Assessment of Abuse Potential of Drugs

Guidance for Industry

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

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Clinical Medical

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I. INTRODUCTION

This guidance is intended to assist sponsors of investigational new drugs and applicants for approval of a new drug in evaluating whether their new drug product has abuse potential. This guidance also provides recommendations to applicants who intend to submit new drug applications (NDAs) for prescription drug products that may have abuse potential.

Drug products with abuse potential generally contain drug substances that have central nervous system (CNS) activity and produce euphoria (or other changes in mood), hallucinations, and effects consistent with CNS depressants or stimulants. Thus, if a drug substance is CNS-active, the new drug product containing that drug substance will likely need to undergo a thorough assessment of its abuse potential and may be subject to control under the Controlled Substances Act (CSA) (*see generally* 21 U.S.C. 811). The CSA contains five schedules of control: Schedules I, II, III, IV and V. Drugs or other substances with a high abuse potential, no currently accepted medical use, and a lack of accepted safety for use under medical supervision are controlled in Schedule I. Drugs or other substances with abuse potential that do have a currently accepted medical use (e.g., the drug or substance is in an FDA-approved product) are placed into Schedule II, III, IV, or V. The specific placement of a drug or other substance within Schedules II-V is determined by the relative abuse potential of the drug or substance and the relative degree to which it induces psychological or physical dependence (21 U.S.C. 812(b)).

In general, FDA's guidance documents 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.

II. BACKGROUND

The assessment of the abuse potential of a drug product under development is generally conducted as a component of its safety evaluation. In this guidance, the term "abuse-related" will be used to designate nonclinical and clinical information that is related to the assessment of abuse potential of a new drug.

As described in Sections III through VI, the results from a broad range of studies and other sources of information contribute to the assessment of a new drug's abuse potential. This includes the results of studies investigating chemistry, pharmacology, pharmacokinetics, animal and human behavior, abuse-related adverse events (AEs) in human studies, and reports of abuse from various sources, such as law enforcement, poison control centers, hospital emergency departments and medical examiners. All abuse-related study protocols and resultant data should be compiled and cross-linked by the applicant to constitute the abuse potential assessment within an NDA submission. The assessment should include a proposal for scheduling under the CSA. (Under 21 CFR 314.50(d)(5)(vii), if the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the CSA, are required.) Following the Agency's review, these data inform both the appropriate labeling of the drug product and our recommendations for drug scheduling under the CSA. In this guidance, this required section of the NDA submission is referred to as the "abuse potential assessment." If an applicant concludes that its new drug product does not warrant scheduling under the CSA, the scheduling proposal in the NDA should state this position, and should provide justification for this position based on relevant data in the NDA.

A. Scope of Guidance

Drug products that are addressed in this guidance include those that contain CNS-active new molecular entities (NMEs) as well as those products that contain CNS-active substances that are already controlled under the CSA.[2] Generic drug products seeking approval under section 505(j) of the Federal Food, Drug & Cosmetic Act are not typically reassessed for abuse potential, and are usually placed in the same schedule of the CSA as the innovator drug product. Drug products that are determined to have abuse potential may contain substances that are chemically or pharmacologically similar to other controlled substances, or they may have novel chemical structures and/or mechanisms of action in the brain.

This guidance provides the following:

- Definitions of *drug abuse, abuse potential*, and other related terminology

[2] The complete list of all scheduled substances can be found in 21 CFR 1308, which is updated following publication in the Federal Register (FR) of a drug scheduling action by the Drug Enforcement Administration.

- A discussion as to which studies we recommend be included in an abuse potential assessment for a CNS-active drug in order to satisfy the requirements of 21 CFR 314.50(d)(5)(vii), with recommendations for the battery of relevant studies that may be conducted in a logical sequence that builds on new data acquired during drug development

- A discussion as to when to conduct the recommended abuse-related studies, and how to appropriately design them

- General administrative recommendations for obtaining FDA advice, consistent with CDER's 21st Century review policies[3] and draft guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*[4]

- A discussion regarding the abuse-related components of a NDA, including a proposal (with justification) addressing whether the drug product should be scheduled under the CSA, and if so, a proposed schedule (see 21 CFR 314.50(d)(5)(vii)). A scheduling proposal may request any of the following: to control a substance in a particular schedule, to decontrol a substance, to transfer a substance to a new schedule, or to not control the substance.

It is beyond the scope of this guidance to discuss the abuse assessment of anabolic steroids (all of which are in Schedule III of the CSA unless subject to an exemption, *see* 21 U.S.C. §§ 811(g)(3)(C), 812). This guidance also does not discuss the studies that should be conducted to demonstrate that a given opioid formulation has abuse-deterrent properties because that is addressed in a separate FDA guidance for industry, *Abuse-Deterrent Opioids – Evaluation and Labeling (2015)*.[5] Biological products that are evaluated by the Center for Drug Evaluation and Research (CDER) are not discussed in this guidance, but are still evaluated for abuse potential based on the principles in Section III.A.[6]

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[3] Available at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf.

[4] Available for notice and comment purposes at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[5] Available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[6] Assessments of abuse for biological products evaluated by the Center for Biologics Evaluation and Research (CBER) are not discussed in this guidance.

B. Definitions

The CSA refers to the assessment of "potential for abuse," "addiction-forming or addiction-sustaining liability," and "dependence" in 21 U.S.C. 802, but does not define these terms. In this guidance, the following definitions are applicable:

Drug abuse is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect. Therefore, *abuse potential* refers to the likelihood that abuse will occur with a particular drug product or substance with CNS activity. Desired psychological effects can include euphoria, hallucinations and other perceptual distortions, alterations in cognition, and changes in mood. Throughout this guidance, the term *abuse potential* will be used, although *abuse liability* represents a similar concept.[7,8]

Dependence refers to *physical or psychological dependence*. *Physical dependence* is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. *Psychological (or psychic) dependence* refers to a state in which individuals have impaired control over drug use based on the rewarding properties of the drug (ability to produce positive sensations that increase the likelihood of drug use) or the psychological distress produced in the absence of the drug.[9]

Tolerance is a state that develops as a result of physiological adaptation characterized by a reduced response to a specific dose of drug after repeated administration of the drug (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

The presence of physical dependence or tolerance does not determine whether a drug has abuse potential. Many medications that are not associated with abuse, such as antidepressants, beta-blockers, and centrally acting antihypertensive drugs, can produce physical dependence and/or tolerance after chronic use. However, if a drug has rewarding properties, the ability of that drug to induce physical dependence or tolerance may influence its overall abuse potential.

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[7] 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).

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

[9] The term "psychological dependence" conveys a similar state to that of "addiction" (American Society for Addiction Medicine (ASAM), 2011) and "substance dependence" (American Society for Addiction Medicine (DSM)-IV-TR, 2000).

III. ASSESSING THE ABUSE POTENTIAL OF A DRUG

This section describes the key decision points in an abuse potential assessment, the types of abuse-related studies that may be important, the recommended time frame within the drug development program for conducting such studies, and the organization of abuse-related information in an NDA submission.

A. Key Decision Points and Recommended Studies in Assessing Abuse Potential

The Controlled Substance Staff (CSS), located in CDER's Office of the Center Director, has the central role in CDER in advising sponsors regarding the abuse potential assessment of a drug product. FDA does not recommend that every drug under development undergo an evaluation of abuse potential. An evaluation of abuse potential is most relevant for NMEs with CNS activity that have not previously been assessed by FDA for abuse potential. However, if a drug substance with CNS activity is already controlled under the CSA and a different dosage strength, dosage form, route of administration, patient population, or therapeutic indication is proposed under an NDA or NDA supplement, a modified abuse potential assessment may be necessary and should be discussed with CSS (see Section III. B).

For NMEs, the decisions regarding whether an abuse potential assessment will be required under 21 CFR 314.50(d)(5)(vii), and what studies should be conducted, as well as the conclusions regarding a drug's abuse potential, generally depend on the answers to the following questions which arise during drug development:

Question 1: Is the new drug (or any major metabolite) active within the CNS?

Drugs with abuse potential almost always have activity within the CNS, so if a new drug or its major metabolite(s)[10] have CNS activity, additional studies will be recommended. Examples of data relevant to the assessment of whether the drug has activity within the CNS include:

- Chemistry studies (drug structure and ability to pass blood brain barrier)
- Receptor binding studies with the drug and major metabolites at CNS sites
- Second messenger system studies (if available) to identify functionality at binding sites
- Pharmacokinetic studies showing the drug's relative distribution to and penetration of the brain

[10]Our use of the term major metabolite is responsive to the following: "Nonclinical characterization of a human metabolite(s) is only warranted when that metabolite(s) is observed at exposures greater than 10% of total drug-related exposure and at significantly greater levels in humans than the maximum exposure seen in the toxicity studies," as described in ICH M3(R2) *Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (2009), available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2_Guideline.pdf.

