Guidance for Industry

Assessment of Abuse Potential of Drugs

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
January 2010

Clinical Medical

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I. INTRODUCTION

This guidance is intended to assist sponsors who are developing drug products with the potential for abuse that may need to be scheduled under the Controlled Substances Act (21 U.S.C. 811(b), 811(c)). Examples of products that are addressed in this guidance include new molecular entities and new dosage forms of drug substances already controlled under the Controlled Substances Act (21 U.S.C. 812(c)). Drugs with abuse potential generally include drugs that affect the central nervous system, drugs that are chemically or pharmacologically similar to other drugs with known abuse potential, and drugs that produce psychoactive effects such as sedation, euphoria, or mood change.[2]

Specifically, the guidance discusses the following:

- The definition of *abuse potential*
- Information on submitting an abuse potential assessment, including a proposal for scheduling
- A description of what constitutes an adequate abuse potential assessment
- Information for sponsors performing an assessment, including (1) the design and conduct of appropriate studies and investigations and (2) general administrative recommendations for submitting a proposal for scheduling

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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[1] This guidance has been prepared by the Controlled Substance Staff (CSS) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970), reprinted in 1970 U.S.C.C.A.N. 4566, 4603.

II. BACKGROUND

The purpose of scheduling substances under the CSA is to minimize abuse and diversion while affording appropriate therapeutic access. Each schedule under the Controlled Substances Act includes a set of regulations that are most restrictive for the Schedule I and II substances and are relatively less restrictive for the Schedule III to V drugs, respectively. Drugs in Schedule I have no accepted medical use in the United States. Depending on the Schedule (II-V), controls may include manufacturing and production quotas, varying degrees of manufacturing and distribution site security requirements, dispensing and prescribing limitations, a range of record-keeping and reporting requirements, and import/export regulations. Prescribers, dispensers, drug manufacturers, and distributors are required to register with the Drug Enforcement Administration (DEA).

Before a drug with a potential for abuse is controlled under the Controlled Substances Act (CSA), the Secretary, Department of Health and Human Services (HHS), must make a recommendation for scheduling under the CSA to the DEA. The regulatory responsibilities for this process are described in 21 U.S.C. 811 and 812, as well as in 21 CFR parts 1300-1316.

Under 21 U.S.C. 811(b) of the CSA, the Secretary of HHS is required to consider, in a scientific and medical evaluation, eight factors determinative of control under the CSA. Following consideration of the eight factors, the Secretary must make three findings and a recommendation for scheduling a substance in the CSA. The eight factors are set out in 21 U.S.C. 811(c) as follows:

1. Its actual or relative potential for abuse

2. Scientific evidence of the drug's pharmacological effects

3. The state of current scientific knowledge regarding the drug or other substance

4. Its history and current pattern of abuse

5. The scope, duration, and significance of abuse

6. What, if any, risk there is to the public health

7. Its psychic or physiological dependence liability

8. Whether the substance is an immediate precursor of a substance already controlled.

The findings relate to a substance's abuse potential, legitimate medical use, and safety or dependence potential, which are factors considered in scheduling drugs under 21 U.S.C. 812.

When a sponsor submits a new drug application (NDA) to the FDA for review, if the drug has a potential for abuse, the sponsor must submit "a description and analysis of studies or information related to abuse of the drug, including a *proposal for scheduling* (emphasis added) under the Controlled Substances Act." (21 CFR 314.50(d)(5)(vii)). In addition, a description must be submitted "of any studies related to overdosage, . . . including information on dialysis, antidotes, or other treatments, if known" (id.).

1. The Controlled Substance Staff evaluates the drug's abuse potential. The Controlled Substance Staff prepares a scientific analysis, including a recommendation for scheduling, based on a scientific and medical evaluation of all relevant and available data (including the public health risk and the sponsor's proposal for scheduling), as required by the CSA.

2. FDA provides the analysis to the National Institute on Drug Abuse (NIDA) for review and comment, as described in the Memorandum of Understanding (MOU) of March 8, 1985 (50 FR 9518-20).

3. The FDA analysis is reviewed and approved by the Office of Chief Counsel, the Center Director, and the FDA Commissioner.

4. FDA then forwards the FDA proposed scheduling recommendation to the Assistant Secretary for Health, who makes the HHS recommendation for scheduling that is transmitted to the DEA.

5. In accepting the HHS recommendation to schedule a drug, DEA publishes a notice of proposed rulemaking in the Federal Register wherein DEA proposes scheduling, describes the proposal and requests comments from the public. After the comment period (usually of 30 to 60 days) has expired, DEA reviews any comments, objections, and requests for a hearing that they have received, and publishes another FR notice, either finalizing the scheduling action with an effective date or responding to the objections and hearing requests.

If the DEA determines that a drug requires scheduling, the sponsor must follow specific regulations related to drug labeling, manufacturing, storage, ordering, prescribing and dispensing. See generally 21 CFR parts 1300-1316. Sponsors are encouraged to contact the DEA early in the drug development process if they believe their drug may have abuse potential and may be controlled and to discuss with the DEA issues related to CSA researcher registration requirements, quotas, and other rules and regulations that concern controlled substances that may be relevant to their product.

