ASSESSMENT OF ABUSE LIABILITY OF BRAIN-PENETRANT COMPOUNDS:

Regulatory Environment, Challenges and Opportunities in View of the Current Opioid Epidemic

Beatriz A. Rocha MD, PhD
Head of Covance Global Regulatory Affairs Clinical Strategy

Background

Abuse liability of a drug refers to its potential use in a non-medical situation for the positive psychoactive effects it produces through its Central Nervous System (CNS) activity.

The assessment of the abuse liability/potential of a drug encompasses all properties of the drug—chemical, pharmacological, pharmacokinetics, usage and diversion history—and is part of the overall assessment of drug safety under the evaluation of a New Drug Application (NDA) in the US or a Market Authorization Application (MAA) ex-US.

In the US, the Comprehensive Drug Abuse Prevention and Control Act, referred to as the Controlled Substance Act of 1970 (CSA) provides the legal basis for the government to control drugs and other substances that have potential for abuse (21CFR801). The CSA refers to “potential for abuse” and “addiction-forming or addiction-sustaining liability” but does not define these terms, which are frequently used interchangeably. The Drug Enforcement Administration (DEA), under the CSA, is responsible for the scheduling of drugs considered to have potential for abuse. All individuals and firms authorized to handle controlled substances are required to be registered by the DEA, to maintain complete and accurate inventories and records of all transactions involving controlled substances, and to comply with security requirements for the storage of controlled substances.

Until 2006, assessment of the abuse potential of New Molecular Entities (NMEs) was required for specific pharmacological classes (i.e., psychostimulants, sedatives, opioids, cannabinoids), but since then, as regulatory guidance became available in the US, EU and Canada, assessment of abuse potential is now required to be completed before NDA/MAA filing for all brain-penetrant compounds and metabolites regardless of the indication. The latest 2015 finalized guidance in the US and the 2016 draft guidance make recommendations for the development of abuse-deterrent formulations (ADF) for new and generic opioids analgesics and is part of the 2016 announced “FDA Opioid Action Plan.”

In regards to the scheduling process of new approved medicines, on November 25, 2015, President Obama signed the Improving Regulatory Transparency for New Medical Therapies Act to amend the CSA with respect to drug scheduling recommendations by the Food and Drug Administration (FDA) and the Secretary of Health and Human Services. The Act determines the time frame for the DEA to issue an interim scheduling determination of drugs with potential for abuse, and redefines the calculation of exclusivity and patent terms.
Regulatory Environment

In 2006, the European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP) adopted the Guideline of the Nonclinical Investigation on the Dependence Potential of Medicinal Products\(^1\).

Subsequently, in 2007, Health Canada published the Clinical Assessment of Abuse Liability for Drugs with Central Nervous System Activity\(^2\).

In 2009, recommendation for the nonclinical investigation was included in the International Conference on Harmonization (ICH) Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (ICH M3 Step 4) finalized in 2009\(^3\). Consistently with the CHMP guideline, ICH M3 reiterates the need to conduct nonclinical evaluation of abuse liability in CNS-active drugs regardless of therapeutic indication, and that these studies should support the design of the clinical evaluation of abuse potential.

In the US, draft guidelines were available from 1990 to 2001, but only in 2010 the revised draft guidance on the assessment of abuse potential of drugs was published\(^4\).

In 2003, the Controlled Substance Staff (CSS) of the FDA was created to oversee the evaluation of abuse liability, drug dependence, risk management and recommendation of drug scheduling of compounds under development. Since then, CSS' active participation in scientific meetings has paved the way for establishing a productive interchange with academia and pharmaceutical companies. Examples of such are dialogue sessions that took place between the CSS and the Cross Company Abuse Liability Council (CCALC), a grassroots initiative formed in 2006 when companies were experiencing common challenges in assessing abuse liability because of the absence of regulatory guidance in the US\(^5\), companies unite to advance regulatory landscape of abuse potential assessment\(^6\). The first dialogue session occurred in 2008 and focused on specific methodological challenges and data interpretation, whereas the second session (2010) focused on comments on the draft guidance published in January 2010\(^5\). Numerous discussion points from the 2008 meeting were incorporated or considered in the development of the 2010 draft guidance, which addresses the chemical, manufacturing, nonclinical, clinical and post-marketing aspects of the assessment of abuse liability, and reiterates how the totality of nonclinical and clinical data are taken into consideration in the overall evaluation of abuse liability during the NDA review.