- Pharmacodynamic studies showing ability of the drug to induce general behavioral changes in animals and humans indicative of CNS activity

If assessment of data from these studies or subsequent studies leads to the conclusion that the new drug has CNS activity, an abuse potential assessment will likely be required under 314.50(d)(5)(vii).

Question 2: For CNS-active new drugs, what is the next step for assessing abuse potential?

For new drugs determined to be CNS-active, the next step for sponsors should be to design and conduct abuse-related animal behavioral studies, such as drug discrimination and self-administration studies. Detailed descriptions and considerations in designing these abuse-related animal behavioral studies are discussed in Section IV.D.

The results from these abuse-related animal behavioral studies are important factors for the third key question:

Question 3: Should a human abuse potential (HAP) study be conducted?

A HAP study (also known as a human abuse liability (HAL) study) assesses abuse potential in individuals with a history of recreational use of drugs of abuse. In determining whether a HAP study should be conducted, it is important to assess whether there is evidence that the new drug produces any of the following:

- Responses in animals in general behavioral studies that are similar to responses to known drugs of abuse
- Generalization (similar effects) to a known drug of abuse in animal drug discrimination studies
- Rewarding properties that support animal self-administration or conditioned place preference
- A profile of abuse-related AEs (including euphoria-related AEs) in clinical studies in healthy individuals (phase 1) and in individuals with the disease of study (phase 2/3)

These studies are discussed in detail in Sections IV and V. If evaluation of the data from these animal and human studies identifies abuse-related signals, it is likely a HAP study will be necessary to conduct. Detailed descriptions and considerations in designing a HAP study are discussed in Section V.C.

If an evaluation of data from animal and human studies does not show evidence of abuse-related signals, a HAP study is not likely to be recommended. However, the sponsor should discuss available data with the Agency to confirm whether or not a HAP study should be conducted.

Once the data from all appropriate abuse-related studies in animals and humans are evaluated, final decisions can be made regarding the fourth key question:

Question 4: Do the animal and human abuse-related data show that the drug has abuse potential, and will it therefore be subject to control under the CSA?

The abuse potential assessment submitted by the applicant in the NDA should include full protocols and primary data, as well as a statistical analysis of the data. The assessment should also include a discussion regarding whether the data show that the drug has abuse potential, proposed labeling for the DRUG ABUSE AND DEPENDENCE section and other relevant sections, and a proposal for scheduling under the CSA, if appropriate (see Section III.E). Following the CSS review of the information submitted in the NDA, CSS determines whether the drug has abuse potential, suggests appropriate labeling, and drafts a CSA scheduling recommendation.

B. When Abuse-Related Studies Should Be Conducted

Sponsors are encouraged to consult with FDA throughout the drug development program regarding the appropriate assessment of abuse potential. In determining whether any specific abuse-related study should be conducted, a sponsor may submit abuse-related questions or issues to CDER's Office of New Drugs (OND) review division, which will request a consultation from CSS. Interaction with CSS through the review divisions can occur from the pre-IND stage through the NDA review cycle.

In general, it is recommended that the specific abuse-related studies be conducted only after the therapeutic dose range is determined. This is not usually known until phase 2 clinical studies are completed, at the earliest. Knowledge of the therapeutic dose range should be used in determining the appropriate doses in the specific abuse-related study. The order of the abuse-related investigations generally starts with *in vitro* studies, followed by animal studies, and then finally by a human abuse potential study, if appropriate. Physical dependence assessments should be conducted first in animals, to provide information about behavioral effects that may inform the design of a human physical dependence study. Assessment of human physical dependence should not commence until information is available regarding the ability to safely discontinue the test drug in study subjects, as discussed in Section V.E. Refer to Sections IV and V for typical study design elements.

Sponsors are advised to discuss their planned abuse-related studies with CSS, or confirm that such studies are not warranted, at the end of phase 2 to ensure the drug is adequately assessed for abuse potential. Sponsors are also advised to summarize all abuse-related data for discussion during a pre-NDA meeting with the OND review division, and to request CSS participation for the meeting. The pre-NDA meeting is generally the appropriate time to confirm the planned content for the abuse potential assessment and to describe the intended organization and data file formats for the NDA submission. FDA will assess the abuse potential of a drug product and determine the Agency's recommendation for its scheduling under the CSA after all study protocols and primary data submitted in the NDA have been reviewed.

C. Preparing the NDA Submission

The content of an abuse potential section of an NDA typically includes (or cross-references) complete study protocols and all primary abuse-related data from the following:

1. Chemistry studies

2. Receptor-ligand binding studies and functional (second messenger) studies

3. Pharmacokinetic studies in animals and humans

4. Abuse–related studies in animals:

    a) General behavioral observations from safety pharmacology studies
    b) Drug discrimination study
    c) Self-administration study
    d) Physical dependence study

5. Abuse-related studies in humans:

    a) Human abuse potential (HAP) study
    b) Physical dependence study

6. Abuse-related AEs from clinical studies

7. Information related to overdose, both intentional and accidental, during clinical studies

8. Assessment of the incidence of abuse during clinical studies

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. Abuse-related studies and data should be submitted in the electronic common technical document (eCTD) as follows:

- The proposal and rationale related to drug scheduling should be placed in Module 1, tab 1.14.1.

- A summary of all abuse-related animal and human data, discussion of these data, and conclusions about the drug's abuse potential should be placed in Module 2. This should occur as a subsection under tab 2.7.4 Summary of Clinical Safety, and should have cross-linking to the proposal for scheduling and product labeling in Module 1, as well as to all abuse-related studies and data in Modules 3, 4, and 5.

- The complete study protocols and primary data from items 1-8 above should be placed in the appropriate sections of the eCTD as follows:

    - Module 3, chemistry
    - Module 4, *in vitro* and animal pharmacology, including behavioral safety studies, pharmacokinetics and pharmacodynamics studies
    - Modules 5, clinical studies, including human abuse potential studies, human pharmacokinetics studies, and integrated summary of safety (ISS)

- Reports of abuse, addiction, and deaths from the U.S. and other sources, including those from outside the U.S., should be placed into Module 5, postmarketing experience.

D. NDA Review and Product Labeling Related to Abuse Potential

NDAs are submitted to the appropriate prescription drug review division in OND, based on the proposed indications and usages of the drug product. CSS is consulted by OND prescription drug review divisions to evaluate abuse-related data submitted in the NDA and to determine whether the drug product has abuse potential. CSS also provides recommendations for the DRUG ABUSE AND DEPENDENCE section of the drug labeling, as well as other sections of labeling with abuse-related information.

Abuse-related information in the labeling is primarily described in the DRUG ABUSE AND DEPENDENCE section which is comprised of three subsections, as described in 21 CFR 201.57(c)(10):

"(i) 9.1 Controlled substance. If the drug is controlled by the Drug Enforcement Administration, the schedule in which it is controlled must be stated.

"(ii) 9.2 Abuse. This subsection must state the types of abuse that can occur with the drug and the adverse reactions pertinent to them, and must identify particularly susceptible patient populations. This subsection must be based primarily on human data and human experience, but pertinent animal data may also be used.

"(iii) 9.3 Dependence. This subsection must describe characteristic effects resulting from both psychological and physical dependence that occur with the drug and must identify the quantity of the drug over a period of time that may lead to tolerance or dependence, or both. Details must be provided on the adverse effects of chronic abuse and the effects of abrupt withdrawal. Procedures necessary to diagnose the dependent state and the principles of treating the effects of abrupt withdrawal must be described."

Sponsors and applicants should engage with CSS via the OND drug review division throughout drug development, pre-IND to pre-NDA, to ensure that all abuse-related studies that may be necessary to inform the required labeling of the drug product are appropriately planned and conducted.

E. The Drug Scheduling Process

Following review of abuse-related data in the NDA submission, FDA makes a determination regarding its recommendation for the appropriate scheduling of the drug under the CSA and makes findings as described in 21 U.S.C. 812(b). If the NDA is approved, scheduling in one of four schedules is based on the drug's relative potential for abuse, accepted medical use in treatment in the United States, and relative potential for psychological or physiological drug dependency.

Drug scheduling is a multi-step process that involves several federal agencies. Under the CSA, a medical and scientific analysis of the abuse potential of the drug is conducted by the Department of Health and Human Services (HHS) *(see* 21 U.S.C. 811(b)). At the conclusion of this analysis, the Secretary of HHS will make a recommendation for scheduling to the Drug Enforcement Administration (DEA),[11] as described in 21 U.S.C. 811 and 812. The role of the Secretary is typically delegated to the Office of the Assistant Secretary for Health (ASH) within HHS. The final decision on whether to control a substance in one of the schedules of the CSA is made by the DEA on behalf of the Attorney General.

HHS designates the role of conducting the medical and scientific analysis to the FDA. The FDA provides the National Institute on Drug Abuse (NIDA) with an opportunity to present its views on drug scheduling during this process.[12] Within the FDA, this medical and scientific analysis is conducted by CSS, and occurs in parallel with the NDA review process.