III. DETERMINING A DRUG'S ABUSE POTENTIAL

A. Definitions

The Controlled Substances Act refers to the assessment of "potential for abuse," "addiction-sustaining liability," and "dependence" 21 U.S.C. 802(1),(9),(18),(29). The Controlled Substances Act does not define these terms. *Abuse potential* and *addiction-sustaining,* or *abuse liability,* can be understood to encompass similar concepts and, as such, are often used interchangeably.[3,4]

Abuse potential refers to a drug that is used in nonmedical situations, repeatedly or even sporadically, for the positive psychoactive effects it produces. These drugs are characterized by their central nervous system (CNS) activity. Examples of the psychoactive effects they produced include sedation, euphoria, perceptual and other cognitive distortions, hallucinations, and mood changes. Drugs with abuse potential often (but not always) produce psychic or physical dependence and may lead to the disorder of *addiction.*

The concept of *abuse potential* encompasses all the properties of a drug, including, for example, chemical, pharmacological, and pharmacokinetic characteristics, as well as fads in usage and diversion history.

Addiction is defined 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 (American Academy of Pain Medicine, American Pain Society, and American Society of Addiction Medicine consensus document, 2001).

B. When Should an Abuse Potential Assessment Be Submitted to FDA?

A sponsor must submit in the NDA an assessment of studies and other information related to the potential abuse of a drug and include a *proposal for scheduling* if the drug affects the central nervous system (CNS), is chemically or pharmacologically similar to other drugs with known abuse potential, or produces psychoactive effects such as sedation, euphoria, and mood changes. See 21 CFR 314.50(d)(5)(vii).

An assessment of abuse potential may be needed for new drugs, including new molecular entities (NME). An abuse potential assessment might also be necessary for a marketed drug product that presents an unexpected adverse event profile that includes events that are related to abuse potential or that is being re-evaluated for a new route of administration that could affect the abuse potential of the drug.

[3] See the DEA Web site for the schedules of drugs, contact information, pertinent information regarding the Controlled Substances Act, and related topics (http://www.deadiversion.usdoj.gov).

[4] "Conference on Abuse Liability Assessment of CNS Drugs," *Drug Alcohol and Dependence*, 70:3 Suppl. 2003.

C. What Should Be Included in an Abuse Potential Submission?

The abuse potential assessment must be submitted as a section of the NDA or a supplement. The section must contain all pertinent preclinical, pharmacological, chemistry, biochemical, human laboratory, and clinical studies, drug formulation data, and a proposal for scheduling, if appropriate (21 CFR 314.50(d)(5)(vii)). The abuse potential section should also include proposed labeling that describes the drug's abuse potential and dependence liability.

The Controlled Substance Staff evaluates all abuse-related data to help FDA review divisions to determine the suitability of a drug's label and labeling and accordingly may make additional recommendations to the sponsor that relate to the CSS evaluation.

Contents of an abuse potential section include the following:

For NMEs, the NDA should include an abuse potential section with the following:

1. A summary, interpretation, and discussion of abuse potential data provided in the NDA
2. A proposal and rationale for placing (or not placing) a drug into a particular schedule of the Controlled Substances Act
3. All primary data related to the abuse potential characterization of the drug, organized under the following subheadings:

    a. Chemistry
    b. Preclinical Pharmacology
    c. Animal Behavioral and Dependence Pharmacology
    d. Pharmacokinetics/Pharmacodynamics
    e. Human Abuse Potential Laboratory Studies
    f. Clinical Trial Data Relative to Abuse and Dependence Potential
    g. Integrated Summaries of Safety and Efficacy
    h. Foreign Experience with the Drug (Adverse Events, Abuse Potential, Marketing and Labeling)

4. Electronic submissions

For an NDA submitted in electronic format, the common technical document (CTD) should address points 1, 2, and 3a-h (above) under the appropriate Modules 1, 2, 3, 4 and 5. These sections should contain links to the summary of abuse data in Module 2 and the proposal for scheduling and product labeling in Module 1. The data and studies supporting sections 3 a-g (above) should be placed in the appropriate sections of the CTD: Chemistry (Module 3), preclinical and animal pharmacology (Module 4), pharmacokinetics/pharmacodynamics (Modules 4 and 5), human abuse and clinical studies (Module 5), and integrated summaries of safety and efficacy (Module 5). Foreign experience has no specific designated location, but would fit most appropriately under Module 5, postmarket experience.

5. Paper submissions

An NDA that will be submitted in paper form should contain the above listed information clearly identified as an abuse potential section.

The scientific overview of the drug's pharmacological activity should include consideration of the drug's pharmacology, a description of its chemical structure and class, its profile of biochemical activity, its pharmacokinetics and metabolism, the production of any active metabolites (and their pharmacological activity profile), and a description of any adverse reactions.

Sponsors are encouraged to consult with the Controlled Substance Staff through the appropriate FDA centers, offices, or divisions responsible for the overall review of the application about the design of studies and data to be included in an abuse potential section. Discussions between the Controlled Substance Staff and sponsors regarding the proposed studies and data can facilitate adequate data submission and full characterization of the abuse potential of the drug substance or product.

