
POLICY AND PROCEDURES

OFFICE OF THE CENTER DIRECTOR

**Consulting the Controlled Substance Staff on Drug Abuse Potential and Labeling,
Drug Scheduling, Dependence Liability and Drug Abuse Risks to the Public Health**

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PURPOSE

This MAPP establishes responsibilities and procedures in the Center for Drug Evaluation and Research (CDER) for consulting the Controlled Substance Staff (CSS) regarding the evaluation of drug abuse potential and labeling, drug scheduling, dependence liability, and drug abuse risks to the public health. This MAPP also provides a description of the role of CSS in the drug abuse assessment and the drug scheduling process within CDER.

BACKGROUND

CSS provides expertise to the Food and Drug Administration (FDA) Centers and CDER Offices and Divisions as part of the review process in assessing drugs for abuse potential and dependence liability. CSS fulfills this unique role within the FDA under the authority of the Controlled Substances Act (CSA) of 1970. The CSA requires the Secretary of the Department of Health and Human Services (HHS) to notify the Attorney General (Department of Justice (DOJ)) through the Drug Enforcement Administration (DEA) if a “new-drug application is submitted for any drug having a stimulant, depressant, or hallucinogenic effect on the central nervous system,” (21 U.S.C. 811(f)) because these effects are signals indicating that the drug may have abuse potential (see also Title 21 Code of Federal Regulations, Section 312.23(a)(10)(i) for investigational new drug (IND) applications). This includes applications for drugs with potentially abuse-deterrent properties. HHS has delegated this function to the FDA and CDER. CSS has performed this role within FDA since 2000.

POLICY

1. CSS performs the abuse potential, dependence liability, and scheduling assessments for CDER. All CDER Offices and Divisions are required to consult CSS to evaluate drugs from an abuse perspective during the review of investigational new drug applications (INDs), new drug applications (NDAs), biological licensing agreements (BLAs), and abbreviated new drug applications (ANDAs). CDER Offices and Divisions are also required to consult CSS to participate on a multidisciplinary team to evaluate new abuse and dependence-related information on currently-marketed drugs.
2. CSS evaluates all drugs submitted under INDs, NDAs, ANDAs, and BLAs that have a stimulant, depressant, or hallucinogenic effect on the central nervous system (CNS). The submissions include those drugs classified as opioids, stimulants, hallucinogens, benzodiazepines, barbiturates, cannabinoids or those classified as anabolic steroids. These drugs must be evaluated for abuse potential as part of the overall assessment of the drug's safety.
3. CSS evaluates IND information relating to the potential for abuse and dependence in clinical studies. This includes evaluating the methodology and data in a nonclinical or clinical protocol or study report. From this information, CSS determines whether a drug under review requires additional nonclinical or clinical studies designed to address questions about the abuse potential of the drug. The nonclinical and clinical abuse-related protocols and study reports evaluated by CSS include:
 - a. Nonclinical drug discrimination protocols and study reports.
 - b. Nonclinical self-administration protocols and study reports.
 - c. Human abuse potential (also called human abuse liability) protocols and study reports.
 - d. Clinical and nonclinical dependence studies.A CSS consultation is required for these assessments.
4. CSS's advice and recommendations will be conveyed to sponsors by the consulting CDER Office or Division. Following the procedures outlined in MAPP 6030.9, *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review*, the review divisions consult CSS at major milestones in drug development.
5. For NDA submissions, sponsors are required to submit and summarize all abuse- and dependence-related information collected during IND development or referenced to support the submission. This information serves as the basis for

CSS's recommendations on the product labeling, particularly *Section 9: Abuse and Dependence*, and on drug scheduling. A CSS consultation request from the reviewing Division is required for NDA evaluations and should occur promptly upon receipt of the NDA. CSS will participate in the NDA filing review.

