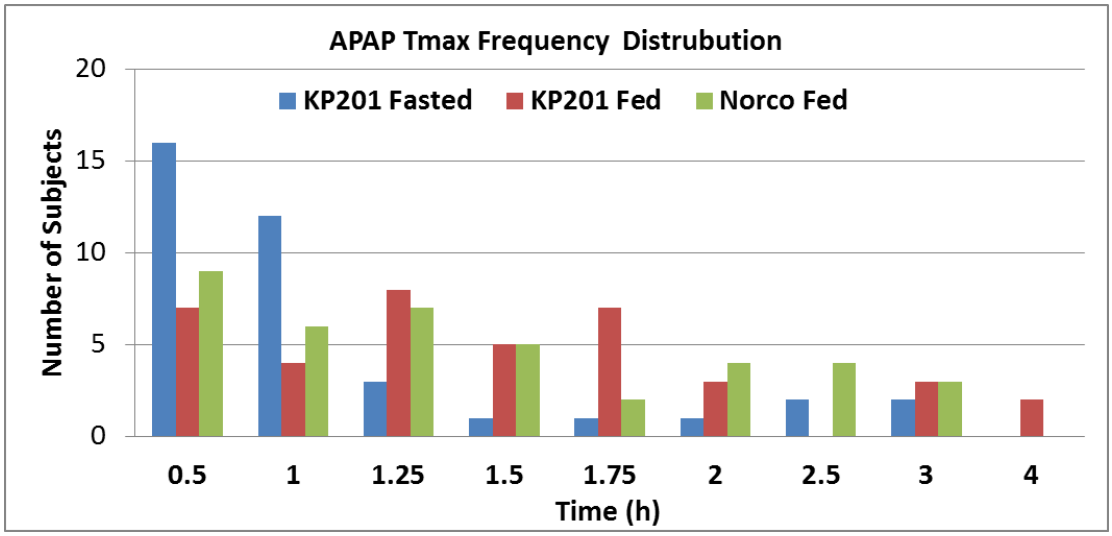
Table 8: Statistical comparison of pharmacokinetic parameters for APAP after oral administration of single doses of KP201/APAP under fed and fasted conditions and Norco under fed condition to healthy subjects (Study KP201.104)

Parameter	Geometric Mean [a]		Geometric Mean Ratio [%]	
	Test	Reference	Estimate	90% Confidence Interval (Lower, Upper)
KP201/APAP, 6.67 mg/325 mg, Fed vs. Fasted				
Cmax	3.23	3.83	84.43	76.64 , 93.01
AUC0-t	14.33	14.00	102.35	97.46 , 107.49
AUCinf	14.84	14.09	105.36	101.30, 109.58
KP201/APAP, 6.67 mg/325 mg, Fed vs. Norco, 7.5 mg/325 mg, Fed				
Cmax	3.23	3.34	96.77	88.00 , 106.40
AUC0-t	14.33	14.46	99.12	94.47 , 103.99
AUCinf	14.84	14.95	99.31	95.60 , 103.17

[a] Least squares geometric means, based on the analysis of natural log-transformed data.

The frequency histogram for Tmax for KP201/APAP under fasted and fed conditions and Norco under fed conditions is presented Figure 10.

Figure 10: Frequency histogram for APAP Tmax following administration of single dose of KP201/APAP under fasted and fed conditions and Norco under fed condition to healthy subjects (Study KP201.104)



Administration of KP201/APAP under fed conditions resulted in slight delay in Tmax of APAP compared to KP201/APAP under fasted conditions. However, KP201/APAP under fed conditions demonstrated comparable Tmax, and equivalent AUC and Cmax for APAP compared to Norco under fed conditions.

Conclusions on Food Effect:

Norco is labeled for use without regard to food. Although KP201/APAP showed a slight delay in Tmax for both hydrocodone and APAP under fed conditions compared to fasted conditions, its PK profiles and parameters under the fed condition are similar to those of Norco under the fed condition. In addition, by evaluating the individual PK profiles, no significant delay of absorption was identified for KP201/APAP under fed conditions. Based on totality of the data, food effect study results support the conclusion that KP201/APAP may be administered without regard to food.

Study KP201.103 – Single- and Multiple-KP201/APAP Dose Study:

The objectives of the study were to assess the pharmacokinetics of KP201, hydrocodone and APAP following a single dose of KP201/APAP (2 × 6.67 mg/325 mg) under fasted conditions and to assess the steady-state pharmacokinetics of KP201, hydrocodone, and APAP following multiple doses of KP201/APAP (2 × 6.67 mg/325 mg) administered every 4 hours under fasted conditions.

Pharmacokinetic parameters of hydrocodone and APAP after administration of KP201/APAP are summarized in Tables 9 and 10.

Table 9: Summary of pharmacokinetic parameters for hydrocodone during oral administration of two KP201/APAP tablets on day 1 followed by two KP201/APAP tablets Q4H × 14 doses (Days 2 to 4) to healthy subjects under fasted conditions (Study KP201.103)

Parameter [a]	**Single dose, Day 1 PK**	**Multiple dose, Q4H × 13 doses (Days 2 to 4), Day 4 PK**
Cmax (ng/mL)	33.95 ± 8.41 (24)	62.79 ± 14.75 (24)
Tmax (h)	1.00 (24) [0.50–4.00]	1.25 (24) [0.50–2.00]
AUC0-4h (h×ng/mL)	92.94 ± 20.16 (24)	195.07 ± 47.66 (24)
AUCinf (h×ng/mL)	219.36 ± 57.28 (24)	-
t½ (h)	4.45 ± 0.59 (24)	4.87 ± 0.63 (24)

[a] Arithmetic mean ± standard deviation (N) except T_{max} for which the median (N) [Range] is reported.

Table 10: Summary of pharmacokinetic parameters for APAP during oral administration of two KP201/APAP tablets on day 1 followed by two KP201/APAP tablets Q4H × 14 doses (Days 2 to 4) to healthy subjects under fasted conditions (Study KP201.103)

Parameter [a]	**Single dose, Day 1 PK**	**Multiple dose, Q4H × 13 doses (Days 2 to 4), Day 4 PK**
Cmax (µg/mL)	7.95 ± 2.16 (24)	11.0 ± 2.34 (24)
Tmax (h)	0.50 (24) [0.50–3.00]	1.00 (24) [0.50–1.50]
AUC0-4h (h×µg/mL)	17.6 ± 4.25 (24)	29.8 ± 6.19 (24)
AUCinf (h×µg/mL)	28.9 ± 7.07 (23)	-
t½ (h)	4.79 ± 1.21 (23)	6.84 ± 2.42 (23)

[a] Arithmetic mean ± standard deviation (N) except T_{max} for which the median (N) [Range] is reported.

The steady-state for hydrocodone was reached at approximately 24 hours after the initiation of multiple dosing. The hydrocodone accumulations for Cmax, AUC0-4, and AUC0-t values (Day 4/Day1 or 14th dose/ 1st dose of KP201/APAP) were 1.85-fold, 2.10-fold, and 2.03-fold, respectively.

The steady-state for APAP was reached at approximately 24 to36 hours after the initiation of multiple dosing. The APAP accumulations for Cmax, AUC0-4, and AUC0-t values (Day 4/Day1 or 14th dose/ 1st dose of KP201/APAP) were 1.38-fold, 1.69-fold, and 1.80-fold, respectively.

Plasma levels of KP201 were not detectable after multiple dosing of KP201/APAP.

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: March 31, 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, May 5, 2016 AADPAC/DSaRM Meeting to Discuss NDA 208653

Overview of the Proposed Product ADF Features:

The drug product is an oral-immediate release (IR) tablet formulation of benzhydrocodone hydrochloride (KP201, 6.67 mg) and acetaminophen (APAP, 325 mg). This drug product does not include any formulation-based mechanisms (e.g., gelling, crush resistance) of abuse deterrence. The proposed deterrent features hinge on 1) poor water solubility of KP201 at physiologic pH and 2) the pharmacologic inactivity of the intact prodrug at opioid receptors. The lower solubility of KP201 is proposed to limit the capacity for preparation of IV-ready solutions of the active pharmaceutical ingredient (API). It is also proposed that gut esterases are more efficient at converting the KP201 prodrug to hydrocodone (HC) than those encountered through non-enteral routes of administration. The intended result is that intravenous (IV) or intranasal (IN) administration of KP201 will lead to altered HC exposures when compared KP201 taken orally and that the resulting slower onset of action would provide less "drug likability" to an abuser. Note that codes for specific in vitro conditions are provided under the closed session presentation; these codes may differ from those used by the applicant.

1. Summary of In Vitro Studies (CMC)

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 hydrocodone bitartrate (HB)/APAP tablets.

A. Physical Manipulation (Size Reduction)

No extensive crushing or grinding studies were carried out for this product since it is an IR tablet with no formulation-based abuse-deterrent features. Particle size for crushed tablets used in extraction studies was determined and indicated that the overall profile was similar to the comparator.

B. Large Volume Extraction Studies

Test 1 – Solubility and Extraction
These studies were designed to determine the extraction potential and solubility of KP201, HC, and APAP when extracted from their respective tablet formulations with Common and Less Common Solvents under Non-Stressing conditions.

Results:
In general, large volume extractions with Common and Less Common Solvents under Non-Stressing conditions led to comparable amounts KP201 and HC extraction from KP201/APAP and HB/APAP tablets, respectively. There were several important exceptions. Common Solvents X, Y, and Z led to negligible KP201 extraction while liberating measurable amounts of HC (8.8-37.1%) from KP201/APAP tablets; under these conditions, levels of extracted HC (72-90%) from HB/APAP tablets remained similar to results observed with other Common Solvents. APAP extraction levels remained comparable across most Common Solvent conditions (see below for exception with Common Solvent O). This observation represents a class effect (i.e., are related) and therefore highlights the fact that under certain conditions, the extraction behavior of KP201 and HB/HC diverges. While the propensity for extraction of KP201 appears to be reduced using these solvents, the fact that APAP continues to partition rapidly into solution may enable facile separation of these two APIs. The fate of the non-extracted KP201 under these conditions was also uncertain (i.e., an analysis of any remaining solid material was not originally provided). Therefore, while solution levels of HC were low with KP201/APAP using Common Solvents X-Z under Non-Stressing conditions, it cannot be categorically concluded that KP201 in any remaining solid was intact. A reverse trend was observed using Common Solvent O, which has considerably different properties from Common Solvents X-Z. Under Non-Stressing conditions, Common Solvent O extracts negligible APAP, low amounts of HC (20-30%) from HB/APAP, and high amounts of KP201 (90-100%). Again, this supports the differential extraction behavior of KP201 and HB/HC from the drug products.

Test 2 – Extraction Variables
These studies were designed to evaluate the effects of Stressing Conditions 1 on the extraction potential and solubility of KP201, HC, and APAP from their respective tablets with Common Solvents only. Additional studies using Stressing Conditions 2 and Common Solvents G & H were requested and developed in agreement with FDA.

Results:
In general, large volume extractions under Stressing Conditions 1 led to higher extraction rates for KP201 and HC from both KP201/APAP and HB/APAP when compared to Non-Stressing Conditions. Increased release (rate and amount) of HC from KP201/APAP was observed with Common Solvents X (59.6%), Y (62.7%), and Z (46.0%) under Stressing Conditions 1; however a decrease in HC titer was observed over time for solutions generated from KP201/APAP or HB/APAP under these conditions. The origin of this decrease over time has not been well-established, although it has been ascribed to HC degradation by the applicant. No release of HC was observed with Common Solvent W under Non-Stressing conditions; however, under Stressing Conditions 1, considerable HC was released (60.9%) although the rate was moderately slow (Time to ~30% = 240 min). Common Solvent W is relevant to solutions that would be used by a typical abuser. Under harsher Stressing Conditions 2, Common Solvents G and H (additionally requested by FDA) released comparable amounts of HC from KP201/APAP (80.3 and 70.4%, respectively) at 180 min. Levels of HC from HB/APAP were similar at 180 min with Common Solvents G and H (80.3 and 89.5% respectively), although higher amounts were observed initially (100% HC at T = 15 min). Note that Common Solvent G in particular is safe and highly relevant to IV use; this solvent supplements the harsher and more toxic conditions used for hydrolysis studies under Test 3. Also notable was the fact that HC extraction with Common Solvent A under Stressing Conditions 1 and with Common Solvent F (requested by FDA) under Stressing Conditions 2 exhibit different results (no HC release under the former conditions at 180 min; 10% HC release at 180 min, 42% at 1440 min under the latter conditions). Common Solvent A and F are nearly identical, but this study indicates that subtle changes may considerably affect hydrolysis of the prodrug. Both solutions are ingestible and injectable.

Test 3 – Hydrolysis
These studies were designed to assess the potential of releasing HC from KP201 tablets (extracted, crushed, and intact) using two major classes of hydrolyzing solvents (Hydrolyzing Solvents 1 and 2) under Stressing Conditions 1 and Non-Stressing conditions.

Results:
In general, stronger class 1 and 2 Hydrolyzing Solvents were required to afford high solution concentrations of HC from KP201/APAP tablets. There were several notable exceptions. Hydrolyzing Solvents HS17 and HS18 are relatively mild and would be commonly available to abusers. While total HC release with these solvents was relatively low (23.4 and 11.4% respectfully at T = 60 using crushed tablets under Stressing Conditions 1), a closely related set of conditions carried out on KP201/APAP tablet extracts (Hydrolyzing Solvent C/HS18) leads to good yields (74%) of HC under Non-

Stressing conditions, although extended times were required (T = 1440 min). Stressing Conditions have not been applied to Hydrolyzing Solvent C/HS18 at this point. This difference in results is likely due to the presence of a solubility-enhancing solvent.

C. Small Volume Extractability and Syringeability Studies

Test 1 – Solubility
These studies were designed to assess the solubility profiles of KP201 and HB in aqueous solutions under various conditions (Solubility Conditions 1). Some concerns with the initial methodology led to a second set of conditions determined in agreement with FDA (Solubility Conditions 2).

Results:
The solubility profile of KP201 and HB/HC differs under certain conditions. In general, KP201 is less soluble than HB/HC.

Test 2 – Extractability and Syringeability
These studies were designed to evaluate the feasibility of creating injectable solutions from KP201/APAP and HB/APAP tablets (Injectable Extracts 1 and 2) under Stressing (Injectable Extracts, Stressing) and Non-Stressing (Injectable Extracts, Non-stressing) conditions that are suitable for IV abuse. Glide forces for the solutions were evaluated using Bracketing Common Needle Gauges.

Results:
Under the majority of the evaluated injectable extraction conditions (Injectable Extracts 1), levels of KP201 (54.9-71.6%) and HC (67.1-78.9%) extracted from KP201/APAP and HB/APAP tablets were similar. Stressing and Non-Stressing conditions did not appear to make a considerable difference in recovery and HC was not observed during extraction of the KP201/APAP tablets. A smaller subset of conditions (Injectable Extracts 2) led to lower solution levels of KP201 (12.6-24.2%) from KP201/APAP tablets than HC from HB/APAP tablets. These conditions are related to Common Solvents X-Z used in the large volume extractions and KP201 was likely precipitated and filtered of during preparation of the IV solution. It is noted that under many of the evaluated conditions, precipitate was formed that made isolation or filtration of IV solutions challenging for KP201/APAP tablets; however, given that the drug product formulation was not designed to prevent abuse, this effect may be of limited impact. This is supported by the negligible difference in glide forces reported for injectable solutions of KP201/APAP and HB/APAP using bracketing common needle gauges.

Test 3 – Injectability
These studies were designed to evaluate the potential for precipitation of KP201 or HC after simulated injections of extracts from both KP201/APAP and HB/APAP tablets into human plasma and blood. Results were compared against ketamine and buprenorphine commercial IV solutions and extracts of buprenorphine/naloxone sublingual film.

Results:
No substantial differences were observed between KP201/APAP, HB/APAP, or other evaluated products.

D. Smoking

Smokability was assessed. Studies were carried out using HC free base, HB, KP201 free base, KP201, the drug product, and the IR comparator tablet. Limited free-basing studies were also carried out.

Results:
Comparable levels of KP201 (2.4%) and HC (4.7%) were obtained from simulated smoking studies with the KP201/APAP and HB/APAP drug products, respectively. Similar levels were observed for KP201 (4.5%) and HB (9.4%) drug substances. Free base KP201 (24.6%) and HC (26.3%) were considerably more volatile. Levels of HC released from simulated smoking of KP201 did not exceed the method LOQs (1.4% for the KP201/APAP drug product, 0.9% for KP201 salt, and 0.8% for KP201 free base). Given the results, smoking may not be a plausible route of abuse for the reference product (IR HB/APAP tablets).

MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 30, 2016

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

Through: Michael Klein, Ph.D., Director M Klein 3/30/16
Controlled Substance Staff

From: James M. Tolliver, Ph.D., Pharmacologist JMT 3/30/16
Controlled Substance Staff

Subject: OPEN SESSION BACKGROUND DOCUMENT on Oral Human Abuse Potential Study KP201.A01, Intranasal Human Abuse Potential Study KP201.A02 and Clinical Study KP201.A03 submitted Under NDA 208-653. Prepared for the FDA Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety & Risk Management Advisory Committee Meeting May 6, 2016.

Background Document

Oral human abuse potential study KP201.A01, intranasal human abuse potential study KP201.A02, and Clinical Study KP201.A03 were submitted by KemPharm Inc. under NDA 208-653 in support of Benzhydrocodone HCl/Acetaminophen (KP201/APAP) Tablets, also known as Apadaz, an intended abuse-deterrent formulation. These types of studies are 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.

Study KP201.A01 entitled "A Randomized, Double-Blind, Placebo-Controlled, Single-Dose, Seven-Way Crossover Study to Determine the Relative Bioavailability, Abuse Potential, and Safety of Equivalent Oral Doses of KP201/Acetaminophen Compared with Hydrocodone/Acetaminophen in Opioid Experienced, Nondependent Subjects."

Description of Study KP201.A01

Study KP201.A01is a single-center, randomized, double-blind, active- and placebo-controlled, 7-period, crossover study. It included a Screening Period, in-clinic Drug Discrimination and Treatment Phases, and a Follow-up Period.

The primary objective was to determine the abuse potential of KP201/APAP relative to HB/APAP when administered orally at three supra-therapeutic doses to nondependent, recreational opioid users.

Sixty-two subjects comprised the pharmacodynamic completer population. Subjects consisted of recreational opioid users who were not currently dependent on opioids (based on Diagnostic and Statistical Manual of Mental Disorders-IV, Text Revision [DSM-IV-TR] criteria) but had used opioids for nontherapeutic purposes (i.e, for psychoactive effects) on at least 10 occasions within the previous year and at least once in the 12 weeks prior to the Screening Visit.

Subjects who successfully completed the Naloxone Challenge Test completed a Drug Discrimination Test to determine whether they can move to the Treatment Phase. In a 2-way crossover, 1:1 ratio, double-blind, randomized design, subjects received a single, oral dose of HB/APAP 45 mg/1, 950 mg (6 over-encapsulated Norco tablets, 7.5 mg/325 mg each) and placebo (6 capsules). Subjects are required to discriminate active treatment from placebo based on the following criteria:

- A minimum peak effect (E_{max}) of 65 points for Drug Liking in response to active treatment during the first 2 hours post-dose;
- A ≥15-point E_{max} difference between active and placebo treatments at 1 or more time points during the first 2 hours following drug administration; and
- A placebo response ≥40 and ≤60 points for Drug Liking during the first 2 hours following drug administration.

Subjects were also required to demonstrate tolerance to the treatments as demonstrated by no emesis within the first 2 hours after dosing.

Products used for treatments in the Treatment Phase included the following:

- Test Drug: KP201/APAP, 6.67 mg/325 mg tablets, over-encapsulated
- Comparator: Hydrocodone Bitartrate (HB)/Acetaminophen (APAP), USP, 7.5/325 mg tablets, over-encapsulated
- Placebo: Microcrystalline cellulose powder in capsules

For the Treatment Phase, subjects were randomized to 1 of 14 treatment sequences using a computer-generated randomization scheme based on a William's pair design. Subjects received the treatments listed below in a double blind, double dummy design following an overnight fast of at least 8 hours and with a separation of at least 72-hours.

- Placebo
- KP201/APAP (80.04mg/3,900mg) – 12 Tablets
- KP201/APAP (53.36 mg/2,400 mg) – 8 Tablets
- KP201/APAP (26.68 mg/1,300 mg) – 4 Tablets
- HB/APAP (90 mg/3,900 mg) – 12 Tablets
- HB/APAP (60 mg/2,600 mg) – 8 Tablets
- HB/APAP (30 mg/1,300 mg) – 4 Tablets

During each Treatment Period of the Double-blind Treatment Phase, serial 3 mL blood samples for pharmacokinetic evaluation were collected pre-dose and at selected times out to 36.0 hours post dose. PK parameters determined for plasma hydrocodone included:

- C_{max} = Maximum plasma level of hydrocodone achieved
- T_{max} = Time to achieve C_{max}
- AUC_{0-x} = Area under the hydrocodone plasma concentration curve from time 0 to x, where x denotes 0.5, 1, 2, 4, 8, and 24 hours

.

The single primary endpoint was maximum Drug Liking (E_{max}) as determined using the 0-100 mm bipolar Drug Liking VAS. For assessing Drug Liking, subjects were asked the question "Do you like the effect that you are feeling now?" The question 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).

Secondary measures included but were not limited to the following:

- Unipolar High VAS in which subjects were asked the question "How high are you now?" Subjects were required to mark a vertical line on a unipolar 0-100 mm VAS anchored on the left by "none" (score of 0) and on the right by "extremely" (score of 100).
- Bipolar Take Drug Again VAS subjects were asked the question, "Would you want to take the drug you just received again, if given the opportunity?" The question was scored using a 0-100 mm bipolar VAS anchored on the left with "definitely would not" (score of 0); "do not care" (score of 50) in the middle; and anchored on the right with "definitely would" (score of 100).

Drug Liking VAS and High VAS, were administered at selected time points out to 24 hours post-dosing. The Take Drug Again VAS was administered at 8 hours and 24 hours post-dosing

Statistical analysis of the pharmacodynamic measures, including Drug Liking VAS, High VAS, and Take Drug Again VAS was conducted by the FDA Center for Drug Evaluation and Research, Office of Biostatistics.

<u>Findings Regarding Study KP201.A01</u>

1. With respect to the primary measure of Drug Liking VAS, KP201/APAP at oral doses of 26.68 mg/1,300 mg (4 tablets), 53.36 mg/2,400 mg (8 tablets), and 80.04mg/3,900mg (12 tablets), as well as HB/APAP at oral doses of 30 mg/1,300 mg (4 tablets), 60 mg/2,600 mg (8 tablets), and 90 mg/3,900 mg, produced maximum Drug Liking statistically significantly above those produced by oral placebo ($p<0.025$). This indicates that following oral administration of either KP201/APAP or HB/APAP at the three dosage levels, subjects liked the treatment they received.
2. With respect to the primary measure of Drug Liking VAS, within each dosage level (4, 8, or 12 tablets), maximum Drug Liking was not statistically significantly different between KP201/APAP and the comparator HB/APAP ($p = 0.4658$, 0.3631, and 0.5315 for one sided test, respectively).
3. With respect to the secondary measures of High VAS and Take Drug Again VAS, all three oral doses of either KP201/APAP or HB/APAP produced mean maximum scores that were statistically significantly higher than the scores produced by oral placebo ($p<0.025$). This indicates that following oral administration of KP201/APAP or HB/APAP at the three doses

examined, subjects did experience some euphoria (High) and that subjects would be willing to take the treatments again if given the opportunity.

4. Within each dosage level (4, 8, or 12 tablets), the mean maximum scores of High ($p = 0.6461$, 0.1401, and 0.5646, respectively) and Take Drug Again ($p = 0.8855$, 0.9497, 0.9658, respectively) were not statistically significantly different between oral KP201/APAP and HB/APAP.
5. As the oral dosages of either KP201/APAP or HB/APAP were increased from 4 to 8 to 12 tablets there was a corresponding increase in the mean maximum plasma levels of hydrocodone. For each dosage level, the maximum plasma hydrocodone concentration (C_{max}) was statistically similar following KP201/APAP and HB/APAP administration. For all six active treatments, times to maximum hydrocodone plasma levels (Tmax) were achieved within about 1 hour. With respect to hydrocodone exposure as reflected by area under the plasma hydrocodone concentration curve (AUC), at the two highest doses (8 and 12 tablets) but not at the low dose of 4 tablets there was a limited, but significant reduction in the $AUC_{0.5hrs}$ and $AUC_{0\text{-}1hr}$ for hydrocodone following oral KP201/APAP compared to HB/APAP. At later time intervals for AUC, no significant reductions were observed.

Intranasal Abuse Potential Study KP201.A02 entitled: A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Single-Dose, Two-Part, Five-Way Crossover Study to Determine the Relative Bioavailability, Abuse Potential, and Safety of Equivalent Doses of Crushed and Intact KP201/APAP Compared with Hydrocodone Bitartrate/APAP and Placebo in Opioid-Experienced, Non-Dependent Subjects Following Intranasal Administration."