IV. APPROACHES AND METHODS FOR ABUSE POTENTIAL ASSESSMENTS

A variety of approaches that can be used to assess the abuse potential of a drug product are discussed in the following sections of the guidance.

A. Preclinical Screening

In vitro receptor binding studies are an important part of the preclinical screening of new drugs with abuse potential because they are very useful in interpreting the results of other animal and human studies, as well as in the planning of future investigations.

In vitro binding studies should be conducted to determine the pharmacological site of action of the drug and active metabolites in the brain (e.g., receptor, transporter, ion-gated channel system). Novel drug mechanisms of action may be associated with previously unrecognized abuse potential in humans.

Although a drug may have a single high-affinity site, it is important that direct and indirect actions and effects of the drug on other neurotransmitter systems associated with abuse potential be assayed. Examples of neurotransmitter systems of interest include the following:

- Dopamine
- Norepinephrine
- Serotonin
- Gamma-aminobutyric acid (GABA)
- Acetylcholine
- Opioid
- N-methyl-D-aspartate (NMDA)
- Cannabinoid

The application of general scientific principles, including the use of appropriate regional brain tissue, positive controls, and internal standards, should be ensured. High selectivity radioligands should be used whenever they are available. Binding sites can also be analyzed using complementary DNA (cDNA), encoding a specific receptor that is expressed in a homogeneous system.

In vivo binding techniques, such as positron emission tomography (PET) or single photon emission computed tomography (SPECT), can also provide information about the localized action of drugs. Studies using these techniques can contribute important information about the whole body pharmacokinetic and pharmacodynamic properties of the drug in question.

Knowledge of the binding profile may suggest which functional in vitro assays can help determine whether the drug is an agonist, antagonist, partial agonist, or mixed agonist-antagonist at specific binding sites. Based on the biochemical pharmacology, behavioral tests relevant to the specific mechanism of action will be more apparent.

Receptor binding data should be submitted as a part of the pharmacology-toxicology section of the NDA and should also be included in, or hyperlinked to, the abuse potential assessment section of the NDA.

B. Chemistry and Manufacturing

1. Consideration of Chemistry Data

Data from the chemistry, manufacturing, and controls (CMC) section of the NDA that are relevant to the abuse potential of the drug under investigation should be submitted as part of, or be hyperlinked to, the abuse potential section. The assessment of abuse potential should include information related to the synthesis of the drug, data on the physical and chemical properties of the substance and proposed drug product, and data related to alternate synthetic pathways and drug characteristics, including yields and impurity profiles.

In addition to the information submitted as part of the CMC section of the NDA, the abuse potential assessment should include an evaluation of the physicochemical properties of the drug substance and product. Information on extractability and solubility of a drug is relevant to the drug's abuse potential and should be addressed.

Assessment of such data is especially relevant when the new drug product is a new formulation of a drug substance, such as a 505(b)(2) NDA submission, of recognized abuse potential, that presents additional safety concerns. Examples of drugs with the highest relative abuse potentials can be found in Schedule II (see 21 CFR 1308.12 for the most current listing). Additional information on the ease or risk of extraction of the drug substance, that is, the active pharmaceutical ingredient (API), from the product formulation should be obtained. In particular, sustained- or extended-release formulations and transdermal systems (patches or mechanical devices containing drugs) that are expected to contain large quantities of a controlled substance should be assessed

to determine the ease of extracting or altering the drug for abuse and diversion. Transdermal and transmucosal drug products in which excess unused drug substance remains after use are a major concern, and the safe disposal of these products should be addressed in the abuse potential assessment.

Studies should be performed that provide information on the performance of the drug product under different conditions, such as application of bandages or heat or multiple applications of a transdermal system. Information should be obtained on how much drug substance might be released and any changes that could take place in the rate of release of the drug from the drug product if it is misused either intentionally or unintentionally. The effects of pH, temperature, and solvent polarity on disruption or destruction of the drug product matrix should be evaluated. Additional experimental variables may include exposure times to the solvent, agitation, varying the surface area (such as from intact to being ground, crushed, or cut up into pieces), and ease of crushing tablets or destroying the dosage form matrix. In general, assay procedures for drug content already reported under CMC may indicate the best conditions for drug extraction and analysis.

2. Abuse Deterrent Formulations

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. For example, a combination product might be developed that contains an FDA-approved drug with abuse potential and a second FDA-approved drug without abuse potential that causes an adverse effect (e.g., sometimes a sponsor may add a substance to limit or reduce abuse of the narcotic). Several different types of abuse deterrent formulations have been proposed in the scientific literature, including formulations with physical barriers to tampering, combinations of an agonist with an antagonist, components that cause adverse events, and alternative methods of administration.[5,6]

Currently, the concept of *abuse deterrence* is viewed as the introduction of some limits or impediments to abuse, as opposed to the outright elimination of abuse. For all dosages of such products, extractability and solubility studies should be designed to determine whether any of the drugs present in the combination might be differentially solubilized and extracted, and thus separated from the API.

