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Developing comprehensive strategies to assess abuse liability/potential of brain-penetrant compounds

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When developing a drug that penetrates or targets sites in the central nervous system (CNS), drug development sponsors must evaluate whether their new product has abuse potential. The assessment of abuse liability of New Molecular Entities (NMEs) represents a complex and challenging aspect of drug development as it encompasses all properties—chemical, pharmacological, pharmacokinetics, usage and diversion history—of brain-penetrant compounds and/or metabolites. The complete assessment is to be included in the New Drug Application (NDA) filing.

To help drug development sponsors develop and execute on their strategy to assess abuse liability during development, this white paper provides an overview of the legal and regulatory frameworks, explains the criteria for scheduling drugs and shares key considerations for conducting abuse liability studies and engaging with regulators during drug development.

Understanding the legal and regulatory framework of the assessment of abuse liability: Scheduling considerations

From a regulatory perspective, abuse potential is a safety issue, and as such, it is part of the standard NDA review. Under the 1938 Food, Drug & Cosmetics (FD&C) Act, the basis of product approval is its safety and effectiveness under the labeled conditions of use. However, a safe and effective product does not mean it is free of risks, but that its clinical benefit is superior to its risks. A product's label is a communication tool to make healthcare providers and patients aware of the potential risks of a product, including its potential for abuse, which is the potential to be used in a non-medical situation based on the positive psychoactive effects the drug produces through CNS activity.

To assist sponsors in writing the DRUG ABUSE AND DEPENDENCE section of labeling, as described in the regulations for the content and format of labeling for human prescription drug and biological products (21 CFR 201.57(c)(10)),[1, 2] the FDA has issued a guidance entitled "Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products – Content and Format Guidance for Industry" on overall labeling content.[3]

Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970, the Controlled Substance Act (CSA), provides the legal basis for the U.S. government to control drugs and other substances—regardless of the indication—that have potential for abuse.

Once the FDA determines that the drug has potential for abuse, it will send the scheduling recommendation to the Drug Enforcement Agency (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 (21 CFR Part 812, 21 CFR Part 802) 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.[4]

See figure 1 on the following page.

Figure 1: An overview of the criteria for scheduling under the CSA

	Schedule I (CI)	Schedule II (CII)	Schedule III (CIII)	Schedule IV (CIV)	Schedule V (CV)
	NO MEDICAL USE	MEDICAL USE			
	Heroin Hallucinogens Marijuana	Opioids Barbiturates Cocaine Amphetamine Methylphenidate Methamohetamine PCP	Opioids (codeine combinations, buprenorphine) Ketamine, GHB Marinol, anabolic steroids	Benzodiazepines and other depressants (Zaleplon, Zolpidem, Eszoplicon) Fenfluramine Modafinil Butorphanol	Pregablin, Orexin antogonist, Lascosamide
Registration	Required	Required	Required	Required	Required
Recordkeeping	Separate	Separate	Readily retrievable	Readily retrievable	Readily retrievable
Distribution restrictions	Order forms	Order forms	Records required	Records required	Records required
Dispensing limits	Research use only	Rx: written, No refills	Rx: written or Oral refills with MD's authorization	Rx: written or Oral refills with MD's authorization	OTC **(Rx drugs limited to MD's order)**
Manufacturing security	Vault/safe	Vault/safe	Secure storage	Secure storage	Secure storage
Manufacturing quotas	Yes	Yes	No **Some drugs limited by Schedule II**	No **Some drugs limited by Schedule II**	No **Some drugs limited by Schedule II**
Import/export narcotic	Permit	Permit	Permit	Permit	Permit to import, declaration to export
Reports to DEA manufacturers & distributors	Yes	Yes	Yes	Manufacturer only	Manufacturer only

Therefore, 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 and the Human Abuse Potential (HAP) study, 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. In this circumstance, reaching an agreement with the Controlled Substance Staff (CSS) of the FDA on the appropriate active comparator should be one of the highest priorities.

FDA approval and DEA scheduling

FDA approval of a new drug product and DEA scheduling are two independent processes under different legislations: the FD&C Act and the CSA, respectively. Commercial availability of the product requires FDA-approved and finalized labeling that includes the DEA's decision on schedule classification.