Description of Study KP201.A02

Intranasal Study KP201.A02 consisted of two parts, namely a dose-selection pilot study (Part A) and the main study (Part B). The pilot study consisted of a Screening Phase, Drug Discrimination Phase, and Dose Selection Phase and was conducted in order to determine a dose of KP201/APAP and HB/APAP for use via insufflation in the main study (Part B). Using cohorts of 9 subjects each, Sponsor evaluated the use of 1, 2, 3, and 4 crushed tablets of KP201/APAP and HB/APAP. Based on criteria including ease of snorting, subjective reinforcing effects observed (i.e. Drug Liking), and safety, the decision was made to use in the main study (Part B) two tablets of KP201/APAP (13.32 mg/650mg) and, as the positive comparator, 2 tablets of HB/APAP (15 mg/650mg).

Part B, consisting of the main study, included a Screening Phase, Qualification Phase, Treatment Phase, and Follow-up Visit.

The Completer Population, consisting of 42 subjects, served as the primary population for PD analysis. Subjects were non-dependent and had experience in both using opioids for non-therapeutic purposes and administering drugs via the intranasal route. Subjects were subjected to Naloxone Challenge Tests to ensure they were and remained non-opioid dependent.

In the Drug Discrimination Phase, subjects were required to distinguish between a single dose of two crushed HB/APAP tablets (15mg/650 mg) and weight-matched placebo powder, each given intranasally. The criteria used to determine the ability to discriminate using the Drug Liking VAS were identical to that described for the Drug Discrimination Phase for study KP201.A01 (See above for study KP201.A01 page 2.)

The Treatment Phase consisted of five treatment periods, each of which involved a single treatment followed by a minimum 96-hour washout. Treatments were administered to subjects using a randomized, crossover, double-blind, double-dummy design. Subjects received each treatment after at least an eight-hour fast according to a randomization scheme. The five treatments are listed below.

- Intranasal Placebo Powder (Microcrystalline Cellulose Powder)
- Oral Intact KP201/APAP (13.34 mg/650 mg)
- Intranasal Crushed KP201/APAP (13.34 mg/650 mg)
- Intranasal Crushed HB/APAP (15 mg/650 mg)
- Oral Intact HB/APAP (15 mg/650mg)

Pharmacokinetic (PK) parameters determined for plasma hydrocodone included C_{max}, T_{max}, and AUC_{0-x}. See definitions for these terms on page 3.

The primary measure of the study was maximum level of drug liking (E_{max}) determined using Drug Liking VAS. (See pages 3 for description of the Drug Liking VAS.)

Secondary measures included but were not limited to High VAS and Take Drug Again VAS, (See page 3 for descriptions of these High VAS and Take Drug Again VAS). For Drug Liking VAS and High VAS, data was collected at selected time points out to 24 hours. The Take Drug Again VAS was administered at 12 hours and 24 hours post-dosing.

Subject rated nasal effects were assess using a four-point Likert Scale with scores ranging from 0 (none), 1 (mild), 2 (moderate, and 3 (severe). Assessments were completed for the following six clinical signs: nasal burning, facial pain/pressure, need to blow nose, nasal irritation, nasal congestion, and runny nose/nasal discharge.

Statistical analysis of the pharmacodynamic measures, including Drug Liking VAS, High VAS, and Take Drug Again VAS was conducted by the FDA Center for Drug Evaluation and Research, Office of Biostatistics.

<u>Findings Regarding KP201.A02</u>

1. All subjects (N=43) were able in insufflate the entire dose (100%) of crushed HB/APAP 15 mg/650 mg, amounting to 850 mg of powder (2 crushed tablets). Thirty-eight out of 44 subjects were able to insufflate the entire dose of crushed KP201/APAP (1,100 mg of powder from 2 tablets). The remaining 5 subjects insufflated between 91.5% and 99.4% of the powder.
2. Intranasal administration of crushed KP201/APAP (13.32 mg/650 mg) and crushed HB/APAP (15 mg/650 mg) produced maximum levels of Drug Liking, representing the

single primary endpoint, that were not statistically significantly different ($p = 0.1654$). At the same time, maximum Drug Liking for both intranasal treatments was statistically significantly larger than placebo ($p<0.025$). The median times to maximum Drug Liking were 0.6 hours and 1.1 hours for intranasal HB/APAP and intranasal KP201/APAP, respectively. The area under the effect curves for Drug Liking at 0 to 0.5 hours ($AUE_{0\text{-}0.5hrs}$), 0 to 1 hour ($AUE_{0\text{-}1hr}$) and 0 to 2 hours ($AUE_{0\text{-}2hrs}$) were significantly lower following KP201/APAP intranasal compared to HB/APAP IN by 5.9 (36.1 – 30.2) (16% reduction), 9.1 (72.6 – 63.5)(13% reduction), and 12 (141.8 – 129.8) (9% reduction) units, respectively. The clinical significance of these reductions is not known.

- With regard to the secondary measure of High VAS, intranasal administration of crushed KP201/APAP and crushed HB/APAP produced maximum levels of High that were statistically greater than that produced by intranasal placebo ($p<0.25$). Thus, subjects experienced euphoria (High). In addition, there were no statistically significant differences between maximum levels of High ($p = 0.7304$) between intranasal KP201/APAP and intranasal HB/APAP. With regard to the area under the effect curves for High VAS over the first half hour ($AUE_{0\text{-}0.5hrs}$), first hour ($AUE_{0\text{-}1}$) and first two hours ($AUE_{0\text{-}2hrs}$), there were no significant differences between the two intranasal treatments ($p= 0.0807$, 0.1161, and 0.4890, respectively).
- With regard to Take Drug Again VAS as measured at 12 or 24 hours, the maximum scores produced by intranasal KP201/APAP or by intranasal HB/APAP were significantly above that produced by placebo, indicating that subjects were willing if given the opportunity to take these treatments again. In addition, there were no statistically significant differences between maximum levels of Take Drug Again ($p=0.1569$), between intranasal KP201/APAP and intranasal HB/APAP.
- In the subject rated Nasal Effects Assessment, mean peak scores for the six nasal effects of nasal burning, facial pain/pressure, need to blow nose, nasal irritation, nasal congestion, and runny nose/nasal discharge ranged from 1.0 to 1.6 following KP201/APAP insufflation and from 0.0 to 1.0 following HB/APAP insufflation. Statistical analysis of least square mean differences between intranasal HB/APAP versus intranasal KP201/APAP as conducted by Sponsor, demonstrated statistically significant ($p<0.0009$) differences for each of the six nasal assessments.
- Intranasal KP201/APAP and intranasal HB/APAP produced statistically similar maximum hydrocodone plasma concentrations (C_{max}), reached with a median time of 1.23 hours. For both treatments, more than 80% of the rise in the mean hydrocodone plasma concentrations was reached within 30 minutes. Following intranasal KP201/APAP as compared to following intranasal HB/APAP, the reduction in systemic exposure to hydrocodone was 50% over the first 30 minutes ($AUC_{0\text{-}0.5hrs}$), 29% over the first hour ($AUC_{0\text{-}1hr}$), 15% over the first 2 hours ($AUC_{0\text{-}2hrs}$).

Study KP201.A03 entitled"A Randomized, Double-blind, Single-dose, Two-way Crossover Study to Determine the Relative Bioavailability of Equivalent Doses of KP201 API Compared with Hydrocodone Bitartrate API in Opioid Experienced, Non-dependent Subjects Following Intranasal Administration"

Description of Study KP201.A03

Study KP201.A03 was a randomized, double-blind, single-dose, two-way crossover, single center study in recreational non-dependent opioid users. Subjects participated in a Screening Phase (Visit 1), Naloxone Challenge Test (Visit 2, Check-in), Treatment Phase (Visit 2, in-patient) and Follow-up Phase (Visit 3).

The primary objective of the study was to compare the rate and extent of absorption of hydrocodone from KP201 API (active pharmaceutical ingredient), 13.34 mg relative to Hydrocodone Bitartrate (HB) API, 15.00 mg when administered intranasally to non-dependent, recreational opioid users. Note that this study did not use the products, KP201/APAP or HB/APAP. Evaluation of the APIs (KP201 and Hydrocodone Bitartrate) alone for intranasal administration was undertaken in part after consideration that abusers may attempt to extract KP201 from the combination formulation thereby removing some of the unwanted excipients or APAP from the formulation, and thereby attempting abuse by intranasal administration of the extracted KP201. A further reason for conducting the study using KP201 API was to maximize exposure to the opioid while reducing the amount swallowed following insufflation compared to administering the crushed KP201/APAP tablet formulation.

Subjects were recreational opioid users who were not dependent on opioids but had experience both in the use of opioids for non-therapeutic purposes (i.e., for psychoactive effects) and the administration of drugs by the intranasal route.

Study KP201.A03 was originally designed as a pharmacokinetic/nasal tolerability study to which was added an assessment for Drug Liking VAS, as an exploratory measure. Drug liking assessments were collected periodically up to 8 hours after each study drug administration. Considering that Drug Liking VAS is a subjective measure, it is important to note that there was no Drug Discrimination Phase and no intranasal placebo arm in the Treatment Phase.

In the Treatment Phase subjects received each of the following treatments in a randomized, double-blind, crossover manner following an overnight fast of at least 8 hours:

- Treatment A: KP201 API (13.34 mg) administered intranasally
- Treatment B: HB API (15.00 mg) administered intranasally

Serial blood samples were obtained pre-dose and up to 24 hours after each study drug administration. Pharmacokinetic parameters, including C_{max}, T_{max}, and $AUC_{0\text{-}xhrs}$ were calculated for plasma concentration data of hydrocodone using non-compartmental methods. See page 3 for definitions of these parameters.

Study utilized 2 cohorts. In the case of the initial Cohort 1, due to incorrect blood sampling processing, no pharmacokinetic data was forthcoming, although Drug Liking VAS was

conducted. A second group of subjects (Cohort 2) was assembled, ultimately consisting of 24 subjects who completed the study. Both pharmacokinetic data and Drug Liking VAS data were obtained from these 24 subjects.

Findings Regarding KP201.A03

Pharmacokinetic data with respect to hydrocodone in plasma was evaluated using Cohort 2 (N=24 subjects). The C_{max} for plasma hydrocodone following intranasal KP201 API was approximately 36% lower compared to that found following intranasal HB API. The time to achieve C_{max} was also significantly delayed following intranasal KP201 API (median of 1.75 hours) compared to following intranasal HB API (median of 0.5 hours). Areas under the hydrocodone plasma concentration versus time curve (AUCs) at all intervals were significantly lower following KP201 API versus HB API.

Although the study was not properly designed to evaluate Drug Liking VAS (see below), exploratory analysis was conducted on Cohort 2 by the FDA, CDER Office of Biostatistics showing no statistically significant difference in mean maximum Drug Liking between intranasal KP201 API and intranasal HB API ($p = 0.0615$). Median time to maximum drug liking was 0.5 hours and 1.1 hours for HB API and KP201 API, respectively.

Study KP201.A03 has a number of design deficiencies listed below which precludes the use of the data in the abuse deterrent evaluation of KP201/APAP Tablets.

- Study is primarily a pharmacokinetic study with Drug Liking added as an exploratory analysis.
- Study involved insufflation of KP201 API and hydrocodone bitartrate API, and not the products KP201/APAP and hydrocodone bitartrate/APAP. As such, this study does not take into account possible effects of either mass of powder to be insufflated or the effects of APAP on the insufflation experience as would occur following insufflation of the products.
- There was no Drug Discrimination (Qualification) Phase intended to select subjects having an appropriate placebo and active comparator response using the Drug Liking VAS.
- There was no placebo treatment in the Treatment Phase of the study. It is not known how subjects might have responded on the Drug Liking VAS when administering placebo intranasally. It also was not possible to validate the Drug Liking VAS.
- There were no additional subjective reinforcing measures (i.e., High VAS or Take Drug Again VAS) conducted which could be used to support observed effects on the Drug Liking VAS.
- A pre-specified statistical analysis plan was not provided for the study.



US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Briefing Material

KP201/APAP: Relevance of Intranasal Abuse of IR Hydrocodone Combination Products

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee
May 05, 2016

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Executive Summary

The sponsor submitted NDA 208653 seeking approval for benzhydrocodone hydrochloride and acetaminophen combination, an abuse-deterrent formulation for hydrocodone/APAP combination. The sponsor is seeking abuse-deterrent labeling claims for both oral and intra-nasal routes of administration. FDA felt that it was important to understand why intra-nasal abuse of IR hydrocodone combination products is a relevant route of administration. The sponsor conducted observational epidemiological studies using data collected by surveillance systems. We evaluated two epidemiological studies.

A study based on a convenience sample of adults assessed by NAVIPPRO's ASI-MV surveillance system shows that within this *sample*,

- the rate of intra-nasal abuse among those who indicated abuse of IR hydrocodone combination products is approximately 23.4%
- the number of intra-nasal abuse among those who indicated abuse of IR hydrocodone combination products is approximately 2122

The sponsor compared the rate and number of intra-nasal abuse of IR hydrocodone combination products with those of other opioid categories such as IR oxycodone combination products and extended-release long-acting opioids (ERLAs). They noted that while the rate of intra-nasal abuse of 23.4% for IR hydrocodone combination products is relatively small compared to other opioid classes, the number of the intra-nasal abuse of IR hydrocodone combination products is comparable to those of other opioid classes:

- IR oxycodone combination products: 2861 (39.5%)
- IR oxycodone single entity: 1856 (56.0%)
- All ERLAs: 2457 (39.4%)

Similar results were observed from a study based on a convenience sample of adolescents assessed by the NAVIPPRO's CHAT surveillance system:

- the rate of intra-nasal abuse among adolescents who indicated abuse of IR hydrocodone combination products is approximately 42.54%
- the number of intra-nasal abuse among adolescents who indicated abuse of IR hydrocodone combination products is approximately 77

These values are relatively large compared to other opioid classes:

- IR oxycodone combination products: 73 (49.0%)
- IR oxycodone single entity: 18 (47.4%)
- All ERLAs: 52 (53.06%)

Based on these results, the sponsor maintained that intra-nasal abuse is a relevant form of abuse.

We approach the question of relevance of intra-nasal abuse of IR hydrocodone combination products using two criteria:

- **Scope**: is this ROA pervasive in the population? How many individuals in the population are abusing IR hydrocodone combination products intra-nasally?
- **Severity**: how severe are the AEs associated with this ROA? What are the health consequences of intra-nasal abuse of IR hydrocodone combination products and how serious are they?

In principle, if intra-nasal abuse of IR hydrocodone combination products satisfies the scope and severity criteria, then it could be considered a relevant route of administration. Unfortunately, what the data enable us to conclude about scope and severity is limited. This limitation stems, in part, from the fact that

- the underlying sampling mechanism that determines how individuals from the underlying populations are captured by the surveillance systems cannot be quantified. Therefore, it is very difficult to determine whether estimated rates of intra-nasal abuse of IR hydrocodone combination products observed in the sample are valid for rates of intra-nasal abuse of IR hydrocodone combination products in the underlying populations.
- the size and specific characteristics of the underlying population is unknown. Therefore, even if the estimated rates generalizes to the underlying population, it is still not possible to know how extensive (scope) is the problem of intra-nasal abuse of IR hydrocodone combination products.

The underlying population from which the ASI-MV data arose can be characterized as consisting of adults who are at high-risk of substance abuse. What we are able to conclude from the data is that a lower bound for the number of intra-nasal abuse of IR hydrocodone combination products within this population is approximately 2122 for the period from 2014Q1 to 2015Q2 or roughly 1415 per year. Using auxiliary data from a 2013 Treatment Episode Data Set (TEDS) report published by the Substance Abuse and Mental Health Administration, we obtained a more informative lower bound for the number of intra-nasal abuse of IR hydrocodone combination products within this underlying population: 34,830 cases per year. This estimate was based on the assumption that the characteristics of individuals captured by TEDS are similar to the characteristics of individuals captured by ASI-MV.

Similarly, the underlying population from which the CHAT data arose can be characterized as consisting of adolescents who are at high-risk of substance abuse. Based on the TEDS 2013 admissions data, a lower bound estimate for the number of intra-nasal abuse of IR hydrocodone combination products within this underlying high-risk adolescent population is approximately 1579 cases per year.

These pieces of information are all we have to make a determination of scope. Whether these numbers satisfy the scope criterion cannot be answered statistically.

Even if intra-nasal abuse of IR hydrocodone combination products satisfies the scope criterion, the other important criterion is severity. The ASI-MV study compares counts of intra-nasal abuse of IR hydrocodone combination products to other opioid categories such as ERLAs. Such a comparison

could be meaningful if the health consequences of snorting IR hydrocodone combination products are similar to the health consequences of snorting other opioids. However, there is little information captured by ASI-MV that could provide a basis for making statements about severity of intra-nasal abuse of IR hydrocodone combination products. Furthermore, the definition of abuse used in the study has several limitations:

- First, the accuracy and usefulness of this definition is subject to debate. The study defines abuse as any non-medical use of prescription opioids within the past-30 days prior to assessment
- Second, the definition does not make any dose-response distinction.
  - A person who snorts IR hydrocodone combination products once within the past 30 days is treated the same way as a person who snorts twice a week within the past 30 days.
  - A person who snorts IR hydrocodone combination products once within the past 30 days and no other time within the past year is treated the same way as a person who snorts IR hydrocodone combination products once within the past 30 days but 10 times within the past year.

The sponsor brought up the notion of progression in an Internet Survey study noting that it may be possible to use it as a surrogate for severity. However, the data are not sufficient to address this issue.

Finally, it is important to understand that estimates of rates and lower bounds for intra-nasal abuse of IR hydrocodone combination products captured by the ASI-MV and CHAT surveillance systems pertain to two different underlying high-risk populations: an adult population at high-risk of substance abuse and an adolescent population at high-risk of substance abuse. For a more general population, the rate of abuse of IR hydrocodone combination products and the rate of intra-nasal abuse among those who abuse IR hydrocodone combination products could be substantially smaller than what were observed in these studies; therefore the issue of intra-nasal abuse of IR hydrocodone combination products may not be as important or as relevant within this more general population.

1 Introduction

On December 09, 2015 KemPharm submitted NDA 208653 seeking approval for benzhydrocodone hydrochloride (HCl) and acetaminophen (APAP) combination (KP201/APAP). KP201/APAP is a fixed-dose (6.67mg/325mg) abuse-deterrent formulation of immediate-release (IR) hydrocodone/APAP (KemPharm, 2015c) with a proposed indication for the short-term (no more than 14 days) management of acute pain. KP201/APAP is abuse-deterrent because benzhydrocodone is an inactive *prodrug*; activation from benzhydrocodone to the opioid analgesic hydrocodone requires interaction with enzymes in the intestinal tract (KemPharm, 2015e, Section 9.2, p. 9). As of this writing, there are currently no approved IR hydrocodone combination products. If approved, KP201/APAP will be the first abuse-deterrent IR hydrocodone combination product.

The sponsor conducted three abuse potential clinical studies:

- KP201/APAP Oral Human Abuse Liability Study
- KP201/APAP Intranasal Human Abuse Liability Study
- KP201/APAP Benzhydrocodone Intranasal Pharmacokinetic Study

Based on the results of these studies, the sponsor claimed (KemPharm, 2015e, Section 9.2, p. 14) that KP201/APAP's abuse-deterrent properties

> ... reduce exposure to active hydrocodone when more than the recommended oral dose is consumed at one time or when benzhydrocodone HCl is administered intra-nasally with or without APAP.

Furthermore,

> ... KP201/APAP and benzhydrocodone HCl are more difficult to snort than hydrocodone/APAP and hydrocodone bitartrate ...

The sponsor also claimed that non-clinical studies show that KP201/APAP is resistant to physical and chemical tampering (KemPharm, 2015c).

Based on the totality of these results, the sponsor is seeking abuse-deterrent labeling claims in accordance with the FDA's abuse-deterrent and labeling guidance (US Food and Drug Administration, 2015).

In the evaluation of this NDA submission, one issue that is important for FDA to consider is whether intra-nasal abuse is a relevant route of administration (ROA) for hydrocodone/APAP combination products and whether the sponsor should obtain labeling for it (Section 9.2 KemPharm, 2015e, page 15)

> *... the clinical data indicate that KP201/APAP has pharmacological properties which reduce exposure to active hydrocodone when more than the recommended oral dose is consumed at one time or when benzhydrocodone HCl is administered intra-nasally with or without APAP. Ease of insufflation scores from both Study 2 and Study 3 indicate that KP201/APAP and benzhydrocodone HCl are more difficult to snort than hydrocodone/APAP and hydrocodone bitartrate, respectively. However, abuse of KP201/APAP by these routes is still possible ...*

The sponsor commissioned three observational epidemiological studies (see Section 2.1) to characterize the patterns of abuse and ROAs among various currently-marketed prescription opioid classes, including IR hydrocodone combination products. Based on the results of these epidemiological studies, the sponsor maintained that intra-nasal abuse of IR hydrocodone combination products is highly prevalent in both absolute and relative terms (Section 2.5.1.1 KemPharm, 2015b, page 4).

To be clear, this statistical review does not address the efficacy question of whether the drug works or the question of whether the abuse-deterrent technology actually leads to reduction of abuse. The primary purpose of this document is to provide a statistical assessment of the sponsor's epidemiological studies with a view towards establishing a principled approach for determining whether intra-nasal abuse of IR hydrocodone combination products is a *relevant* route of administration. Section 2 provides a summary of two of the sponsor's observational epidemiological studies. Methodological limitations of these studies are discussed in Section 3. Section 3.3 establishes a framework for thinking about relevance. Sections 4 and 5 discuss whether the epidemiological studies are able to provide information for using the framework for determining whether intra-nasal abuse of IR hydrocodone combination products is a relevant route of administration.

2 Epidemiological Studies

2.1 Overview

Before discussing whether the results of the epidemiological investigations submitted by the sponsor can be used to make statements about relevance, it is useful to review the sponsor's studies. The sponsor commissioned observational epidemiological studies to examine prevalence and patterns of abuse of IR hydrocodone combination products and other opioid classes. Each of the studies are based on separate data sources captured by the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) surveillance systems:

- NAVIPPRO Addiction Severity Index - Multimedia Version (ASI-MV®)
- NAVIPPRO Comprehensive Health Assessment for Teens (CHAT®)
- NAVIPPRO Internet Survey Report: Use and Abuse of Hydrocodone Combination Products Internet Survey 2014

We discuss the design of the ASI-MV and CHAT studies and their results below. We do not discuss the internet study because the question of progression, which is indirectly related to the concept of severity (see Sections 3.3 and 5), is very difficult to address given the small sample size (see KemPharm, 2015d, page 5).

Note, while the ASI-MV and CHAT studies span 2012Q1 to 2015Q2, the focus of this document will only cover 2014Q1 to 2015Q2. This does not imply that results based on data within this interval are incompatible with results based on data from 2012Q1 to 2015Q2. Our reason for focusing on the 2014Q1 to 2015Q2 interval is because we felt that relevance should be evaluated with the most recent data.

2.2 ASI-MV

The NAVIPPRO ASI-MV surveillance system obtains information on abuse, ROA, and the prescription opioids being abused when individuals are assessed for substance abuse. Individuals are said to be assessed for substance abuse if they take the ASI-MV computerized self-administered questionnaire. The settings under which these assessments are performed include the following treatment modalities:

- Residential/Inpatient
- Outpatient/non-Methadone
- Methadone
- Corrections
- Other

To illustrate, suppose 10 individuals visited substance abuse treatment centers that are part of the NAVIPPRO network. They are asked to take the ASI-MV questionnaire. Suppose

- 8 individuals took the questionnaire: 2 indicated that they did not abuse prescription opioids
- 4 individuals reported abusing IR hydrocodone combination products: 3 indicated abuse via oral ROA, 1 indicated abuse via intra-nasal ROA.
- 2 individuals reported abusing extended release long-acting opioids (ERLAs): both indicated abuse via intra-nasal ROA

Based on the information,

- the number of assessments is 8
- the number of individuals who indicate abuse of IR hydrocodone combination products is 4
- the number of individuals who indicate abuse of ERLAs is 2

Note, in this example, the 3 individuals who indicated oral ROA are distinct from the individual who indicated intra-nasal ROA. Note, however, that in the ASI-MV sample, an individual who indicated oral ROA may also indicate intra-nasal ROA. For example, it is possible that among the 4 individuals who indicated abuse of IR hydrocodone combination products, 1 contributes to only the total oral count while 3 contribute to both the total oral count and intra-nasal count. Similarly, it is also possible that an individual who indicated abuse of IR hydrocodone combination products also indicated abuse of ERLAs and in this case the individual contributes to both the total IR hydrocodone combination products count and ERLAs count. It is important to keep these distinctions in mind when examining results in Sections 2.4.1 and 2.4.2.

2.2.1 Capturing Abuse, ROA, and Opioid Information

When individuals are assessed for substance abuse (i.e., takes the self-administered computerized ASI-MV questionnaire), a question asks whether they have used prescription opioids non-medically in the past 30 days prior to being assessed. For the purpose of the ASI-MV epidemiological study, abuse is defined as non-medical use of a product in ways that are not consistent with how the product was prescribed to the individuals. If they indicated abuse of prescription opioids, they are presented with a screen where they are asked to select pictures of the drugs that they used. In addition, they are asked to identify all the relevant ROA.