Under 21 U.S.C. 811(b) of the CSA, the medical and scientific analysis considers the following eight factors determinative of control of the drug under the CSA (21 U.S.C. 811(c)):

1. Its actual or relative potential for abuse.
2. Scientific evidence of its pharmacological effect, if known.
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.

[11] The Administrator of the DEA receives the scheduling recommendations and acts on behalf of the Attorney General of the Department of Justice with regard to these scheduling actions.

[12] Memorandum of Understanding with the National Institute on Drug Abuse (Notice; 50 FR 9518-20; March 8, 1985).

7. Its psychic or physiological dependence liability.

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

Following the medical and scientific analysis of abuse-related data submitted in the NDA, an Eight Factor Analysis (8FA) document is drafted by CSS on behalf of the Secretary of HHS that addresses the eight factors listed above. This 8FA takes into consideration the "description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act" submitted in the NDA in accordance with 21 CFR 314.50(d)(5)(vii), along with all relevant and available data. CSS and NIDA staff work together with the goal of gaining concurrence on the 8FA and scheduling recommendations.

The 8FA is then provided to CDER's Office of the Center Director at FDA, and finally to the FDA Commissioner for review and comment. The finalized 8FA is transmitted from the Office of the Commissioner at FDA to the ASH at HHS. NIDA may provide to the ASH/HHS the basis for a separate recommendation. After the ASH/HHS considers the 8FA and recommendations, the ASH/HHS transmits the final 8FA and scheduling recommendation to DEA.

After DEA receives the 8FA and recommendations, DEA may respond by issuing a notice of proposed rulemaking, an interim final rule, or final rule on the HHS scheduling recommendation in the Federal Register. After allowing time for public comment, DEA generally responds with a scheduling order or respond to issues raised by the public. The final rule may respond to any comments received from the public, and confirms a scheduling placement for the drug and the effective date *(see generally* 21 U.S.C. 811, 21 CFR 1308.43).

With the enactment of the Improving Regulatory Transparency for New Medical Therapies Act in 2015, FDA approval of a new drug may not take effect until DEA issuance of an interim final rule under 21 U.S.C. 811(j) establishing schedule placement for the drug, in accordance with 21 U.S.C. 355(x). *See* Pub. L. No. 114-89, 129 Stat. 698 (Nov. 25, 2015).

Once DEA has issued a final scheduling decision and assigned a controlled substance schedule, the controlled substance symbol, e.g., C-II, C-III, C-IV or C-V, must be included in the product labeling as required under 21 CFR 201.57(c)(10)(i) and 1302.03. In order to update the labeling following the scheduling action, a supplement to the NDA must be submitted by the applicant to update product labeling to reflect the DEA scheduling action described in the final rule or interim final rule. *See* 21 CFR 314.70. The appropriately labeled FDA-approved drug product may then be marketed.

IV. ABUSE-RELATED DATA FROM CHEMISTRY AND NONCLINICAL STUDIES

Abuse-related data can be obtained from a variety of chemistry studies and nonclinical studies, including those that investigate pharmacology, pharmacokinetics, general animal behavioral effects, self-administration, drug discrimination, and physical dependence in animals.

A. Chemistry and Manufacturing

Data from the chemistry, manufacturing, and controls (CMC) section of the NDA that are relevant to the abuse potential of the drug substance and drug product under investigation should be submitted as part of, or be cross-referenced to, the abuse potential assessment section.

The chemistry part of the abuse potential assessment section for an NME should include the following information about the drug substance:

- Chemical structure
- Molecular formula and molecular weight (salt and base, as applicable)
- Chemical Abstracts Service (CAS) Registry Number(s)
- Chemical name (such as the name generated using the nomenclature conventions of the International Union of Pure and Applied Chemistry (IUPAC), the name listed in the United States Adopted Names (USAN) Counsel dictionary, drug development program codes, and established or generic names)
- Description of isomers, e.g., optical, existence of diastereomers, geometric, and positional isomers
- Physicochemical properties of the drug substance, for both salt and free acid/base forms, e.g., melting point, boiling point, dissociation equilibrium constants, and solubility in various solvents, such as aqueous media, buffered solutions, alcohol, and organic solvents
- Description of the manufacturing process for the drug substance, specifically addressing whether it involves a precursor that is a controlled substance or a List I or List II chemical (21 CFR 1310.02)[13]

The composition and physicochemical properties of the drug product should be discussed in the abuse potential assessment section in the context of their possible impact on the abuse potential of the drug substance, and relative to the drug schedule of already-marketed formulations containing the same drug substance if it is a controlled substance.

[13] Note that if the new drug involves an immediate precursor to a drug already controlled under the CSA it may be subject to scheduling by a different process than that described above at III.E. *See* 21 U.S.C. 811(e), 21 CFR 1308.47.

B. Screening with Receptor-Ligand Binding Studies

Comprehensive screening using *in vitro* receptor-ligand binding studies should be conducted to determine the pharmacological site(s) of action of the test drug, as well as its major human metabolites, in the brain. Possible CNS sites of action include receptors, transporters, and ion-gated channel systems. Notably, novel pharmacological mechanisms of action may be associated with previously unrecognized abuse potential in humans. The outcome of receptor-ligand binding studies can help determine which *in vitro* functional assays should be conducted.

Although a CNS-active drug may have a single high-affinity site, it is often the case that drugs have multiple mechanisms of action with varying degrees of affinity. Some examples of neuronal systems related to abuse potential that should be assayed include the following:

- Dopamine
- Serotonin
- Gamma-aminobutyric acid (GABA)
- Opioid
- Cannabinoid
- N-methyl-D-aspartate (NMDA)
- Ion-channel complexes (e.g., calcium, potassium, chloride)
- Transporters (e.g., dopamine, serotonin, GABA)

A comprehensive binding assay typically assesses many dozens of sites in the CNS, only some of which are currently known to be associated with abuse potential. However, mechanisms of action not previously associated with abuse potential may produce abuse-related signals with a novel drug. Even though most of the assayed sites will not be predictive of drug abuse, they can be predictive of certain animal behaviors and AEs in humans that may be observed during abuse-related studies.

General scientific principles, including the use of appropriate positive controls and internal standards, should be applied. Highly selective radioligands should be used whenever available. The concentration of the ligand should be at least 10 μM (or should be equivalent to many-fold greater than the anticipated therapeutic exposure).

In vivo receptor-ligand 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. These studies are typically conducted in humans (where they have been validated), although animal applications are possible. Studies using these techniques may be useful in contributing important information about the whole-body pharmacokinetic and pharmacodynamic properties of the drug.

Data from receptor-ligand binding assays should be evaluated on the basis of both specificity (whether the ligand binds at one or many sites) and selectivity (the relative affinity of a ligand for different binding sites).

Knowledge of the binding profile may suggest whether functional *in vitro* assays should be conducted to determine whether the drug is an agonist, antagonist, partial agonist, or mixed agonist-antagonist at specific binding sites. Once the mechanisms of action of the test drug are known, it can be determined which animal behavioral tests may be relevant.

C. Use of Nonclinical Pharmacokinetic Data in Animal Abuse-Related Studies

PK data that are generated during nonclinical evaluations of a test drug are important in appropriately designing and interpreting animal abuse-related studies. The main PK parameters for this purpose are peak plasma concentration (C_{max}), time to maximum concentration (T_{max}), time to onset of drug effects, and terminal half-life ($T_{½}$) for the parent drug and any major CNS-active metabolites (>10% of parent concentration). Other elements, such as area under the curve ($AUC_{0-\infty}$), bioavailability, and CNS concentration and drug clearance, may be important, depending on the drug product. Animal PK data may also be useful in determining relative distribution of the test drug to the brain.

The use of nonclinical PK data in designing animal abuse-related studies is described in detail below. Protocols for animal abuse-related studies should include a justification of design elements based on nonclinical PK data, when appropriate. All PK parameters utilized should be based on actual measurements, not estimations. When the NDA is submitted, all nonclinical PK studies and resultant data that informed the design and interpretation of animal abuse-related studies should be cross-linked.

D. Animal Abuse-Related Behavioral Pharmacology Studies

Abuse-related animal behavioral studies should be conducted when it has been determined that a test drug or any of its major metabolites are CNS-active. These studies evaluate whether a test drug produces behavioral changes in animals that suggest the drug may have abuse potential in humans. Safety studies that measure whether the drug influences or interferes with general behavior (e.g., Irwin test, motor performance test) show whether a drug produces abuse-related signals (e.g., hyperactivity indicative of stimulation). Specific abuse-related studies evaluate whether a drug has rewarding or reinforcing properties (self-administration study and conditioned place preference study), and whether a drug has effects that are similar to known drugs of abuse (drug discrimination study). The results of these animal studies are used (in conjunction with an evaluation of abuse-related AEs from clinical studies) to determine whether a human abuse potential study will likely be necessary and how the study protocol should be designed. Additionally, the ability of a drug to produce physical dependence after chronic administration should be evaluated. This ability can be demonstrated by the appearance of withdrawal signs upon abrupt drug discontinuation.