A new formulation that is designed with a possible claim of abuse deterrent qualities should be studied for relative abuse potential in human pharmacology studies. The abuse potential of the new formulation should be compared to a previously approved product that serves as a positive control. The positive control in these studies may be an immediate release product, an extended-release product, and possibly an extract of the new formulation that is believed not to be abusable (see section V.A below). In addition to the above assessments, robust assessments of efficacy, safety, biopharmaceutics

[5] N. Katz. "Abuse-Deterrent Opioid Formulations: Are They a Pipe Dream?" *Curr. Rheumatol. Rep.* 10(1): 11-8, 2008.

[6] N. Katz et al., "Challenges in the Development of Prescription Opioid Abuse-deterrent Formulations," *Clin. J. Pain*, 23(8), pp 648-60, Oct 2007.

(including alcohol interaction), and epidemiologic studies should be performed to demonstrate that a new formulation is an abuse deterrent. Long-term epidemiological studies may also be necessary to support an abuse deterrent claim.

C. Animal Behavioral Pharmacology Studies

The behavioral assessment of drugs in animals is a continually evolving field that seeks to assess drugs using the latest scientific advances. The main goal of animal studies is to provide an indication early in drug development of a drug's abuse potential. The information gained can guide the sponsor and FDA in determining what additional studies should be conducted in animals and humans. The recommendations in the sections that follow address the conduct of animal abuse potential studies, recognizing that new methodologies may be developed.

1. Principles in Study Design

Animal abuse potential studies use *several species*, usually rodents and primates. Sponsors should provide (1) justification for the selection of an animal model and (2) the prior drug history of the animals selected. The *sample size* in animal studies should be adequate to accurately characterize the ability of the drug to induce the particular behavior of interest. The number of animals included in a study depends on the anticipated effect size and the desired power of the statistical test used.

Route of administration can significantly affect behavior because of psychophysiological and pharmacodynamic effects. Given that drugs are commonly abused by more than one route, the proposed clinical route of administration as well as other routes should be tested when feasible.

A determination of *plasma levels* of the parent drug and its major metabolites in animals over a time course are important when assessing similarities to human plasma levels. Pharmacodynamic and pharmacokinetic considerations should guide the selection of *time points for measurements*, including appropriate pretreatment times. A correlation between the pharmacokinetic profile and the appearance and resolution of behavioral effects for parent and psychoactive metabolites is often observed in abuse potential assessments.

The experimental design should include appropriate *negative and positive control groups*, with suitable justification provided. A negative control could include a drug without abuse potential that is approved for treatment of the same condition proposed for the new drug. The positive control should be in the same pharmacological class as the test drug when possible. Doses for negative and positive controls should be behaviorally equivalent to the test drug. For drugs that are new molecular entities or are not pharmacologically similar to a known drug of abuse, an appropriate comparator can be a drug approved for treatment of the same condition for which the new drug is proposed.

Generally, studies should explore the behavioral effects of a *range of doses*, including high doses that produce plasma levels that are multiples of the therapeutic dose. Doses

should be chosen on the basis of the drug's characteristics as the plasma levels of the drug increase. Additional principles of dose selection can be found in the DHHS/Public Health System document entitled *Policy on Humane Care and Use of Laboratory Animals*.[7] Information resulting from adverse effects or other safety concerns should be used to set dose level limits or indicate that further investigation is appropriate.

2. Types of Animal Abuse Potential Studies

A variety of approaches exist to study the abuse potential of drugs in animals. When choosing a behavioral test, the chemical and pharmacological properties of the drug, its pharmacological class, and existing knowledge about its abuse potential should be considered.

Self-administration tests assess the rewarding properties of a drug. If animals actively work at a behavioral task to receive a dose of the drug, it is likely that the drug will be rewarding in humans.

Conditioned place preference is a method related to self-administration in which animals choose to spend time in one of two distinct environments, that is, the site where they previously received a drug or where they previously received placebo. Conditioned place preference is not as rigorous a behavioral test as self-administration in determining the rewarding properties of a drug.

A positive result with a drug in self-administration or conditioned place preference tests in animals can have some predictive value in identifying drugs that might have abuse potential in humans. However, a negative result does not necessarily mean that the drug does not have abuse potential. This is because certain classes of drugs used by humans do not induce self-administration or conditioned place preference in animals. Examples of such drug classes include 5-HT2 agonist hallucinogens, cannabinoids, NMDA antagonists, and other drugs that produce effects broadly characterized as "psychedelic." When a drug could produce effects that are similar to these classes of drugs, other behavioral tests should be relied on to assess abuse potential.

Drug discrimination is a method in which animals indicate whether a test drug produces physical or psychic perceptions similar to those produced by a known drug of abuse. In this test, an animal learns to press one bar when it receives the known drug of abuse and another bar when it receives placebo. A challenge session with the test drug determines which of the two bars the animal presses more often, as an indicator of whether the test drug is recognized or perceived by the animal as the known drug of abuse.