We would like to elaborate on what it means to use the drug non-medically and on how abuse is defined based on non-medical use. According to a submitted report (Section 3.3 KemPharm, 2015a, page 22), a series of questions is used to establish whether

- the individual has a current chronic pain problem and has taken prescribed opioid medication for pain in the past 30 days
- he/she has obtained his/her medications only from his/her own physician
- he/she have not used the drug via an alternate ROA

The individual is also asked if he/she has used prescription opioids in the past 30 days "not in a way prescribed by your doctor, that is, for the way it makes you feel and not for pain relief." A proprietary algorithm[1] is applied to answers of these questions resulting in

- the individual being classified as having engaged in non-medical use and are assumed to be abusing the medication or
- the individual being classified as not abusing the medication

2.3 CHAT

The NAVIPPRO CHAT surveillance system obtains information on abuse, ROA, and prescriptions opioids being abused when adolescents ($\leq$ 18 years of age) are assessed for substance abuse. Individuals are said to be assessed for substance abuse if they take the CHAT self-administered computerized questionnaire. The settings in which the assessments are performed include

- substance abuse treatment centers (drug or alcohol) that are part of the NAVIPPRO network
- alternative schools
- mental health programs
- others

[1] We do not have access to this algorithm and therefore cannot evaluate its properties.

2.3.1 Capturing Abuse, ROA, and Opioid Information

When individuals are assessed for substance abuse (i.e., take the self-administered computerized CHAT questionnaire), they are asked whether they have used any prescription opioids in the past 30 days prior to assessment and if so, whether they have done so in ways not prescribed by a doctor. Those who indicated that they have used prescription opioid products in such a way are classified as having abused prescription opioids. Like ASI-MV, CHAT also asks individuals to identify all prescription opioids they have used in the past 30 days and ROAs in which they have used the products.

2.4 Main Results from Epidemiological Studies

The sponsor presented some important results from their ASI-MV and CHAT epidemiological studies to support their position that intra-nasal abuse of IR hydrocodone combination products is a relevant form of abuse. We present the main results below. Note that the study period for these observational epidemiological studies spans 2012Q1 to 2015Q2. However, we present only information from 2014Q1 to 2015Q2.

2.4.1 ASI-MV

Table 1 displays the counts and rates of abuse for each opioid class. Consider row 1. There were 96357 individuals that were assessed by NAVIPPRO's ASI-MV from 2014Q1 to 2015Q2. Out of these 96357 individuals, 9064 individuals indicated that they abused IR hydrocodone combination products within the past 30 days prior to being assessed. Thus, the rate of IR hydrocodone combination products abuses is 9.41 per 100 assessments. This is obtained by $9064/96357 \times 100$.

Table 2 displays route-specific abuse rates for each opioid class. Consider for example IR hydrocodone combination products. Among 9064 individuals assessed by ASI-MV and who indicated abusing IR hydrocodone combination products, 8184 indicated oral abuse of IR hydrocodone combination products within the past 30 days prior to assessment, resulting in a rate of 0.903 or 90.3%. This is obtained by 8184/9064. Similarly, among the 9064 individuals who indicated abusing IR hydrocodone combination products, 2122 reported intra-nasal abuse resulting in a snorting rate of 0.234 or 23.4% among those who indicated abuse of IR hydrocodone combination products. The sponsor noted that the 23.4% of intra-nasal abuse of IR hydrocodone combination products is relatively small compared to

- oral abuse of IR hydrocodone combination products (90.3%)
- intra-nasal abuse of other opioid classes

However, the sponsor further noted that the intra-nasal abuse counts for IR hydrocodone combination products are comparable to other opioid classes. For example, among the 7250 individuals who indicated abuse of IR oxycodone combination products, 2861 (39.5%) indicated intra-nasal abuse. Also, among the 6234 individuals who indicated abuse of ERLAs, 2457 (39.4%) indicated intra-nasal abuse (see Table 2).

Table 1: Rates and counts of abuse of various prescription opioid classes among individuals assessed by ASI-MV from 2014Q1 to 2015Q2. Within this time-frame, 96357 individuals were assessed by ASI-MV. Rates are expressed as number of individuals who indicated abuse per 100 individuals assessed for substance abuse.

Opioid Classes	**Counts**	**Rates**	**Lower 95%**	**Upper 95%**
IR HCP	9,064	9.41	9.22	9.59
IR OCP	7,250	7.52	7.36	7.69
IR OSE	3,314	3.44	3.32	3.55
All Other IR	2,732	2.84	2.73	2.94
All ERLAs	6,234	6.47	6.31	6.63
All ADF ERLAs	3,493	3.63	3.51	3.74
All Non-ADF ERLAs	4,602	4.78	4.64	4.91

HCP: hydrocodone combination products
OCP: oxycodone combination products
OSE: oxycodone single-entity products
ADF: abuse-deterrent formulation
ERLA: extended-release long-acting products

Source: Reproduced by statistical reviewer from sponsor's report (Table 8 KemPharm, 2015a, page 39)

Table 2: ROA-specific rates and counts of abuse of various prescription opioid classes among individuals assessed by ASI-MV from 2014Q1 to 2015Q2. Under each opioid column heading, the value in parentheses is the denominator used in the calculation of rates.

	IR HCP (9064)		IR OCP (7250)		IR OSE (3314)		Other IR (2732)		ERLAs (6234)		ADF ERLAs (3493)		Non-ADF ERLAs (4602)	
ROA	**Cases**	**Rates**[†]	**Cases**	**Rates**	**Cases**	**Rates**	**Cases**	**Rates**	**Cases**	**Rates**	**Cases**	**Rates**	**Cases**	**Rates**
Oral	8,184	90.3	5,455	75.2	1,387	41.9	727	26.6	3,632	58.3	2,080	59.5	2,216	48.2
Snort	2,122	23.4	2,861	39.5	1,856	56.0	620	22.7	2,457	39.4	987	28.3	2,004	43.5
Inject	139	1.5	913	12.6	1,206	36.4	1,766	64.6	2,164	34.7	1,206	34.5	1,742	37.9
Smoke	99	1.1	261	3.6	218	6.6	44	1.6	248	4.0	110	3.1	180	3.9
Other	271	3.0	252	3.5	51	1.5	186	6.8	269	4.3	121	3.5	169	3.7

[†]: Rates are expressed in %
HCP: hydrocodone combination products
OCP: oxycodone combination products
OSE: oxycodone single-entity products
ADF: abuse-deterrent formulation
ERLA: extended-release long-acting products

Source: Reproduced by statistical reviewer from sponsor's report (Table 14 KemPharm, 2015a, page 56)

2.4.2 CHAT

Table 3 displays the proportion of abuse for each opioid class among adolescents assessed by CHAT. Consider row 1. There were a total of 4965 individuals that were assessed by NAVIPPRO's CHAT from 2014Q1 to 2015Q2. Out of these 4965 individuals, 181 individuals indicated that they abused IR hydrocodone combination products within the past 30 days prior to being assessed. Thus, the rate of IR hydrocodone combination products abuses is 3.65 per 100 assessments. This is obtained by $181/4965 \times 100$.

Table 4 displays route-specific abuse rates for each opioid class. Consider for example IR hydrocodone combination products. Among 181 individuals assessed by CHAT and who indicated abusing IR hydrocodone combination products, 147 reported oral abuse of IR hydrocodone combination products within the past 30 days prior to assessment resulting in a rate of 0.8122 or 81.22%. This is obtained by 147/181. Similarly, among the 181 individuals who indicated abusing IR hydrocodone combination products, 77 reported intra-nasal abuse resulting in a snorting rate of 0.4254 or 42.54%.

Table 3: Rates and counts of abuse of various prescription opioid classes among individuals assessed by CHAT from 2014Q1 to 2015Q2. Within this time-frame, 4965 adolescents were assessed by CHAT. Rates are expressed as number of individuals who indicated abuse per 100 individuals assessed for substance abuse.

Opioid Classes	**Counts**	**Rates**	**Lower 95%**	**Upper 95%**
IR HCP	181	3.65	3.12	4.17
IR OCP	149	3.00	2.53	3.48
IR OSE	38	0.77	0.52	1.01
All Other IR	38	0.77	0.52	1.01
All ERLAs	98	1.97	1.59	2.36
All ADF ERLAs	52	1.05	0.76	1.33
All Non-ADF ERLAs	72	1.45	1.12	1.78

HCP: hydrocodone combination products
OCP: oxycodone combination products
OSE: oxycodone single-entity products
ADF: abuse-deterrent formulation
ERLA: extended-release long-acting products

Source: Reproduced by statistical reviewer from sponsor's report (Table 23 KemPharm, 2015a, page 77)

Table 4: ROA-specific rates and counts of abuse of various prescription opioid classes among individuals assessed by CHAT from 2014Q1 to 2015Q2. Under each opioid column heading, the value in parentheses is the denominator used in the calculation of rates.

	IR HCP (181)		IR OCP (149)		IR OSE (38)		Other IR (38)		ERLAs (98)		ADF ERLAs (52)		Non-ADF ERLAs (72)	
ROA	**Cases**	**Rate**[†]	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**	**Cases**	**Rate**
Oral	147	81.22	110	73.83	24	63.16	23	60.53	74	75.51	37	71.15	52	72.22
Snort	77	42.54	73	48.99	18	47.37	17	44.74	52	53.06	25	48.08	39	54.17
Smoke	9	4.97	7	4.70	2	5.26	1	2.63	5	5.10	4	7.69	3	4.17
Inject	2	1.10	7	4.70	4	10.53	5	13.16	8	8.16	5	9.62	6	8.33
Other	2	1.10	3	2.01	1	2.63	2	5.26	0	0.00	0	0.00	0	0.00

[†]: Rates are expressed in %
HCP: hydrocodone combination products
OCP: oxycodone combination products
OSE: oxycodone single-entity products
ADF: abuse-deterrent formulation
ERLA: extended-release long-acting products

Source: Reproduced by statistical reviewer from sponsor's report (Table 26 KemPharm, 2015a, page 87)

2.5 Conclusions

Based on the results of the epidemiological studies (see Table 2), the sponsor concluded that (KemPharm, 2015a, page 97)

> *These data suggest that snorting of hydrocodone IR combination products may be a route of abuse used by a significant number of abusers of these products.*

In stating this conclusion, the sponsor maintains that intra-nasal abuse of IR hydrocodone combination products is a relevant route of abuse.

3 Statistical Considerations

3.1 Overview

In discussing the relevance of intra-nasal abuse of IR hydrocodone combination products, the sponsor estimated the rate of intra-nasal abuse among those who indicated abuse of IR hydrocodone combination products within the sample of individuals assessed by NAVIPPRO's ASI-MV surveillance system. Among the 9064 individuals who indicated abuse of IR hydrocodone combination products, 2122 or 23.4% indicated intra-nasal abuse. These values are comparable to intra-nasal abuse of other prescription opioids. For example, among the 6234 individuals who indicated abuse of ERLAs, 2457 or 39.4% indicated intra-nasal abuse.

The sponsor noted a similar pattern among adolescents assessed by NAVIPPRO's CHAT surveillance system. Among 181 adolescents who indicated abuse of IR hydrocodone combination products, 77 or 42.54% indicated intra-nasal abuse. From Table 4, the IR hydrocodone combination products intra-nasal abuse rate are similar in magnitude to other opioid categories. On an absolute basis, 77 individuals indicated intra-nasal abuse of IR hydrocodone combination products. This value is larger than any of the other prescription opioid categories.

Whether these numbers reflect what goes on in the underlying populations depends in a very important way on how the ASI-MV and CHAT surveillance systems collect the data. Section 3.2 provides an in-depth discussion of this issue which we refer to as the estimability issue. Furthermore, even if patterns observed in the data could be generalizable to the underlying populations, whether that is sufficient for concluding relevance will have to depend on how these numbers are able to shed light on the scope and severity of the problem of intra-nasal abuse of IR hydrocodone combination products. Section 3.3 introduces the principles of scope and severity as criteria for assessing relevance.

3.2 Estimability

To understand why the estimability issue is important, we need to first make the distinction between population and sample. For convenience, we focus only on the NAVIPPRO ASI-MV study. However, the principles raised in the discussion are also applicable to the CHAT study, with the understanding that the underlying population captured by CHAT is different than the underlying population captured by ASI-MV.

The data gathered by the NAVIPPRO ASI-MV surveillance system constitute a sample from some population[2]. In this case, the actual population is unknown and difficult to define. One way of thinking about this population is to consider the kinds of people that are assessed by ASI-MV for substance abuse. These are individuals

- who are likely to make contact with substance abuse treatment centers
- who are likely to make contact with law enforcements via paroles, drug courts, DUIs, etc...

It is then not unreasonable to characterize the underlying population as some subset of the US population that consist of individuals who are at high risk of substance abuse and that the ASI-MV data constitute a sample from this population. The estimability issue has to do with whether the ASI-MV sample can be used to make statements about this underlying high-risk population. For example, does the 23.4% intra-nasal abuse rate among those who indicated abuse of IR hydrocodone combination products observed in the ASI-MV sample represent a valid estimate of the corresponding quantity in the underlying high-risk population? Similarly, does the relative magnitude of intra-nasal abuse between IR hydrocodone combination products and ERLAs (2122 versus 2457, respectively) represent the relative magnitude observed in the high-risk population?

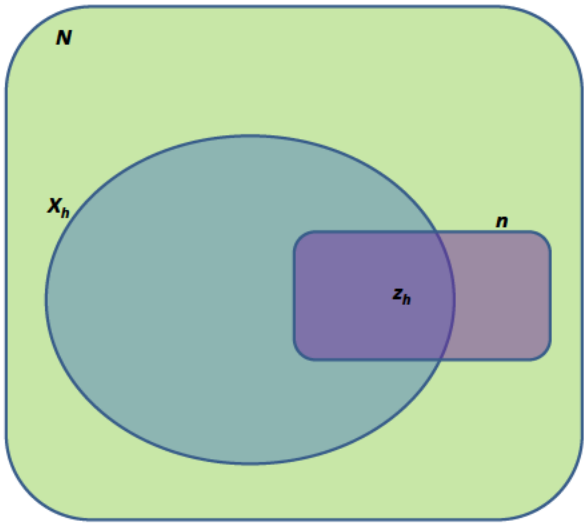

Figure 1: *Relationship between sample and population. The outer square, denoted by N, represents the high-risk population. The inner circle, denoted by X_h, represent the number of individuals abusing IR hydrocodone combination products in N. The inner rectangle, denoted by n, represents the number of individuals assessed by the NAVIPPRO ASI-MV surveillance system. The number of abuses of IR hydrocodone combination products captured by ASI-MV, denoted by z_h, is the intersection of n and X_h. Note, we are using the letters N and n not only to distinguish between population and sample but also to indicate the actual size; i.e., there are N individuals in the underlying population and ASI-MV assessed n individuals.*

Source: *Figure generated by the statistical reviewer.*

[2]**Note.** The term *population* does not refer to the entire US. As used here, it refers to some subset of the US population.

These questions are very difficult to answer because it is not possible to quantify the selection mechanism that determines how individuals end up being assessed by ASI-MV. To clarify, consider the diagram in Figure 1:

- N is used to denote the underlying high-risk population and also its size.
- X_h is used to denote a subset of this population and its size who abuse IR hydrocodone combination products.

Suppose we are interested in making statements about the population quantity $R_h = X_h/N$. We can think of R_h as the proportion of individuals in the underlying high-risk population who indicated abusing IR hydrocodone combination products. It is not possible to know N because the individuals in this population are hidden and it is not possible to know X_h because not all those who abuse IR hydrocodone combination products in the population are captured by ASI-MV. What is available to us is the ASI-MV sample, the individuals who are assessed by ASI-MV for substance abuse. In Figure 1

- n is used to denote both the set of individuals assessed by ASI-MV and its size.
- z_h is used to denote a subset of this sample and its size who indicated abusing IR hydrocodone combination products.

Thus, the proportion of individuals in the sample who abuse IR hydrocodone combination products is $r_h = z_h/n$. Statistically, the estimability question reduces to whether $r_h = R_h$.

There are two situations where the sample proportion r_h is a valid estimate of the population proportion R_h. This happens when the set of individuals assessed by the ASI-MVsystem is a

- random sample from the underlying high-risk population
- weighted sample from the underlying high-risk population where the weights are known

Unfortunately, ASI-MV is neither a random sample nor a weighted sample; it is a convenience sample. This in itself is not a limitation if we have some idea about the sampling scheme. Unfortunately, it is not possible to quantify how individuals in the underlying high-risk population ended up being selected by the ASI-MV surveillance system. Therefore, it is difficult to conclude that r_h is a valid estimate of R_h. What we can say however is that r_h estimates $\pi_h/\pi \times R_h$ in the sense that the expected value of r_h is

$$E(r) = \left(\frac{\pi_h}{\pi}\right) R_h \tag{1}$$

where

- π_h is some fraction of X_h such that the number of ASI-MV assessments who indicated abuse of IR hydrocodone combination products is equal to $\pi_h \times X_h$; that is, $z_h = \pi_h X_h$. Note that π_h is unknown.
- $\pi = n/N$. Note that π is unknown because N is unknown.

From (1), observe that

- if $\pi_h > \pi$, then r_h tends to overestimate R_h. This can happen for example if individuals who ended up being assessed by ASI-MV are more prone to abuse IR hydrocodone combination products than the population N as a whole.
- if $\pi_h < \pi$, then r_h tends to underestimate R_h. This can happen if individuals who ended up being assessed by ASI-MV are less prone to abuse IR hydrocodone combination products than the population N as a whole.
- if $\pi_h = \pi$, then $r_h = R_h$. This happens under random sampling.

We emphasize that it is not possible to know which of the first two scenarios the ASI-MV surveillance system falls in, only that we know it is not a random sample. Therefore, it is unknown whether the sample rate r_h estimates the population rate R_h.

The sponsor acknowledges that quantities such as proportion of individuals assessed by ASI-MV who indicated abuse of specific prescription opioids do not necessarily represent the corresponding quantities in the population:

> It is important to note that data collected via the ASI-MV do not necessarily relate to incidence, prevalence, or to increases or decreases in trends of abuse in the general population, including those who abuse but do not seek treatment.

(See KemPharm, 2015a, page 17.). This holds true even if we interpret *general population* as the underlying high-risk population. However, the sponsor noted that *relative* statements made about the sample is valid for the underlying population:

> ... these data have a variety of strengths in that evaluation of abuse prevalence among the ASI-MV sample affords the ability to measure the relative prevalence or burden of abuse of currently marketed hydrocodone IR combination products compared to a range of comparator opioid products/compounds within an experienced abuser population. Data sources for both ASI-MV and CHAT provide a profile of abuse within the context of a number of comparator opioid compounds with varying levels of utilization, lengths of market history, and opioid strengths.

(See KemPharm, 2015a, page 13.).

Whether conclusions based on relative comparisons made within the ASI-MV sample applies to the underlying high-risk population is also difficult to justify. To see why this is so, suppose we are interested in comparing intra-nasal abuse rates between IR hydrocodone combination products and ERLAs in the underlying high-risk population and that

- $r_{h,in} = z_{h,in}/z_h$ is the proportion of individuals who indicated intra-nasal ROA among those who indicated abuse of IR hydrocodone combination products within the ASI-MV sample.
- $r_{e,in} = z_{e,in}/z_e$ is the proportion of individuals who indicated intra-nasal ROA among those who indicated abuse of ERLAs within the ASI-MV sample.

The sample rate ratio $r_{h,in}/r_{e,in} = z_{h,in}/z_{e,in}$ measures the size of intra-nasal abuse of IR hydrocodone combination products relative to ERLAs. In Table 2 for example, 2122 individuals

indicated intra-nasal ROA among those who indicated abuse of IR hydrocodone combination products and 2457 indicated intra-nasal ROA among those who indicated abuse of ERLAs. Thus,

$$\frac{r_{h,in}}{r_{e,in}} = \frac{2122}{2457} = 0.86$$

This suggests that *within the ASI-MV sample*, the size of intra-nasal abuse of IR hydrocodone combination products is nearly as large as the size of intra-nasal abuse of ERLAs.

Whether this relative statement based on the ASI-MV sample also hold for the underlying high-risk population depends on the *unknown* underlying sampling scheme. Only under certain conditions will statements based on the sample generalizes to the underlying population. To see this, we need to introduce additional notation and quantities. Let

- X_h denote the number of individuals abusing IR hydrocodone combination products within the underlying high-risk population
- $X_{h,in}$ denote the number of individuals who abuse intra-nasally among the X_h individuals
- X_e denote the number of individuals abusing ERLAs within the underlying high-risk population
- $X_{e,in}$ denote the number of individuals who abuse intra-nasally among the X_e individuals
- π_h denote the proportion of X_h detected by the ASI-MV surveillance system
- π_e denote the proportion of X_e detected by the ASI-MV surveillance system
- $\pi_{h,in}$ denote the proportion of $X_{h,in}$ detected by the ASI-MV surveillance system
- $\pi_{e,in}$ denote the proportion of $e_{h,in}$ detected by the ASI-MV surveillance system

In order for the rate ratio $r_{h,in}/r_{e,in}$ observed in the sample to apply to the underlying population we must have

$$\frac{\pi_{h,in}}{\pi_h} = \frac{\pi_{e,in}}{\pi_e} \ .$$

Roughly speaking, this means that the underlying sampling mechanism cannot in any way prefer IR hydrocodone combination products over ERLAs or the other way around. In other words, the representativeness of IR hydrocodone combination products and its ROA cannot be different from the representativeness of ERLAs and its ROA within the sample. Unfortunately, there is insufficient information to make a determination regarding whether the ASI-MV system preferentially selects one over the other.

3.3 Criteria for Assessing Relevance

Whether intra-nasal abuse of IR hydrocodone combination products is a *relevant* ROA is a difficult question to answer. For the ASI-MV study, the sponsor noted that among those who indicated abuse of IR hydrocodone combination products, 23.4% indicated intra-nasal ROA. For the CHAT study, the sponsor noted that among adolescents assessed by CHAT and who indicated abuse of IR hydrocodone combination products, 42.5% indicated intra-nasal ROA. If we ignore the estimability issue for the moment, what these numbers suggest is that the IR hydrocodone combination products

intra-nasal abuse rates can vary depending on the underlying population. It is not inconceivable that another surveillance system may capture data that could suggests an intra-nasal abuse rate for IR hydrocodone combination products that is even smaller, for example 5%. This would not be incompatible with the two numbers observed in the ASI-MV and CHAT studies because it may be describing a different underlying population.

From a public health perspective however, it seems incomplete to try to interpret relevance based on the how large or how small these rates are. The reason is this: an outcome due to drug exposure can have a very small incident rate but if the drug is widely-prescribed or widely-used, a small rate can translate into a large number of events for the outcome. However, having a large number of events is neither sufficient nor necessary for determining relevance. It could be argued that some outcomes such as headaches and nausea are highly prevalent but may not be relevant from a public health perspective. On the other hand, it could be argued that other outcomes such as myocardial infarction (MI), although not as prevalent as headaches and nausea, are relevant from a public health perspective. These examples suggest that relevance has two components: scope and severity. Headaches and nausea could be considered as having scope but not severity. On the other hand, MI could be considered as having less scope but very severe.

Guided by these examples, we approach the question of relevance in a principled way using these two criteria:

- **scope** - how pervasive or how large is intra-nasal abuse of IR hydrocodone combination products in the population?
- **severity** - how serious are the consequences of intra-nasal abuse of IR hydrocodone combination products?

If intra-nasal abuse of IR hydrocodone combination products satisfies the criteria of scope and severity, this may provide a justification for making the determination that it is a relevant ROA. We acknowledge that this raises more questions:

- What is the threshold beyond which we say that the scope criterion is satisfied?
- What is the threshold beyond which we say that the severity criterion is satisfied?

These are very important public health questions but unfortunately, ones that cannot be answered statistically. As such, we leave them unanswered, relying on the readers' expertise to make his or her own judgment. The statistical narrative is intended to provide a basis for thinking about these questions and to evaluate whether the studies provide any useful information that we can use to make statements about scope and severity of intra-nasal abuse of IR hydrocodone combination products.

4 Scope

4.1 Scope of Intra-nasal Abuse of IR Hydrocodone Combination Products

The previous discussion about estimability underscores the difficulty of generalizing beyond the sample to the underlying population when the surveillance system captures data using a convenience sampling scheme. For the ASI-MV study, we know that

- among 96357 individuals assessed by ASI-MV from 2014Q1 to 2015Q2, 9064 indicated abuse of IR hydrocodone combination products (9.41%).
- 2122 of these 9064 (23.4%) individuals indicated abuse via intra-nasal ROA.