Abuse-related animal studies are not typically conducted until the end of phase 2, when the final therapeutic doses are usually selected. This is because doses selected for testing in animal abuse-related studies should be based on the plasma levels produced in humans by the highest proposed therapeutic dose (see discussion below). If these animal studies are conducted with doses that do not reflect final therapeutic and supratherapeutic exposure, they will not be valid for assessing abuse potential and may need to be repeated using appropriate doses.

Animal abuse-related studies generally utilize classic designs that are adapted as appropriate for regulatory purposes. A sponsor is responsible for proposing and justifying all design parameters of an abuse-related animal study. If a study is not appropriately designed, the resulting data may not be relevant to the assessment regarding the abuse potential of the test drug.

Sponsors may propose additional methods of assessing abuse potential, which should include justifications that demonstrate the scientific validity and reliability of these methods, especially with regard to assessing drugs with unknown abuse potential.

As described below, each study should incorporate design parameters that facilitate the collection of data that are consistent with the regulatory goals of the specific study.

1. General Considerations

Selection of Animals. Typically, abuse-related animal studies are conducted in rats, because this species has been validated for use in these studies. Although nonhuman primates have often been used for abuse assessments, the ICH guidance for industry, *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (2010)[14] (*M3(R2)* guidance), states that, "When the metabolite profile and the target for drug activity in rodents are consistent with that of humans, the nonclinical abuse liability evaluations should be conducted in rodents. Nonhuman primates should be reserved only for those limited cases where there is clear evidence that they would be predictive of human abuse liability and the rodent model is inadequate." The study protocol should justify the species selected, especially if a non-rodent species is proposed. Typically, a single animal species is used for animal abuse-related studies. It is appropriate to use animals of both sexes in these studies. The experimental drug history of the animals (classes of drugs, as well as extent and recency of exposure) should be provided, if it is known and available, since prior exposure to drugs may influence responsivity to the current test drug. The number of animals used in the study should be based on a statistical power analysis in order to ensure that the sample size is appropriate to detect changes in behavior that can be attributed to the test drug.

Selection of Drug Doses. The doses used in animal abuse-related studies should be selected on the basis of the specific test being conducted (see below). For regulatory purposes, the doses of a test drug that will be evaluated in animal abuse-related studies should be derived from the C_{max} produced by the highest proposed therapeutic dose, rather than on the basis of characterizing an entire dose-response curve (e.g., no effect level to incapacitating level). This is because most animal abuse-related studies are specialized safety studies, not studies that investigate the

[14] Available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073246.pdf. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. Available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073246.pdf.

toxicological properties of the test drug. Recreational drug users tend to use drugs at doses that are multiples of the medically-recommended dose, so abuse-related studies in animals typically test doses that produce C_{max} levels that are equivalent to, as well as at least 2-3 times greater than, the C_{max} produced by the highest proposed therapeutic dose. (This principle does not apply for a self-administration study, see below). If a test drug has partial agonist activity at a site associated with abuse potential (where higher doses tend to produce antagonist activity, while lower doses produce agonist activity), evaluating decrements in dose may be more appropriate when assessing the abuse-related properties of the drug, if the therapeutic indication relies on receptor antagonism.

Control Groups. Abuse-related studies should include a positive control drug group and vehicle group for comparison with the test drug group. In order for a study to be considered valid, the positive control group should produce results that are statistically significantly different from the vehicle group to establish that the study has "assay sensitivity" (i.e., the ability to demonstrate that an abuse signal can be produced under study conditions, to ensure that the abuse potential of the test drug can be determined). Although unscheduled psychoactive drugs are sometimes proposed as a "negative control", they are unlikely to fulfill this condition because they have not typically undergone a thorough abuse potential assessment. Thus, for animal studies, we expect that the only appropriate negative control will be vehicle. The drug selected as the positive control should be in the same pharmacological class as the test drug, whenever possible, and should be scheduled under the CSA. The dose of the positive control is typically based on a dose utilized in published abuse-related studies, to ensure adequate abuse-related behavioral responses in the specific animal test. For a test drug with a mechanism of action that is novel or does not correspond to a drug currently controlled under the CSA, the Agency will consider sponsor proposals for an alternative positive control. This may be a drug that has a therapeutic indication or behavioral profile that is similar to the test drug, even if the mechanism of action is different. The statistical evaluation should compare the test drug to both the positive control and vehicle.

Timing of Data Collection. Data collection in animal behavioral studies should occur at T_{max}, with additional measurements made before and afterward to ensure full characterization of the test drug. Since T_{max} is determined by route of administration, data from animal PK studies should inform the time points at which observations are made. The time to onset will be dependent on the specific animal behavior being evaluated, since various responses may occur at different times while the drug is active.

Of special interest is the role of tolerance in determining study time points. The direct evaluation of tolerance is not typically required for an abuse potential assessment in animals. However, sponsors should be aware of whether the pharmacological mechanism of a test drug is associated with the development of tolerance. If so, this should influence the timing of the behavioral training and testing, so that drug exposure is not frequent enough to induce tolerance. When the possibility of tolerance is not controlled, a negative result in the test often cannot confidently be interpreted as failing to show a signal of abuse. For test drugs with novel mechanisms of action, the likelihood of preventing the development of tolerance is increased if drug testing is conducted no more frequently than every other day.

Schedules of Reinforcement for Operant Studies. When animals are first being trained in the test procedures for self-administration and drug discrimination studies, they typically receive a reward each time they respond appropriately, corresponding to a fixed ratio 1 (FR1) schedule of reinforcement. The requirement for the number of correct responses (e.g., lever presses) to receive a reward is then increased with continued training. However, final testing should be conducted using a standard FR10, rather than schedules of reinforcement with greater response requirements (e.g., use of fixed ratio values greater than 10, or use of progressive ratio).

***Application of Good Laboratory Practice (GLP*).** Abuse-related nonclinical studies must be conducted using GLP, as these are nonclinical laboratory studies conducted to support approval of a drug for use in humans. See 21 CFR 58.1. Sponsors should refer to the following guidances, as well as to 21 CFR Part 58 (*Good Laboratory Practice for Nonclinical Laboratory Studies*),[15] to ensure compliance with GLP requirements when conducting abuse-related nonclinical studies:

- *M3(R2) guidance*
- ICH guidance for industry, *S7A Safety Pharmacology Studies for Human Pharmaceuticals* (2001).[16]

2. General Behavioral Tests

Irwin Test. This is a study of general behavior in which animals are observed in an open cage after acute administration of a test drug over a period of time that covers C_{max}. Observations may include body posture (flat, rearing), grooming, vocalization, mobility, chewing, appearance and ease of handling. Data from this study can provide initial indications of whether a drug produces abuse-related effects such as stimulant or sedative properties. This test should be conducted as part of the toxicology safety battery, so the doses used reflect a broad range of doses that produce plasma levels that are similar to, as well as greater than or less than, those produced by the proposed human therapeutic dose. The route of administration often parallels

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[15] Note that 21 CFR 58.10 states, "When a sponsor conducting a nonclinical laboratory study intended to be submitted to or reviewed by the Food and Drug Administration utilizes the services of a consulting laboratory, contractor, or grantee to perform an analysis or other service [such as abuse-related studies], it shall notify the consulting laboratory, contractor, or grantee that the service is part of a nonclinical laboratory study that must be conducted in compliance with the provisions of [the regulations in *Good Laboratory Practice for Nonclinical Studies*]. See also FDA's Proposed Rule in the Federal Register (8/24/16), "Good Laboratory Practice for Nonclinical Laboratory Studies", available at https://www.federalregister.gov/documents/2016/08/24/2016-19875/good-laboratory-practice-for-nonclinical-laboratory-studies.

[16] Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074959.pdf. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

that of the proposed therapeutic route. Given that the Irwin test is a safety pharmacology study, it will usually include a comparison with vehicle but will not usually include a positive control.

Motor Performance Tests. These tests evaluate the ability of a test drug to interfere with normal motor functioning after acute administration. Some of these tests may overlap with measures evaluated in the Irwin study. Examples of these tests include observations of locomotor behavior in a test cage (including stereotypy), ability of an animal to maintain itself on a rotating rod (rotarod performance), ability to turn over when an animal is placed on its back (righting reflex), observations of muscle tone (tail suspension test), and ability for an animal to maintain itself on an elevation (inclined plane test). These tests may be conducted as part of the safety pharmacology evaluation of a drug and may provide relevant information about behavioral similarities of a test drug relative to known drugs of abuse.