Psychomotor tests assess the effects of the test drug on motor functioning in comparison with the effects of well-characterized drugs of abuse.

[7] This document is available on the Internet at http://grants1.nih.gov/grants/olaw/references/phspol.htm.

Dependence potential of a substance is the propensity of a substance, as a consequence of its pharmacological effects on physiological or psychological functions, to give rise to a need for repeated doses of the substance. Physical dependence is often characterized by withdrawal symptoms.[8] Psychological or psychic dependence refers to impaired control over drug use, such as craving.

Dependence potential can be determined by measuring the pharmacological properties during animal and human drug testing. Tests for *tolerance* and *physical dependence* examine the responses to repeated administration of a drug. Repeated doses over a wide range are needed to attain the same effects observed at starting doses or, as an alternative, to avoid symptoms of *withdrawal* or "bad feelings." Studies should start at doses, as compared to placebo, showing no behavioral effects, and doses should be increased several times to produce a dose-effect curve. Correlation of results with plasma concentration measurements can provide useful insight when interpreting the studies. An assessment of *tolerance* or *physical dependence* should be performed as part of the safety assessment of a drug and should be considered in drug scheduling. The demonstration of dependence in animals can influence the human safety and the abuse potential evaluations.[9]

3. Timing of Studies During Preclinical Development

Sponsors are encouraged to consult with the Agency early in the development of new molecular entities about the need for, and optimal timing of, animal abuse potential studies. The consultation will be most useful before the end of phase 2 of the development to facilitate planning of late stage clinical trials. Conducting any necessary animal abuse potential studies early in development will provide the sponsor with more information for consideration in the overall development of the drug. However, during phase 1, a drug's clinically effective dose may not be known, and animal abuse potential studies that do not use an appropriate dose may not be useful for assessing abuse potential or in the design of human abuse potential studies later in development. See section V.A below.

[8] Physical dependence is a state of adaptation manifested by a drug class-specific withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug and/or administration of an antagonist. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. The presence of tolerance does not determine whether a drug has abuse potential, in the absence of other abuse indicators such as rewarding properties (American Academy of Pain Medicine, American Pain Society and American Society of Addiction Medicine consensus document, 2001).

[9] M3 (R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, current *Step 2* version, July 15, 2008, pp. 16-17.

D. Application of Good Laboratory Practice (GLP)

The good laboratory practice (GLP) principles described in the guidance for industry *S7A Safety Pharmacology Studies for Human Pharmaceuticals* (ICH S7A) and in FDA regulations, 21 CFR part 58, apply to abuse potential studies in animals.[10] The scope of ICH S7A includes new chemical entities and biotechnology-derived products for human use. Sponsors should find ICH S7A useful in ensuring quality and reliability of animal safety studies.

E. Pharmacokinetics/Pharmacodynamics

Characterization of the pharmacokinetic (PK)/pharmacodynamic (PD) properties of a substance and product is important for determining the abuse potential of a drug or product. Measures of systemic exposure to the drug product from preclinical and clinical studies should be considered when assessing the abuse potential of the drug.[11] Data should include information on maximum concentration (C_{max}), time to onset, time to maximum concentration (T_{max}), area under the curve ($AUC_{0-\infty}$), and the terminal elimination half-life ($T_{½}$) of the parent drug and any psychoactive metabolites. In addition, data on bioavailability, distribution volume, and drug clearance should be included. The PK information relevant to abuse potential and described in the abuse potential section of the NDA should include or be hyperlinked to data that have also been submitted under the PK section of the NDA.

Information on PD should also be included if available. This information will be of value because it can help to correlate psychoactive drug effects with achieved plasma concentrations.

Information on factors that might change the properties of a product, such as crushing a tablet or taking the product with alcohol and inducing rapid release and absorption of the active drug, should be collected not only to characterize the abuse potential of the product, but also to identify any safety concerns associated with misuse of the product (see section IV.B.1).

V. HUMAN LABORATORY STUDIES

The abuse potential assessment of a new drug should be based on a composite analysis of chemistry, pharmacology, and clinical data, and the public health risk that the drug presents. One study alone generally would not be considered sufficient for an adequate abuse potential assessment. Data from human abuse potential studies will contribute to the development of product labeling and drug scheduling recommendations. If the human abuse potential studies and the adverse events profile from clinical studies do not show the presence of rewarding effects or other abuse-related behaviors or similar pharmacology, a recommendation for scheduling would be unlikely. (General information on conducting clinical studies can be

[10] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at http://www.fda.gov/cder/guidance/index.htm.

[11] See FDA's guidance on *Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application,* available on the CDER guidance page.

obtained from the FDA guidance on *General Considerations for the Clinical Evaluation of Drugs*.[12])

A. Human Abuse Potential Study in Recreational Drug Users

The human abuse potential study consists of pharmacology assessments that provide unique information relevant to central nervous system-active drugs, especially opioids, stimulants, depressants, cannabinoids, and hallucinogens (see also section IV.B.2). The objectives of such studies are to provide information on the relative abuse potential of a new drug in humans and to contribute to predicting the likelihood of abuse when the drug becomes available. The studies are typically conducted in a population experienced in using drugs recreationally after sufficient data related to safety and efficacy in a patient population have been acquired. Sponsors are encouraged to proactively interact with FDA in planning and conducting such studies, often by the end of phase 2. Sponsors are encouraged to submit protocols to FDA for review and advice on design, as well as safety issues, before beginning the study.