One topic of particular interest for sponsors is the sequence in which nonclinical and clinical abuse liability studies are to be conducted during drug development. To that extent, following publication of the draft guidance, FDA and National Institute of Drug Abuse (NIDA) organized a workshop on the science of the assessment of abuse potential and proposed a decision tree for discussion and further comments from the public NIDA, FDA\(^7\).

Even though the 2010 draft guidance has not yet been finalized, it is clear that one recipe does not fit all and that sponsors need to consider each NME on its own when planning for the assessment of abuse liability. Start planning the overall strategy and engage with the FDA/CSS early in development is still the best approach.

Impact of Prescription Opioid Abuse in the Assessment of Abuse Liability

Prescription opioids, stimulants and CNS depressants are the three classes of medications with the highest potential for abuse. However, in terms of abuse and mortality, opioids account for the greatest proportion of the prescription drug abuse problem. Deaths related to prescription opioids began rising in the early part of the 21st century. By 2002, death certificates listed opioid analgesic poisoning as a cause of death more common than heroin or cocaine\(^8\)
In 2012, under the scope of the Food and Drug Administration Safety and Innovation Act (FDASIA), the FDA was mandated to develop guidance on abuse-deterrent formulation (ADF) for opioid analgesics. The ADF draft guidance was published in 2013 and finalized in 2015, and has recommendations on studies necessary to demonstrate that a given formulation has abuse-deterrent properties, on how those studies will be evaluated by the agency, and what labeling claims may be approved based on the results of those studies. Since then, five products with abuse-deterrent labeling have been approved in the US—OxyContin® (oxycodone, crush/extraction resistant) [Purdue Pharma, L.P.], EMBEDA® (morphine/naltrexone, naltrexone is an antagonist, blocks euphoria) [Alpharma Pharmaceuticals], Targiniq (oxycodone hydrochloride and naloxone, naloxone antagonist), Hysingla® (hydrocodone, crush/extraction resistant) [Purdue Pharma, L.P.], and MorphaBond® (morphine, crush/extraction resistant) [Inspirion Delivery Technologies, LLC]—which provide information on the studies conducted and the corresponding supported labeling. Once the ADFs of these products were approved, the original formulations were discontinued from the market.

A draft guidance with recommendations for evaluating abuse-deterrent formulations of generic (solid oral) opioid drugs has recently been published.

The draft guidance recommends comparative nonclinical studies to demonstrate that a generic (solid oral) opioid drug is no less abuse-deterrent than the innovator drug with respect to all potential routes of abuse.

Despite all government efforts, 18,893 overdose deaths related to prescription pain analgesics, and 10,574 overdose deaths related to heroin were reported in the US in 2014 (Center for Disease Control and Prevention, 2015), and in February 2016 the FDA announced a “far-reaching action plan to approach opioid medications” (FDA News Release, 2016) that aims at implementing policies to reverse the epidemics while still assuring that pain patients have access to effective therapy. The FDA’s Opioid Action Plan includes measures to encourage the development of abuse-deterrent formulations of opioid products, the development of newer pharmacotherapies for pain, the development of warnings and safety information for immediate-release (IR) opioid labeling, strengthened post-market requirements, updated of the Risk Evaluation and Mitigation Strategy (REMS) Program, reassessment of the risk-benefit approval framework for opioid use and the expansion of the use of advisory committees.