3. Evaluation of Rewarding Drug Effects

Self-Administration Study. This study evaluates whether a test drug has rewarding properties that are sufficient to produce reinforcement (i.e., the likelihood that an animal will repeatedly self-administer the test drug after initial exposure). Animals are first trained to press a bar in the test cage in order to receive a food reward, using a schedule of reinforcement that typically increases over the training period from FR1 to FR10. After animals consistently bar-press in response for food, they begin to receive an intravenous dose of a known drug of abuse (training drug) as the reward, instead of food. They are also tested with vehicle to ensure that bar-pressing is not maintained for a substance without rewarding properties. Once animals stably bar-press (self-administer) the training drug, they are then allowed to self-administer intravenous doses of the test drug.

If the test drug produces a high level of self-administration compared to vehicle, there is a good probability that the drug will produce rewarding properties in humans that are supportive of drug abuse. The intravenous route of administration should be used in order to optimize the temporal association between active lever-pressing and immediate drug effects. The doses of the test drug should be fractions of the doses that produce plasma levels similar to those produced by the human therapeutic dose. This is done to allow for the repeated administration of the test drug without the risk of immediate overdose, and to prevent immediate satiation from a single dose, which would obscure the ability to assess reinforcement.

Any drug of abuse that is scheduled under the CSA may serve as the animal training drug for the self-administration study. However, in order to validate the study, a positive control drug should produce self-administration levels in challenge sessions that are statistically significantly different from vehicle. The ideal positive control drug is in the same pharmacological class as the test drug and is scheduled under the CSA. The dose of the positive control should be consistent with that used in published self-administration studies. When the test drug has a novel mechanism of action, the positive control drug may be one in the same therapeutic class or one that produces similar behavioral effects. The appropriate negative control is vehicle.

Certain classes of drugs with hallucinogenic properties do not typically produce animal self-administration (e.g., 5HT2A agonists), or are only self-administered by animals under limited

conditions (e.g., cannabinoids), even when they are known to be taken by humans for their rewarding effects. Sponsors may propose that a self-administration study is not appropriate, based on similarity in mechanism of action or behavioral effects to these classes of drugs.

Conditioned Place Preference (CPP). This study evaluates whether a test drug produces rewarding effects that are demonstrated by an animal's preference to be on the side of a cage where it received the test drug, as opposed to the side where it received vehicle. Notably, CPP differs from self-administration in that it does not measure whether the rewarding effects of a drug produce reinforcement. It is also not considered to be as sensitive or reliable as self-administration. The dose of the test drug should produce plasma levels that are equivalent to and greater than those produced by the proposed therapeutic doses. The positive control is ideally a scheduled drug in the same pharmacological class as the test drug, with the dose consistent with that used in published CPP studies. Route of administration is not critical as long as testing is conducted at T_{max}.

4. Evaluation of Similarity of Effects to Known Drugs of Abuse

Drug Discrimination. This study evaluates whether a test drug produces "interoceptive cues" (bodily sensations) that are similar to those produced by a known drug of abuse that is scheduled under the CSA (the training drug). Animals are trained in separate sessions to press one bar in the test cage after receiving a training drug and the other bar after they receive vehicle, followed by receipt of a food reward. Animals are typically trained up to a fixed ratio-10 (FR10) schedule of reinforcement. Once animals reliably associate the interoceptive cues from training drug and vehicle with correct lever pressing (>80% accuracy), they are given challenge sessions with a range of doses of the test drug, the positive control, and vehicle. During challenge sessions, if animals have been trained using FR10, they are allowed to lever press a total of 10 times on either lever before removal from the test cage. Animals are not typically rewarded during challenge sessions in order to maintain appropriate associative training.

Animals press the two different levers in the test cage based on the similarity of the interoceptive cue produced by the test drug to the two separate training conditions. "Full generalization" to the training drug occurs when the animal lever presses >80% (8 of 10 times) on the lever associated with training drug. "No generalization" occurs when the animal lever presses <20% on the training drug lever (e.g., >80% on the vehicle lever). "Partial generalization" occurs in between these poles. For regulatory purposes, partial generalization between 60-80% suggests that the test drug produces an interoceptive cue that has some similarity to the training drug. In order to validate the study, the positive control drug should produce full generalization to the training drug and the vehicle should produce no generalization to the training drug. If the test drug produces full or partial generalization to the training drug (a known drug of abuse), it may have abuse potential.

Drug discrimination is dependent on mechanism of action, so only those test drugs that have pharmacological activity similar to that of the training drug will likely produce a significant degree of generalization to the training drug. Thus, if the test drug has a novel mechanism of action, sponsors may prefer to propose an alternative approach for identifying an appropriate training drug.

5. Evaluation of Physical Dependence and Withdrawal Behaviors

Physical Dependence Study. This study evaluates whether chronic administration of a drug at therapeutic plasma levels produces a withdrawal syndrome upon drug discontinuation. This assessment may be conducted in animals at the conclusion of a toxicology study or in a dedicated study. Drug administration should typically occur for at least four weeks at stable doses that produce plasma levels similar to those produced by therapeutic (and possibly supratherapeutic) doses. Withdrawal is preferentially initiated in animals through abrupt drug discontinuation, although tapered drug discontinuation and antagonist precipitation may provide additional safety information. Behavioral observations should begin several days before drug discontinuation and continue daily for at least 7 days or for a duration equivalent until the test drug is eliminated. A standardized checklist of expected withdrawal behaviors for pharmacological drug classes should be used. Different pharmacological classes of drugs tend to produce different withdrawal syndromes (although there can be overlapping responses). These withdrawal signs often are opposite to the signs observed during drug administration (e.g., benzodiazepine withdrawal may produce hyperactivity and seizures, while stimulant withdrawal may produce hypoactivity and sleep). In order to validate the study, a positive control (a scheduled drug with known abuse potential, preferably in the same pharmacological class as the test drug) should produce withdrawal behaviors that are greater than those produced by vehicle.

Although physical dependence should be assessed during the safety evaluation of a drug, it is also considered to be part of the abuse potential assessment because of the role aversive withdrawal can play in maintaining abuse of certain classes of drugs. Also, dependence liability is a factor FDA must consider when recommending whether a drug should be controlled under the CSA.*(see* 21 U.S.C. 811(c)(7)). Additionally, the scheduling placement of a drug with abuse potential under the CSA includes consideration of its ability to induce physical or psychological dependence, relative to other scheduled drugs *(see* 21 U.S.C. 812(b)).

V. ABUSE-RELATED DATA FROM HUMAN STUDIES

Abuse-related data can be obtained from numerous human studies, including a human abuse potential study, human studies that evaluate cognition and performance, abuse-related AEs from clinical studies, and human physical dependence studies.

A. Use of Clinical Pharmacokinetic Data in Human Abuse-Related Studies

Pharmacokinetic data that are generated during phase 1 and 2 clinical studies with the test drug are important in appropriately designing and interpreting data from human abuse-related studies. The main PK parameters for this purpose are C_{max}, T_{max}, time to onset of drug effects, and $T_{½}$ for the parent drug and any major CNS-active metabolites (>10% of parent concentration). Other elements, such as $AUC_{0-\infty}$, bioavailability, and CNS concentration and drug clearance, may be important, depending on the drug product. Human pharmacokinetic data may be useful in determining relative passage of the test drug into the brain.

The recommended use of the clinical PK data in designing human abuse-related studies is described in detail below. The protocols for human abuse-related studies should include a justification of design elements based on phase 1 and 2 clinical PK data. All PK parameters utilized should be based on actual measurements, not estimations. When the NDA is submitted, all clinical PK studies and resultant data that informed the design and interpretation of human abuse-related studies should be cross-linked.

B. Abuse-Related Adverse Events in Clinical Safety and Efficacy Studies

All clinical safety and efficacy studies should be evaluated for CNS-related AEs that may suggest the test drug produces effects that will be sought out for abuse purposes. A positive signal from abuse-related AEs does not inherently mean that a test drug has abuse potential. However, evaluation of clinical AE data, in conjunction with nonclinical abuse-related data (chemistry, receptor binding, animal studies), will determine whether a human abuse potential study should be conducted.

The presence of a euphoria-like response is a key observation in the clinical assessment of whether a test drug has abuse potential. If euphoria-related AE(s) are reported, it will be important to further characterize the profile of the abuse-related signals to determine if the drug is similar to other known drugs of abuse (a stimulant, sedative, hallucinogen, etc.). In the absence of euphoria-related signals, AEs such as hallucination and dissociative state may also be indicative of abuse potential. If any of these abuse-related AEs are present, the test drug will likely need to be evaluated in a human abuse potential study before the FDA can approve it.

Abuse-related AEs should be interpreted in the context of the proposed therapeutic indication of a drug. Thus, not all CNS-related AEs are equally relevant for purposes of abuse assessment. For example, an antidepressant that produces "elevated mood" or a sleep aid that produces "somnolence" in the absence of a clear euphoric signal is not likely to be interpreted from these AE data alone as having abuse potential. Additionally, even though "dizziness" is listed under euphoria-related terms, this AE is not by itself indicative of abuse potential. At the time of publication of this guidance document, a ranking of relevant AEs as signals of abuse risk is not available, and all AEs are of interest for the Agency to consider in the overall assessment of risk to the public health. The Agency's interest extends to information about the timing of the AEs and the narratives from case report forms (CRFs), which are important in interpretation of the drug effects.