Until 2015, the time between FDA approval of a new therapy with potential for abuse and DEA scheduling was inconsistent. In some instances, scheduling after NDA approval took more than one year, preventing drug companies from marketing their drug during this period, and consequently, preventing patients in need from having access to an FDA-approved therapy. In 2015, the "Improving Regulatory Transparency for New Medical Therapies Act" amended the CSA by tasking the DEA to make an interim scheduling decision within 90 days of the FDA's approval and scheduling recommendation. The date of the DEA's interim scheduling decision is considered the date of the NDA's approval and permits the drug to be marketed. The drug's marketing exclusivity, therefore, starts when the interim final rule controlling the drug is issued in accordance with section 201(j) of the CSA.

Evaluating abuse potential during drug development

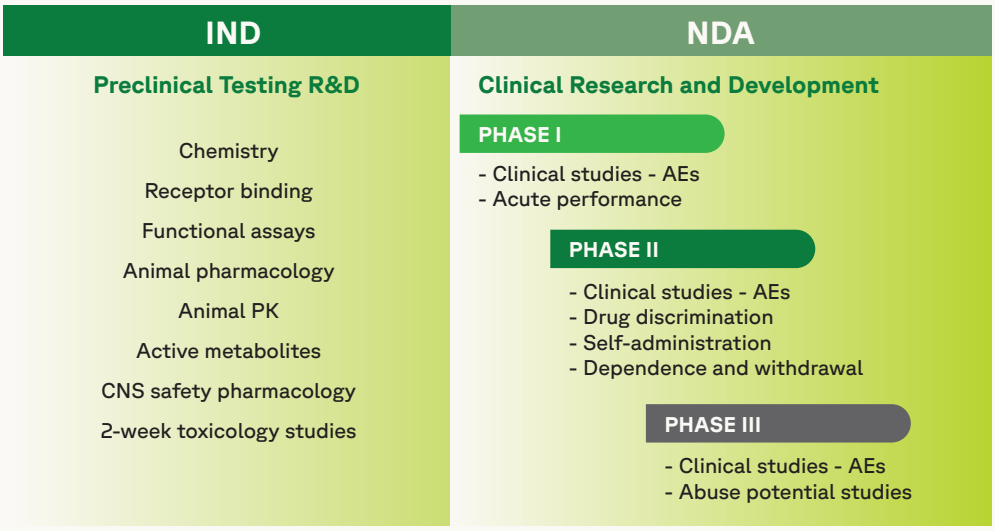
Integrating the assessment of abuse potential in drug development is a critical exercise that sponsors and regulators are called to face. While sponsors must identify the risk of abuse and frequently are called to prove the null hypothesis, regulators are challenged to evaluate the probability that such risk (i.e., the exposure to the chance of abuse) could be extrapolated from the confined clinical trial environment to the real world. There is no ideal pre-set procedure to follow, and one strategy does not fit all.

The assessment of abuse potential is complex and a multidisciplinary approach needs to be integrated in the overall nonclinical and clinical regulatory strategies. The 2017 FDA Guidance on the Assessment of Abuse Potential of Drugs[5] recommends several nonclinical studies and what data may indicate that the HAP study is required. However, given such assessment is required for the NDA filing of all brain-penetrant and active CNS drugs and/or metabolites, regardless of the indication, it is critical for sponsors to obtain agreement with the CSS on the timing and adequacy of the abuse-related studies. The earlier sponsors engage with the CSS the better the outcome, and the higher the probability of removing potential roadblocks to development, ensuring that assessment of abuse potential is not in the critical path for NDA filing.

