



Assessing Drugs with Potential for Abuse

FDA's new guidance to aid sponsors with CSA

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OVER THE PAST YEAR, THE FDA has been focusing efforts on the regulation of controlled substances to ensure the ongoing safety of existing products. It has determined that certain opioid drugs required Risk Evaluation and Mitigation Strategies (REMS) and has held a number of public and stakeholder meetings related to the development of the REMS. It has also held an advisory committee hearing to determine that propoxyphene could safely remain on the market with strengthened warnings, a Medication Guide, and development of additional safety data, and it wrote several warning letters to companies marketing controlled substances, both to those marketing unapproved drugs and those marketing approved products contrary to product labeling. While these actions may signal additional scrutiny of post-market products, FDA recently released a draft guidance document suggesting additional consideration of such products prior to marketing.

In January 2010, FDA released a draft guidance document entitled, "Guidance of Industry: Assessment of Abuse Potential of Drugs," intended to aid sponsors in developing drug products with potential for abuse that may require scheduling under the Controlled Substances Act (CSA). The CSA balances minimizing abuse potential and diversion of scheduled substances with allowing access to scheduled products with therapeutic value, by assigning drugs with abuse potential to Schedules I-V, oriented from most to least restrictive. While there is no accepted medical use of Schedule I drugs in the U.S., Schedules II-V are permitted for use with varying controls, which include manufacturing and production quotas and security requirements, prescribing and dispensing restrictions, and record-keeping, reporting, and registration obligations. The draft guidance document addresses the definition of "abuse potential," submission of an abuse potential assessment, what constitutes an adequate abuse potential assessment, and how such assessment should be performed.

The Department of Health and Human Services (HHS) is tasked with reviewing drugs with abuse potential and recommending to the Drug Enforcement Agency (DEA) whether they should be scheduled according to the CSA. In its scientific and medical assessment, HHS must consider eight criteria triggering control under the CSA:

- the drug's actual abuse potential,
- scientific evidence of the product's pharmacologic effects,
- the current scientific knowledge regarding the drug,
- its history and current pattern of abuse,

- the scope, duration, and significance of abuse,
- the potential public health risk,
- the psychic or physiological dependence liability, and
- whether the substance is an immediate precursor of an already-controlled substance.

To facilitate HHS' evaluation of the drug's abuse potential, legitimate medical use, and safety potential, sponsors must submit a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling, known as an abuse potential assessment. While the CSA does not define "abuse potential," "abuse liability," and other, similar terms, the draft guidance specifies that these terms can be understood to encompass similar concepts, and may often be used interchangeably. According to the draft guidance, "abuse potential" refers to drugs used in non-medical situations, repeatedly or sporadically, for the positive psychoactive effects they produce and are characterized by their central nervous system effects. Drugs with abuse potential often lead to psychic or physical dependence, including the possible disorder of addiction. "Abuse potential" refers to all the properties of the substance, including its chemical, pharmacological, and pharmacokinetic profiles, and its usage and diversion history. The draft guidance document defers to the American Academy of Pain Medicine, American Pain Society, and American Society of Addiction Medicine 2001 consensus document in defining the term "addiction" as a "chronic, neurobiological disorder with genetic, psychosocial, and environmental aspects, characterized by one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving."

Sponsors should be aware that an abuse potential assessment — an evaluation of studies and other information related to the potential abuse of a drug and including a proposal for scheduling if the drug affects the CNS, is chemically or pharmacologically similar to other drugs with known abuse potential, or produces psychoactive effects — may be needed for new drugs, including new molecular entities or for marketed drug products presenting an unexpected safety profile implicating abuse potential or being evaluated for a new administration route that could affect the product's abuse potential. The abuse

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potential assessment, submitted as a section of the application, should contain pertinent preclinical, pharmacological, chemistry, biochemical, human laboratory, clinical study, and drug information data, as well as the scheduling proposal, which describes the drug's abuse potential and dependence liability.

The draft guidance document outlines several approaches and methods that may be used in evaluating the abuse potential of a drug product, including preclinical screening, chemistry and manufacturing, animal behavioral pharmacology studies, application of good laboratory practice, and product pharmacokinetics/pharmacodynamics. At preclinical screenings of new drugs with abuse potential, *in vitro* receptor binding studies can be used in determining the pharmacological site of action for the product and its active metabolites, including assays of not only high-affinity sites, but also other neurotransmitter systems associated with abuse potential. *In vivo* binding techniques may also provide useful data regarding the localized action of drugs.

