Assessing the Clinical Abuse Potential of Abuse Deterrent Opioid Formulations

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Disclosure

I am an employee of INC Research, and in this role I consult with various pharmaceutical and biotech companies.
Prescription Opioid Abuse Epidemic

• In 2014, an estimated 4.3 million people (≥ 12 years of age) were current nonmedical users of pain relievers in the US.¹
• In 2015, an estimated 3.8 million people (≥ 12 years of age) were current misusers of pain relievers in the US.²
• There has been a shift in the demographic of opioid users over the last few decades.
  – In the 1960s, more than 80% of people who began using opioids initiated with heroin.
  – In the 2000s, 75% of opioid users reported that their first regular opioid was a prescription pain reliever.³

Abuse Deterrent Opioids

• One of many tools to mitigate opioid abuse/misuse
• Formulations that deter abuse may be useful in ensuring access to drugs for purposes of medical treatment while limiting abuse and the consequences of abuse\(^1\)
• Introduce some impediments to abuse, as opposed to the outright elimination of abuse

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Types of Tampering & Abuse

- Prescription drugs can be abused by swallowing whole or the product can be tampered with (e.g., crushing) for abuse by swallowing, snorting, dissolving in solution and injecting, or smoking.
Types of Abuse Deterrent Formulations

- Technologies include:
  - Physical/chemical barriers to tampering
  - Agonist/antagonist combinations
  - Aversion - substances combined to produce unpleasant effects if manipulated/administered at high doses
  - Delivery system - e.g., depot injectable formulations and implants
  - New molecular entities and prodrug - lacks activity until transformed in GI tract
  - Combination - two or more of the above methods
  - Novel approaches - this category encompasses novel approaches or technologies that are not captured in the previous categories

Progression of Abuse

AD technologies should consider how a particular product is abused.

Opioids can be abused by:

- increasing oral dose
- crushing/chewing + swallowing
- crushing + snorting
- crushing + smoking
- crushing + dissolving + injecting

Often there is a progression of abuse
Regulatory Guidances

Abuse-Deterrent Opioids —
Evaluation and Labeling
Guidance for Industry

General Principles for
Evaluating the Abuse
Deterrence of
Generic Solid Oral Opioid Drug
Products
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Division of Decision Management (SPA-203), Food and Drug Administration, 5600 Fisher Lane, Room 301, Rockville, MD 20852. All comments should be identified with the docket number issued in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document, contact (CDER) Robert Linnberger at 240-402-7907.

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

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When Is Abuse Potential Assessed?

- An abuse potential assessment is conducted for **new drugs**, including new molecular entities, when the drug:
  - Affects the central nervous system (CNS),
  - Is chemically or pharmacologically similar to other drugs with known abuse potential,
  - Produces psychoactive effects e.g., sedation, euphoria, mood changes, or
  - Is a new formulation designed with a possible claim of abuse deterrent qualities

- An abuse potential assessment may also be necessary for a marketed product that:
  - Presents an unexpected adverse event profile that includes events related to abuse potential, or
  - Is being re-evaluated for a new route of administration that could affect its abuse potential
Abuse Deterrence Evaluation and Labeling

- Based on 4 categories of evidence

<table>
<thead>
<tr>
<th>Category</th>
<th>Type of Study</th>
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<tbody>
<tr>
<td>Category 1</td>
<td>Laboratory-based in vitro manipulation and extraction studies</td>
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<tr>
<td>Category 2</td>
<td>Pharmacokinetic studies</td>
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<tr>
<td>Category 3</td>
<td>Clinical abuse potential studies</td>
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<tr>
<td>Category 4</td>
<td>Post-marketing data – demonstration of ADFs ability to case persistent and relevant reduction in abuse</td>
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</table>
In Vitro (Category 1)

- In vitro (laboratory manipulation and extraction) studies determine likelihood of:
  - Defeating or compromising a controlled-release mechanism
  - Preparing an immediate-release formulation for alternative routes of administration
  - Separating the aversive/antagonist ingredients from the opioid
Manipulation Evaluation to Support Clinical Studies