6. CSS conducts additional scientific and medical evaluations (Eight-Factor Analyses, see 21 U.S.C. 811(b) and (c)) to determine if a drug warrants control under the CSA and thus require the preparation of scheduling recommendations. When necessary, CSS drafts scheduling recommendations, which will proceed through a clearance process that includes CDER's Office of the Center Director, FDA's Office of the Commissioner, and the Office of the Assistant Secretary for Health (OASH) at HHS. Scheduling recommendations from HHS are ultimately transmitted from OASH to the DEA. CSS makes recommendations on labeling to the consulting Office or

Division consistent with the scheduling recommendation and the drug's abuse and dependence liabilities.
7. CSS participates in the review of pre-marketing data on drugs with potentially abuse-deterrent properties and proposed labeling claims related to abuse deterrence for products submitted under INDs and NDAs and for products that are currently marketed (Reference #6). A CSS consultation is required for these evaluations.
8. Under some rare circumstances, the Office of Generic Drugs (OGD) should consult CSS, such as when an ANDA involves a drug product for which a new Eight-Factor Analysis and scheduling recommendation is necessary. OGD may also need to consult CSS for generic products referencing a reference listed drug (RLD) for an abuse-deterrent opioid product, e.g., when clinical studies were conducted to demonstrate that the generic opioid drug product is no less abuse-deterrent than the RLD (References #7 and #10).
9. CSS participates in the evaluation of currently marketed drugs when new safety information pertaining to abuse or dependence is submitted to the Agency. Such information could be derived from a clinical trial, an adverse event report, a postapproval study, or peer-reviewed biomedical literature and data. A CSS consultation is required for these evaluations.
10. CSS participates in the evaluation of IND submissions involving use of Schedule I substances (including marijuana (cannabis), heroin, lysergic acid diethylamide (LSD), peyote, methaqualone, and 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") and their derivatives). See 21 CFR, Section 1308.11 for a complete list of Schedule I substances. CSS also reviews nonclinical and clinical protocols referred to FDA by the DEA under the provisions of 21 CFR 1301 (Reference #8).

PROCEDURES**Preapproval Consultations with CSS****CDER Offices and Divisions will:**

11. Complete the general consult request form (FRM-CONSULT-01).
12. Attach the following supporting documents if applicable, place the consult request documents in the formal archival system, and ensure the consult is forwarded to the CSS Project Manager:
 - a. Links to sections of the IND/NDA/ANDA/BLA related to drug abuse as well as drug scheduling and dependence, and abuse deterrence.
 - b. Citations to pertinent electronic NDA sections.
 - c. Letters from sponsors on drug abuse, scheduling and dependence issues.
 - d. Data from additional studies conducted at the request of CSS or any other information pertinent to the abuse potential or scheduling of the drug.
13. Notify CSS promptly when a consultation involves INDs and information regarding the study of abuse, dependence, and scheduling needs to be conveyed. For INDs, NDAs, BLAs, and ANDAs, provide the desired completion date, and justification for the date in the consult, including the user fee goal date, pertinent internal or industry meetings, Advisory Committee (AC) meetings, and meetings with other groups. CSS generally needs 30 days to prepare for industry meetings, to perform IND reviews, and to prepare for filing meetings. Consultations on NDAs, scheduling actions, and abuse-related risk management issues require longer preparation times.
14. Inform IND sponsors and NDA applicants that information and communication related to abuse, addiction, scheduling, dependence, and abuse deterrence must be submitted to CSS through the review division.
15. Coordinate industry meeting requests and consultation with CSS in a timely manner when the meeting is requested.
16. Consult CSS for input and clearance, as appropriate, when drafting abuse potential-related sections of sponsor communications.
17. Send CSS a courtesy copy of final actions or sponsor communications via an appropriate electronic method.

The CSS Project Manager will:

18. Serve as the point of contact for the review Divisions' assigned project managers regarding assignment of CSS reviewers, status of consult requests, and the CSS calendar.

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19. Keep accurate records of pending consult review projects.
 20. Ensure that the CSS reviewer enters completed consultations into the formal archival system.
 21. Notify the DEA, as mandated by the CSA, if a new drug submitted under a marketing application appears to have abuse potential.
 22. Coordinate with the Office of Chief Counsel (OCC), CDER, FDA, and HHS, and transmit scheduling recommendations to DEA.