1. Subjects

Human abuse potential studies are usually conducted in experienced, recreational drug users who have a recent or current history of using a drug in the pharmaceutical class of the test drug. The subjects in the study should have experience with drugs with similar psychoactive properties, regardless of the pharmacologic mechanism of action.

The characteristics of the study population with respect to past and current drug use and abuse should be presented in detail with respect to drugs abused, preferred drug(s) of abuse, and duration of abuse and abstinence. Screening for substance abuse during the study is often necessary to ensure that subjects are not currently abusing other substances. Exclusion criteria should include a current diagnosis of substance dependence, current abuse, and current treatment for a substance-related disorder.

Recently, some abuse potential studies have also been conducted in drug naïve healthy subjects and this is an area of needed research. These two populations may differ in important ways, including in their ability to identify subtle differences in drug effects that are relevant to abuse assessment.

For the study to be interpretable, the subjects should be able to reliably report "drug-liking" and be able to provide ratings of drug experiences related to the drug's subjective effects and similarity to specific classes of known drugs of abuse. Study subjects should be able to distinguish the effects of the test drug and similar drugs and should be able to demonstrate that they can discriminate the effects of the positive control from the placebo. Some investigators may consider prescreening subjects for their ability to detect and report subjective drug effects, and to distinguish the effects of the appropriate positive control. Other factors that influence the significance of study results include

[12] Available on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

demographic range with respect to age, sex, and race, drug of choice, frequency of participation in drug abuse studies, duration of drug abuse, variety of drugs used, and duration of drug abstinence.[13]

2. Design

The design of the study should be based on the study objective and statistical analysis model. The human abuse study measures repeated single-dose administrations over a period of time, determined by the time course of the drug's effects. Doses should range from minimally effective to supratherapeutic, if safety is known and precautions are taken to deal with safety concerns.

Human abuse potential studies are usually double blind, double dummy, placebo, and positive comparator controlled, and are crossover designs. The abuse potential of the test drug is assessed by comparing responses of the test drug with those of placebo and with those of the positive control. A result of *no abuse potential* should be validated by showing a significant difference in response between the positive control and the placebo. All subjects are tested under all drug conditions. Drug conditions would typically involve placebo and multiple doses of the new drug and positive control. A repeated Williams square design is recommended. Subjects should be randomly assigned to one of the sequences in the Williams square. Thus, the number of replicates of the Williams square depends on the desired sample size. The assessment of abuse potential can include co-primary endpoints and some secondary endpoints of interest, if appropriate. However, no more than three primary measures should be recommended. Although the use of 12 to 25 subjects has been seen in past studies, in some recent studies as many as 40 subjects have been used. We don't recommend a specific number of subjects for a study; however, the study should be sufficiently powered such that we can determine the statistically significant relationship of the test drug to placebo and positive control to the primary and secondary outcome measures. The investigator and the staff who interact with subjects should not know the sequence of substances administered.

Procedures for managing adverse events should be explicit and appropriate for the drug class being tested. The washout period of a crossover designed study should be at least five times the maximum $t_{1/2}$ of the longest acting drug in the study.

3. Study Site

Studies should be conducted under controlled laboratory settings, preferably in a closed residential unit. The subject population is at risk for abuse of the same type of drugs being tested, and subjects with histories of drug abuse may be more likely to dropout or miss visits. Therefore, it is recommended that subjects stay overnight following administration of each dosage. The laboratory setting should provide control over variables related to sleep and nutrition that can lead to greater variability in outcome. The controlled setting also provides greater safety at the higher than therapeutic doses

[13] "Conference on Abuse Liability Assessment of CNS Drugs," *Drug and Alcohol Dependence*, 70:3 Suppl., 2003.

that are usually administered and can help prevent other forms of drug abuse and possible drug carryover effects.

4. Selection of Doses and Controls

Study protocols should be specific as to proposed dosing and monitoring of subjects. The test drug should be compared to the positive control under identical conditions for assay of abuse potential. The positive control should have measurable abuse potential previously established through experimental studies and epidemiological data. The positive control should be a drug of abuse in the same pharmacological class as the test drug. Additional useful information can be obtained if the positive control has the same medical indication as the test drug. Limits of sensitivity of the assay to lower doses should be determined. Slopes of the dose effect functions across different measures should be determined. Within a given study, a positive control should have its anticipated effects on the parameters of abuse potential that are being studied. Failure to demonstrate the expected effects would invalidate the study.

A dose run-up pilot study in a drug abuser population can provide an empirical basis for dose selection. This preliminary study potentially provides an opportunity to evaluate and modify procedures in subsequent dose effect studies.