• In vitro data is critical to inform manipulation techniques for clinical studies
  – Equipment for manipulation (e.g., mortar pestle, coffee grinder, grater)
  – Duration of grinding/manipulation time
  – Particle size distribution
  – Appearance of ground powder (blinding)
  – Identification of appropriate placebo and comparator
  – Number of capsules/tablets per grind
  – % recovery
  – Stability and storage of ground material
Pharmacokinetic Studies (Category 2)

• Evaluate the in vivo properties of the formulation by comparing PK profiles of manipulated vs. intact formulation through one or more routes of administration.
  - Routes should be relevant to drug and safe to administer
  - Manipulation techniques guided by in vitro data - resulting in greatest release
  - Consider what claims will be made (chewing ≠ crushing)

• Assessment of food/alcohol should be included
  - When food is expected to increase exposure, subsequent abuse potential studies by the oral route should be conducted in the fed state

• Typically conducted in healthy volunteers; adverse events and tolerability assessed

• Special attention should be given to:

<table>
<thead>
<tr>
<th>Manipulation techniques</th>
<th>Food effects</th>
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<tr>
<td>Routes of administration</td>
<td>Alcohol effects</td>
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</table>

FDA Guidance: Pharmacokinetic Studies (Category 2) – Study Types

- Pharmacokinetic profile for the oral route of administration should be studied
  - Chewed or crushed
  - Healthy volunteers as long as naltrexone is used to block the pharmacodynamic effects of the opioids
- Intranasal pharmacokinetic profile may be important to assess (product dependent)
  - Should be done in subjects experienced with intranasal opioid
  - Need to consider the risks of the excipients in the product and if IN administration is justified
  - Collect adverse events related to tolerability
- Intravenous
- Food and alcohol effects if such an effect is expected
  - Assess if food effect is result of API or excipients
  - Human abuse potential study may need to be done in fed state if food increases release
  - Best to do in separate study and prior to Category 3 study if it may be a concern
FDA Guidance:
Clinical Planning

• Results from PK studies can influence HAP studies
  – e.g., if the extended-release characteristics of an AD opioid formulation cannot be defeated and PK profile remains unchanged following oral or nasal administration of the manipulated product, oral and nasal HAP studies may not be necessary

• 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.
  – For the approved ADFs so far, this has been the preferred route
Clinical Abuse Potential Studies (Category 3)

• For drugs with abuse-deterrent properties, the purpose of a clinical abuse potential study is to assess the impact of the potentially abuse-deterrent formulation on measures that predict how probable it is that the formulation will be attractive to abusers (“liked”).

• Preferred design is a randomized, double-blind, placebo-controlled, and positive comparator-controlled crossover study.

• Generally conducted in a drug-experienced abuse population that is further selected using a pre-qualification phase (enrichment strategy).

• Various pharmacodynamic, pharmacokinetic, and safety measures implemented to assess subjective drug effects and exposure.
How Is a Human Abuse Potential Study Conducted?

• These studies are typically conducted as single dose studies that are blinded (identity of drug is masked)
• The studies are usually crossover designs, in that each subject receives all treatments in a random order
• Typically, the study drug is compared to a placebo and a comparator that is usually the same opioid (immediate- or extended-release)
• The routes of administration can vary and can include both intended (as directed for therapy) and unintended routes used for the purpose of abuse (e.g., snorting, injection)
• Doses are chosen based on past experience with specific opioids in the study population
• Assessments are conducted during the time course of the drug’s effects

What Type of Subjects are Selected for Human Abuse Potential Studies?