Fortrea encourages sponsors to incorporate abuse liability strategies into their development plan in the very early stages of development of active CNS drugs. These strategies should be revisited and refined throughout development, but at a minimum should be presented to the CSS at the three key points of development:

1. **Pre-IND meeting** - review the chemical structure and *in vitro/in vivo* binding profile and discuss with the CSS plans for the nonclinical evaluation, which is to be performed under Good Laboratory Practice (GLP) conditions in compliance with ICH S7A guideline (Safety Pharmacology Studies for Human Pharmaceuticals). If nonclinical protocols are not yet finalized, it is recommended to obtain CSS agreement on the timing of the protocols review.
2. **End-of Phase II (EOP2) meeting** - review the entire safety database obtained to date (clinical pharmacology program and Phase II studies), with a focus on adverse events (AE) interest, such as hallucinations and mood swings occurring at the expected clinical efficacious dose(s). During the EOP2 meeting, it is expected that sponsors will present a complete review of the strategy for assessing abuse potential (completed and planned studies), including considerations about conducting the HAP study. It is recommended to obtain CSS agreement on the timing of the HAP protocol review.
3. **Pre-NDA meeting** - summarize and present all abuse-related data (nonclinical and clinical) for discussion with the review division and request participation of the CSS. The discussion around the entire abuse-related dataset generated during development helps confirm the planned content for the abuse potential assessment and describes the intended organization and data file formats for the NDA submission.

Figure 2. An overview of studies to conduct by phase



Performing a Human Abuse Potential study

HAP studies present additional challenges compared to traditional Phase I studies, mostly due to the complexity of the target population, design and assessments. In study execution, using specialized subjective assessment scales (e.g., visual analog scale [VAS]) requires well-trained clinical staff and subjects, and multiple assessments in the clinic, which can be challenging. "Drug liking" is the most common primary outcome measure, but several others, such as "take drug again" and behavioral and cognitive performance assessments are included. To assess early exposure, duration of exposure and Tmax, several blood samples are required to define the PK profile in relation to the subjective outcomes and the AEs associated with abuse potential, such as mood-related AEs.

The vast amount of data generated in a HAP study requires extensive data management. Due to the many complexities involved in the design and execution of a human abuse potential study, obtaining concurrence with the CSS on the protocol is a critical step to ensure that human abuse potential data will be acceptable and satisfy CSS review expectations. The CSS recommends that sponsors submit a well-developed protocol synopsis to gain agreement on the overall study design, and on the doses of the test drug, the proposed active comparator and the study population.

Preparing for an NDA submission

The FDA's 2017 guidance, Assessment of Abuse Potential of Drugs, outlines how to prepare the abuse potential section of an NDA submission.[6] At a high level, the abuse potential section of the NDA should include (or cross-reference) the Integrated Summary of Safety (ISS) along with 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 (eCTD) and offers the list of modules where the appropriate information is to be included.

During the NDA review, the totality of available nonclinical and clinical data is taken into consideration in the overall evaluation of abuse liability. These data may include specific nonclinical experiments, such as drug discrimination and self-administration, as well as the HAP study. Sponsors should develop strategies to engage with the DEA, understand how to respond to questions from the CSS and effectively engage with the FDA in scheduling and labeling discussions.

Fortrea's recommendations

Based on a vast body of literature on the subject and experience over multiple interactions with the CSS, Fortrea has defined the following questions to guide sponsors as they evaluate 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 known drug of abuse?
    c. Is the agonist or antagonist function similar to a known drug of abuse?

2. **Which nonclinical behavioral studies should be conducted?**
    a. Which behavioral pharmacology study(ies) (i.e., physical dependence/withdrawal, drug discrimination, self-administration) is(are) necessary?
    b. Which comparator(s) should be used? This can be challenging for new mechanisms of action given that this agreement with agencies is recommended before initiating the studies.

3. **Should the HAP study be conducted?**
    a. Is the clinical abuse potential study needed?
    b. Which comparator(s) should be used? Behavioral pharmacology tests(s) will likely inform on the comparator of the clinical study, but it is strongly recommended to seek agreement with regulators before initiating the study. The CSS staff is available to review the protocol.

4. **Does the totality of the data in the NDA suggest that the drug has abuse potential (i.e., how has the new compound compared to the controlled substances of reference [active comparators] in the nonclinical and clinical abuse-related studies conducted)?**

    If the response to this question is positive, according to the CSA, sponsors are required to include a recommendation on scheduling in the NDA.

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