5. Outcome Measurements

The primary method for evaluating the subjective effects of drugs is through the use of standardized questionnaires. Study participants are asked to rate their response to a drug that has been administered to them in a laboratory in terms of whether the drug produces sensations such as "good," "high," or "spacey." The "drug liking" rating can be measured on a Visual Analog Scale during a drug session or at the end of the drug session.

Measures most directly related to likelihood of abuse include the following:

- Ratings of liking ("Do you like the drug?") and other subject-rated effects
- Determining the subjects' disposition to take the drug again
- Drug identification (that is, subjects are able to categorize the effects of the test drug as similar to those of numerous classes of psychoactive drugs)

Measures of drug effect typical of drug class include the following:

- Subject-rated strength of drug effect
- Behavioral and cognitive performance assessment
- Measurement of relevant physiological effects
- Assessment of mood state changes using Profile of Mood States (POMS) and the Addiction Research Center Inventory (ARCI)

6. Analysis of Data

If the study consists of a heterogeneous population of identifiably unique groups, analyses of the data subsets corresponding to each group should be conducted. For example, a population of recreational users of central nervous system depressants could include individuals who prefer to abuse sedative-hypnotic drugs over alcohol. In a study evaluating a new central nervous system stimulant, the study population could include individuals identified as cocaine abusers, for example. These individuals are often polydrug abusers and may prefer to abuse drugs from other pharmacological classes. The differences in preference of each population group to the drug class could yield different results. Further research in this area of analysis would help determine under what circumstances these subgroup analyses can be performed and are useful.

Information about the subjective effects of drugs in humans can also be obtained through drug discrimination studies, in which subjects are first trained to recognize the effects of a known drug of abuse compared to placebo. Subjects then receive a blind challenge with different doses of a test drug to determine whether they can identify the effects of the test drug as being similar to those of the known drug of abuse.

Self-administration studies in humans can be a useful method for determining the probability of abuse potential. In this test, subjects are given the opportunity to request additional doses of a drug after initial exposure to that drug, often in conjunction with a requirement for a certain amount of work before the subsequent dose is offered. The major advantage of self-administration in humans compared to that in animals is that human subjects can communicate the reasons a drug is desirable to them, and specifics about the full range of sensations that a drug induces.

B. Related Pharmacology Studies

Other aspects of human pharmacology of the test drug (e.g., cognitive and performance impairment) should be investigated.

Certain tests that might be conducted during clinical studies to assess the therapeutic potential of a new drug can give indications of similarities between the new drug and known drugs of abuse. Psychomotor tests that determine whether the effects of a drug increase or decrease normal motor functioning can suggest that a drug may be like a known stimulant or depressant. Similarly, cognitive tests that assess whether memory, perception, attention, language ability, or consciousness are altered by a drug can indicate the presence of certain effects that drug abusers might find desirable.

As with animal tests, human investigations with new drugs should assess whether a drug produces tolerance upon repeated administration, as well as whether a drug produces withdrawal symptoms following discontinuation of drug administration, which is indicative of physical dependence.

686 **C. Clinical Trial Data Relative to Abuse Potential Assessments**
687
688 The evaluation of the adverse events profile of a drug from clinical trials can provide a signal of
689 abuse potential. The systematic categorization, tabulation, and analysis of safety data for mood
690 elevation, sedation, and psychotomimetic events can provide useful information. The incidence
691 of euphoria-type adverse events (including euphoria, euphoric mood, elevated mood, mood
692 alteration, feeling drunk, feeling abnormal) and hallucination (visual and auditory) are a few of
693 the more prominent MedDRA terms that should be considered. MedDRA 12 terms for
694 inappropriate affect, which include the following lower level terms: elation inappropriate,
695 exhilaration inappropriate, feeling happy inappropriately, inappropriate affect, inappropriate
696 elation, inappropriate laughter, inappropriate mood elevation, should also be considered. A
697 prospective evaluation of withdrawal adverse events after abrupt discontinuation of treatment
698 can provide information relevant to dependence. Various quantitative measurements will be
699 useful in providing objective data to assess dependence (e.g., opioid and benzodiazepine
700 withdrawal scales and psychiatric rating scales). Data related to serious psychiatric and
701 neurological adverse events and the need for hospitalization is relevant to the public health risks
702 and abuse potential of the drug.
703
704 Phase 3 clinical trials evaluate the safety and efficacy of a product for a specific condition in
705 large multi-center trials involving the intended patient populations. Phase 3 trials provide
706 support for therapeutic dose recommendations; dose response data; and data relevant to abuse,
707 dependence potential, drug diversion, and accountability, as related to study subjects (completers
708 and dropouts).