The list below is a compilation of abuse-related AE terms, related to the drug's pharmacology, as provided in the MedDRA (Medical Dictionary for Regulatory Activities) System Organ Classifications (SOC). We recommend sponsors and applicants use these terms when describing abuse-related AEs. Each of the lower level terms that are shown are coded on the basis of a longer list of verbatim terms, words or phrases from a patient or observer. Most preferred abuse-related terms relate to the drug's pharmacology and fall under SOC General disorders and administration site conditions, SOC Nervous system disorders, and SOC Psychiatric disorders.

Below are examples of MedDRA Preferred Terms (PTs), which may provide abuse-related information about a drug. This list is not exhaustive, however. A MedDRA search should

include additional PT terms that reflect any specific effect of a drug being abused and events that could be observed during drug abuse (for example, overdose, seizure), etc., coded in current MedDRA PTs.

Euphoria-related terms

Euphoric mood; Elevated mood*;* Feeling abnormal; Feeling drunk; Feeling of relaxation; Dizziness; Thinking abnormal; Hallucination*;* Inappropriate affect

Terms indicative of impaired attention, cognition, and mood

Somnolence; Mood disorders and disturbances

Dissociative/psychotic terms

Psychosis; Aggression; Confusion and disorientation

Related terms not captured elsewhere

Drug tolerance; Habituation; Drug withdrawal syndrome; Substance-related disorders

Abuse-related AE data from clinical safety and efficacy studies should be systematically categorized, tabulated, and analyzed to determine if AE patterns exist within different human populations following administration of the test drug. These AEs should be presented as both pooled studies and individual studies, separated by dose. When appropriate, full CRFs should be evaluated in order to understand the incident that led to the AEs, establish the time at which AEs appear following drug administration, the duration of the AEs, and which AEs overlap temporally. CRFs are also important to determine if other drugs were present at the time of the incident or whether the individual had other extenuating circumstances during the incident. All incidents that lead to hospitalization for serious neurological or psychiatric abuse-related AEs may provide relevant information about abuse potential. The history of a subject may be important in interpreting any abuse-related event. Clinical studies can also provide information about the incidence of signals suggestive of abuse, such as substance use disorders, overdose, drug diversion or drug loss.

Differences in AE profiles can occur between different phases of clinical drug development. For example, it is not unusual for there to be a greater incidence of abuse-related AEs from a test drug in healthy volunteers who participate in phase 1 studies, compared to the subject populations who participate in phase 2 and 3 studies. Several possibilities may account for this. One possibility is that phase 1 studies test a much broader range of doses than those tested in phase 2 and 3, including the larger doses that tend to produce a greater degree of abuse-related AEs. Another possibility is that phase 2 and 3 studies test individuals who may have an altered responsivity to a test drug because of their underlying disease state. For this reason, the tabulation of abuse-related AEs should occur not only by dose, but also by population tested. If a human abuse potential study is conducted later, the resultant data should be tabulated with other phase 1 data in the NDA.

C. Human Abuse Potential Study in Recreational Drug Users

The primary objective of a HAP study is to provide information on the relative abuse potential of a test drug (generally an NME) in humans. Data from HAP studies are important in developing abuse-related drug product labeling and in determining whether the drug product will be scheduled under the CSA. As noted above in Section III.A, a HAP study will likely be necessary when abuse-related signals occur in nonclinical studies or if abuse-related AEs are observed in clinical studies. HAP studies that are designed to specifically test the effectiveness of a new opioid formulation in providing meaningful abuse deterrence, are described in the guidance for industry, *Abuse-Deterrent Opioids – Evaluation and Labeling (2015).*

During drug development, it is generally advised that HAP studies not be conducted prior to the end of phase 2 clinical studies. This should ensure that the doses used in the HAP study are based on the final proposed therapeutic doses and have established safety following phase 1 studies in healthy individuals and phase 2 studies in individuals with the disease of interest. Typically, HAP studies evaluate the highest proposed therapeutic dose of the test drug as well as doses that are multiples of the highest proposed therapeutic dose (usually 2-3 times greater, if this can be done safely) in comparison to a positive control(s) and placebo.

1. Study Site

HAP studies are typically conducted in an inpatient or outpatient human pharmacology laboratory setting. In the outpatient setting, subjects should be screened for drugs of abuse when returning to the laboratory unit prior to the administration of a study treatment. Given that supratherapeutic doses are tested in these studies, medical personnel and equipment should be available to adequately respond to AEs that could compromise the safety of the subjects enrolled in the study. Safety measures should be in place to ensure that subjects are not released from the laboratory unit until they are no longer impaired by drugs administered during the study.

2. Subjects and Sample Size

HAP studies should be conducted in experienced recreational drug users who have a recent history of using drugs in the same general pharmacological class as the test drug (e.g., sedative, stimulant, opioid, or hallucinogen). Typically, subjects who qualify for the study have had numerous recent recreational experiences with the drug class. This drug history ensures that subjects are so familiar with the psychoactive effects of the drug class that they can both identify and tolerate the drug class. Ideally, subjects should prefer this drug class for recreational use. It is not recommended that drug-naïve subjects be used in HAP studies because this population has not been validated scientifically as being able to provide accurate information on the abuse potential of a drug.

During screening, a thorough recreational drug history should be taken from each potential subject that details the drugs used, the frequency of use (overall number of times used and typical amount used), and the time since last use. Individuals should be excluded from participation in the study if they are currently dependent on a drug (other than caffeine or

nicotine) or if they are in drug treatment or recovery. Additional exclusionary criteria specific to a HAP study should include positive drug urine screen, positive breath alcohol test, signs of drug withdrawal, serious psychiatric or neurological conditions, and any medical condition that could be exacerbated by drug exposure or interfere with study procedures.

Sponsors should include a fair representation of races and sexes as participants in clinical trials so that clinically significant differences in response can be detected. The FDA *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs (1993)*[17] should be followed. The age of HAP study subjects typically ranges from 18 to 55 years old.

Study power is of special concern with HAP studies, given that the sample size is typically small. In order to determine the correct sample size, a power analysis should be conducted, with a justification of the power level that is used in the sample size calculation. The statistical analysis should be based on the data from those subjects who complete the study. The number of completers can be influenced by AEs related to drug administration such as sedation, somnolence, mental status changes, or nausea/vomiting, all of which may interfere with the collection of data. Thus, the definition of the completer population should include the criterion that randomized subjects must have at least one response on the visual analog scale (VAS) for Drug Liking within 2 hours of T_{max} for each treatment in the study. To ensure adequate power, the sponsor should take into account that there will be subjects who drop out of the study early and plan the sample size calculation accordingly. Proper planning should avoid any need to replace subjects who discontinue without completing the study. The data from all subjects who begin the study should be evaluated for safety signals, including ones indicative of abuse potential.

3. Study Design

The design of a HAP study typically includes a Screening Phase, a Qualification Phase, a Treatment Phase, and Follow-up. The drug administration phases are detailed below:

Qualification Phase

The purpose of the Qualification Phase is to select subjects who report drug liking in response to the positive control and demonstrate a meaningfully different response from that produced by placebo. Each subject should be primarily evaluated using a bipolar Drug Liking VAS of 0-100, such that placebo should produce a score between 40-60 points, the positive control should produce a score outside of the placebo range, and there should be a difference of at least 15 points between placebo and positive control response. Only those subjects who produce these results should participate in the Treatment Phase.

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[17] Available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126835.pdf. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

The Qualification Phase is generally conducted with only two study treatments: the positive control to be used in the Treatment Phase (at a single dose known to produce drug liking, preferably from previously conducted HAP studies) and placebo. If two positive control drugs are used in the Treatment Phase, each of them should be included in the Qualification Phase. The Qualification Phase is typically conducted in a double-blind fashion. However, if the positive control has a very long half-life that could necessitate an extended washout period between drug sessions, the placebo session may be scheduled before the positive control session to reduce intersession timing. In such a case, subjects should remain blind to the study treatment order.

For studies in which an opioid will be administered, it is recommended that subjects undergo a naloxone challenge prior to initiation of the Qualification Phase (and prior to the Treatment Phase, if they have left the laboratory unit) in order to demonstrate that they are not physically dependent on opioids. In a naloxone challenge test, subjects are administered naloxone and evaluated for 2 hours using the Clinical Opiate Withdrawal Scale (COWS) and vital sign monitoring. Those subjects who display no signs of opioid withdrawal and have a COWS score of <5 after each naloxone administration should be considered to be non-dependent on opioids.

