ASSESSMENT OF ABUSE LIABILITY OF BRAIN-PENETRANT COMPOUNDS:

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

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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 U.S. or a Market Authorization Application (MAA) ex-U.S.

In the U.S., 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 U.S., EU and Canada, assessment of abuse potential is required to be completed before NDA/MAA filing for all brain-penetrant compounds and metabolites regardless of the indication. Finalized and Draft guidances for industry in the U.S. make recommendations for the overall nonclinical and clinical assessment of abuse potential (2017 guidance), and the development of abuse-deterrent formulations (ADF) for new and generic opioids analgesics (2015 guidance and 2016 draft guidance, respectively). Taken together these guidances are part of the "FDA Opioid Action Plan" announced in 2016 in response to the alarming increase in the number of opioid related overdoses and deaths (Callif et al., 2016).

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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 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. (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003360.pdf).

Subsequently, in 2007, Health Canada published the Clinical Assessment of Abuse Liability for Drugs with Central Nervous System Activity. (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guideld/abus/abuse_liability_abusif_usage_clin%20eng.php).

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. (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf). Consistent 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 U.S., draft guidelines were available from 1990 to 2001, but only in 2010 was the revised draft guidance on the assessment of abuse potential of drugs published. It was finalized in January 2017. (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf).

In 2003, the Controlled Substance Staff (CSS) of the FDA was created to oversee the evaluation of abuse liability, drug dependence, risk management and the recommendation of drug scheduling of compounds under development. Since then, CSS' active participation in scientific meetings has facilitated 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 U.S. (Rocha BA et al., (2011) Companies unite to advance regulatory landscape of abuse potential assessment. Reg Focus 16:8–13).

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 (Rocha, BA et al., 2011). 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 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 (National Institute on Drug Abuse [NIDA], Food and Drug Administration [http://www.seiservices.com/nida/ 1014102/agenda.aspx]).

The final 2017 guidance includes a discussion as to when to conduct the recommended abuse-related studies, and indicates the key decision points for sponsors to consider when planning the assessment of abuse potential. In addition, the guidance provides recommendations on how to appropriately design abuse-related nonclinical and clinical studies, and when to conduct them during the development process. Even though the final guidance significantly expands on concepts introduced in the 2010 draft guidance, it is clear that sponsors need to consider each NME on its own when planning for the assessment of abuse liability. The best approach is still considered to be to start planning the overall strategy and engaging with the FDA/CSS early in development.

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 commonly than heroin or cocaine (Paulozzi et al. [2006] Increasing deaths from opioid analgesics in the United States Pharmacoepidemiol. Drug Saf., 15; pp. 618–627).

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 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf), and has recommendations on studies necessary to demonstrate that a given formulation has abuse-deterrent (AD) 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. However, the guidance also acknowledges that the science of abuse deterrence is relatively new, and formulation technologies, analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. Therefore, the Agency is taking a flexible approach to the evaluation and labeling of potentially ADF products.

As of May 8, 2017, the FDA has approved ten products with AD formulations of Extended Release (ER) opioids: OxyContin Neo® (oxycodone, crush/extraction resistant), Embeda® (morphine/naltrexone), Targiniq™ ER (oxycodone hydrochloride/naloxone), Hysingla® ER (hydrocodone, crush/extraction resistant), MorphaBond™ (oxycodone/ naloxone), Xtampza® ER (oxycodone, intravenous/inhalation resistant), Troxyca® ER (oxycodone/naltrexone), Arymo™ ER (morphine, cutting/crushing/grinding/breaking resistant), and Vantrela™ ER (hydrocodone, crushing/breaking/extraction resistant). The first oxycodone hydrochloride immediate release oral tablets (RoxyBond™) was approved on April 20, 2017. RoxyBond™ is formulated using SentryBond(TM) abuse-deterrent technology to make the product more difficult to manipulate and abuse by the intranasal and intravenous routes.

A draft guidance to industry with recommendations for evaluating abuse-deterrent formulations of generic (solid oral) opioid drugs, (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM492172.pdf) published in 2016, 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. Currently, there are no approved generic versions of opioids with AD labeling.

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 U.S. in 2014 (Center for Disease Control and Prevention, 2015). In 2015, more than 15,000 people died from overdoses involving prescription opioids (CDC 2016 Wide-ranging online data for epidemiologic research [WONDER]).