Whether these 23.4% and 9.4% rates also hold for the underlying population is unlikely to be true given the discussion in Section 3.2. With respect to intra-nasal abuse of IR hydrocodone combination products, the data enable us to say that the number of individuals who intra-nasally abuse IR hydrocodone combination products in the underlying high-risk population is likely to be greater than 1415 per year[3]. If this lower bound is sufficient for determining that intra-nasal abuse is pervasive, then we may consider the scope criterion satisfied. However, if this information is insufficient, then we need recourse to other studies or data sources to evaluate scope.

Similarly, for the CHAT study, the data enable us to say that the number of adolescents who intra-nasally abuse IR hydrocodone combination products in the underlying high-risk population is likely to be greater than 52 per year[4]. If this lower bound is sufficient for determining that intra-nasal abuse is pervasive, then we may consider the scope criterion satisfied. However, if this information is insufficient, then we need recourse to other studies or data sources to evaluate scope.

4.2 Scope of Intra-nasal Abuse of IR Hydrocodone Combination Products: A Lower Bound From External Data

At the end of Section 4.1, we stated that within the underlying high-risk population from which the ASI-MV sample arose, there's roughly 1415 or more intra-nasal abuses of IR hydrocodone combination products per year. There are, however, auxiliary data that could be used with the ASI-MV data to estimate a more informative lower bound.

The Substance Abuse and Mental Health Administration (SAMHSA) publishes the Treatment Episode Data Set (TEDS) which contains demographic characteristics and substance abuse problems of admissions to primarily publicly-funded treatment facilities in the US (SAMHSA, 2016). In 2013, there were 1581786 admissions to treatment facilities captured by TEDS who are at least 18 years old (See Table 2.1b SAMHSA, 2013, page 53). Note that while it is possible to think of the 1581786 admissions as a sample from the underlying high-risk population, this sample cannot be viewed as a random sample from that population for the same reason that the ASI-MV sample cannot be viewed as a random sample. However, if we can reasonably assume that individuals admitted to TEDS treatment centers are similar to individuals assessed by ASI-MV, then we can apply the estimates from the ASI-MV study to estimate a more informative lower bound for the number of intra-nasal abuse of IR hydrocodone combination products in the underlying high-risk population:

- From Table 1, 9.4% of those assessed by ASI-MV indicated abusing IR hydrocodone combination products.
- If the individuals captured by TEDS in 2013 are similar in characteristics to those assessed by ASI-MV, then we can expect roughly 148,846 cases of abuse of IR hydrocodone combination products in TEDS: 0.094×1581786.

[3] There were 2122 intra-nasal abuse of IR hydrocodone combination products per 6 quarters or 1415 per year.
[4] There were 77 intra-nasal abuse of IR hydrocodone combination products per 6 quarters or 52 per year.

- From Table 2, 23.4% of those who indicated abuse of IR hydrocodone combination products also indicated that they abuse IR hydrocodone combination products intra-nasally.
- If the individuals captured by TEDS in 2013 are similar in characteristics to those assessed by ASI-MV, then we can expect roughly 34,830 cases of intra-nasal abuse in TEDS: 0.2340×148846.

Ignoring the sampling variability of the ASI-MV estimates, we can reasonably conclude, based on TEDS 2013 admissions data, that although we do not know the extent of intra-nasal abuse of IR hydrocodone combination products in the underlying high-risk population, it is roughly *at least* 34,830. How far this value is away from the true value cannot be determined with the available information.

This exercise can also be repeated for the CHAT study. Within the TEDS 2013 admissions, there were 101665 admissions that were between the ages of 12 and 18, not including 18. If we can reasonably assume that adolescents admitted to TEDS treatment centers are similar to adolescents assessed by CHAT then we can apply the estimates from the CHAT study to estimate a more informative lower bound for the number of intra-nasal abuse of IR hydrocodone combination products in the underlying high-risk adolescent population:

- From Table 3, 3.65% of those assessed by CHAT indicated abusing IR hydrocodone combination products.
- If the adolescents captured by TEDS in 2013 are similar in characteristics to those assessed by CHAT, then we can expect roughly 3711 cases of abuse of IR hydrocodone combination products in TEDS: 0.0365×101665.
- From Table 4, 42.54% of those who indicated abuse of IR hydrocodone combination products also indicated that they abuse IR hydrocodone combination products intra-nasally.
- If the adolescents captured by TEDS in 2013 are similar in characteristics to those assessed by CHAT, then we can expect roughly 1579 cases of intra-nasal abuse in TEDS: 0.4254×3711.

Ignoring the sampling variability of the CHAT estimates, we can reasonably conclude, based on TEDS 2013 admissions data, that although we do not know the extent of intra-nasal abuse of IR hydrocodone combination products in the underlying adolescent high-risk population, it is roughly *at least* 1579. How far this value is away from the true value cannot be determined with the available information.

4.3 A Note on the Differences Between TEDS and ASI-MV

The sponsor noted that there are some differences between individuals captured by TEDS and ASI-MV(KemPharm, 2015a, page 18):

- ASI-MV has a larger proportion of Hispanics than TEDS (19% vs 13%).
- ASI-MV has a smaller proportion of unemployed than TEDS (19.9% vs 39.7%).

To this, we also add that the TEDS sample consists primarily of admissions to publicly funded substance abuse treatment centers whereas the ASI-MV sample consists of assessments by privately and publicly funded substance abuse treatment centers and assessments captured in parole, drug court, DUI/DWI, and other settings. Whether these differences biased the 34830 lower bound estimate cannot be determined.

5 Severity

As discussed in Section 3.3, the assessment of relevance of a specific route of abuse should not only include scope but also severity. That is, we should also consider the health consequences of snorting IR hydrocodone combination products.

The sponsor noted that the number of intra-nasal abuse of IR hydrocodone combination products are comparable to other opioid classes such as ERLAs. Such comparisons would be reasonable if the consequences of snorting IR hydrocodone combination products are similar to the consequences of snorting ERLAs (or other opioid classes). In other words, there is an underlying assumption that consequent AEs such as overdose and death from snorting IR hydrocodone combination products is similar to snorting other opioids. Unfortunately the data do not provide any information on the distributions of AEs from snorting of IR hydrocodone combination products and other opioids. As such, assessment of severity based on consequent AEs is not possible.

Furthermore, the definition of abuse used in the studies is any non-medical use of prescription opioids within the past-30 days prior to assessment. There are two concerns with this definition:

- First, the accuracy and usefulness of this definition is debatable.
- Second, the definition does not make any dose-response distinction.
  - A person who snorts IR hydrocodone combination products once within the past 30 days is treated the same way as a person who snorts twice a week within the past 30 days.
  - A person who snorts IR hydrocodone combination products once within the past 30 days and no other time within the past year is treated the same way as a person who snorts IR hydrocodone combination products once within the past 30 days but 10 times within the past year.

If severity of snorting IR hydrocodone combination products depends on some sort of dose-response relationship between frequency of snorting and AEs, the data provide little information to elicit such a relationship.

6 Summary

The sponsor submitted NDA 208653 seeking approval for benzhydrocodone hydrochloride and acetaminophen combination, an abuse-deterrent formulation for hydrocodone/APAP combination. Based on the results from three abuse potential clinical studies, the sponsor is seeking abuse-deterrent labeling claims for both oral and intra-nasal routes of administration. FDA felt that it was important to understand why intra-nasal abuse of IR hydrocodone combination products is a relevant route of administration. The sponsor conducted observational epidemiological studies

using data collected by surveillance systems. A study based on a convenience sample of adults assessed by NAVIPPRO's ASI-MV surveillance system shows that

- the rate of intra-nasal abuse among those who indicated abuse of IR hydrocodone combination products is approximately 23.4%
- the number of intra-nasal abuse among those who indicated abuse of IR hydrocodone combination products is approximately 2122

The sponsor compared the rate and number of intra-nasal abuse of IR hydrocodone combination products with those of other opioid categories such as IR oxycodone combination products and extended-release long-acting opioids. They noted that while the rate of intra-nasal abuse of 23.4% for IR hydrocodone combination products is relatively small compared to other opioid classes, the number of the intra-nasal abuse of IR hydrocodone combination products is comparable to those of other opioid classes:

- IR oxycodone combination products: 2861 (39.5%)
- IR oxycodone single entity: 1856 (56.0%)
- All ERLAs: 2457 (39.4%)

Similar results were observed from a study based on a convenience sample of adolescents assessed by the NAVIPPRO's CHAT surveillance system:

- the rate of intra-nasal abuse among adolescents who indicated abuse of IR hydrocodone combination products is approximately 42.54%
- the number of intra-nasal abuse among adolescents who indicated abuse of IR hydrocodone combination products is approximately 77

These values are relatively large compared to other opioid classes:

- IR oxycodone combination products: 73 (49.0%)
- IR oxycodone single entity: 18 (47.4%)
- All ERLAs: 52 (53.06%)

Based on these results, the sponsor maintained that intra-nasal abuse is a relevant form of abuse.

We approach the question of relevance of intra-nasal abuse of IR hydrocodone combination products using two criteria:

- **Scope**: is this ROA pervasive in the population? How many individuals in the population are abusing IR hydrocodone combination products intra-nasally?
- **Severity**: how severe are the AEs associated with this ROA? What are the health consequences of intra-nasal abuse of IR hydrocodone combination products and how serious are they?

In principle, if intra-nasal abuse of IR hydrocodone combination products satisfies the scope and severity criteria, then it could be considered a relevant route of administration. Unfortunately, what the data enable us to conclude about scope and severity is limited. This limitation stems, in part, from the fact that

- the underlying sampling mechanism that determines how individuals from the underlying populations are captured by the surveillance systems cannot be quantified. Therefore, it is very difficult to determine whether estimated rates of intra-nasal abuse of IR hydrocodone combination products observed in the sample are valid for rates of intra-nasal abuse of IR hydrocodone combination products in the underlying populations.
- the size and specific characteristics of the underlying population is unknown. Therefore, even if the estimated rates generalizes to the underlying population, it is still not possible to know how extensive (scope) is the problem of intra-nasal abuse of IR hydrocodone combination products.

The underlying population from which the ASI-MV data arose can be characterized as consisting of adults who are at high-risk of substance abuse. Within this population, we are interested in assessing the scope of the problem of intra-nasal abuse of IR hydrocodone combination products. What we are able to understand from the sample however is that a lower bound for the number of intra-nasal abuse of IR hydrocodone combination products within this population is approximately 2122 for the period from 2014Q1 to 2015Q2. Using auxiliary data from a 2013 TEDS report published by the Substance Abuse and Mental Health Administration, we obtained a more informative lower bound for the number of intra-nasal abuse of IR hydrocodone combination products within this underlying population: 34,830 cases per year. This estimate was based on the assumption that the characteristics of individuals captured by TEDS are similar to the characteristics of individuals captured by ASI-MV.

We can also obtain a lower bound for the underlying adolescent population from which the CHAT data arose. This underlying population can be characterized as consisting of adolescents who are at high-risk of substance abuse. Within this population, we are interested in assessing the scope of the problem of intra-nasal abuse of IR hydrocodone combination products. Within the TEDS 2013 admissions, there were 101665 individuals between the ages of 12 and 18, not including 18. After applying the estimates from the CHAT study, a lower bound for the number of intra-nasal abuse of IR hydrocodone combination products within the underlying high-risk adolescent population is approximately 1579.

Whether these lower bound information on intra-nasal abuse of IR hydrocodone combination products are sufficient to make a determination of scope is beyond the capabilities of the statistical analyses.

Even if intra-nasal abuse of IR hydrocodone combination products satisfies the scope criterion, the other important criterion is severity. The ASI-MV study compares counts of intra-nasal abuse of IR hydrocodone combination products to other opioid categories such as ERLAs. Such a comparison could be meaningful if the health consequences of snorting IR hydrocodone combination products are similar to the health consequences of snorting other opioids. However, there is little information captured by ASI-MV that could provide a basis for making statements about severity of intra-nasal abuse of IR hydrocodone combination products. Furthermore, the definition of abuse used in the study has several limitations:

- First, the accuracy and usefulness of this definition is subject to debate. The study defines abuse as any non-medical use of prescription opioids within the past-30 days prior to assessment
- Second, the definition does not make any dose-response distinction.
  - A person who snorts IR hydrocodone combination products once within the past 30 days is treated the same way as a person who snorts twice a week within the past 30 days.
  - A person who snorts IR hydrocodone combination products once within the past 30 days and no other time within the past year is treated the same way as a person who snorts IR hydrocodone combination products once within the past 30 days but 10 times within the past year.

The sponsor brought up the notion of progression in their Internet Survey study noting that it may be possible to use it as a surrogate for severity. However, the data are not sufficient to address this issue.

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

Review of Multiple Epidemiologic Studies

Date:	March 28, 2016
Reviewer(s):	Jana McAninch, MD MPH MS Alex Secora, MPH *Division of Epidemiology II*
Team Leader:	Cynthia Kornegay, PhD *Division of Epidemiology II*
Acting Associate Director:	Judy Staffa, PhD RPh *Office of Surveillance and Epidemiology*
Subject	Review of hydrocodone combination product postmarketing abuse studies, with focus on intranasal route of abuse
Drug Name(s):	KP201/APAP
Application Type/Number:	NDA #208653
Submission Number:	EDR: \\CDSESUB1\evsprod\NDA208653\208653.enx
Applicant/sponsor:	KemPharm
OSE RCM #:	2016-61

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EXECUTIVE SUMMARY

KemPharm, Inc. (Sponsor) is currently seeking approval of KP201/APAP (benzohydrocodone and acetaminophen, NDA #208653), a prodrug of an immediate-release (IR) hydrocodone in combination with acetaminophen, formulated with properties intended to reduce abuse, particularly through the nasal route. As part of the NDA submission, the Sponsor has included epidemiologic studies examining patterns of hydrocodone combination product (HCP) abuse in the community, including abuse via non-oral routes. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) has asked the Division of Epidemiology II (DEPI) to evaluate these studies and, specifically, to comment on whether the studies support the Sponsor's assertion that snorting is a relevant route of abuse for HCPs. DAAAP also asked DEPI to review and provide comment on the Sponsor's proposed postmarketing study plan to evaluate the impact of KP201/APAP's abuse-deterrent properties in community settings.

DEPI reviewed three epidemiologic study reports submitted by the sponsor, including two reports from the Addiction Severity Index—Multimedia Version (ASI-MV®) and the Comprehensive Health Assessment for Teens (CHAT®) abuse surveillance programs, which collected data from adults and adolescents being assessed for substance abuse treatment, as well as an internet survey of visitors to a peer-to-peer online drug discussion forum. In addition, DEPI reviewed four published epidemiologic studies relevant to the question of intranasal abuse of HCPs.

Overall, the studies demonstrated that oral ingestion was reported consistently as the most common route of HCP abuse, while the estimated prevalence of intranasal abuse among HCP abusers varied widely—from approximately 6% to more than 70%—depending on the characteristics of the study population, how the questions about route of abuse were asked, and the referent time frame. The available data suggest that snorting is not an uncommon route of HCP abuse in populations with more advanced opioid addiction, those with polysubstance abuse, and high-risk adolescents. However, snorting is infrequently identified as the preferred or the exclusive route for abusing HCPs, and limited data suggest that regular (a few times a week or more) intranasal HCP abuse may be uncommon. Parenteral abuse of HCPs is reported very infrequently in all populations studied. Because of the widespread availability and abuse of HCPs, even a relatively low prevalence of intranasal abuse among HCP abusers translates to large absolute numbers of individuals exposed to the potential harms associated with this behavior. The epidemiologic data are extremely limited with regard to estimating the harms associated with intranasal HCP abuse, but the totality of the available epidemiologic data, interpreted within the context of the known pharmacologic properties of HCPs, suggests that intranasal abuse of HCPs may contribute relatively little to the overall public health burden of morbidity and mortality associated with HCP abuse, misuse, and addiction.

1 INTRODUCTION

Hydrocodone combination products (HCPs) are a widely prescribed class of products formulated with hydrocodone, an opioid, in combination with a specified amount of therapeutically active non-opioid ingredients, most commonly the analgesic acetaminophen. Upon enactment of the Controlled Substances Act (CSA) in 1971, HCPs were listed as Schedule III products; however, in August 2014, the Drug Enforcement Administration (DEA) rescheduled HCPs from Schedule III to the more highly controlled Schedule II of the CSA. The new regulation went into effect on October 6, 2014.

KemPharm, Inc. (Sponsor) is currently seeking approval of KP201/APAP (benzohydrocodone and acetaminophen, NDA #208653), a prodrug immediate-release (IR) HCP formulated with properties intended to reduce abuse, particularly through the nasal route. The Sponsor has submitted experimental data to support its claim of reduced abuse potential, including tamper resistance and safety features such as reduced exposure at supratherapeutic oral doses and when isolated for parenteral administration. The Sponsor also asserts that crushed KP201/APAP tablets have lower intranasal abuse liability due to delayed and reduced bioavailability of the active drug and more severe nasal effects such as nasal irritation and burning, runny nose, congestion, and facial pain/pressure compared to crushed hydrocodone/acetaminophen tablets.

As part of the NDA submission, the Sponsor has included epidemiologic studies examining patterns of HCP abuse in the community, including abuse via non-oral routes. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) has asked the Division of Epidemiology II (DEPI) to evaluate these studies and, specifically, to comment on whether the studies support the Sponsor's assertion that snorting is a relevant route of abuse for HCPs. DAAAP also asked DEPI to review and provide comment on the Sponsor's proposed postmarketing study plan to evaluate the impact of KP201/APAP's abuse-deterrent properties in community settings.

2 REVIEW METHODS AND MATERIALS

DEPI reviewed three separate epidemiologic study reports (#1-3), and data submitted in response to FDA's Information Request (#4):

1. National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-9/30/2014
2. NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015
3. NAVIPPRO® Internet Survey Report: Use and abuse of Hydrocodone Combination Products Internet Survey 2014

4. Response to February 4, 2016 FDA Information Request (IR), received February 12, 2016.

Study reports #1 and #2 above cover different time periods but analyze data from the same two data sources, the Addiction Severity Index—Multimedia Version (ASI-MV®) and the Comprehensive Health Assessment for Teens (CHAT®) surveillance programs. In this review, we will present results of the first two study reports together (Section 3.1). The third study report contains analyses of data from a separate, internet-based survey and will be discussed separately (Section 3.2). The study reports contain results from a large number of analyses; therefore, in this review we present and discuss in detail only the findings deemed to be most relevant to the objectives of this review.

In addition, DEPI conducted a PubMed search for any epidemiologic studies relevant to the question of intranasal abuse of HCPs using combinations of the following search terms: "hydrocodone," "opioid," "snorting," "inhalation," "intranasal," "route," and "abuse." Studies included all years and were limited to human studies and to studies published in English. Identified studies are summarized and discussed briefly to provide additional context for the results of the submitted studies (Section 3.3).

Appendix B (Section 7.2) briefly presents and interprets relevant findings from a second internet study report, "NAVIPPRO Internet Survey Report: Progression of Hydrocodone Combination Products Use Internet Survey 2015," that was submitted by the Sponsor on March 17, 2016, just prior to finalization of this review.

In Section 4, we summarize and interpret all the available evidence to attempt to characterize the scope and public health relevance of intranasal HCP abuse.

Finally, in Appendix C (Section 7.3), we briefly summarize and comment on the proposed postmarketing study plan for assessing abuse of KP201/APAP and the impact of its potentially abuse-deterrent properties on abuse and related outcomes in post-approval settings. In particular, we discuss whether the proposed study plan would be likely to fulfill post-marketing requirements were abuse-deterrent labeling to be approved for KP201/APAP.

3 REVIEW RESULTS

3.1 NAVIPPRO ASI-MV AND CHAT INVESTIGATIONS

3.1.1 Study Overview

The two NAVIPPRO® Drug Abuse Surveillance Reports present data describing and characterizing abuse of HCPs among individuals assessed within the ASI-MV and CHAT networks, including analyses of routes of administration among abusers. These

surveillance programs collect information on recent abuse of prescription and illicit drugs in a large sample of individuals being assessed for substance abuse problems and treatment planning in the U.S. using the ASI-MV and CHAT proprietary computerized assessment tools. The ASI-MV population includes adults aged 18 years and older, while the CHAT program includes adolescents under 18 years old.

3.1.2 Study Methods

3.1.2.1 Data source, setting, and study populations

The National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) is a cross-sectional surveillance system that measures patterns of abuse for selected prescription and illicit drugs. The ASI-MV is a proprietary data collection instrument used in the NAVIPPRO system to collect information on substances used and abused from adults within a network of substance abuse treatment centers and other assessment settings using a self-administered, structured, computerized interview. The ASI-MV assessment captures product-specific data related to past 30-day use and abuse for over 60 brand and generic prescription opioid products using visual images of prescription opioid products, as shown below in Figure 1.

Figure 1. ASI-MV screen for hydrocodone products (updated March 2015)



Source: NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015

The Comprehensive Health Assessment for Teens (CHAT) is a computerized behavioral health assessment targeted to adolescents age 18 years and younger being assessed for treatment of drug or alcohol abuse. Similar to the ASI-MV, CHAT collects data on the use and abuse of opioids, as well as factors related to substance abuse that are specific to this younger population. Also like the ASI-MV, data related to route(s) of administration, source for obtaining the products and geographic location are collected. Questions unique to CHAT are focused on adolescent experiences in five domain areas: self and personality factors, family and peer relations, physical and emotional health, psychological issues, and drug use experiences. The CHAT network of participating sites comprises treatment centers and other facilities, such as alternative schools and mental health programs. CHAT monitors the same prescription medications tracked by ASI-MV and began data collection and surveillance in June 2009.

Sites within the NAVIPPRO systems are not randomly recruited to join the network. Therefore, results of the analyses conducted on the patient data collected from these centers may not be generalizable to all patients assessed for substance abuse treatment in the U.S. Almost half of the ASI-MV program sites are in the South U.S. census region, whereas only a tiny proportion are in the Northeast region, as shown in Table 1. During the same time period, approximately 72% of assessments in the smaller CHAT network came from sites in the state of Missouri, as shown in Table 2.

Table 1. Number of assessments within the ASI-MV by U.S. Census region, 1/1/2012-6/30/2015

Region	*n*	*%*
Northeast	9,279	4.1
South	110,703	48.9
West	52,959	23.4
Midwest	53,413	23.6

Source: NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015

Table 2. ASI-MV and CHAT networks—number of states, sites, and assessment, 1/1/2012-6/30/2015

	Total States	*Total Sites*	*Total Assessments*	*Number (%) of Assessments from Missouri*
ASI-MV	44	831	226,357	--
CHAT	26	180	12,096	8,683 (72%)

Source: NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015

Both the ASI-MV and CHAT are dynamic systems where new sites are added to the network on a regular basis and some attrition in participating sites occurs over time. In addition, changes are made periodically to the computerized ASI-MV and CHAT assessment tools. In March 2015, an update was made to the ASI-MV screens that present prescription opioid products, including the addition of new products and a change in the order of presentation of opioid product screens, as shown Table 3.

Table 3. Previous and updated ASI-MV opioid product screen order

Previous opioid product screen order (before 03/14/2015)	Updated opioid product screen order (after 03/14/2015)
1. Oxycodone ER	1. Hydrocodone
2. Oxycodone IR single-entity	2. Oxycodone IR Combination
3. Oxycodone IR combination	3. Oxycodone IR single-entity
4. Hydrocodone	4. Oxycodone ER
5. Methadone	5. Tramadol
6. Meperidine	6. Buprenorphine
7. Fentanyl	7. Morphine
8. Hydromorphone	8. Fentanyl
9. Morphine	9. Methadone
10. Oxymorphone	10. Hydromorphone
11. Tramadol	11. Oxymorphone
12. Buprenorphine	12. Tapentadol
13. Tapentadol	13. Meperidine

Source: NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015

Drug utilization data source: Prescription volume data were obtained from IMS Health Vector One National (VONA_ Pain Market Prescription Tracking database), which comprises approximately 59,000 retail pharmacies and includes cash, Medicaid, and third-party retail transactions.

3.1.2.2 Study Design

NAVIPPRO's ASI-MV and CHAT studies are ecologic time series, based on cross-sectional data and using convenience sampling.

3.1.2.3 Definition of Abuse Outcomes

Abuse is defined as any non-medical use of a prescription opioid product within the past 30 days prior to assessment, as determined by responses to a series of follow-up questions, asking whether (1) they have a current pain problem and have taken the medication as prescribed, (2) they have obtained the medication only from their own physician, and (3) they have not used the drug via an alternate route of administration (ROA). Respondents who indicate use of pharmaceutical substances are presented

follow-up questions that make specific inquiries for each product on ROA used and sources of procurement for each product.

With regard to route of administration, respondents are asked ***"How have you usually used [DRUG]? Please select all that apply,"*** followed by the following choices:

- Swallowed it whole
- Dissolved it in my mouth like a cough drop
- Chewed it, and then swallowed it
- Drank it after it dissolved in liquid
- Snorted it
- Smoked it
- Injected it with a needle into my vein
- Injected it with a needle into my skin or muscle
- Other

3.1.2.4 Study time frame

The first study report includes data from 1/1/2012-9/30/2014. The second study report focuses on the more recent time period 1/1/2014-6/30/2015, although analyses included in the appendix of the second study report present data for the entire study period of 1/1/2012-6/30/2015. For this review, data for the entire study period of 1/1/2012-6/30/2015 will be presented when available.