Treatment Phase

The Treatment Phase is usually designed as a randomized, double-blind, double-dummy, placebo- and active-controlled, crossover study.

The study treatments should include placebo, one or two doses of the positive control and at least three doses of the test drug. If the test drug has multiple mechanisms of action that may produce a constellation of abuse-related psychoactive effects, or has a CNS-active major metabolite with a different mechanism of action, it may be appropriate to consider including a second positive control.

In the interests of safety and assurance of successful results, the positive control should be an FDA-approved drug that is pharmacologically similar to the test drug and scheduled under the CSA. When the test drug has a novel mechanism of action that presents a difficult selection for positive control, sponsors should explore and justify use of alternative positive control candidates that have been shown to be safe and elicit similar psychoactive properties as the test drug.

The dose(s) of the positive control are ideally selected on the basis of previously-conducted HAP studies, in which those doses produced positive psychoactive effects indicative of abuse potential. When the positive control is a drug that has not been evaluated in a HAP study before, it may be useful to first conduct a separate dose-finding study, to ensure that the dose selected for the HAP study produces positive subjective responses that differentiate statistically from placebo.

For regulatory purposes, the doses of a test drug that will be evaluated in human abuse-related studies should be based on the highest proposed therapeutic dose in humans, as well as a dose 2-

3 times that dose, if this can be done safely. Lower doses may be appropriate when the drug has a narrow therapeutic index or produces differences in the pharmacokinetic profile between subject subgroups (e.g., sex, race, or age). If a test drug has partial agonist activity at a site associated with abuse potential, evaluating decrements in dose may be more appropriate when assessing the abuse-related properties of the drug, if the therapeutic indication relies on receptor antagonism.

The protocol design should address any potential impact of food on test drug absorption or the collection of subjective measures. For example, consideration should be given as to whether orally-administered drugs should be ingested while fasting or on high fat diets. The imposition of restrictions on subjects who smoke cigarettes during the study session may need to be considered.

Most HAP studies will be conducted using an oral route of administration for all treatments. However, if the test drug is to be medically administered through a non-oral route, or if it is liable to be used for recreational purposes via a non-oral route, it may be appropriate to conduct the HAP study using both an oral and non-oral route of drug administration. In this case, the protocol should clearly describe study procedures for the non-oral drug administration, including preparation of the treatments for use and training of the subjects in the procedures so that the entire drug dose is delivered. The safety of alternative routes of administration should be demonstrated prior to the initiation of the study.

Each study treatment should be administered once to each subject, using a repeated Williams square design. A standard washout period between sessions should be calculated on the basis of the drug with the longest half-life, so that adequate drug elimination between study sessions will be achieved (typically within 5 half-lives). If the test drug has a CNS-active major metabolite with a half-life that is longer than the parent drug, that metabolite's half-life should be part of the calculation of the length of the washout period. The length of the washout period may also be extended if information from animal or human studies shows that tolerance develops with repeated exposure to a test drug within a brief time period.

4. Outcome Measurements

Outcome measures for a HAP study should include subjective measures, safety and physiological measures, pharmacokinetic data, and abuse-related AEs.

Subjective Measures

In HAP studies, standardized questionnaires should be used for evaluating the subjective effects of drugs. Typically, study participants are asked to provide information about their responses to a test drug through the use of specific VAS at specific time points following drug administration. The VAS for "Drug Liking" should be selected as the primary measure. One or two additional primary measures may be selected, such as VAS for "High". Secondary measures may include VAS that are specific for the pharmacological effects of the test drug, such as "Stoned" for cannabinoids, "Hallucinations" for hallucinogens, "Sedation" for CNS depressants, and "Stimulated" for CNS stimulants. VAS for "Overall Drug Liking," "Take Drug Again" and

"Drug Similarity" are secondary measures that evaluate subjective responses after peak drug effects have occurred, as well as next day responses. The data from the secondary measures should be considered with the primary measures in determining whether the HAP study shows signals of abuse. On a unipolar VAS, the scale ranges from 0 ("No Response") to 100 ("Highest Response"). On a bipolar VAS, a score of 50 represents "No Response," with 0 and 100 representing the poles of the two choices (e.g., "Drug Liking/Disliking" or "Sleepy/Awake").

The timing of the subjective measures should be established based on the pharmacokinetics of the test drug (as well as any CNS-active major metabolites). Since T_{max} is determined by route of administration, data from previously-conducted human PK studies should inform the time points at which observations are made. Following oral administration of a drug, measures are typically taken every 30 minutes for the first several hours, and thereafter at more extended intervals through 24 hours after drug administration. The timing of subjective measure collection should occur most frequently around the time of peak plasma level (T_{max}).

For drugs that have rapid onset, it may be appropriate to collect measurements earlier and more frequently than 30 minute intervals. In contrast, for drugs with a very long half-life with persistent effects, continuing to evaluate subjective responses well after peak drug effects occur may be appropriate. The time to onset is dependent on the specific human behavior being evaluated, since various effects may occur at different times while the drug is active. For example, in a human study, signs of euphoria (assessed through a subjective measure or reported as an AE) may start or end at a time different from signs indicative of stimulation or hallucination. Evaluating the time course of the different subjective measures in relation to each other (and to abuse-related AEs) can provide important information regarding why subjects may report positive or negative assessments of the drug before, during and after the peak of drug effects (T_{max}).

Safety and Physiological Measures

Safety measures should be collected throughout the study session. These may include clinical laboratory parameters, vital sign measurement, electrocardiogram, and oxygen saturation. Other measures can be proposed, based on the physiological effects of the test drug. Depending on the safety risks posed by the study drugs, qualified emergency response personnel and appropriate safety equipment should be available.

Changes in physiological measures such as heart rate, blood pressure and pupil size are often indicative of responses to a specific drug class (e.g., miosis following opioid administration or tachycardia following stimulant administration). These physiological effects can be monitored over the course of the study session and correlated to both the drug dose administered and the PK of the drug.

Abuse-Related Adverse Events

AEs, as observations pertinent to the investigation on each individual administered the investigational drug or employed as a control, must be collected in all clinical studies of investigational new drugs (*see* 21 CFR 312.62(b), (c), *see also* 312.60, 312.64(b)), and can

provide critical information regarding the abuse potential of a test drug. However, in HAP studies, it is possible to directly correlate the appearance and duration of abuse-related AEs in relation to responses on VAS subjective measures such as "Drug Liking" and "High". If specific abuse-related AEs are reported in earlier clinical studies, HAP study staff should be informed of the need to increase appropriate monitoring of these AEs, as well as medical or psychiatric responses, during or after a study session.

A test drug may induce AEs that can modulate subjective measure outcomes or interfere with the collection of the measures. Examples of such AEs include sedation that prevents data collection or mobility related to frequent urination that may heighten the subject's awareness of the effects of the drug. Considerations should be given in advance regarding how to reduce interruptions to study procedures because of AEs.

Detailed case narratives for abuse-related AEs should be included with the study report. Narratives for each AE should include time of onset and duration of the event, dose of drug taken, severity and outcome. If available, pharmacokinetic values for each individual subject who experienced these AEs should be provided to determine whether there is a temporal correlation between drug plasma levels and AEs.

Pharmacokinetic Data

Many HAP studies include an analysis of blood samples collected throughout a study session in order to monitor drug PK. This is done primarily to confirm that plasma levels of the drug are equivalent between subjects and to evaluate whether subjective measures and AEs can be correlated with drug levels over time. Typically, blood is drawn immediately after the collection of subjective measures is completed at each time point. If an analysis shows that a subject had low plasma levels of a drug, it may account for a lack of subjective responses in a drug session.

5. Analysis of Data

The statistical analysis of a HAP study should address whether:

- The known drug of abuse (positive control) produces reliable abuse-related responses compared to placebo.
- The test drug produces abuse-related responses that are smaller than the positive control.
- The test drug produces abuse-related responses that are similar to placebo.

To address these issues, the following hypotheses should be tested:

1. Validation test of the sensitivity and integrity of the study: Does the positive control (C) produce mean responses that show greater abuse potential compared to placebo (P)? Thus, the hypothesis should be tested as following:

$$H_0 : \mu_C - \mu_P \le \delta_1 \text{ versus } H_a : \mu_C - \mu_P > \delta_1 \text{ where } \delta_1 > 0.$$

2. Does the test drug (T) produce mean responses that show less abuse potential compared to positive control?

$$H_0 : \mu_C - \mu_T \leq \delta_2 \text{ versus } H_a : \mu_C - \mu_T > \delta_2 \text{ where } \delta_2 \geq 0 .$$

3. Does the test drug produce mean responses that show similar abuse potential compared to placebo?

$$H_0 : \mu_T - \mu_P \geq \delta_3 \text{ versus } H_a : \mu_T - \mu_P < \delta_3 \text{ where } \delta_3 > 0 .$$

The actual values of δ_1, δ_2, *and* δ_3 vary according to such factors as subjective measures, drug class, and route of drug administration. All the margins should be pre-specified and justified in the protocol. The statistical tests yield multiple comparisons (all doses of positive control drug versus placebo; all doses of the test drug versus each dose of the positive control drug; and all doses of the test drug versus placebo) for each of the subjective measures collected. For each hypothesis, the statistical significance of the test should be achieved on all doses. Thus, no multiplicity adjustment is recommended.