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 Opioids 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, strengthens post-market requirements, updates of the Risk Evaluation and Mitigation Strategy (REMS) Program, reassesses the risk-benefit approval framework for opioid use, and expands the use of advisory committees. (http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm).

Accordingly, on March 1, 2016, the FDA sought advice from the agency's Science Board (http://www.fda.gov/AdvisoryCommittees/Calendar/ucm487034.htm) 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 U.S. 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 (http://www.cdc.gov/media/modules/dpk/2016/dpk-pod/rr6501e1er-ebook.pdf).

Since April 2014, the Agency finalized a 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 AD properties, used for the management of chronic pain now have a harmonized indication intended to emphasize the need to balance risk with benefit: "the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate." Besides the harmonized indication, the safety labeling changes included 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 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.

Drug Scheduling under the Controlled Substance Act (CSA)

When the FDA reviews the safety and efficacy of a NDA under the 1938 Food, Drug & Cosmetics (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 is categorized according to a schedule (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 (http://www.deadiversion.usdoj.gov/schedules/). Scheduling categorization is a comparative exercise between the test drug and known drugs of abuse. Given that nonclinical and clinical comparability assays, such as drug-self-administration, were developed and validated for known drugs of abuse, for NMEs with new mechanisms of action, identifying the appropriate controlled substance for comparison (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 legislation, 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 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 registration of manufacturers and distributors seeking to conduct clinical trials, as noted previously (https://www.congress.gov/bill/114th-congress/house-bill/639/text).

This law tasks the DEA to make an interim scheduling decision within 90 days of the FDA creating a scheduling recommendation. The date of the DEA's interim scheduling decision is now to be considered the date of the NDA's approval, 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.

For the first time in a regulatory document, the 2017 Guidance on the Assessment of Abuse Potential of Drugs clearly describes the drug scheduling process and the consequences of the 2015 Improving Regulatory Transparency for New Medical Therapies Act .

Regulatory Expectations

Assessment of Abuse Potential (AP) of CNS-Active NMEs and Products That Contain CNS-Active Substances That Are Already Controlled Under the CSA

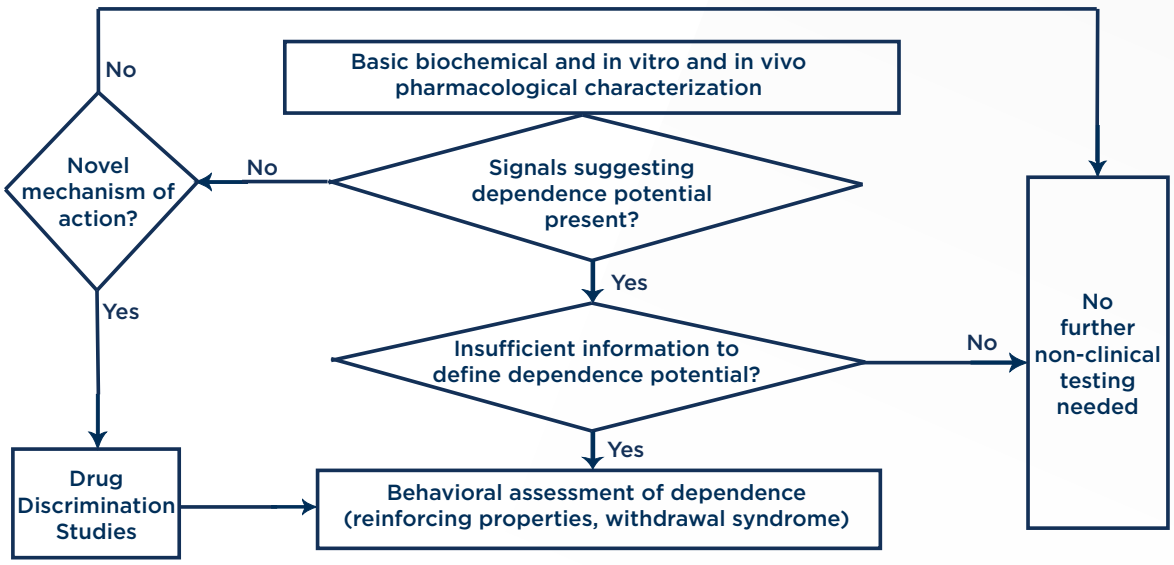
Assessment of abuse potential of NMEs during drug development is a very complex and expensive process. It takes into consideration the totality of nonclinical and clinical data available at filing, which may include specific nonclinical experiments, such as drug discrimination and self-administration, as well as a dedicated clinical study in poly-drug users (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 to obtain agreement on timing and adequacy of studies.