3.1.2.5 Target and comparator opioid products

A full list of HCP (target) and comparator opioid products is provided in ***Appendix A.*** Briefly, these include the following drug groupings:

- Hydrocodone immediate-release (IR) combination products (brand and generic formulations)
- Oxycodone IR combination products (brand and generic formulations)
- Oxycodone IR single entity (SE)
- All other IR prescription opioids (both single-entity and combination excluding Schedule III products)
- All extended-release/long-acting (ER/LA) opioids (both ADF and non-ADF products excluding patch and buprenorphine products)
- All ADF ER/LA opioids
- All non-ADF ER/LA opioid (excluding patch and buprenorphine products)

3.1.2.6 Statistical Analyses

*Please see review by the Division of Biometrics VII for full description and evaluation of statistical methods.

Calculation of Prescription Opioid Abuse Rates

Prevalence of past 30-day abuse was calculated three ways for HCPs and selected comparator opioid categories:

1. Number of abuse cases per 100 ASI-MV or CHAT assessments
2. Number of abuse cases per 100,000 prescriptions dispensed
3. Number of abuse cases per 10,000,000 morphine equivalent milligrams (MEMs) dispensed,

where the number of prescriptions dispensed was determined based on the states that contributed data to the ASI-MV or CHAT networks during the time period evaluated (i.e. January 2012 through June 2015).

For ROA and procurement source analyses, results also are presented as the percentage of individuals who report a specific ROA for a product or group of products among all individuals who reported past 30-day abuse of these products during the specified time period.

To examine changes following rescheduling of HCPs in October 2014, a log-binomial model was employed to estimates changes in linear trends in abuse of HCPs and comparator opioids from January 2012 through June 2015. Log–Poisson regression models were used to estimate compound-specific linear trends of abuse adjusted for morphine-equivalence, during each year of the study period.

3.1.3 Study Results

3.1.3.1 ASI-MV

3.1.3.1.1 Study population characteristics

Characteristics of the ASI-MV study population are shown in Table 4. The large majority of individuals were between 21 and 54 years of age, and the majority was male. Of note was that respondents reporting past 30-day prescription opioid abuse were more likely than the study sample as a whole to be entering residential, outpatient, or methadone treatment programs, with approximately 75% entering one of these types of treatment programs. Those reporting prescription opioid abuse were also more likely to have a more severe drug problem, as measured by the ASI-MV severity score.

Table 4. ASI-MV participant characteristics (1/1/2012-6/30/2015)

		All respondents (N = 226,357)		Respondents reporting any past 30-day Rx opioid abuse (n = 51,116)	
	Response	**n**	**%**	**n**	**%**
Age	Under 21 years	16,388	7.2	3,513	6.9
	21 - 34 years	117,503	51.9	30,185	59.1
	35 - 54 years	80,063	35.4	15,560	30.4
	55+ years	12,403	5.5	1,858	3.6
	Missing	0	0.0	0	0.0
Gender	Male	144,977	64.0	26,718	52.3
	Female	81,357	35.9	24,395	47.7
	Unknown/no response	20	< 1.0	3	< 1.0
Race	Caucasian	140,594	62.1	38,875	76.1
	African American	41,757	18.4	5,336	10.4
	American Indian/Alaskan Native	11,494	5.1	1,475	2.9
	Asian	1,722	< 1.0	257	< 1.0
	Hispanic/Latino	29,952	13.2	5,005	9.8
	Other race	821	< 1.0	166	< 1.0
	Unknown/no response	17	< 1.0	2	0.0
Marital status	Married	43,512	19.2	10,114	19.8
	Separated, divorced, widowed	52,636	23.3	11,728	22.9
	Never married	129,626	57.3	29,113	57.0
	Unknown/no response	583	< 1.0	161	< 1.0
Employment	Professional	24,262	10.7	5,069	9.9
	Administrative, clerical, sales	28,709	12.7	6,866	13.4
	Skilled or semi-skilled	70,362	31.1	14,604	28.6
	Student	9,708	4.3	1,695	3.3
	Homemaker	11,299	5.0	3,613	7.1
	Other manual/unskilled	23,903	10.6	5,186	10.1
	Did not work for pay in last 3 years	15,262	6.7	3,717	7.3
	Disabled	13,676	6.0	3,937	7.7
	No occupation	28,260	12.5	6,234	12.2
	Unknown/no response	916	< 1.0	195	< 1.0
Criminal justice system prompted substance abuse treatment*	Yes	135,775	60.0	18,467	36.1
	No	90,152	39.8	32,533	63.6
	Unknown/no response	430	< 1.0	116	< 1.0
Chronic medical problem	Yes	66,576	29.4	20,176	39.5
	No	159,296	70.4	30,832	60.3
	Unknown/no response	485	< 1.0	108	< 1.0
Self-reported pain problem	Yes	73,995	32.7	25,405	49.7
	No	152,038	67.2	25,641	50.2
	Unknown/no response	324	< 1.0	70	< 1.0
Treatment Modality	Residential/Inpatient	53,550	23.7	22,675	44.4
	Outpatient/non-Methadone	63,155	27.9	12,773	25.0
	Methadone/LAAM	5,200	2.3	2,523	4.9
	Drug Court	6,874	3.0	783	1.5
	Probation/Parole	37,324	16.5	4,998	9.8
	DUI/DWI	21,013	9.3	1,173	2.3
	Other Corrections	3,971	1.8	422	< 1.0
	TANF (Welfare)	3,207	1.4	414	< 1.0
	Other	28,864	12.8	4,456	8.7
	Unknown/no response	3,199	1.4	899	1.8
Drug Severity‡	0-1	87,946	38.9	5,066	9.9
	2-3	23,313	10.3	3,238	6.3
	4-5	31,007	13.7	6,282	12.3
	6-7	55,326	24.4	18,963	37.1
	8-9	24,218	10.7	15,823	31.0
	Unknown/no response	4,547	2.0	1,744	3.4

*"Criminal justice system prompted substance abuse treatment" indicates that admission to substance abuse treatment was required or encouraged of the respondent by a judge, probation or parole officer, or other criminal justice official.

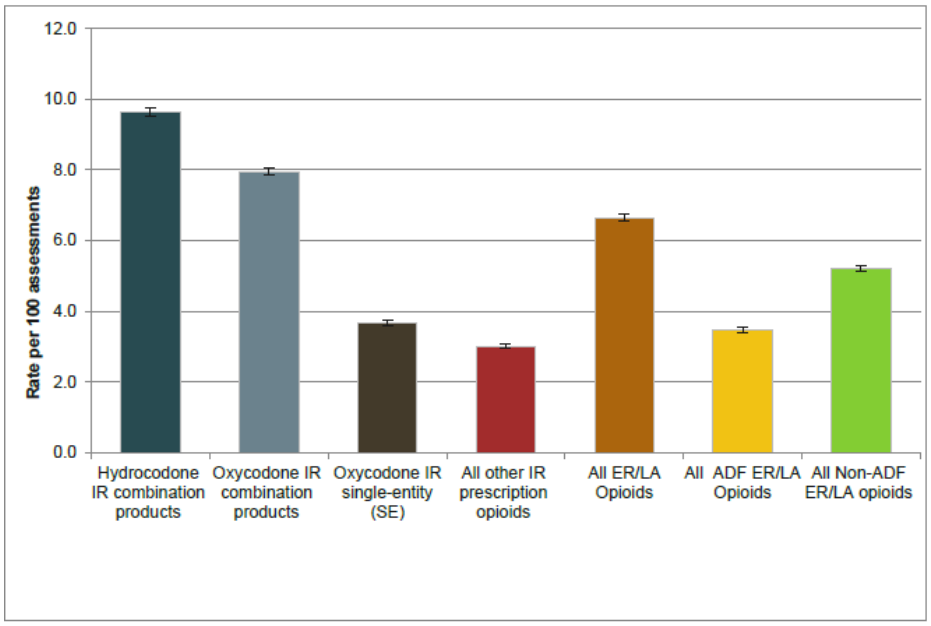
‡ASI-MV severity score category definitions include 0-1: No real problem, treatment not indicated; 2-3: Slight problem, treatment probably not indicated; 4-5: Moderate problem, some treatment indicated; 6-7: Considerable problem, treatment necessary; 8-9: Extreme problem, treatment absolutely necessary.

Source: NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015

3.1.3.1.2 Prevalence of abuse of HCPs and comparator opioids

Figure 2 below demonstrates that HCPs are the most commonly reported drug of abuse among those being assessed for substance abuse treatment within the ASI-MV network, with 9.6% (95% CI 9.5% - 9.7%) reporting abuse of HCPs in the past 30 days.

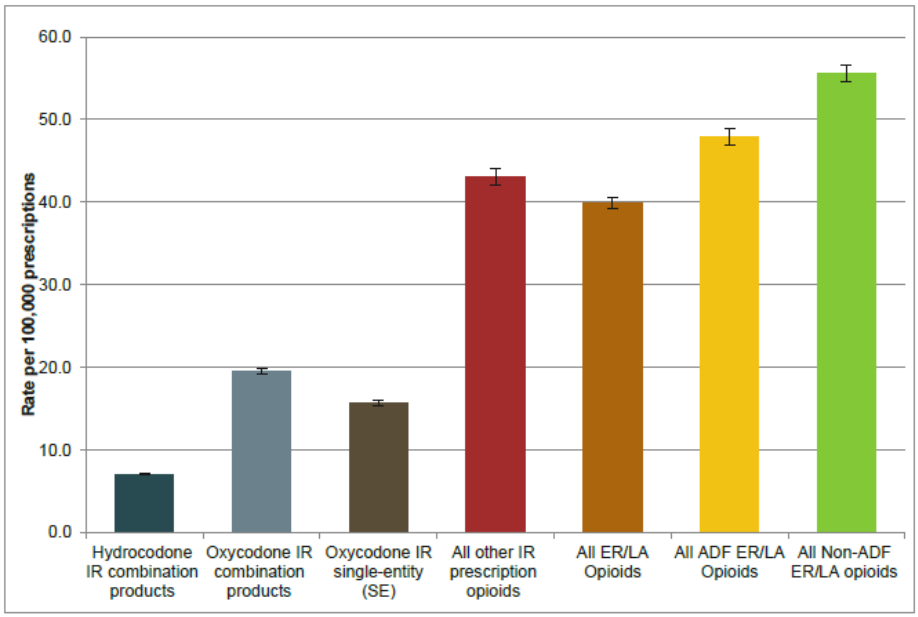
Figure 2. Past 30-day abuse per 100 assessments for hydrocodone combination products and comparator opioids within the ASI-MV network (1/1/2012-6/30-2015)



Source: NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015

However, when adjusted for the number of prescriptions dispensed, HCPs have the lowest abuse rates among the opioid product groups analyzed (Figure 3).

Figure 3. Past 30-day abuse per 100,000 prescriptions dispensed for hydrocodone combination products and comparator opioids within the ASI-MV network (1/1/2012-6/30-2015)



Source: NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015

Table 5 below indicates that of the 21,796 assessments in which HCP abuse was reported, 9,262 (42.4%) reported HCP abuse only. The data below also suggest that, compared to those who abuse only HCPs, those who abuse HCPs in addition to other opioids have indicators of more severe opioid use disorders, including a higher likelihood of being assessed in a substance abuse treatment setting, considering opioids their primary problem substance, higher addiction severity scores, and a higher prevalence of illicit drug use. The large majority of past 30-day HCP abusers also reported past 30-day illicit drug or alcohol abuse.[1]

[1] Past 30-day abuse of at least one of the following substances: heroin, methadone, barbiturates, sedatives, cocaine/crack, amphetamines, marijuana, hallucinogens, inhalants, and/or past 30-day abuse of alcohol.

Table 5. Severity of drug problem indicators among those reporting hydrocodone combination products as the only opioid abused and among those indicating abuse of one or more additional opioids, 1/1/2012-6/30/2015

		Hydrocodone combination product abuse only (n = 9,262)	Hydrocodone combination product and one or more other opioid abuse (n = 12,534)
	Response	**%**	**%**
Expected Treatment Modality	Residential/Inpatient	31.3	56.4
	Outpatient/non-Methadone	30.9	22.9
	Methadone	2.5	3.4
	Corrections*	20.5	7.8
	Other	14.6	9.5
Considering all the alcohol and drugs you use, how would you rank the opiate pain medications you selected? ∓	Primary problem	18.6	55.3
	Secondary problem	11.0	17.5
	Tertiary problem	6.3	7.2
	Not a problem for me	62.5	19.5
	No response	1.5	< 1.0
Drug severity rating ∓∓	0-1: No real problem, treatment not indicated	23.1	3.1
	2-3: Slight problem, treatment probably not necessary	9.6	2.7
	4-5: Moderate problem, some treatment indicated	14.8	7.9
	6-7: Considerable problem, treatment necessary	31.3	34.0
	8-9: Extreme problem, treatment absolutely necessary	18.3	48.2
	No response	2.8	4.0
Illicit drug use**	Yes	79.5	92.4
	No	20.5	7.6

* Corrections represents individuals assessed by the ASI-MV who were evaluated in one of the following settings: drug court, probation/parole, DUI/DWI, or other corrections

** Past 30-day abuse of at least one of the following substances: heroin, methadone, barbiturates, sedatives, cocaine/crack, amphetamines, marijuana, hallucinogens, inhalants, and/or past 30-day abuse of alcohol.

∓ Ranking of problem with opiate pain medication is based on self-report by individual respondents at the time of assessment.

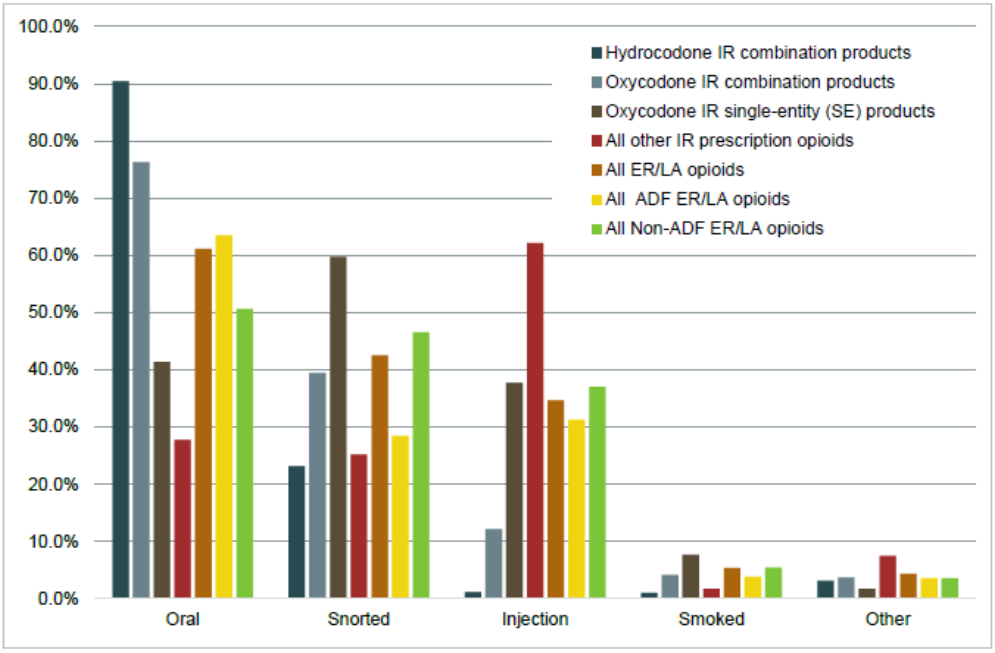
∓∓ Drug severity rankings are calculated estimates of problem status based on several items measured from the ASI-MV interview regarding drug use, duration of use, and current need for treatment.

Source: NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015

3.1.3.1.3 Route of abuse for HCPs and comparator opioids

Figure 4 depicts the ROA for HCPs and comparator opioids among individuals reporting abuse of those products in the past 30 days. Of those individuals indicating past 30-day abuse of an HCP, oral routes were by far the most common ROA, but 23.3% reported snorting HCPs. In comparison, 39%, 58.1%, and 41.3% of abusers reported snorting oxycodone IR combination products, oxycodone IR single-entity (SE) products, and extended-release/long-action (ER/LA) opioids, respectively. The percentage of HCP abusers reporting injecting, smoking, or other ROAs was extremely small. Because respondents could report multiple ROAs for a product or product group, percentages do not add to 100%.

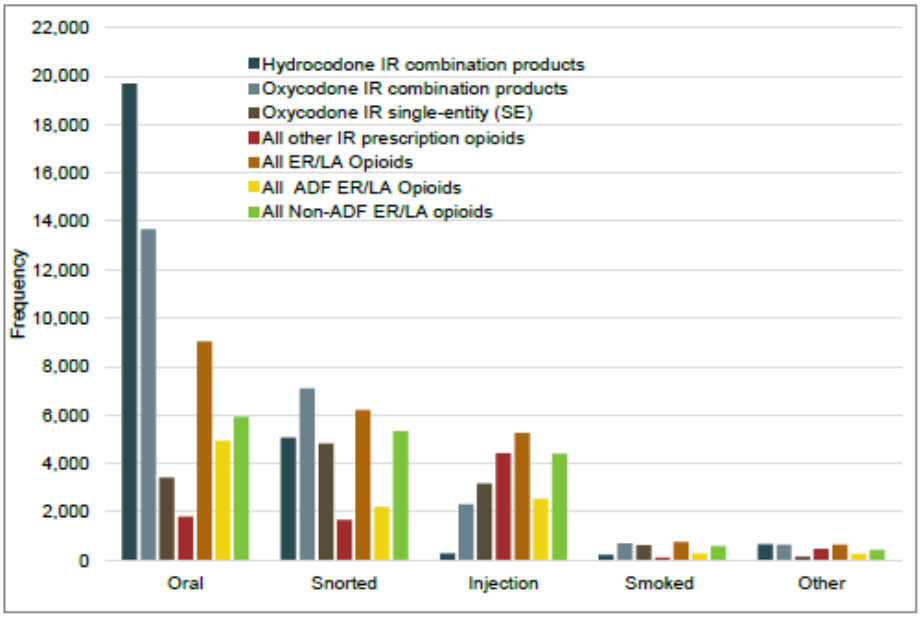
Figure 4. Route of administration for hydrocodone IR combination products and comparator opioids within the ASI-MV network (1/1/2012-6/30/2015)



Source: NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015

Figure 5 below shows the total number of ASI-MV assessments indicating abuse of HCPs and comparator opioids, by ROA, during the study period 1/1/2012 – 6/30/2015. Again, oral abuse of HCPs and oxycodone IR combination products account for the greatest number of abuse reports. However, the absolute number of individuals reporting snorting HCPs (5,071) was similar to the number reporting snorting oxycodone IR SE products (4,812), and non-ADF ER/LA opioid products (5,326).

Figure 5. Frequency of abuse by route of administration for hydrocodone IR combination products and comparator opioids within the ASI-MV network (1/1/2012-6/30/2015)



Source: NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015

The percentage of HCP abusers who report abuse via snorting varied widely within the ASI-MV network, depending on the setting in which the individual is being assessed and on whether HCPs are the only opioid abused in the past 30 days (Table 6).

Table 6. Abuse of HCPs via snorting, by treatment modality and combination with other opioids within the ASI-MV network (1/1/2012- 6/30/2015)

	Total number of past 30-day HCP abusers	Number reporting past 30-day HCP abuse via snorting	Percent of HCP abusers who report past abuse via snorting
Residential/inpatient	9,968	2,877	28.9%
Outpatient/non-methadone	5,732	1,300	22.7%
Methadone	657	133	20.2%
Corrections	2,877	329	11.4%
Other	2,543	432	17.0%
Abused only HCPs past 30 days	9,262	903	9.7%
Abused HCPs and ≥1other opioid past 30 days	12,534	4,168	33.3%

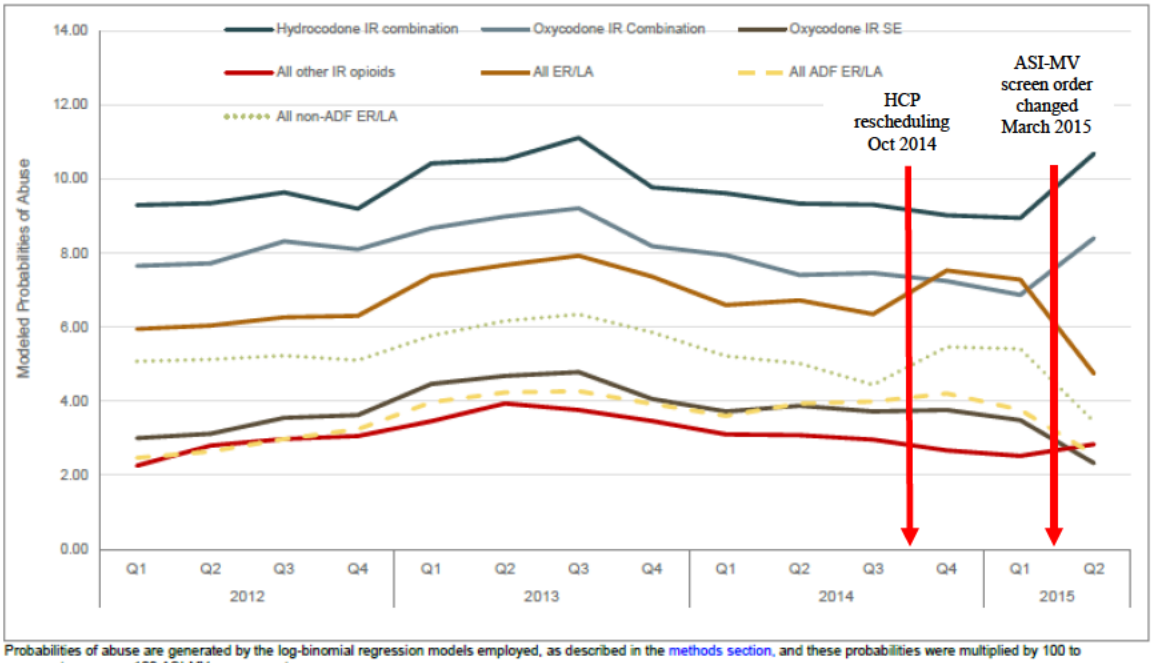
Source: Table based on data contained in NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015 and IR response, received 2/12/16.

Those who report HCP abuse via snorting tend to have higher drug severity ratings, compared to those who abuse HCP orally. Among those who report abusing HCPs via snorting, 85% are determined to have a "considerable" or "extreme" drug problem, as compared to 69.1% of those who report oral HCP abuse, based on multiple items measured in the ASI-MV interview regarding drug use, duration of use, and current need for treatment. In addition, 82.2% of those indicating HCP abuse via snorting also reported abusing one or more other opioid products, and 78.3% reported abusing one or more other opioid products *and* one or more illicit drugs. For those indicating oral HCP abuse, these percentages were considerably lower, 55.5% and 51.3% respectively (data not shown).

3.1.3.1.4 Trend analyses

Figure 6 depicts trends in abuse prevalence for HCPs and comparator opioids within the ASI-MV network. Overall, the rank order of opioids remained fairly stable across the time period. However, changes in abuse estimates are seen immediately following the changes made to the order of drugs in the ASI-MV assessment tool in March 2015, with the abuse estimates for drugs that were moved to earlier screens (HCP and oxycodone IR combination) increasing, and drugs that were moved to later screens (ER/LA opioids, e.g. oxycodone ER and methadone) decreasing.

Figure 6. Modeled trend analysis estimates for past 30-day abuse per 100 ASI-MV assessments (1/1/2012-6/30/2015)



Probabilities of abuse are generated by the log-binomial regression models employed, as described in the methods section, and these probabilities were multiplied by 100 to represent cases per 100 ASI-MV assessments.

Source: NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015

3.1.3.2 CHAT

3.1.3.2.1 Study population characteristics

Table 7 shows the characteristics of the CHAT study population. The large majority of participants was 15-18 years old, and most were male. More than one third had been living in a controlled environment such as a juvenile justice center or substance abuse treatment center in the past 30 days, and almost one third were currently taking medication for an emotional or behavioral problem.