709 Sponsors should make every effort to do the following:

710
711 1. Set criteria, collect data, and tabulate the abuse, misuse, noncompliance, and diversion
712 cases across the studies and study sites with special attention to aberrant drug behaviors
713 that may be indicative of drug abuse, misuse and/or diversion.[14,15]
714
715 2. Provide complete information, including case report forms and final outcomes, on all
716 instances of addiction, abuse, misuse, overdose, drug diversion/drug accountability,
717 discrepancies in amount of the clinical supplies of the study drug, noncompliance,
718 protocol violations, lack of efficacy, individuals lost to follow-up, and any other reasons
719 why subjects dropped out of the study.
720
721 3. Provide information on the risks of addiction, abuse, misuse, overdose, and drug
722 diversion in the study populations.
723
724 Pertinent data can include measurements of drug accountability, tolerance, physical dependence,
725 or withdrawal symptoms, and the presence of signs or symptoms of drug abuse, misuse,

[14] S.D. Passik, K.L. Kirsh, K.B. Donaghy, R.K. Portenoy, "Pain and Aberrant Drug-Related Behaviors in Medically Ill Patients With and Without Histories of Substance Abuse," in *J. Pain*, 2(2):173-81, Feb 2006.

[15] http://sbirt.samhsa.gov/ Screening and brief intervention (SBI) can identify the severity of the "problem" in study participant and identify the appropriate level of intervention.

overdose, or drug diversion. Evidence from clinical trials suggesting that a drug has reinforcing effects can warrant a prospective abuse potential study (as described above, under section V.A).

Abuse-relevant adverse event data for non-patient healthy populations can be obtained from single and multiple dose pharmacokinetic studies and electrocardiographic studies.

VI. POSTMARKET EXPERIENCE/DATA

Foreign postmarket experience and epidemiological data regarding misuse and abuse of a drug under review by the FDA may be useful in decisions about scheduling a substance under the CSA and labeling a drug under the Food, Drug, and Cosmetic Act (FDCA). Information from countries outside the United States can contribute to the abuse potential assessment of a drug, especially if there has been substantial postmarket experience. Adverse events reports associated with appropriate medical use, misuse, or illicit use, as well as data on abuse and diversion of a drug can be relevant. In addition, English translations of labels approved in other countries can provide relevant information regarding safe use, abuse, and dependence.

For active pharmaceutical ingredients that are formulated into new drug products, postmarket data on abuse, misuse, overdose, and diversion in the United States provide valuable insight. Sponsors should search publicly available databases, including the Drug Abuse Warning Network (DAWN), the National Survey on Drug Use and Health (NSDUH), the Treatment Episode Data Set (TEDS), Monitoring the Future (MTF), and other databases, to characterize and monitor risks associated with the misuse and abuse of a drug and to estimate the extent of use and abuse of a particular drug.[16] Because these databases have limitations, the scope of each individual database should be described to clarify the applicability and limitations of the data that are provided.

Raw counts and weighted estimates from the above databases should be put into the context of relative exposure, especially for purposes of comparisons and assessing trends. The ratio of the number of abuse events (*numerator*) relative to the number of prescriptions or number of patients or amount of drug produced during the specified time period (the *denominator*) should be calculated to provide an abuse indication corrected for exposure. Such a calculated ratio for a test drug can provide useful information when compared with pharmacologically similar drugs covering the same time period. This calculation would be relevant to the overall assessment of relative abuse for a drug and may be useful in providing meaningful trends over a period of several years.

Information from other sources that is neither systematically acquired nor statistically significant can provide only anecdotal information that a substance is being illicitly used, purchased, sold, or diverted. Such sources include substance abuse clinics, poison control centers, state boards of pharmacy, medical examiners (ME), police diversion units, local departments of public health,

[16] More information and statistics on substance abuse are available from the Substance Abuse and Mental Health Services Administration Web site at http://www.oas.samhsa.gov and the National Institute on Drug Abuse Web site at http://www.nida.nih.gov.

and national or field offices of the DEA. DAWN ME data can provide important information related to drug mortality. Determining whether there are increasing or decreasing trends in abuse can provide valuable information about the postmarket experience with a drug product.

VII. LABELING AND DRUG SCHEDULING

Labeling and drug scheduling play different roles in encouraging safe and appropriate use of drugs with abuse potential, as well as in minimizing the actual abuse, misuse, and diversion that may result from their availability.

Information on the abuse potential of a drug is generally conveyed to healthcare professionals and patients through appropriate labeling. The *Drug Abuse and Dependence* section of the label should describe the abuse potential and symptoms of withdrawal of the drug and provide information on its safe use. The label may not reflect that a drug is scheduled, or that it will be scheduled, until the scheduling process is complete. When the scheduling process is completed, a supplement must be submitted to reflect the schedule. The regulations require that the label of a drug that has been scheduled bear the C-X symbol, where X is the schedule II, III, IV or V (21 CFR 201.57(a)(2)). Labeling is the cornerstone of risk minimization efforts for most of the drugs approved by FDA.

ABBREVIATIONS

AERS	Adverse Events Reporting System
ASH	Assistant Secretary of Health
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CNS	Central nervous system
CSA	Controlled Substances Act
CSS	Controlled Substance Staff
DAWN	Drug Abuse Warning Network
DEA	Drug Enforcement Administration
DHHS	Department of Health and Human Services
DOJ	Department of Justice
FDA	Food and Drug Administration
IND	Investigational New Drug
NDA	New Drug Application
NSDUH	National Survey on Drug Use and Health
NIDA	National Institute on Drug Abuse
SAMHSA	Substance Abuse and Mental Health Services Administration
U.S.C.	United States Code

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