• The study subjects are:
  − Experienced, recreational drug users who have recent or current history of using the drug in the same class as the test drug (e.g., opioids, amphetamines)
  − Healthy males and females (18 years or older)
  − No current/prior addictive disorder and are non-dependent on the drug of abuse

• Non-dependence can be confirmed by using
  − Diagnostics and Statistical Manual (DSM-IVR) criteria
  − Pharmacological challenge (e.g., naloxone to precipitate withdrawal in opioid-dependent individuals)

• Past recreational drug use experience is confirmed by:
  − Subject reported history
  − Pharmacological challenge (e.g., subject’s ability to tell the difference between the effects of a comparator (abuse drug) vs. placebo)


What Is Measured in a Human Abuse Potential Study?

• Visual Analog Scales (VAS) are commonly used to assess subjective drug effects

• VAS for drug liking should be the primary measure, appears to correlate most directly with potential for abuse

• Other measures of particular interest include:
  − Assessment of overall drug liking
  − Assessment of high
  − Assessment of likelihood to take the drug again

• Measure can be assessed using either a unipolar or bipolar scale, and a rational should be provided for the choice of a particular scale

• Training subjects on pharmacodynamic measures is critical in ensuring comprehension and appropriate subject selection

Measuring Drug Effects

• Ratings of drug liking and other subjective effects are measured on Visual Analog Scales (0-100 point scale)

Figure. Presentation of bipolar VAS Drug Liking scales

At this moment, my liking for this drug is
# Additional Measures in Human Abuse Potential Studies

<table>
<thead>
<tr>
<th>Subjective drug effects:</th>
<th>Physiological/ behavioral e.g.</th>
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<tbody>
<tr>
<td>e.g.</td>
<td>• Pupil diameter</td>
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<td>• Psychomotor activity</td>
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<td>• Cognitive performance</td>
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<td>• Profile of mood states</td>
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<td></td>
<td>• Nasal effects (intranasal route)</td>
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<tr>
<td>• Positive drug effects (e.g. Good Drug Effects, High)</td>
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<tr>
<td>• Negative drug effects (e.g. Bad Drug Effects, Nausea, Feel Sick, Dysphoria)</td>
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<tr>
<td>• Other drug effects (e.g. Alertness/Drowsiness)</td>
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<tr>
<td>• Take Drug Again</td>
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<tr>
<td>• Subjective Price/Street Value</td>
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<tr>
<td>• Strength of drug effect</td>
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<tr>
<th>Pharmacokinetic</th>
<th>Safety</th>
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<td>• Plasma drug/metabolite concentration</td>
<td>• Adverse events</td>
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<td>• Vital signs</td>
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<td>• Pulse oximetry</td>
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Examples of Relative Reductions in Drug Liking for Two Test Drugs Compared to a Positive Comparator and Placebo

Time course data presented on a bipolar 100 mm Visual Analog Scale for Drug Liking where 0 is Strong Disliking, 50 is neutral, and 100 is Strong Liking.
How Is Human Abuse Potential Data Interpreted?

- Primary analysis is typically the difference in means of the peak effects ($E_{\text{max}}$)\(^1\)
- Take Drug Again considered a key secondary endpoint
- Consider pattern of findings across all of the measures
- Examine profile of subjective effects produced in terms of onset, peak duration of activity, and offset
- Qualitative aspects of the findings should be considered e.g., steepness of the drug liking response, duration of the liking effects, positive vs. negative effects
- What is clinically meaningful?
  - Some studies suggest that a 10 point difference may be clinically meaningful\(^2,3\)
  - A recent study demonstrated that ‘Overall Drug Liking’ was significantly associated with reduced real-world nonmedical use, healthcare utilization, and costs\(^4\)

Summary

• Evaluation of abuse deterrent opioids requires careful consideration of the intended routes and tampering methods that are meant to be mitigated.

• Pre-marketing claims can be supported by Category 1-3 studies which include in vitro (laboratory), pharmacokinetic, and human abuse potential studies.

• Studies are surrogates for determining the attractiveness or abuse potential of an abuse deterrent formulation, under conditions of study.

• Study limitations must be carefully considered.
Thank you
Questions

For more information on Abuse Potential evaluation, please contact:

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