Table 7. CHAT participant characteristics (1/1/2012-6/30/2015)

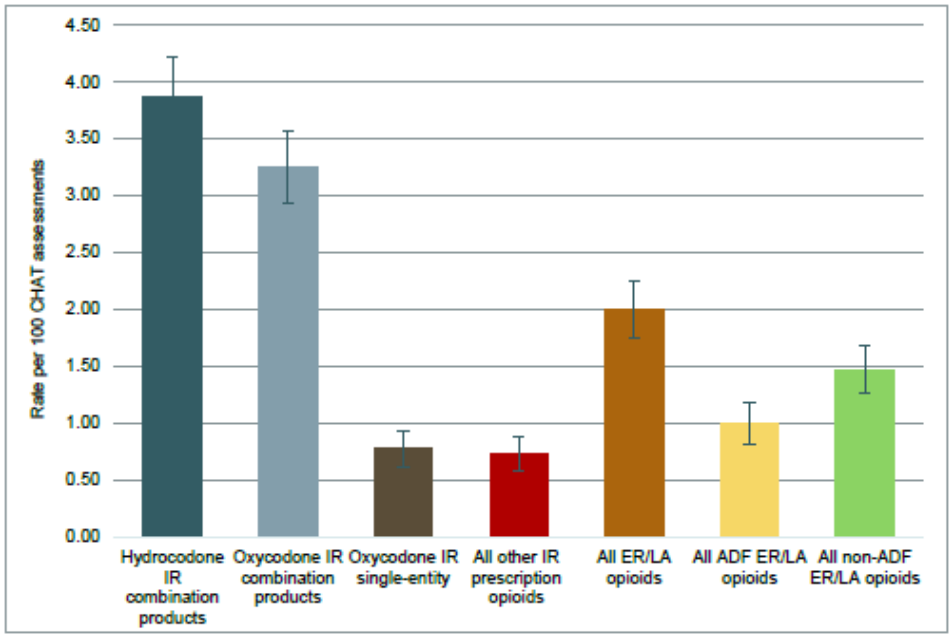
	Response	Number (N = 12,096)	Percent (%)
Age	Age distribution		
	Under 10 years	24	< 1.0
	10 - 14 years	2,378	19.7
	15 - 18 years	9,626	79.6
	Over 18 years	68	< 1.0
Gender	Male	8,255	68.2
	Female	3,841	31.8
	Unknown/no response	0	0.0
Race (not mutually exclusive)	Caucasian	8,206	67.8
	African American	2,629	21.7
	American Indian/Alaskan Native	624	5.2
	Asian	123	1.0
	Pacific Islander/Native Hawaiian	52	< 1.0
	Hispanic/Latino	1,419	11.7
	Middle Eastern	40	< 1.0
	Other Race	498	4.1
	Unknown/no response	11	< 1.0
Current living situation	One or both biological or adoptive parents	9,655	79.8
	Other relatives	720	6.0
	Legal guardian	737	6.1
	Friends	126	1.0
	Partner or spouse	40	< 1.0
	Foster family	358	3.0
	Alone	39	< 1.0
	Other	415	3.4
	Unknown/no response	6	< 1.0
Currently enrolled in school	Yes	10,072	83.3
	No	2,024	16.7
School program (n = 10,072)	Public school	7,297	72.4
	Private school	184	1.8
	GED program	258	2.6
	Alternative school or program	1,590	15.8
	Home school	189	1.9
	Technical, trade/beauty, vocational school	63	< 1.0
	Treatment or detention center	283	2.8
	College	72	< 1.0
	Other	129	1.3
	Unknown/no response	7	< 1.0
Past 30 days in a controlled environment (juvenile justice center, substance abuse treatment, etc.)	Yes	4,237	35.0
	No	7,853	64.9
	Unknown/no response	6	< 1.0
Currently taking medication for emotional, behavioral, or learning problems.	Yes	3,901	32.3
	No	8,169	67.5
	Unknown/no response	26	< 1.0
Current physical problems or illnesses	Yes	3,432	28.4
	No	8,664	71.6
	Unknown/no response	0	0.0
Current pain problem	Yes	2,357	19.5
	No	9,718	80.3
	Unknown/no response	21	< 1.0

Source: NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015

3.1.3.2.2 Prevalence of abuse of HCPs and comparator opioids

Figure 7 shows the prevalence of abuse for HCPs and comparator opioids within the CHAT network during the study period. Similar to the ASI-MV study, HCPs are the most prevalent drugs of abuse, followed by oxycodone IR combination products.

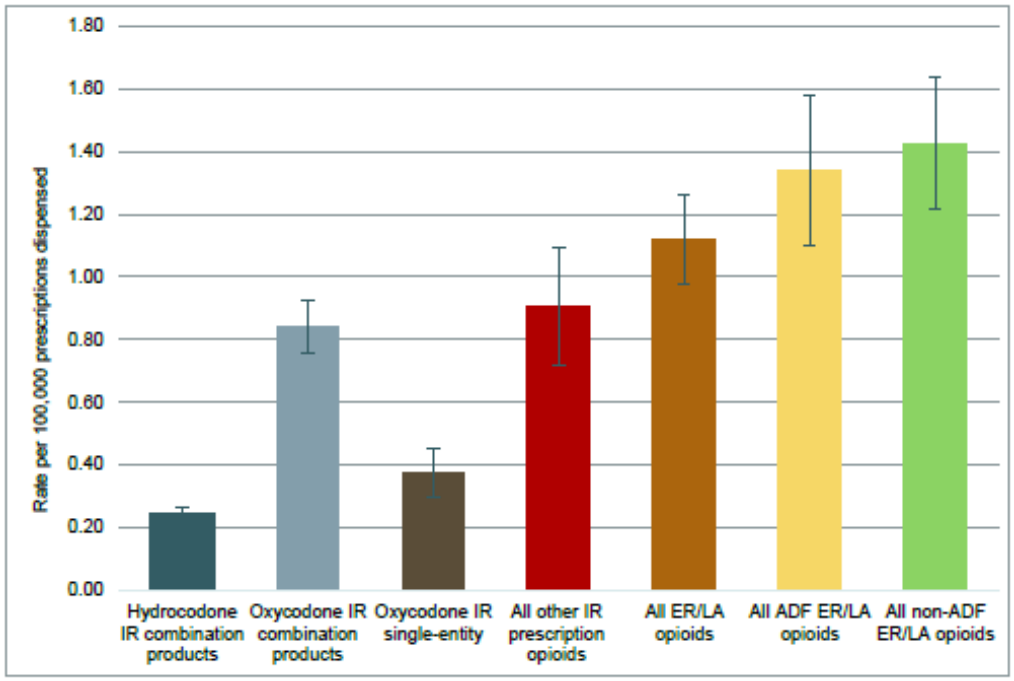
Figure 7. Past 30-day abuse per 100 assessment for hydrocodone IR combination products and comparator opioids within the CHAT network (1/1/2012-6/30/2015)



Source: NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015

Figure 8 shows the prescription volume-adjusted abuse estimates for HCPs and comparator opioids in the CHAT network. Again, after adjusting for the larger prescription volume of HCPs, these estimates are the lowest of all the opioid product groups.

Figure 8. Past 30-day abuse per 100,000 prescriptions for hydrocodone IR combination products and comparator opioids within the CHAT network (1/1/2012-6/30/2015)

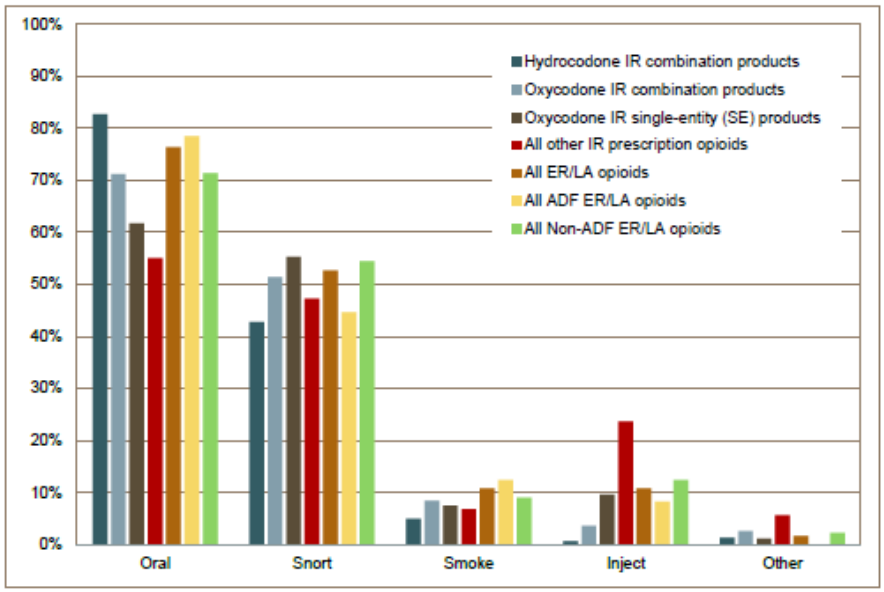


Source: NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015

3.1.3.2.3 Route of abuse for HCP and comparator opioids

Figure 9 shows the ROA profile for HCP and comparator products, among those who report past 30-day abuse of an opioid in each product grouping. The percentage of HCP abusers in CHAT who reported snorting the drug (42.7%) was higher than in the ASI-MV population, and unlike in the ASI-MV was only slightly lower than the percentage reporting intranasal abuse of other opioids in this analysis. The percentage of HCP abusers reporting smoking, injecting, and other ROAs remained very low.

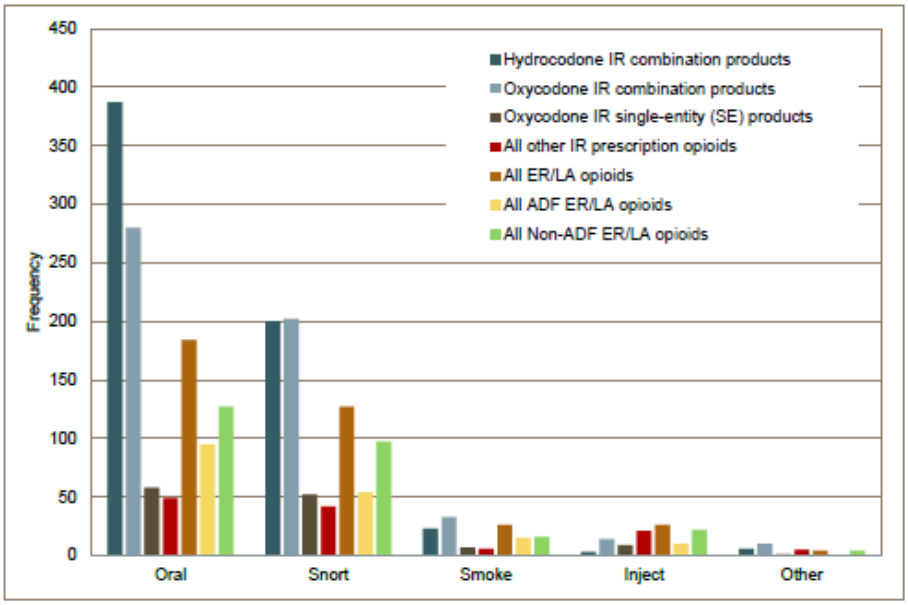
Figure 9. Percent of abusers of HCPs and comparator opioids within the CHAT network reporting abuse of that product by specific routes of administration (1/1/2012-6/30/2015)



Source: NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015

Figure 10 shows the total numbers of CHAT assessments in which abuse of HCPs and comparator opioids was reported during the study period, by ROA. Here, intranasal abuse of both HCPs and oxycodone IR combination products was higher, in absolute terms, than intranasal abuse of any other opioid grouping.

Figure 10. Frequency of abuse by route of administration for hydrocodone IR combination products and comparator opioids within the CHAT network (1/1/2012-6/30/2015)

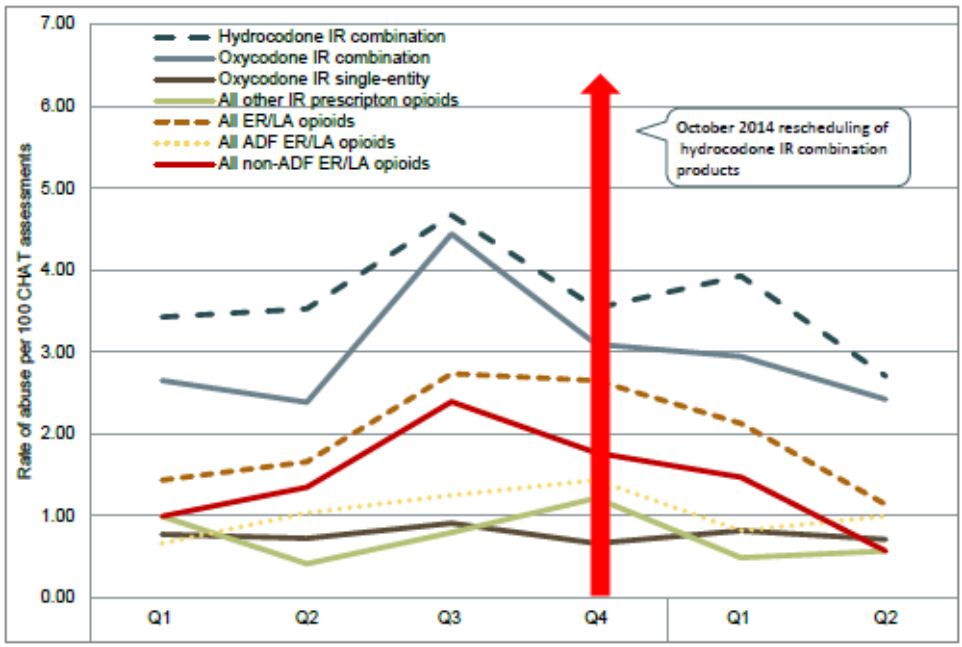


Source: NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015

3.1.3.2.4 Trend analyses

Figure 11 shows quarterly past 30-day abuse estimates for HCPs and comparator opioids within the CHAT network before and after the October 2014 rescheduling of HCPs. Due to the smaller sample size in CHAT, quarter-to-quarter variability was greater than in the ASI-MV data. Unlike in the ASI-MV, which showed increases in abuse estimates for both HCPs and oxycodone IR combination products, increases were not seen for any opioids in the CHAT study.

Figure 11. Past 30-day abuse per 100 assessment for hydrocodone IR combination products and comparator opioids within the CHAT network by quarter (1/1/2012-6/30/2015)



Source: NAVIPPRO® Drug Abuse Surveillance Report: Analysis of Data for Hydrocodone Combination Products 1/1/2012-6/30/2015

3.1.4 DEPI Comments on the NAVIPPRO ASI-MV and CHAT Studies

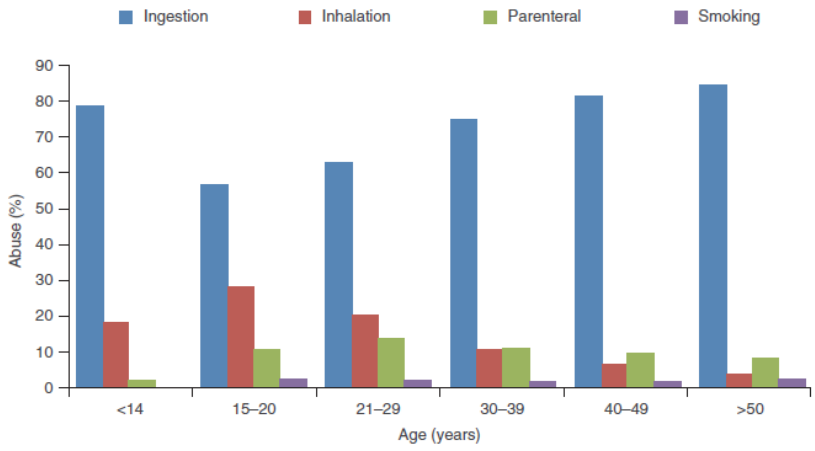
Both the ASI-MV and CHAT studies suggest that, among individuals being assessed for substance abuse problems in a variety of settings, HCPs are the most commonly abused prescription opioids, with 9.6% reporting past 30-day abuse of HCPs in the ASI-MV network and a smaller proportion (3.9%) in the CHAT network. This finding is not surprising, given the widespread availability of HCPs, as well as the documented widespread misuse and abuse that led to the CSA rescheduling of these products in 2014.

Among past 30-day abusers of HCPs, 23.3% of adults assessed in the ASI-MV network and 42.7% of adolescents assessed in the CHAT network reported snorting the drug,

either as the only route or in combination with other ROAs. However, oral abuse was the dominant ROA for HCP abuse in both populations. In the CHAT program, the proportion of HCP abusers who reported snorting was fairly similar to the proportion reporting snorting as a route of abuse for other prescription opioids, which ranged from 44.6% to 55.3%. In the ASI-MV study, the proportion of HCP abusers reporting use via snorting was considerably lower than the proportion of abusers of other prescription opioids who reported snorting as a route of abuse. However, because of the high prevalence of HCP abuse in this population relative to other prescription opioids, the absolute number of respondents who reported snorting HCPs was similar to the number who reported snorting IR combination oxycodone, IR single-entity oxycodone, or ER/LA opioids.

The higher prevalence of snorting among HCP abusers in the CHAT study, as compared to the ASI-MV, is not surprising. Previous work has found that, among individuals entering publically-funded substance abuse treatment programs, those aged 15-20 years were the most likely to report snorting prescription opioid analgesics, as shown in Figure 12 below.

Figure 12. Route of abuse of prescription opioid analgesics according to age—2006 Substance Abuse and Mental Health Services Administration, Treatment Episode Data Set (TEDS).



Source: Katz et al., 2011

The prevalence of snorting among HCP abusers within the ASI-MV network varied considerably by treatment modality, ranging from 11.4% - 28.9%. Snorting prevalence was also substantially lower among those reporting HCPs as the exclusive opioids abused (9.7%), compared to among those abusing HCPs in addition to at least one other prescription opioid (33.3%).

The ASI-MV and CHAT studies provide potentially valuable information on route of abuse for HCPs and other opioids. However, the outcome metric used for measuring the prevalence of the various routes of abuse in the ASI-MV and CHAT assessments is not

well defined. In the assessment, those indicating past 30-day use of HCPs or other drugs are prompted to answer the following question: "*How have you usually used [DRUG]? Please select all that apply*," followed by a number of choices, including "Snorted it." Respondents might easily be confused by the seemingly contradictory requests to indicate the route most commonly used ("usually"), and the instructions to "select all that apply." It is also unclear what the referent time period is for this question. We are not aware of work that has been completed to evaluate the validity of this aspect of the ASI-MV and CHAT assessments.

Relative to recreational prescription opioid abusers in general, the ASI-MV and CHAT study populations represent a high-risk subgroup enriched with individuals with more advanced addiction and social disruption, resulting in criminal justice referrals, engagement with social service agencies, and entry into substance abuse treatment programs. It is difficult to know to what degree the abuse patterns in this population reflect abuse patterns in the larger population of prescription opioid abusers. It seems possible that, in both these populations, the proportion of HCP abusers who abuse HCPs via snorting could be substantially different from that in a broader population of recreational drug abusers.

The ASI-MV and CHAT program also lack generalizability even to those being assessed for substance abuse nationally in that the geographic distribution of the study samples do not reflect the geographic distribution of the U.S. population or of substance abuse assessment or treatment sites. Approximately 65% of the CHAT assessments, for example, occurred in the state of Missouri, and therefore, results will be heavily weighted toward abuse patterns occurring in that state. Compared to the U.S. population distribution, the ASI-MV has less representation from the Northeast and more from the South.[2] Because drug abuse patterns have been shown to vary considerably by geographic region and degree of urbanization (Young et al., 2010), estimates from these studies, including the relative abuse prevalence of various drugs and routes of abuse, may not reliably reflect those in the larger population of individuals being assessed for substance abuse nationally.

For several reasons, the analyses conducted to assess changes in abuse estimates following the rescheduling of HCPs in October 2014 are problematic. First, it appears that the trends may be confounded by changes in the order in which opioid products are presented in the ASI-MV assessment, with both HCPs and oxycodone IR combination products showing increasing abuse prevalence after being moved to earlier screens in the computerized assessment in March 2015. Similar increases were not seen in the CHAT program, although it was unclear whether this program underwent the same assessment

[2] http://www.census.gov/

modifications at this time. Second, because both the ASI-MV and CHAT networks are convenience samples that change over time, shifts in the study populations can affect abuse trends as well. For example, shifts in site characteristics, such as geographic region and treatment modality, can affect abuse patterns over time, making it difficult to determine the effect of any particular intervention on abuse rates without somehow accounting for these shifts.

3.2 NAVIPPRO INTERNET SURVEY REPORT

3.2.1 Study Overview

In this study, investigators conducted an anonymous web-based survey of individuals who participate in peer-to-peer online discussions of various drugs on the Bluelight.org website, inquiring about lifetime and current abuse of HCPs and other opioids.

3.2.2 Study Methods

3.2.2.1 Data source, Setting, and Study Population

This report presents data from a novel survey offered to visitors to a popular online drug discussion forum, Bluelight.org, specifically targeting non-medical prescription opioid users. The purpose of the survey was to characterize non-medical use of hydrocodone IR combination products among a subgroup of abusers who visit such online drug forum websites. Bluelight.org describes itself as "an international, online harm-reduction community, committed to reducing the harm associated with drug use. Bluelight neither condones nor condemns the use of drugs."[3]

On Bluelight.org's homepage, site visitors are invited to participate in a 5-10 minute survey "to help fund Bluelight," with the following link to the informed consent and survey: *Have you ever used hydrocodone IR combination products?*[4] The survey was adapted from similar internet-based surveys created for use in other studies investigating prescription opioid abuse and misuse (Katz et al., 2008).

To be eligible to participate, individuals must have met the following criteria: (1) ability to read and understand English; (2) visit Bluelight.org or been directed to Bluelight.org for the purposes of taking the survey; (3) be willing to "agree" to participate in the survey; and (4) be at least 18 years of age. Respondents residing outside the U.S. were excluded for this analysis.

[3] http://bluelight.org/vb/content/128-BLUELIGHT-ORG-Reducing-Harm-by-Educating-the-Individual

[4] http://bluelight.org/vb/content/

3.2.2.2 Study Design

This is a cross-sectional study, using convenience sampling.

3.2.2.3 Abuse outcome definitions

No information was provided regarding definitions or validation of abuse outcomes, routes of abuse, etc.

3.2.2.4 Study timeframe

Participants were recruited between December 2014 and March 2015.

3.2.2.5 Statistical Analyses

Descriptive statistics were reported, using frequency and percentage for categorical variables and mean, standard deviation and range for continuous variable. The sponsor stated that 95% Confidence Intervals (CIS) would be reported where appropriate; however none were included in the submitted study report. Data analyses were carried out suing IBM SPSS Statistics 20.0 (IBM Corp., Armonk, New York. USA).

3.2.3 Study Results

3.2.3.1 Survey response rate and description of survey participants

Of the 634 individuals who viewed the survey consent form, 631 agreed to participate, 461 met eligibility criteria (>18 years old and U.S. resident), and 319 completed the survey. Of these, 307 reported using one or more opioids in their lifetime. Three participants had discrepancies in their age and year of birth responses, resulting in an analytic sample of 304 individuals.

As shown in Table 8, the majority of participants were 21-34 years old, with a fifth being under 21 years of age and only about one fourth of participants being over 34 years old. More than two thirds of participants were male. Geographic distribution was fairly similar to that of the U.S. population overall.[5]

[5] http://www.census.gov/

Table 8. Demographic characteristics of survey participants (N=304), NAVIPPRO Internet Survey

		Survey participants	
Category	**Response**	**n**	**%**
Age	Under 21 years	61	20.1
	21 - 34 years	161	53.0
	35 - 54 years	66	21.7
	55 + years	16	5.3
Gender	Male	216	71.1
	Female	82	27.0
	Other	1	< 1.0
	Prefer not to answer	5	1.6
Race	White	258	84.9
	Black or African-American	4	1.3
	Hispanic or Latino	5	1.6
	American Indian	2	< 1.0
	Alaskan Native	1	< 1.0
	Asian	2	< 1.0
	Other or multi-racial	21	6.9
	Prefer not to answer	11	3.6
Region*	Northeast	63	20.7
	South	100	32.9
	Midwest	66	21.7
	West	75	24.7
Education	Less than High School	6	2.0
	High School/GED	48	15.8
	Some College	122	40.1
	2-Year College Degree (Associates)	35	11.5
	4-Year College (BA, BS)	59	19.4
	Master's Degree	22	7.2
	Doctoral Degree	8	2.6
	Prefer not to answer	4	1.3
Current employment status	Full-time student	67	22.0
	Employed full-time	105	34.5
	Employed part-time (not a part-time student)	25	8.2
	Employed contractually	12	3.9
	Unemployed	43	14.1
	Retired	6	2.0
	Disability	16	5.3
	Other	21	6.9
	Prefer not to answer	9	3.0

Source: NAVIPPRO® Internet Survey Report: Use and abuse of Hydrocodone Combination Products Internet Survey 2014

3.2.3.2 Lifetime users of HCPs and other prescription opioids

Table 9 further characterizes the study population in terms of their reasons for using prescription opioid products during their lifetime. Although 58.2% of respondents indicated that they had used these drugs as prescribed for medical reasons, 71% reported use of opioids not prescribed for them for reasons other than pain. Almost half (48%) of lifetime prescription opioid users reported using prescription opioids via a route other than the intended route (e.g. snorted, injected) and 36.5% reported attempting to extract the active ingredient.