On March 1, 2016, the FDA sought advice from the agency's Science Board for the hearing and discussion of the following topics:

▶ The role of opioids in pain management
▶ Scientific challenges facing the FDA in supporting the development of pain medications, including opioids, that have reduced risks of being abused
▶ Scientific challenges facing the FDA in seeking to understand the real-world use of opioids to treat pain, including the impact of opioids with potentially less risk for abuse
▶ The role that the FDA plays as a part of a larger federal, state and local response to the challenges of providing appropriate pain treatments while reducing opioid abuse
▶ Post-market surveillance activities related to opioids

Several Board recommendations open new opportunities for innovative clinical trials and labeling reviews. Some panelists encouraged the agency to explore research tools in poorly defined chronic pain conditions, such as phenotyping in fibromyalgia, with subsequent genotyping that can be used to develop decision points and predict treatment responses. Another recommended focus is in expanding the risk/benefit model to include function as well as pain, and collect long-term risk/benefit information that might support changes to labels and limits on dose.
On March 15, 2016 the US Centers for Disease Control and Prevention (CDC) released new voluntary clinical guidelines asking primary care providers treating adults with chronic non-cancer related pain to consider alternatives to prescription opioid analgesics, limit treatment length and monitor their patients to see if the opioids are the best choice for them\textsuperscript{11}.

**Drug Scheduling under the Controlled Substance Act (CSA)**

When the FDA reviews the safety and efficacy of a NDA under the 1938 Food, Drug and Cosmetic Act (FD&C Act), it also determines whether the drug has potential for abuse, and if so, it will send the scheduling recommendation to the DEA for their evaluation and subsequent scheduling decision under the CSA. The CSA establishes five schedules (I, II, III, IV and V) for drugs and substances with abuse potential, based upon the substance's medicinal value, harmfulness and potential for abuse or addiction (21CFR812, 21CFR802) when compared to a controlled substance. Under the CSA, a “controlled substance” implies that a drug or substance or precursor included in schedules I-V, each one of which is associated with different levels of regulation, with schedule I drugs being those with high potential for abuse and no accepted medical use in the United States\textsuperscript{14}. However, nonclinical and clinical comparability assays, such as drug self-administration, were developed and validated for known drugs of abuse. Therefore, for NMEs with new mechanisms of action, the comparison with the appropriate controlled substance (i.e., active comparator) is challenging, and adds significant complexity to the overall evaluation. Reaching agreement with the CSS on the appropriate active comparator is one of the highest priorities in these circumstances.

FDA approval of a new drug product and DEA scheduling are two independent processes under different legislature, and commercial availability of the product requires finalized approved labeling including schedule classification. Historically, the time between FDA approval of a new therapy with potential for abuse and DEA scheduling has been inconsistent and in some instances has taken more than one year, preventing drug companies from marketing their drug, and patients in need from having access to an FDA-approved therapy. A long-time expected improvement of this process recently occurred on November 25, 2015, when President Obama signed the Improving Regulatory Transparency for New Medical Therapies Act, that amends the CSA with respect to drug scheduling recommendations by the Secretary of Health and Human Services, and with respect to registration of manufacturers and distributors seeking to conduct clinical trials\textsuperscript{15}.

This new law tasks the DEA to make an interim scheduling decision within 90 days of the FDA making a scheduling recommendation. The date of the DEA's interim scheduling decision is now to be considered the date of approval of the NDA and permits the drug to be marketed. The drug's marketing exclusivity therefore is to start when the interim final rule controlling the drug is issued in accordance with section 201(j) of the CSA.

**Regulatory Expectations**

**Assessment of Abuse Potential of NMEs**

Assessment of abuse potential of NMEs during drug development is a very complex and expensive process. It takes into consideration the totality of nonclinical and clinical data available at filing, which may include specific nonclinical experiments, such as drug discrimination and self-administration, as well as a dedicated clinical study in poly-drug abusers (i.e., Human Abuse Liability (HAL)). In order to ensure that adequate evaluation is completed before filing, sponsors need to proactively engage with regulatory agencies early in development for obtaining agreement on timing and adequacy of studies.
Abuse potential of a drug is considered a safety issue, and consequently the nonclinical evaluation is done under toxicology/safety pharmacology and Good Laboratory Practice (GLP) conditions apply, in compliance with the ICH S7A guideline (Safety Pharmacology Studies for Human Pharmaceuticals). The clinical evaluation takes into consideration the entire safety database (Phases I-III/IV) including the HAL study.