With respect to chemistry and manufacturing data the following should be included in the abuse potential assessment: information related to the drug's synthesis, data on the physical and chemical properties of the substance and the drug, and data on alternate synthetic pathways and drug characteristics. Additionally, the assessment should appraise the physicochemical properties of the drug substance and product, including information on extractability and solubility. The draft guidance document also recommends the sponsor conduct studies to provide information on the product's performance under different conditions, e.g., application of heat or multiple applications of a transdermal system. Abuse deterrent formulations should be subject to additional scrutiny, and a new formulation designed with a possible abuse deterrent claim should be studied for relative abuse potential in human pharmacology studies wherein the abuse potential of the study formulation should be compared to a previously approved product as a positive control. The study should include robust assessments of efficacy, safety, biopharmaceutics including alcohol interaction, and epidemiologic studies to support an abuse deterrent claim.

While the field of animal behavioral studies continues to evolve, FDA believes information derived from such studies can help determine what additional studies, if any, should be conducted in animals or humans. These studies use several species, typically rodents and primates; sponsors will need to justify the animal model selection and the prior drug history of the animals selected. The study design must consider the appropriate sample size, the effect of the route of administration, the correlation of plasma levels of the drug and its metabolites in the animal versus in humans, the use of appropriate negative and positive control groups, the behavioral effects of a range of doses, and the pharmacokinetic profile. A variety of approaches may be used to study abuse potential in animals, including self-administration tests, conditioned place preference, drug discrimination methods, and psychomotor tests, based on the chemical and pharmacological properties of the drug, its pharmacological class, and current knowledge of its abuse potential. Dependence potential may also be considered, including tests for tolerance and physical dependence, as part of the safety assessment of a drug and should be considered in drug scheduling. The draft guidance

document specifically informs industry that good laboratory practices, as described in "S7A Safety Pharmacology Studies for Human Pharmaceuticals" and FDA regulations, apply to abuse potential studies in animals.

Finally, the draft guidance document describes the importance of characterizing the substance and drug product's pharmacokinetic and pharmacodynamic properties in determining abuse potential. System exposure to the drug from preclinical and clinical studies — including information on maximum concentration, time to onset, time to maximum concentration, area under the curve, and the terminal elimination of the parent drug and any psychoactive metabolites — should be considered in the abuse potential assessment, as well as data on bioavailability, distribution volume, and drug clearance. Information on pharmacodynamic properties should be included if available, and factors that may change the product's properties (e.g., crushing a tablet) should also be collected.

The draft guidance document also discusses human laboratory studies, including human abuse potential study in recreational drug users, related pharmacology studies, and clinical trial data relative to abuse potential assessments. The human abuse potential studies consist of pharmacology assessments of CNS-active drugs to provide information on the relative abuse potential of the product in humans. The studies are typically conducted in a population experienced in recreational drug use after sufficient data on safety and efficacy have been developed. Sponsors are strongly encouraged to proactively involve FDA in such studies, including submitting protocols for FDA review and advice on design and safety issues before beginning the study. Related pharmacology studies, e.g., psychomotor tests, should be done to test other aspects of human pharmacology such as cognitive and performance impairment. Finally, the evaluation of clinical trial adverse event data through systematic categorization, tabulation, and analysis can illuminate an abuse potential signal. In support of this, as part of Phase III trials, sponsors should

- set criteria and collect data on abuse, misuse, noncompliance, and diversion cases,
- provide complete information on all instances of addiction, abuse, misuse, overdose, drug diversion/accountability, noncompliance, protocol violations, lack of efficacy,
- list individuals lost to follow-up, and other reasons why subjects dropped out of the study, and
- provide information on the risks of addiction, abuse, misuse, overdose, and drug diversion in the study population.

The importance of the draft guidance document and the concept it contains is readily apparent: based in part on the information submitted in the application, FDA prepares a scientific analysis with a recommendation for scheduling, which is forwarded to DEA for consideration in the final scheduling of the drug and in turn, results in specific regulatory requirements relating to the drug's labeling, prescribing, advertising, manufacturing, promotion, marketing, and use in the practice of medicine. Industry members are encouraged to review and submit comments on the draft document by March 29, 2010. ■