Table 9. Reasons for lifetime use of prescription opioid products, NAVIPPRO Internet Survey

Reasons* for use (N=304)	n	%
Prescribed to me for medical reasons and used as prescribed only	177	58.2
Prescribed to me for medical reasons but used a higher dose than was prescribed	206	67.8
To relieve pain but it was not prescribed to me	163	53.6
Prescribed to me for reasons other than the pain it was prescribed for (e.g., to relax, feel less stressed, feel more outgoing, to get high or stoned)	90	29.6
Not prescribed to me and used it for reasons other than pain (e.g., to relax, feel less stressed, feel more outgoing, to get high or stoned)	217	71.4
Via an alternate route (e.g., snorted, injected, or other route not intended)	146	48.0
By attempting to extract the active ingredient	111	36.5
To avoid or relieve withdrawal symptoms	132	43.4
To taper use of prescription or illicit drugs	89	29.3
To enhance the effect of prescription or illicit drugs	98	32.2
To enhance the effect of alcohol	58	19.1
In combination with prescription or illicit drugs	172	56.6
To ease comedown from using prescription or illicit drugs	94	30.9
Other reasons[Ŧ]	12	3.9
Prefer not to respond	2	< 1.0

* Response options are not mutually exclusive. Therefore, individual response categories may sum to greater than total sample.
Ŧ Respondents that selected the 'Other' response option were provided a text box to enter their own response option. These responses were manually sorted (if applicable) into one of the other response option categories.

Source: NAVIPPRO® Internet Survey Report: Use and abuse of Hydrocodone Combination Products Internet Survey 2014

Of the 304 participants, 288 (94.7%) indicated that they used HCPs in their lifetime. Among those participants reporting lifetime use of a HCP, most (59.7%) reported their age at first prescription opioid use to be between 14 and 18 years of age, and 13 (7.3%) reported first using the product via an alternate route (e.g. snorted, injected, or other route not intended).

Of the total 288 lifetime users of HCPs, 210 (72.9%) reported using the drugs non-medically (other than as prescribed for medical reasons) at some point in their lives. Table 9 describes the lifetime and preferred routes of administration of HCPs among these non-medical users. Almost all (96.2%) non-medical users of HCPs reported having ever swallowed the pills whole, while 44.8% reported chewing, 36.2% drinking in solution, and 34.3% snorting. Only 3.8% reported ever injecting HCPs. When asked to select a single preferred route of administration for HCPs, 58.6% chose swallowing whole, 11.4% chewing, 9.5% drinking in solution, and 6.7% snorting. Only four respondents (1.9%) preferred injecting HCPs.

Table 10. Lifetime and preferred routes of administration used for hydrocodone IR combination products among non-medical users of HCPs, NAVIPPRO Internet Survey

n = 210	Response	n	%	Lower 95% CI	Upper 95% CI
Routes of administration used for hydrocodone IR combination products in lifetime	Swallowed whole	202	96.2	93.6	98.8
	Chewed	94	44.8	38.0	51.5
	Buccal (in cheek)	10	4.8	2.3	8.8
	Sublingual (under tongue)	28	13.3	8.9	19.3
	Drank in solution	76	36.2	29.7	42.7
	Parachuted*	62	29.5	23.4	35.7
	Snorted	72	34.3	27.9	40.7
	Injected	8	3.8	1.6	7.5
	Smoked	5	2.4	0.8	5.5
	Rectal (plugging)	18	8.6	5.1	13.5
	Other route	7	3.3	1.3	6.9
	Prefer not to respond	2	1.0	0.1	3.4
Preferred route of administration for hydrocodone IR combination products**	Swallowed whole	123	58.6	51.9	65.2
	Chewed	24	11.4	7.3	17.0
	Buccal (in cheek)	1	0.5	0.0	2.7
	Sublingual (under tongue)	3	1.4	0.3	4.2
	Drank in solution	20	9.5	5.8	14.7
	Parachuted*	9	4.3	2.0	8.1
	Snorted	14	6.7	3.6	11.2
	Injected	4	1.9	0.5	4.9
	Smoked	0	0.0	0.0	0.0
	Rectal (plugging)	3	1.4	0.3	4.2
	Other route	7	3.3	1.3	6.9
	Prefer not to respond	2	1.0	0.1	3.4

*Parachuted: rolled powdered or crushed tablet in a piece of toilet paper to ingest.
**Response options are mutually exclusive

Source: NAVIPPRO® Internet Survey Report: Use and abuse of Hydrocodone Combination Products Internet Survey 2014

One-hundred eighty-eight participants (61.8%) reported that the *first* prescription opioid product they ever used was a HCP. In this group, most (59.6%) reported their age at first prescription opioid use to be between 14 and 18 years of age. About half (51.6%) indicated non-medical use of the product during first use. Within this group, 5.2% indicated that they first snorted the HCP. In contrast, 16% of first lifetime non-medical users of oxycodone combination products reported first snorting the product (data not shown).

3.2.3.3 Current users of HCPs

Among the 288 lifetime users of HCPs, 113 (39.2%) responded that they were still using HCPs, with 14 (12.4%) of current users reporting use only as prescribed for medical reasons. Among current users of HCPs, 14 (12.4) reported using them via an alternate route (e.g. snorted, injected, or other route not intended) and 11 (9.7%) report attempting to extract the active ingredient (Table 11). Excluding HCP users who report only medical use as prescribed, the 14 respondents reporting HCP use via an alternate route therefore represent 14.5% of the 99 current HCP non-medical users.

Table 11. Current use of hydrocodone IR combination products, NAVIPPRO Internet Survey

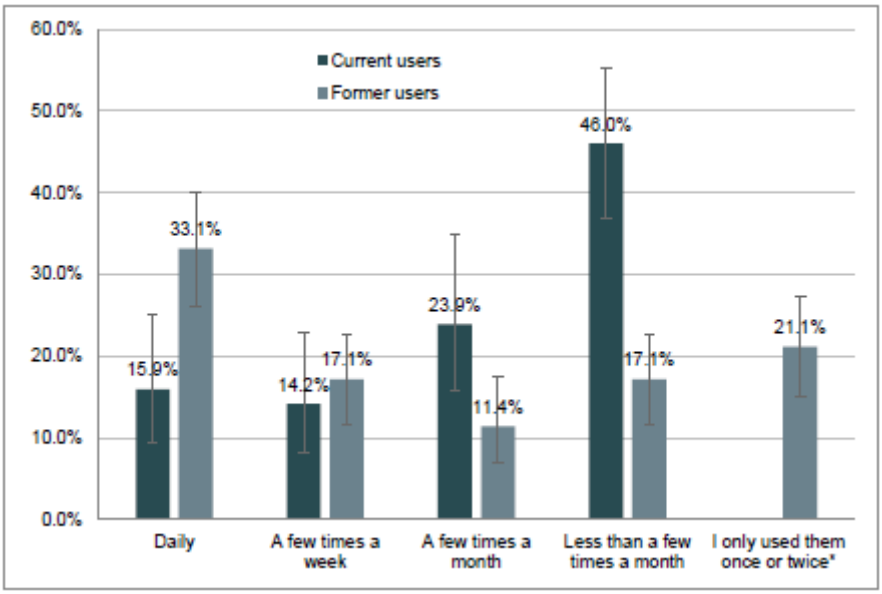
Reasons* for current use (n = 113)	n	%	Lower 95% CI	Upper 95% CI
Prescribed to me for medical reasons and use as prescribed only *(exclusive response option)*	14	12.4	6.8	20.8
Prescribed to me for medical reasons but use a higher dose than was prescribed	33	29.2	20.8	37.6
To relieve pain but it was not prescribed to me	42	37.2	28.3	46.1
Prescribed to me for reasons other than the pain it was prescribed for (e.g., to relax, feel less stressed, feel more outgoing, to get high or stoned)	16	14.2	8.1	22.9
Not prescribed to me and use it for reasons other than pain (e.g., to relax, feel less stressed, feel more outgoing, to get high or stoned)	61	54.0	44.8	63.2
Via an alternate route (e.g., snorted, injected, or other route not intended)	14	12.4	6.8	20.8
By attempting to extract the active ingredient	11	9.7	4.9	17.4
To avoid or relieve withdrawal symptoms	21	18.6	11.5	28.4
To taper use of prescription or illicit drugs	15	13.3	7.4	21.9
To enhance the effect of prescription or illicit drugs	25	22.1	14.3	32.7
To enhance the effect of alcohol	9	8.0	3.6	15.1
In combination with prescription or illicit drugs	34	30.1	21.6	38.5
To ease comedown from using prescription or illicit drugs	21	18.6	11.5	28.4
Other reasons*	6	5.3	1.9	11.6
Prefer not to respond	3	2.7	0.5	7.8

* Of the 'other' responses, 15 respondents indicated they used these products because they were prescribed to them.

Source: NAVIPPRO® Internet Survey Report: Use and abuse of Hydrocodone Combination Products Internet Survey 2014

When asked about the frequency of their current use of HCPs, most current users indicated that their current use was less than a few times a month (46.0%) or a few times a month (23.9%). Former users were more likely to report daily use than current users. (Figure 13).

Figure 13. Frequency of use among current and former hydrocodone IR combination product users, NAVIPPRO Internet Survey



Source: NAVIPPRO® Internet Survey Report: Use and abuse of Hydrocodone Combination Products Internet Survey 2014

None of the 14 current users reporting use via alternate routes were daily HCP users, as shown in Table 12. Three respondents, corresponding to approximately 3% of current non-medical HCP users, reported HCP use a few times a week, and 11 reported use a few times a month or less. Confidence intervals were not provided for these estimates.

Table 12. Distribution of frequency of hydrocodone IR combination product use among current users who report use via an alternate route (e.g. snorted, injected, or other route not intended), n=14

	n	%
Daily	0	0.0
A few times a week	3	21.4
A few times a month	3	21.4
Less than a few times a month	8	57.1

Source: IR Response, Received 2/12/16

3.2.4 DEPI Comments on the NAVIPPRO Internet Survey Report

This study report presents descriptive data from an anonymous survey administered to visitors to an online peer-to-peer drug discussion forum, Bluelight.org. Users of HCPs were specifically recruited. Of particular interest for this review are the data presented on non-oral routes of abuse. The survey results indicate that, in this population, a substantial minority (34.3%; 95% CI 27.9%-40.7%) of lifetime non-medical users of HCPs have

tried snorting the drugs at least once, although few (6.7%; 95% CI 3.6%-11.2%)) reported that snorting was their preferred route for taking HCPs. Among current users of HCPs, 12.4% reported using the drug via an alternate route (e.g. snorting, injecting, other), although it was not stated what proportion of this use was via snorting. Among those reporting any current use via alternate routes, most reported using HCPs a few times month or less and none reported daily use of HCPs.

This study provides novel information in an area with very limited data resources and is therefore a valuable new contribution to efforts to better understand patterns of HCP abuse, particularly with regard to ROA. However, the study has a number of limitations that affect interpretation of the results. First, no information was provided on validation of the survey questions, other than noting that it was adapted from similar online surveys and specifically referencing one (Katz et al., 2008) that also provided minimal information on survey development or validation of questions related to non-medical use of prescription opioids. Some of the measures in the current survey, particularly related to alternate ROAs, were difficult to interpret with regard to timeframe of use.

Second, the small sample size resulted in very small cell counts and imprecise estimates particularly for subgroup analyses, for example looking at snorting among more frequent versus less frequent HCP abusers. Confidence intervals were not provided for these subgroups analyses, but given the very small sample size and event counts, they would be expected to be quite wide.

Another consideration with this study is its limited generalizability. The study population was quite young, a demographic group shown in previous studies of individuals entering treatment to be most likely to report prescription opioid abuse via snorting (Katz et al, 2011). It is also not known how representative visitors to online drug forums are of the broader population of prescription drug abusers, or how similar those who opt to participate in this online survey are to other visitors to the site. These online discussions often include sharing information and speculation on tampering methods, preferred routes of administration, and desirable and undesirable effects of various drugs. In this survey, almost half of participants reported using prescription opioids via an alternate ROA, and more than a third report having tampered with a prescription opioid to extract its active ingredient. It is unclear how often the site is accessed by casual recreational or experimental prescription opioid users as opposed to those with more severe opioid use disorders or addiction. Although it is possible that the survey sample would be more likely to engage in tampering or alternative ROAs than the general population of HCP abusers, it is difficult to predict whether, overall, these types of selection bias are likely to result in over- or underestimation of the prevalence of snorting and other non-oral routes of HCP abuse.

3.3 PUBLISHED EPIDEMIOLOGIC LITERATURE

3.3.1 Butler et al., 2011

This 2011 study presents one year of data (2009) from the NAVIPPRO ASI-MV program, the same data source as two of the study reports submitted by the Sponsor. During 2009, 795 out of 4,136 (19.2%) of individuals reporting past 30-day abuse of hydrocodone indicated that they had snorted it.

In 2014, FDA contacted one of the authors of this study, inquiring about the percent of HCP abusers who report snorting as their only route of abuse. The following data table (Table 13) was provided to FDA, showing that for the years 2010-2013, between 5.5% and 7.5% of HCP abusers reported snorting as the *only* route of abuse for these products.

Table 13. Past 30-day abuse of hydrocodone IR combination products among adults assessed for substance abuse treatment within the NAVIPPRO ASI-MV network

Year	Past 30-day Abuse Hydrocodone IR Combination (Total Cases)	Any Snorting (non-exclusive ROA[F]) Percent*	Only Snorting (exclusive ROA[FF]) Percent*
2010	6,994	22.5%	5.9%
2011	6,835	21.4%	5.5%
2012	6,777	23.0%	6.7%
2013	5,911	24.1%	7.5%

* Percent is calculated as the total number of individuals who indicate the specific route of administration (ROA) as the numerator among only the individuals who indicated abuse of the opioid group of interest (i.e., hydrocodone IR combination products) as the denominator.
[F] Non-exclusive ROA = individuals who indicate snorting and may also indicate other ROA for abuse of the opioid group of interest
[FF] Exclusive ROA = individuals who indicate snorting as the only ROA for abuse of the opioid group of interest

Source: Email communication between Silvia Calderon, FDA Controlled Substances Staff, and study co-author Teresa Cassidy, Inflexxion, Inc., on June 12, 2014

3.3.2 Cicero et al., 2013

This was a cross-sectional survey conducted in the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system Survey of Key Informants' Patients (SKIP) program, an ongoing program that collects information from a sample of individuals entering non-methadone substance abuse treatment centers. The study population included those aged 18 years or older who met DSM-IV criteria for substance abuse with a primary drug that was a prescription opioid and who used prescription opioids to get high within the 30 days prior to entering treatment.

In this survey, of the 912 individuals who indicated that hydrocodone was their primary drug of abuse, 94.6% reported oral, 26.6% reported inhalation, and 4.2% reported injection as routes of administration.

3.3.3 Katz et al., 2008

This paper presents results from a 2007 cross-sectional survey of visitors to an online drug information website, Erowid.org. Of the 896 participants included in the final

analytic sample, 201 (22.4%) reported having used Vicodin in the past 30 days non-medically ("*in a way not prescribed by your doctor*"). Of these, 31 (15.4%) reported snorting Vicodin, although the referent timeframe for reported routes of administration was unclear, for example if it referred to lifetime ("ever"), past 30-days, or even usual or preferred routes.

3.3.4 Young et al., 2010

In this 2010 cross-sectional study, a small sample of 212 prescription drug users was recruited from two Kentucky counties, one a rural Appalachian county (n=101) and a one a major metropolitan area on (n=111), to examine differences in ROA for nonmedical prescription opioid use. Participants were recruited initially with flyers and key informants, then these participants were asked to refer additional participants. The demographics of the two samples differed considerably, with the vast majority of the rural sample being white and less than 10 percent of the urban sample being white, although the populations of both counties were predominantly white. The rural sample was also younger, and scores from the Addiction Severity Index indicated that rural participants had more severe drug problems than did their urban counterparts (data not shown).

As shown in Table 14, the two samples were also very different with regard to patterns of nonmedical prescription opioid use. Although more than 90% of participants in both groups had used hydrocodone nonmedically in their lifetime, 74.3% of rural participants indicated that they had snorted the drug, while only 6.3% of urban participants reported snorting. No participants in either group reported injecting hydrocodone. Rural participants were also much more likely to have used other prescription opioids, both orally and via non-oral ROAs. Nearly twice as many rural participants reported lifetime use of heroin as did urban participants.

Table 14. Age-, gender-, and race-adjusted comparisons for route of drug administration among rural (n=101) and urban (n=111) drug users

Table 2 Age-, gender-, and race-adjusted comparisons for route of drug administration among rural (n = 101) and urban (n = 111) drug users

	Rural %	Urban %	Adjusted* *P*-values
Buprenorphine (sublingual tablets)	50.5	0	—
Swallowing	31.7	0	—
Snorting	26.7	0	—
Injecting	3.0	0	—
Fentanyl (patch)	35.6	0	—
Swallowing	25.7	0	—
Snorting	1.0	0	—
Injecting	14.9	0	—
Hydrocodone (tablets)	90.1	91.9	0.408
Swallowing	68.3	91.9	**0.046**
Snorting	74.3	6.3	**<0.001**
Injecting	0	0	—
Hydromorphone (all formulations)	32.7	4.6	**0.001**
Swallowing	6.9	4.5	0.524
Snorting	5.9	0.9	0.472
Injecting	21.8	0	—
Methadone (tablets)	77.2	3.6	**<0.001**
Swallowing	27.7	3.6	0.083
Snorting	64.4	0	—
Injecting	1.0	0	—
Morphine (all formulations)	53.5	4.6	**0.007**
Swallowing	14.9	3.6	0.652
Snorting	17.8	0.9	0.547
Injecting	33.7	0	—
OxyContin® (generic/tablets)	86.1	23.6	**0.002**
Swallowing	25.7	22.5	0.442
Snorting	68.3	3.6	**<0.001**
Injecting	44.6	0	—
Other Oxycodone** (tablets)	83.2	50.0	0.374
Swallowing	31.7	47.7	**0.026**
Snorting	68.3	1.8	**<0.001**
Injecting	3.0	0	—

*p-values adjusting for age, race, and gender.
**Includes, for example, Tylox®, Percocet®, and Percodan®.

Source: Young et al., 2010

3.3.5 DEPI Comments on the Published Literature

These studies further illustrate the wide range of estimates for the proportion of HCP abusers who abuse it via intranasal routes. The Young study in particular noted lifetime prevalence estimates for HCP snorting ranging from 6.3% in a sample of urban abusers to 74.3% among rural HCP abusers with more advanced substance use disorders. Like the submitted study reports, most of the published literature is comprised of studies using highly selected convenience samples that may not well represent abuse patterns in a

broader population of prescription opioid abusers. In addition, the published studies suffered from poorly defined outcome measures with respect to route of administration.

4 DISCUSSION

4.1 PREVALENCE OF INTRANASAL HCP ABUSE

As summarized in Table 16 below, the estimated prevalence of intranasal abuse among HCP abusers varies considerably, depending on the setting and characteristics of the study population, how the questions about ROA are asked, and the referent time frame. Overall, the available data suggest that snorting is not an uncommon route of administration in certain selected populations of HCP abusers. The highest prevalence estimates for current intranasal HCP abuse were in the CHAT study, which samples a very high-risk group of adolescents being assessed for substance abuse treatment. This finding is troubling, but not surprising, as nasal abuse of prescription opioids overall has been shown to be highest in adolescents, among individuals entering treatment centers (Katz et al., 2011)

The evidence also suggests that the prevalence of snorting HCPs is higher in those with more advanced addiction. In the ASI-MV study, intranasal abuse of HCPs was most common among those who are abusing other opioids in addition to HCPs and in those entering residential/inpatient substance abuse treatment; 85% of those snorting HCPs were determined to have a "considerable" or "extreme" drug problem in need of treatment. The Young study was consistent with these findings, in that the rural cohort, who had a high prevalence of severe drug use disorders, had a far higher lifetime prevalence of HCP snorting than an urban cohort with less severe drug problems. Again, this observation is not surprising. Epidemiologic data suggest that there is a progression from ingestion of prescription opioids (in inexperienced users) to snorting and/or injecting the drugs (when the abuser is more experienced). In one study, whereas a majority (87%) of surveyed opioid-dependent individuals reported ingestion as their initial route of administration of ER oxycodone, at the time of admission to a treatment center, the most prevalent route was inhalation (58.1%) (Katz et al, 2011).

Snorting is infrequently identified as the preferred or the exclusive route for abusing HCPs, and a large majority of those who report snorting HCPs also report abuse of other opioids and illicit drugs. The NAVIPPRO internet survey suggests that in a population of visitors to an online peer-to-peer discussion forum, the prevalence of current, regular (a few times a week or more) abuse of HCPs via an alternate route is low (Table 12). The small sample size limits inferences that can be drawn from these results, however. Additional information from the recently submitted 2015 NAVIPPRO Internet Survey (see Appendix B) provides slightly different estimates, indicating that that approximately

3% of non-medical users snort these products daily, and just under 6% snort a few times a week during continued non-medical HCP use. In addition, when asked about their most recent non-medical use of HCPs, only 6.3% reported that they had snorted the products. Although the precision of these estimates was not provided and the time frame difficult to interpret, these findings are consistent with the hypothesis that ongoing daily or frequent abuse of HCPs via the intranasal route may be quite uncommon.

Table 16. Summary of prevalence estimates for intranasal HCP abuse

	Population/setting	***Measure/definition of intranasal abuse***	***Estimated percent of HCP abuse that is via intranasal route***
NAVIPPRO: ASI-MV	Adults being assessed for drug or alcohol abuse problems in treatment centers and other settings within the ASI-MV network	Of those reporting past 30-day HCP abuse, percent who selected "snorted it" in response to the question: *"How have you usually used [DRUG]? Please select all that apply."*	
		Overall	23.3%
		Among those entering residential/inpatient treatment	28.9%
		Among those assessed in corrections settings	11.4%
		Among those reporting past 30-day abuse of HCPs and ≥ 1 other prescription opioid	33.3%
		Among those reporting past 30-day abuse of ONLY HCPs	9.7%
		Of those reporting past 30-day HCP abuse, percent who selected "snorted it" as their *only* route	5.5 - 7.5%
NAVIPPRO: CHAT	Adolescents < 18 years being assessed for treatment of drug or alcohol abuse within the CHAT network	Of those reporting past 30-day HCP abuse, percent who selected "snorted it" in response to the question: *"How have you usually used [DRUG]? Please select all that apply."*	42.7%
NAVIPPRO: Internet Survey	Visitors to the online drug discussion forum, Bluelight.org	Of those ever using HCPs nonmedically, percent indicating that routes used for HCPs in lifetime include "snorted"	34.3%

		Of those ever using HCPs nonmedically, percent indicating that preferred route for HCPs is "snorted"	6.7%
		Of current HCP non-medical users, percent who reported using it via an alternate route, *AND* reported use of HCPs that is	14.1%
		Daily	0.0%
		A few times a week	3.0%
		A few times a month	3.0%
		Less than a few times a month	8.0%
Cicero, 2013	Adults entering non-methadone treatment for prescription opioid addiction	Of individuals reporting hydrocodone as their primary drug of abuse, percent who reported snorting it	26.6%
Katz, 2008	Adults completing internet survey on Erowid.org	Of past 30-day Vicodin non-medical users, percent who reported snorting it	15.4%
Young, 2010	Survey of prescription opioid abusers recruited in two Kentucky counties	Of those who reported ever using hydrocodone non-medically, percent who reported snorting it	
		Urban (less severe addiction)	6.3%
		Rural (more severe addiction)	74.3%

4.2 RELEVANCE AND PUBLIC HEALTH BURDEN OF INTRANASAL HCP ABUSE

Determining the relevance and public health burden of intranasal HCP abuse requires consideration of both the number of individuals potentially affected and the risk associated with snorting, particularly any excess risk beyond that associated with misuse and abuse via the oral route. Given the widespread availability and abuse of HCPs in the U.S., even a small percentage abusing through the intranasal route translates to a large absolute number of individuals exposed to potential harms associated with intranasal abuse. This number remains dwarfed, however, by the much larger number exposed to potential harms of misuse and abuse via oral ingestion of HCPs, which is consistently reported as a ROA by more than 90% of abusers and abuse cases across multiple populations and study settings.

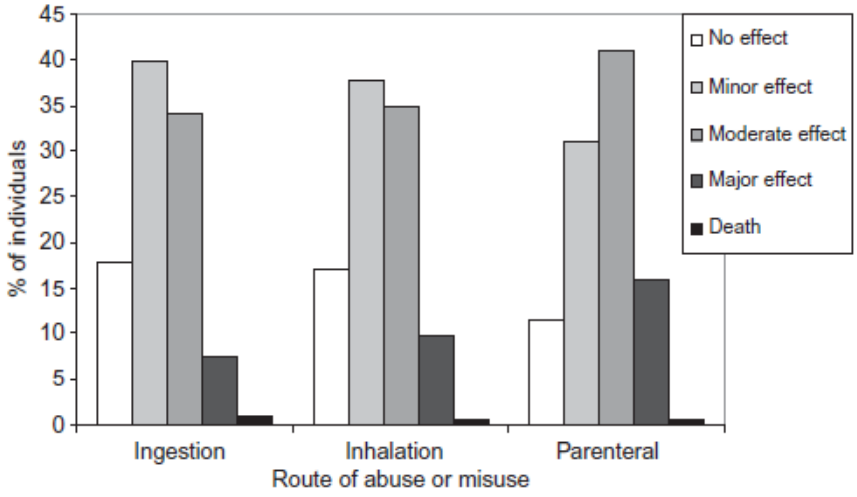
With respect to the risk of adverse outcomes associated with HCP snorting specifically, the data are quite limited. Alexander et al. (2012) describe 35 cases identified between 2004 and 2011 in three otolaryngology practices in Kentucky presenting with orofacial-nasal symptoms and nasal tissue damage, including necrosis and perforated nasal septum, associated with intranasal HCP abuse. Although little information was available on the

actual history of HCP nasal abuse in these cases, the nature of the tissue damage described suggests that repeated, or chronic intranasal drug abuse (of HCPs and/or other drugs) likely was involved. We are unaware of any study that estimates the risk of nasal tissue damage in the setting of acute or chronic intranasal HCP abuse.