In the EU, the CHMP guidance recommends a two-tiered approach of the nonclinical evaluation of abuse potential for all substances and corresponding metabolites that enter the CNS, including those for which no class-specific standards are available and for which the dependence potential has yet to be determined. The recommendation is to initially evaluate the substance’s pharmacological profile (receptor binding and in-vitro activity (tier 1)) and to subsequently conduct animal behavioral studies to determine the substance’s discriminative stimuli, reinforcing properties and physical dependence and withdrawal (tier 2).

EMA’s recommendations are illustrated in the CHMP Guidance as below:

In the US, the CSS proposed a decision tree with the main goal of aligning nonclinical and clinical evaluation throughout development, and consequently identified three decision points where sponsors should pause and review their plans for assessment of abuse potential:

1. **Nonclinical Phase** – review of chemical structure and in vitro/in vivo binding profile. Plans for the nonclinical evaluation need to be put in place at this stage, and can be reviewed with the CSS during a pre-IND meeting.

2. **Early Clinical** – review of the entire safety database to date (Clinical Pharmacology program and Phase II studies), with focus on Adverse Events of interest, such as hallucinations and mood swings occurring at the expected clinical efficacious dose(s). It is expected that sponsors will present a complete review of the strategy for assessing AP (completed and planned studies) during the end-of-phase II meeting. In the case that a clinical AP study is to be conducted, sponsors should obtain CSS’ agreement on the timing of protocol review.

3. **Late Clinical** – review of the entire dataset generated during development (nonclinical and clinical) that will be described in the NDA, as per eCTD format indicated in the table below. This is to be discussed with the CSS and the FDA division during the pre-NDA meeting.
<table>
<thead>
<tr>
<th>eCTD Module</th>
<th>Content</th>
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<tbody>
<tr>
<td>1.11.4</td>
<td>Summary, interpretation and discussion; provide data table links; proposal for scheduling recommendations</td>
</tr>
<tr>
<td>2.4</td>
<td>Outline of preclinical studies performed</td>
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<tr>
<td>2.5</td>
<td>Outline of clinical studies performed</td>
</tr>
<tr>
<td>3.2.P.1</td>
<td>Additional studies performed to examine extraction under various conditions</td>
</tr>
<tr>
<td>3.2.P.2</td>
<td>Development of any component of drug product included to address accidental or intentional misuse</td>
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<tr>
<td>4.2.1.1</td>
<td><em>In vitro</em> and <em>in vivo</em> studies reports</td>
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<tr>
<td>4.2.37.4</td>
<td>Complete discussion – 8-factor analysis</td>
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<tr>
<td>5.3.5.4</td>
<td>Complete study reports of all clinical abuse potential studies</td>
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**Regulatory Expectations for the Development of Opioid Analgesics and Pain Therapies**

In view of the current regulatory environment and the Opioids Action Plan, development of abuse-deterrent formulations is required for new and generic opioids. Even though so far five products with ADF have been approved in the US, setting a regulatory precedent, the FDA recognizes the need for additional technology research on abuse-deterrent formulations and expects that from sponsors. Evaluation of the ability of the abuse-deterrent technology to reduce the potential for abuse of the drug requires a series of *in vitro* laboratory manipulation, extraction and syringe use studies, and *in vivo* clinical abuse potential study (i.e., HAL). The results of these studies are summarized in the label to support statements on the expected reduction of abuse or misuse via the administration routes tested. Working closely with the FDA from the early stages of development is critical for the successful development of acceptable abuse-deterrent technologies and formulations. The 2016 FDA draft guidance on the evaluation of the abuse deterrence of generic solid oral opioids provides a series of examples of nonclinical studies that need to be completed before the filing of the Abbreviated New Drug Application (ANDA) in order to ensure that generic forms of abuse-deterrent opioids are no less abused and no less abuse-deterrent than their brand name drugs.

Developers of extended-release opioids are expected to face more post-marketing commitments to generate data on the long-term impact of using opioids for better evidence on the serious risks of misuse and abuse associated with long-term use of opioids.