Statistically, HAP studies should be evaluated as safety studies. Thus, the null hypotheses for the test drug should be constructed based on the presumption that the test drug produces abuse potential similar to the positive control and therefore differentiates from placebo. In order to demonstrate that the drug has no abuse potential, the null hypotheses should be rejected statistically. This is in contrast to the statistical evaluation used in efficacy studies, in which the null hypothesis is constructed on the presumption that the test drug is not efficacious and does not differentiate from placebo.

The statistical analysis of the data from a HAP study should begin with descriptive statistics of the mean, standard error, and other summary statistics such as minimum, first quartile (Q1), median, third quartile (Q3) and maximum for each subjective measure, each treatment and each paired difference among treatments. These data should then be used to create tables and graphs.

Primary Analyses

The statistical model that should be used in HAP studies is a linear mixed-effects model, which includes period, sequence, and treatment as fixed effects, and subject as a random effect. The primary analyses of abuse potential should be based on testing the differences between the means from the primary measure(s) at the peak of drug response effects (E_{max}) produced by the test drug, the positive control, and placebo, using proper tests and appropriate statistical methods at a significance level of 0.05 (1-sided).

Secondary Analyses

Secondary analyses should include the secondary subjective measures and objective measures (such as pupil size) and time to peak effect. The analyses should follow the same procedure as the primary analyses.

It is important to note that although the abuse-related AEs observed during HAP studies do not undergo a statistical evaluation, they are still an important component in assessing the abuse signals produced during the HAP study.

All statistical analyses including primary, secondary, any alternative and supportive analyses should be pre-specified.

D. Clinical Studies That Evaluate Cognition and Performance

Clinical studies that evaluate cognition and performance can provide additional safety information regarding the psychoactive effects of drugs that may have abuse potential. If a sponsor wishes to evaluate these parameters, the testing may occur during a HAP study with recreational drug users. Alternatively, the testing may occur during separate studies in healthy individuals who do not have experience with recreational drugs. Cognitive tests include those that assess the effects of a test drug on memory, perception, attention, language ability, or consciousness. Performance tests generally evaluate psychomotor abilities such as response time or amount of sway while standing.

If a test drug interferes with cognition or performance, this does not inherently mean that the drug has abuse potential, but it does provide important information related to the drug's CNS pharmacology. These responses may also suggest ways in which a test drug could endanger the health or safety of individuals who take the drug (or those around them). Data from these studies may be useful in predicting public health risks, which is a critical area discussed in the 8FA*(see* 21 U.S.C. 811(c)(6)).

The ability of a drug to induce changes in cognition or performance may alter the attractiveness of a drug for abuse purposes. Research regarding methods of assessing whether a particular drug product has more or less attractiveness to recreational drug users is ongoing. However, for regulatory purposes, any evaluation of the attractiveness of a drug product should be based on a method that is scientifically validated and reliable in terms of its ability to predict abuse potential.

E. Clinical Evaluation of Physical Dependence

An abuse potential assessment should include an evaluation of whether a drug produces physical dependence, in order to: 1) provide accurate information in labeling regarding the risks associated with abrupt drug discontinuation (and the possible need for tapered discontinuation), and 2) provide information that FDA will use in determining whether a drug will be recommended for scheduling under the CSA, and if so, which schedule should be recommended (s*ee* 21 U.S.C. 811(c)(7)).

In humans, discontinuation of many CNS-active drugs produce drug withdrawal symptoms indicative of physical dependence, including headache, anxiety, nausea/vomiting, tremor, chills, decreased concentration, agitation/irritability, sleep disturbances, and mood changes. However, different pharmacological classes of drugs may produce unique withdrawal symptoms that are often opposite to the responses produced during drug administration. For example, opioids may produce constipation during drug administration but diarrhea during drug discontinuation, while amphetamines may produce mental acuity during administration but cognitive impairment during drug discontinuation.

The Agency recognizes that physical dependence does not inherently indicate that a drug has abuse potential. Indeed, some drug classes (such as beta-blockers and monoamine reuptake inhibitors) that are known to produce physical dependence are not abused and are not scheduled under the CSA.

The assessment of physical dependence in humans does not typically involve a dedicated study. Instead, physical dependence is usually assessed at the conclusion of a phase 2/3 clinical efficacy study through a monitored discontinuation period. Use of abrupt drug discontinuation rather than tapered discontinuation, or precipitated withdrawal through antagonist administration, is generally preferable in order to produce naturalistic conditions under which patients stop taking medication. The duration of observation during drug discontinuation should persist for a period equivalent to at least 5 half-lives of the test drug when the drug has been fully eliminated.

A human physical dependence evaluation may include:

- Use of drug class-specific withdrawal scales
- Use of disease-specific scales for evaluation of potential symptom rebound
- Assessment of AEs before and after drug discontinuation
- Use of VAS assessing withdrawal symptoms and mood states
- Use of daily diary by study subject
- Collection of physiological measures and vital signs
- Blood sampling for association of pharmacokinetics and withdrawal signs/symptoms

When clinical efficacy studies with the test drug are conducted in a vulnerable population, or when abrupt discontinuation of a test drug may pose a safety concern due to return of disease symptoms (e.g., seizures in study subjects with epilepsy or psychotic responses in subjects with schizophrenia), a dedicated physical dependence study conducted in healthy controls may be recommended. In the design of such a study, the highest proposed therapeutic dose can be tested in comparison to placebo (with evaluation of withdrawal AEs and relevant scales). If the abrupt withdrawal of the drug is likely to cause serious AEs in healthy subjects, an animal physical dependence study may be sufficient. For a drug with a novel mechanism of action, an animal physical dependence study should be conducted prior to a human study, to obtain information about which signs and symptoms should be monitored during drug discontinuation in a human study.

A sponsor should propose and justify all design elements of a physical dependence study.

VI. POST-MARKETING AND ILLICIT DRUG ABUSE DATA

When a drug substance in the new drug product has been included in drug products legally marketed in the U.S. or elsewhere, post-marketing data may provide information regarding whether the drug substance produces abuse-related signals and potential risks. Similarly, if a drug substance in the new drug product has been used for abuse purposes, information may be available regarding the rewarding effects and safety issues associated with the drug substance. These data may contribute to a broader understanding of the abuse potential of a drug, in conjunction with animal and human laboratory data collected during drug development.

Post-marketing data may include, but is not limited to, abuse-related information obtained from:

- Summaries of AEs reported during clinical studies, as detailed in drug labeling for a legally marketed drug (including English translations for labeling used in other countries)

- Drug abuse reports in the FDA's Adverse Events Reporting System (FAERS), company drug safety databases and World Health Organization (WHO) VigiBase

- Publicly available federally-funded HHS databases such as the National Survey on Drug Use and Health (NSDUH), the Treatment Episode Data Set (TEDS), and Monitoring the Future (MTF)

- Proprietary databases containing data on prescription drug abuse and diversion, or on entry into substance abuse treatment centers

- Databases reporting on drug abuse in state or local communities such as poison control centers, treatment programs, state boards of pharmacy, medical examiners, prison systems, syringe service programs, local departments of public health

- Databases containing information on drug diversion and drug seizures, such as the DEA's National Forensic Laboratory Information System (NFLIS)

- State or local law enforcement reports

- Scientific and medical literature

- Internet forums and social media sites through which drug experiences are reported and discussed

Each of these potential sources of abuse-related information has limitations,[18] which should be delineated in an NDA submission if data from these sources are used. Not all of these data sources are expected to be useful for all products. Post-marketing abuse data should be presented within the context of prescription volume for the product(s) of interest. Where feasible and appropriate, data on relevant comparator products should be included. Applicants should also refer to CDER's *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005)*[19] for recommended methods of assessing and reporting safety through observational studies.

Although post-marketing data from US or foreign sources can provide important abuse-related information, they are not a substitute for a thorough abuse potential assessment conducted prior to submission of an NDA.

[18] Secora, A.M. et al, "Measures to quantify the abuse of prescription opioids: a review of data sources and metrics" Pharmacoepidemiology and Drug Safety 2014; 23: 1227- 1237.

[19] Available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

ABBREVIATIONS

ASH	Assistant Secretary for 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
DEA	Drug Enforcement Administration
DOJ	Department of Justice
FAERS	FDA's Adverse Events Reporting System
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
IND	Investigational New Drug Application
NDA	New Drug Application
NIDA	National Institute on Drug Abuse
NSDUH	National Survey on Drug Use and Health
SAMHSA	Substance Abuse and Mental Health Services Administration
U.S.C.	United States Code