Arguably, of greatest concern are outcomes related to addiction and overdose. Although snorting is associated with more advanced drug use disorders, as noted above, the existing data shed little light on whether snorting is more a cause or a consequence of worsening substance use disorder, or on whether an opioid formulation that reduced intranasal abuse would decrease the likelihood of an individual becoming addicted. Population data are extremely limited with regard to non-fatal and fatal overdose associated with HCP abuse via the intranasal route, as most population data sources for clinical data—for example electronic healthcare data or the Drug Abuse Warning Network (DAWN)[6] surveillance system of drug-related emergency department visits—do not capture ROA well, if at all, particularly for specific drug products. Although route of exposure may not always be accurately captured in poison control exposure calls, these data may provide some window into clinical outcomes associated with intranasal prescription opioid abuse. A published analysis of 2007-2008 call data from U.S. poison centers suggests that intranasal and parenteral opioid exposures may be associated with more severe outcomes, as shown in Figure 14. Unfortunately, the data do not indicate to what degree this pattern applies to HCPs specifically. Although this analysis could theoretically be conducted using poison center call data, FDA does not have access to these data, and we are unaware of any published study or publically available data that can answer this question. In addition, severe overdoses resulting in unattended or pre-hospital death may never result in a call to a poison center and therefore would not be captured in these data.

[6] http://www.samhsa.gov/data/emergency-department-data-dawn

Figure 14. Medical outcome severity associated with ingestion, inhalation, or parenteral routes of administration, intentional misuse or abuse of, or withdrawal from prescription opioids that led to poison center calls, 2007-2008



Notes: Data courtesy of Richard Dart and Elise Bailey; RADARS® System Poison Center Data, 2007-2008; Rocky Mountain Poison & Drug Center, Denver Health, Denver, Colorado.

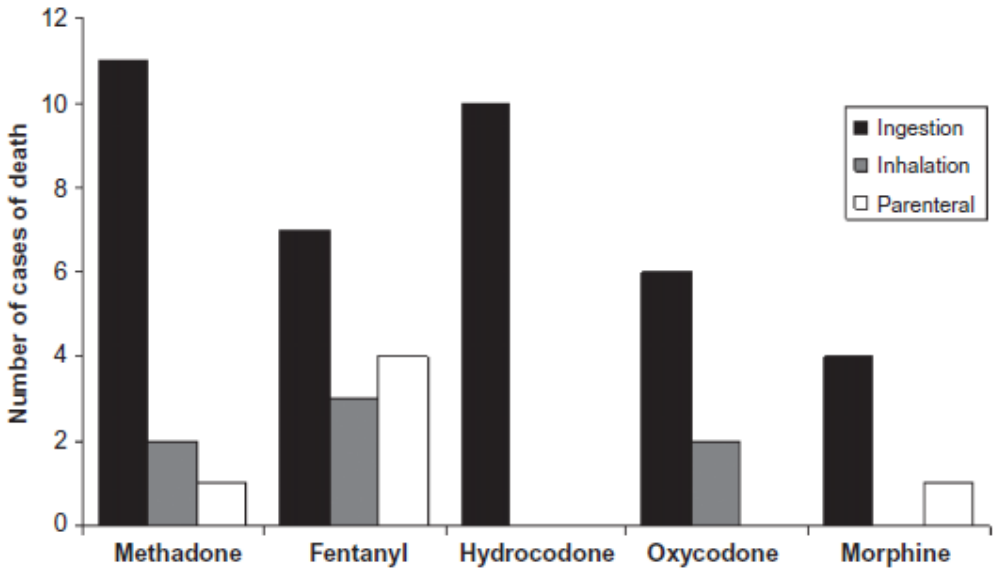
Suicide data were removed from the dataset. Data are for prescription opioids only: buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tramadol. Definitions of associated medical outcomes are: *Minor effect*: The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient. *Moderate effect*: The patient exhibited symptoms as a result of the exposure; symptoms are more pronounced, more prolonged, or more of a systemic nature than minor symptoms. Usually, some form of treatment is or would have been indicated. Symptoms were not life-threatening. *Major effect*: The patient has exhibited symptoms as a result of the exposure; they were life-threatening or resulted in significant residual disability or disfigurement. *Death*: The patient diedas a result of the exposure or as a direct complication of the exposure when the complication was unlikely to have occurred had the toxic exposure not preceded the complication.

Source: Katz et al., 2011

Medical examiner data suggest that alternate routes of exposure account for a substantial minority of unintentional prescription opioid overdose deaths. A 2008 West Virginia study found that out of 295 unintentional overdose deaths involving prescription pharmaceuticals, 66 (22.4%) involved a nonmedical route of administration (Hall et al, 2008). However, as shown in Figure 15, a published analysis of 2006 U.S. poison control center call data indicated that no fatal poisonings attributed to intentional misuse or abuse of hydrocodone involved inhalation or parenteral exposures (Katz et al., 2011). Again, it should be noted that overdoses resulting in severe respiratory depression and rapid death may never result in a call to a poison control center, and therefore intranasal and parenteral abuse cases may be under-represented in poison center data, particularly for the more potent opioids. Also, a caller (e.g. bystander or healthcare provider) may not always recognize or report non-oral routes of exposure, even when they had in fact occurred. These reasons may explain the somewhat surprising finding that the parenteral

route was not identified in any oxycodone misuse or abuse exposure calls resulting in death.

Figure 15. Deaths due to the intentional misuse or abuse of prescription opioids, by product suspected to have caused death, by route of administration of the product



Note: The figure compiles individual case data collected on fatal exposure for opioid drugs by route of exposure (ingestion, inhalation, parenteral) and by reason of exposure (intentional abuse, misuse, suicide). Deaths for which the reason was "intentional misuse" or "intentional abuse" were selected. Only cases that had a known route of abuse/misuse were taken into account. Opioid products were selected if they were considered the primary substance that caused death; opioid products included single and combination opioids, and all formulations reported. A single death may have been counted twice if multiple routes were suspected (e.g., a death that was reported to have occurred through parenteral and/or ingestion was counted under each of the routes) or if two opioid products were suspected to have caused death (e.g., a death that was reported to have been caused by hydrocodone/oxycodone was counted under each product). Hydromorphone deaths = 0. Number of deaths per route of abuse/misuse (all products combined): ingestion: 38; inhalation: 7; parenteral: 6.
Source: Data from Bronstein et al. [Table 21] (22).

Source: Katz et al., 2011

In summary, the epidemiologic data are extremely limited with regard to the public health burden of morbidity and mortality from intranasal HCP abuse. However, the available epidemiologic data do appear to support the hypothesis that the vast majority of the harm associated with HCPs is due to oral ingestion of these products. Furthermore, this hypothesis is plausible, considering (1) the limited amount of material that can be administered intranasally and absorbed at any one time, (2) the relatively low dose of hydrocodone in HCPs, compared to the higher dosage forms available for single-ingredient opioids, particularly those formulated as extended-release/long-acting products where intranasal administration has the potential to result in rapid absorption and bioavailability of a very high dose of opioid, and (3) the substantial harms associated with oral ingestion of high doses of acetaminophen-containing opioid analgesics.

5 CONCLUSION

The estimated prevalence of intranasal abuse among HCP abusers varies widely—from approximately 6% to more than 70%—depending on the setting and characteristics of the study population, how the questions about ROA are asked, and the referent time frame. The available data suggest that snorting is not an uncommon route of administration in certain populations of HCP abusers, particularly those with more advanced opioid addiction, those with polysubstance abuse, and high-risk adolescents. However, snorting is infrequently identified as the preferred or the exclusive route for abusing HCPs, and limited data suggest that regular (a few times a week or more) intranasal HCP abuse may be uncommon. Parenteral abuse of HCPs is reported very infrequently in all populations studied. Because of the widespread availability and abuse of HCPs, even a relatively low prevalence of intranasal abuse among HCP abusers translates to large absolute numbers of individuals exposed to potential harms associated with this behavior. Unfortunately, population data on harms associated with intranasal HCP abuse are very limited. However, the totality of the available epidemiologic data, interpreted in the context of the known pharmacologic properties of HCPs, suggests that intranasal abuse of HCPs may contribute relatively little to the overall public health burden of morbidity and mortality associated with HCP abuse, misuse, and addiction.

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7 APPENDICES

7.1 APPENDIX A: TARGET AND COMPARATOR PRODUCTS FOR ASI-MV AND CHAT ANALYSES

Target and comparator products	ASI-MV and CHAT monitored product categories
Hydrocodone IR combination products (brand and generic formulations)	Lorcet Lortab Vicodin Vicoprofen Norco Other hydrocodone (includes specific images of generic hydrocodone IR combination products) Other hydrocodone not shown (includes any other short acting hydrocodone combination product not presented with an image of the medication)
Oxycodone IR combination products (brand and generic formulations)	Percocet Tylox Percodan Combunox Roxicet Other Roxicet not shown Other short acting oxycodone (includes specific images of other generic oxycodone IR combination products) Other short acting oxycodone not shown (would include Oxecta and any other short acting oxycodone not presented with an image of the medication)
Oxycodone IR single-entity (SE)	OxyIR Roxicodone Other Roxicodone not shown
All other IR prescription opioids (both single-entity and combination excluding Schedule III products)	Actiq Fentora Onsolis Dilaudid Other IR hydromorphone (includes images of generic hydromorphone IR products) Other IR hydromorphone not shown MSIR Other IR morphine not shown Opana Generic IR oxymorphone not shown Nucynta
All ER/LA Opioids (both ADF and non-ADF products excluding patch and buprenorphine products)	Original OxyContin Reformulated OxyContin Xartemis XR Other non-combination ER oxycodone not shown Other ER oxycodone w/ acetaminophen not shown

Target and comparator products	ASI-MV and CHAT monitored product categories
	Exalgo MS Contin KADIAN AVINZA Oramorph SR EMBEDA Other ER morphine not shown Original/Old Opana ER Reformulated/New Opana ER Generic ER oxymorphone (Actavis) Generic ER oxymorphone (Impax) Other generic ER oxymorphone not shown Nucynta ER Zohydro ER
All ADF ER/LA opioids	Reformulated OxyContin Xartemis XR Exalgo EMBEDA Reformulated Opana ER Nucynta ER
All non-ADF ER/LA opioids (excluding patch and buprenorphine products)	Original OxyContin Other non-combination ER oxycodone not shown Other ER oxycodone w/ acetaminophen not shown MS Contin KADIAN AVINZA Oramorph SR Generic ER morphine products not shown Original Opana ER Generic ER oxymorphone (Actavis) Generic ER oxymorphone (Impax) Other generic ER oxymorphone not shown Zohydro ER

7.2 APPENDIX B: BRIEF REVIEW OF NAVIPPRO 2015 INTERNET STUDY REPORT FINDINGS

7.2.1 Description of study and relevant findings

On March 17, 2016, the Sponsor submitted to FDA the following study report: "NAVIPPRO Internet Survey Report: Progression of Hydrocodone Combination Products Use Internet Survey 2015." Some of the analyses in this study report were found to be relevant to DEPI's review of hydrocodone combination products (HCP) abuse patterns, particularly the relevance of the intranasal route of abuse. These findings are therefore presented and briefly discussed below.

This report describes an additional web-based survey of visitors to the peer-to-peer drug discussion forum Bluelight.org. The sampling, inclusion criteria, survey administration, and analytic methods were similar to those used in the previously submitted "NAVIPPRO Internet Survey Report: Use and abuse of Hydrocodone Combination Products Internet Survey 2014." After exclusion criteria were applied, the final analytic sample for this study consisted of 472 respondents aged 18 or older who reported ever having used HCPs for non-medical reasons. The demographic characteristics of the sample (Table 1a) were similar to that of the study population in the 2014 internet survey, in which the majority of respondents were between 21 and 54 years of age, three quarters were male, the large majority was white, and most had at least some college education.

Table 1a. Demographic characteristics of survey participants (N=472).

		Survey participants	
Category	**Response**	**n**	**%**
Age	Under 21 years	102	21.6
	21 - 34 years	251	53.2
	35 - 54 years	96	20.3
	55 + years	23	4.9
Gender	Male	355	75.2
	Female	103	21.8
	Other	10	2.1
	Prefer not to answer	4	< 1.0
Race	White	409	86.7
	Black or African-American	1	< 1.0
	Hispanic or Latino	18	3.8
	American Indian	7	1.5
	Alaskan Native	0	0.0
	Asian	4	< 1.0
	Other or multi-racial	26	5.5
	Prefer not to answer	7	1.5
Education	High School/GED or less	99	21.0
	Some College	207	43.9
	4-Year College (BA, BS)	101	21.4
	Master's Degree	46	9.7
	Doctoral/Professional Degree (MD, JD, PhD, EdD)	12	2.5
	Prefer not to answer	7	1.5

Source: NAVIPPRO Internet Survey Report: Progression of Hydrocodone Combination Products Use Internet Survey 2015

Of the 472 respondents who had ever used HCPs non-medically, 394 reported continued non-medical use of these products following initial use. The duration of continued use was not specified. Of these 394 respondents who reported continued non-medical use of HCPs following initial use, 102 (25.9%) indicated snorting among the routes of administration used during continued use of HCPs. Of these, 13 (12.7%) reported snorting daily and 22 (21.6%) a few times a week. Thirty-two (31.4%) reported snorting HCPs only once or twice (Table 2a).

Therefore, of the 394 respondents reporting continued use of HCPs following their initial use, 3.3% reported daily snorting and 5.6% reported snorting a few times a week for an undetermined period of time.

Table 2a. Frequencies of routes of administration when continuing to use hydrocodone IR combination products non-medically (N=394)

	Total responses	Daily		A few times a week		A few times a month		Less than a few times a month		I only used this route once or twice	
		n	%	n	%	n	%	n	%	n	%
Swallowed whole	336	98	29.2	70	20.8	92	27.4	60	17.9	16	4.8
Chewed	139	30	21.6	33	23.7	35	25.2	26	18.7	15	10.8
Drank in solution	104	9	8.7	17	16.3	21	20.2	23	22.1	34	32.7
Snorted	102	13	12.7	22	21.6	19	18.6	16	15.7	32	31.4
Parachuted (rolled powdered or crushed tablet in a piece of toilet paper to ingest)	67	6	9.0	11	16.4	14	20.9	16	23.9	20	29.9
Rectal (plugging)	42	1	2.4	7	16.7	6	14.3	5	11.9	23	54.8
Sublingual (under tongue)	31	3	9.7	9	29.0	5	16.1	3	9.7	11	35.5
Injected	15	5	33.3	3	20.0	3	20.0	2	13.3	2	13.3
Buccal (in check)	10	1	10.0	4	40.0	2	20.0	1	10.0	2	20.0
Smoked	8	1	--	1	--	1	--	1	--	4	--
Other route	18	3	16.7	5	27.8	3	16.7	3	16.7	4	22.2

Percentages not calculated for routes with fewer than 10 responses

Source: NAVIPPRO Internet Survey Report: Progression of Hydrocodone Combination Products Use Internet Survey 2015

The 394 respondents indicating continued use of HCPs after their initial use were also asked about their most recent non-medical use of HCPs. Slightly more than one third of continuing non-medical HCP users had used these products within the past 30 days, while approximately 15% had used them within the past 3 months, as shown in Table 3a.

Table 3a. Timeframe of most recent non-medical use of hydrocodone IR combination products (n=394)

	n	%
Within the past 30 days	142	36.0
Within the past 3 months	58	14.7
Within the past 6 months	34	8.6
Within the past year	53	13.5
Within the past 3 years	61	15.5
Longer than 3 years ago	46	11.7

Source: NAVIPPRO Internet Survey Report: Progression of Hydrocodone Combination Products Use Internet Survey 2015

Table 4a describes the routes used during the most recent non-medical use of HCPs, in comparison to the routes used during the first non-medical use of HCPs. At their last episode of non-medical HCP use, 6.3% of respondents indicated that they had snorted the product, while 4.9% reported snorting during their first non-medical HCP use.

Table 4a. Routes of administration respondents used during most recent non-medical use of hydrocodone IR combination products

	Routes of administration respondents used during first non-medical use of HCPs (n = 472)*		Routes of administration respondents used during most recent non-medical use of HCPs (n = 394)	
	n	%	n	%
Swallowed whole	374	79.2	265	67.3
Chewed	33	7.0	45	11.4
Drank in solution	17	3.6	25	6.3
Snorted	23	4.9	25	6.3
Rectal (plugging)	2	< 1.0	8	2.0
Injected	2	< 1.0	7	1.8
Parachuted (rolled powdered or crushed tablet in a piece of toilet paper to ingest)	17	3.6	4	1.0
Sublingual (under tongue)	1	< 1.0	3	< 1.0
Smoked	0	0.0	3	< 1.0
Buccal (in cheek)	0	0.0	2	< 1.0
Other route	3	< 1.0	7	1.8

Response options within each question are mutually exclusive.
*Source: Table 3

Source: NAVIPPRO Internet Survey Report: Progression of Hydrocodone Combination Products Use Internet Survey 2015

7.2.2 DEPI Comments

In general, the findings of this additional internet survey are consistent with the conclusions made in the body of this review. This survey does, however, add some useful pieces of information on patterns of HCP abuse in this population of non-medical HCP users, particularly abuse via the intranasal route. First, 26% of respondents reported snorting as a route of administration used at least once during continued non-medical use of HCPs. However, only 6.3% reported that they had snorted a HCP during their most recent non-medical use, suggesting that while it is not uncommon for non-medical HCP users in this population to snort them at some point in their lifetime, this may not be a regular or ongoing practice for most. The data on frequency of non-medical HCP use supports this hypothesis, in that only approximately 3% of continuing non-medical HCP users report snorting it on a daily basis, and less than 6% report snorting a few times a week.

The 2015 NAVIPPRO internet survey discussed here has similar strengths and limitations to the 2014 NAVIPPRO internet survey discussed in the body of this review, including issues with survey validation and data quality, small cell sizes and unknown estimate precision, and limited generalizability of the findings. The duration of "continued use" is not well defined, making the findings somewhat difficult to interpret. Also, in the 2015 survey, the data on most recent use is somewhat problematic, in that the majority of individuals may have been recalling details of a single episode of non-medical HCP use that occurred more than one month prior to the survey. It is questionable how accurate the recall of the specific route of administration would be for the more distant episodes of use.

7.3 APPENDIX C: COMMENTS ON SPONSOR'S PROPOSED POSTMARKETING STUDY PLAN

The sponsor submitted a proposed postmarketing study plan, and below DEPI provides comment on this plan, particularly as it relates to postmarketing requirements (PMRs) that would likely be issued if this product were to be approved with abuse-deterrent labeling language.

7.3.1 Summary of Sponsor's submitted study plan

7.3.1.1 Stated Objectives

1. Evaluate abuse and route of administration (ROA) patterns for KP201/APAP among populations considered at high-risk for abuse of opioid analgesics
2. Evaluate the potential impact of the market introduction of KP201/APAP in relation to the abuse prevalence of other hydrocodone immediate-release (IR) combination products currently on the market
3. Assess the extent to which the physicochemical properties of KP201/APAP may present a deterrence for abuse of the product when compared to other hydrocodone IR combination products, and other relevant opioids within the marketplace
4. Evaluate the recreational desirability of the product relative to other hydrocodone IR combination products and/or relevant opioids within the market

7.3.1.2 Study Approach

The design and methodology for these studies will be provided in study protocols to be submitted for Agency review and approval. Briefly summarized, the study plan is as follows.

The sponsor proposes using two NAVIPPRO® (National Addictions Vigilance Intervention and Prevention Program) surveillance system data sources:

1. ASI-MV® (Addiction Severity Index – Multimedia Version) survey of those being assessed for substance abuse at treatment centers and other settings, and
2. WIS (Web Informed Services) Internet Monitoring archive of online posts written on drug-related discussion forums,

and proposes a two-phase approach similar to that required in new FDA language for PMRs to evaluate the impact of abuse-deterrent products in post-market settings.

Phase I

The first phase will focus on the time period beginning with commercial introduction of KP201/APAP and follow the product as it develops market share. Phase I will consist of

post-market surveillance monitoring for KP201/APAP through examination of WIS Internet Monitoring data of online discussions among recreational drug users . Phase I will also include surveillance monitoring of the number of abuse cases of KP201/APAP within the ASI-MV data stream. Regular monitoring of these measures will be necessary to determine at what point sufficient data are obtained to warrant initiation of a formal post-marketing epidemiology study.

Phase 2

Phase II of the post-market study program for KP201/APAP will be to conduct formal epidemiologic studies to determine whether the product's abuse-deterrent properties result in meaningful reductions in abuse in the post-approval setting. KemPharm proposes to conduct two studies to assess abuse-deterrence of KP201/APAP: 1) a primary formal post-market epidemiology study among a high-risk population of adults entering or assessed for substance abuse treatment using ASI-MV data, and 2) a supportive study of drug-related discussion among recreational drug abusers on Internet websites and forums using WIS data. The study will employ a cross-sectional, observational design that compares the prevalence of both overall abuse and prescription-adjusted abuse for KP201/APAP in the period after its introduction to that of other relevant opioid comparator products or compounds.

7.3.2 DEPI Comments

The Sponsor's current study proposal adheres to the general principles described in FDA's "Guidance for Industry Abuse-Deterrent Opioids – Evaluation and Labeling;" however, as currently constructed, the post-market epidemiology program would not meet all of the Sponsor's stated objectives, nor would it be sufficient to fulfill FDA-imposed post-marketing study requirements to assess the impact of abuse-deterrent properties on abuse, misuse, and related adverse clinical consequences. Consistent with the guidance, the Sponsor proposes to use data from large geographic areas, intends to focus on high-risk patients and use relevant comparator data, and has plainly demarcated formal and supportive investigations. The proposed data sources for the formal and supportive studies are acceptable. Despite these strengths, at present, this study lacks any assessment of trends in abuse over time or "hard" clinical outcomes related to abuse such as fatal and non-fatal overdose, and diagnosed addiction. At a minimum, any post-marketing study program assessing the effectiveness of abuse-deterrent formulations in reducing abuse must present data on abuse trends and/or rates of change over time (relative to comparator products), and must include data on clinical outcomes, specifically addiction, overdose, and death.

The two-phase post-marketing study approach proposed by the sponsor is appropriate for understanding the landscape of KP201/APAP abuse shortly after the product is launched and ensuring sufficient utilization before hypothesis-driven studies are initiated to assess

abuse deterrence. The Sponsor should consider expanding the number of data sources used in Phase I and also provide data on selected appropriate comparators to provide context. Additional data sources, such as internet chat rooms and forums, spontaneous adverse event reporting, or smaller interview- or survey-based data may provide additional contextual information during Phase I to help better understand abuse of this product, including routes of abuse, in various populations.

The Phase I data will help determine appropriate timelines, objectives, and designs for formal epidemiologic assessment of abuse deterrence (Phase II). Phase II investigations will require formal statistical analyses in addition to descriptive data. These studies should include formal assessments of temporal changes in rates of outcomes—including route-specific abuse and the clinical outcomes addiction, overdose, and death—relative to appropriate comparators. If studies to achieve these objectives use large electronic healthcare databases, they should follow guidelines laid out in FDA's "Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data." Some important features include validation of outcomes and/or use of well validated medical code algorithms (such as those being developed in the ER/LA opioid PMRs); measurement of and control for potential confounders; and linkages to other data sources, the National Death Index or other source of overdose death data being a critical linkage in this context. Non-traditional pharmacoepidemiologic approaches to evaluating overdose death should also be explored. One example might be a study linking state medical examiner overdose death data to Prescription Drug Monitoring Program dispensing data to assess the risk of overdose death associated with recent receipt of specific opioid products. Work is ongoing at the state and national level to improve the quality, detail, and consistency of drug-related death data, and we encourage sponsors to become engaged in these efforts and to explore novel approaches to evaluating the impact of abuse-deterrent formulations on the incidence of overdose death.

The impact of abuse-deterrent formulations on the risk of addiction is a challenging but important question. The anticipated completion of the ER/LA opioid consortium PMR study to validate an instrument for assessing opioid addiction in patients with chronic pain may open new avenues for evaluating this outcome in prospective studies. Retrospective study designs could also conceivably explore the risk of addiction associated with specific products through recruitment in patient populations seeking treatment for opioid addiction. Electronic healthcare data may also prove useful for assessing addiction outcomes, with adequate validation of substance use disorder medical codes and adherence to other pharmacoepidemiologic best practices.