Abuse potential of a drug is considered a safety issue, and consequently the nonclinical evaluation is conducted to support approval and must be done under Good Laboratory Practice (GLP) conditions, 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 guideline 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 (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003360.pdf)

Non-clinical Testing of Dependence Potential of CNS-active Compounds



In the U.S., following the publication of the draft guidance in 2010, several discussions between industry, academia and the FDA/CSS occurred, with the CSS proposing a decision tree aligning nonclinical and clinical evaluation throughout development. The FDA 2017 final guidance formalizes these recommendations and recommends sponsors to discuss their planned abuse-related studies with the CSS via the review division throughout development, from the pre-IND through the NDA review cycle as appropriate.

Three decision points where sponsors are advised to pause and review their plans for assessment of abuse potential are:

1. **Nonclinical Phase –** review of chemical structure and in vitro/in vivo binding profile. Plans for the nonclinical evaluation need to be established 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 Abuse Potential (completed and planned studies) during the EOP2 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 –** summarize all abuse-related data (nonclinical and clinical) for discussion during a pre-NDA meeting with the review division, and request participation of the CSS. The discussion around the entire abuse-related dataset generated during development is to confirm the planned content for the abuse potential assessment and to describe the intended organization and data file formats for the NDA submission.

Directions for preparing the NDA submission with details on the content of an abuse potential section of the NDA are now part of the 2017 Guidance. Overall, the abuse potential section of the NDA should also include (or cross-reference) the Integrated Summary of Safety (ISS), as well as data reflecting abuse of the drug substance contained in the new drug (or similar drugs) in the form of an approved drug product or as an illicit substance. The guidance also indicates that abuse-related studies and data should be submitted in the electronic common technical document (e-CTD), and offers the list of modules where the appropriate information is to be included.

eCTD Module	Content
1.11.4	Proposal and rationale related to drug scheduling
2.7.4	Outline of all abuse-related animal and human data, discussion of the data and conclusions about the drug's abuse potential (cross-link to the proposal for scheduling and product labeling in Module 1 and all abuse-related studies and data in Modules 3, 4 and 5.
3	Chemistry
4	In vitro and animal pharmacology, including behavioral safety studies, pharmacokinetics and pharmacodynamics studies
5	Clinical studies including human abuse potential studies, human pharmacokinetics studies and ISS
5	Post-marketing experience including reports of abuse, addiction, and deaths from the U.S. and outside U.S. sources

Regulatory Expectations for the Development of Opioid Analgesics and Pain Therapies

In view of the current epidemic of opioid abuse, its impact in public health epidemics, the regulatory environment and the government's initiatives, such as the FDA Opioid Action Plan, the development of abuse-deterrent formulations is required for new and generic opioids. Even though, as of May 2017, ten opioid products with abuse-deterrent formulation (ADF) have been approved in the US, the FDA recognizes the need for additional technology research on ADF 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 syringeability studies, and in vivo clinical abuse potential studies (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 abuseable 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 FDA Extended-Release/Long-Acting 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 is strongly recommend seeking agreement with regulators before initiation of the study. In the U.S., 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 CSA, if the response to this question is positive.

Covance Abuse Liability Expertise in Regulatory Strategy

Global Regulatory Affairs Strategy
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- 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 14 years.
- Recognized expert in the development of overall regulatory strategy on the assessment of abuse potential of drugs; she is the Chief Operating Officer of the Cross Company Abuse Liability Consortium in which capacity she has 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 sitting on the Board of Directors of the College on Problems of Drug Dependence.
- As Executive Director and Head 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

- Developing overall nonclinical and clinical regulatory strategies for assessing abuse potential of compounds throughout development – Working in collaboration with Covance Early Development.
- Supporting engagement with the Controlled Substance Staff (CSS)/FDA at all stages of development (pre-IND, End-of-Phase II, pre-NDA).
- Supporting preparation of Human Abuse Liability (HAL) 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

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