Furthermore, the current REMS program that applies to all extended-release opioids is expected to be expanded in order to increase the number of prescribers who receive training on pain management and safe prescribing of opioid drugs.

The FDA is willing to work closely with sponsors towards developing more reliable pain nonclinical models and clinical study designs to facilitate the development of novel analgesics. Therefore, there is a significant opportunity for the development of novel analgesics with lower potential of abuse.
Regulatory Challenges

While developers have the burden to identify the risk of abuse and frequently are called to prove the null hypothesis, regulators are challenged to evaluate the probability that such risk (i.e., the exposure to the chance of abuse) could be extrapolated from the confined clinical trial environment to the real world.

Integrating the assessment of abuse potential in drug development is a critical exercise that sponsors and regulators are called to face, and the earlier the collaboration is established between the parties, the better the outcome. There is no ideal recipe to follow and one strategy does not fit all. However, based on several publications on the subject and experience over multiple interactions with the CSS, we defined the following questions to guide sponsors on their evaluation of major decision points throughout drug development.

1. Is the drug or metabolite CNS-active?
   a. Is the chemistry structure similar to a known drug of abuse?
   b. Is the binding similar to a drug of abuse?
   c. Is the agonist or antagonist function similar to a known drug of abuse?

2. Which behavioral pharmacology study(ies) (i.e., drug discrimination and self-administration) is(are) necessary? Which comparator(s) to use? This can be challenging for new mechanisms of action given that this agreement with agencies is recommended before initiation of the studies.

3. Is the clinical abuse potential study needed? Which comparator(s) to use? Behavioral pharmacology tests(s) will likely inform on the comparator of the clinical study but it would be strongly recommended to seek agreement with regulators before initiation of the study. In the US, the CSS staff is available for review of the protocol.

4. Does the totality of the data in the NDA suggest that the drug has abuse potential? Sponsors are required to make a recommendation on scheduling, according to the Controlled Substance Act, if the response to this question is positive.

Covance Abuse Liability Expertise in Regulatory Strategy

Global Regulatory Affairs Strategy
Beatriz A. Rocha MD, PhD
Executive Director
Head of Global Regulatory Affairs Clinical Strategy

▶ More than 30 years of professional experience that spans from academia and government to industry, and includes clinical practice in anesthesia and pain management, clinical research, basic research and regulatory affairs strategy during the last 12 years.
▶ Recognized expert in the development of overall regulatory strategy on the assessment of abuse potential of drugs in development; she is the Chair of the Regulatory Workgroup of the Cross Company Abuse Liability Consortium in which capacity she been involved in policy discussions with the Controlled Substance Staff/FDA since 2006.
▶ Currently serving as a reviewer for NIH/NIDA Medications Development Division, and on the Board of Directors of the College on Problems of Drug Dependence, where she also chairs the Industry/Academia Government Relations Committee.
▶ As Executive Director of Global Regulatory Affairs Clinical Strategy at Covance Inc., she provides leadership on the overall abuse liability strategy in preparation for NDA filing during drug development and support for negotiations during NDA review.
During Drug Development (Pre-NDA filing)

- Developing overall nonclinical and clinical regulatory strategies for assessing abuse potential of compounds throughout development—Working in collaboration with Covance Market Access
- Supporting engagement with the Controlled Substance Staff (CSS)/FDA at all levels of development (pre-IND, End-of-Phase II, pre-NDA)
- Supporting preparation of Human Abuse Liability protocols and CSS review of protocol
- Developing 8-Factor Analysis and corresponding eCTD Modules

During NDA review

- Developing strategies to engage with the DEA
- Supporting responses to questions and interactions with the CSS/FDA
- Supporting scheduling and labeling discussions with the FDA

References and Additional Suggested Reading


FDA News Release, February 5, 2016
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm484765.htm


11 http://www.fda.gov/NewsEvents/FactSheets/ucm484714.htm
12 http://www.fda.gov/AdvisoryCommittees/Calendar/ucm487034.htm
13 http://www.deadiversion.usdoj.gov/schedules/

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