The CSS Reviewer will:

23. Review submitted documents and respond to the consultation request under the supervision of their Team Leaders or the CSS Director, or designated individual.
24. Attend meetings, as requested by the consulting Offices, the CSS Team Leaders, CSS Director, or other appropriate designee.
25. Contact other Offices for additional support in clarifying consultation questions, if necessary, and coordinate with the other Offices development of the final work product.
26. Assess the need for additional information on abuse, and dependence. Participate in the review and discussions pertaining to proposed labeling.
27. Advise the Offices and Divisions on drug scheduling, proposed labeling, and proposed postmarketing studies or clinical trials.
28. Prepare scheduling recommendations, as appropriate.
29. Enter consultation reviews into CDER's electronic document archival system.

Postapproval Consultations with CSS

The CDER Offices and Divisions will:

30. Consult CSS if abuse, dependence or related events are reported as postmarketing adverse events.
31. Include CSS in meetings on abuse, scheduling, dependence, and REMS, as well as on products that have or could have abuse-deterrent properties.
32. Consult CSS on labeling revisions for drugs when abuse, scheduling, dependence, and abuse deterrence topics are concerned.
33. Consult CSS when drafting risk communications to the public about abuse, diversion and dependence.

REFERENCES

1. Controlled Substances Act (CSA) of 1970, as amended.
2. 21 Code of Federal Regulations (CFR) parts 5.10, 200, 312.23, 314, and 1300.
3. 21 U.S.C. 811(b) and (f).
4. FDA draft *Guidance for Industry: Assessment of Abuse Potential of Drugs*, 01/2010.
5. *Abuse-Deterrent Opioids - Evaluation and Labeling, Guidance for Industry*, 04/2015.
6. FDA draft *Guidance for Industry, General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Product*, 03/2016.
7. FDA, 2013, CDER MAPP 6030.9, *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review*.
8. FDA, 2003, CDER MAPP 4200.1, *Consulting the Controlled Substance Staff on INDs and Protocols That Use Schedule I Controlled Substances and Drugs*.
9. FDA, 2003, CDER MAPP 4200.2, *Forecasting Schedule I and II Substance and Drug Needs*.
10. FDA, 2011, CDER MAPP 4200.4, *Office of Generic Drugs (OGD) Consultation with the Controlled Substance Staff (CSS) on Subject Abbreviated New Drug Application (ANDA) Submissions*.
11. MOU 225-15-01, *Memorandum of Understanding between the U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research and the U.S. Department of Justice, Drug Enforcement Administration*, 03/24/2015.

DEFINITIONS

Abuse: The intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect.

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..

Adverse Events: Any health related event associated with the use of a nonprescription drug that is adverse, including: (A) an event occurring from an overdose of the drug, whether accidental or intentional; (B) an event occurring from abuse of the drug; (C) an

event occurring from withdrawal from the drug; and (D) any failure of expected pharmacological action of the drug (21 U.S.C. 379aa).

Controlled Substance: A drug or other substance, or immediate precursor, included in schedule I, II, III, IV, or V of part B of this subchapter. The term does not include distilled spirits, wine, malt beverages, or tobacco, as those terms are defined or used in subtitle E of the Internal Revenue Code of 1986 (21 U.S.C. § 802(6)).

Controlled Substance Staff (CSS): Located within FDA's Center for Drug Evaluation and Research, CSS assesses preclinical, clinical, and actual abuse data to determine whether a drug under review requires abuse potential studies, scheduling under the CSA, and appropriate information in drug labeling to convey abuse-related messages. In addition, international drug control treaties to which the United States is a signatory may affect the regulation of new drugs with abuse potential. CSS assesses this aspect, and notifies the appropriate government agencies

Dependence Liability: The propensity of a substance, as a consequence of its pharmacological effects on physiological or psychological functions, to give rise to a need for repeated doses of the substance. Physical dependence is often characterized by withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Psychological or psychic dependence refers to impaired control over drug use, such as craving 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.

Drug Abuse Assessment: An assessment of a drug's abuse potential that includes "a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act." (21 CFR 314.50(d)(5)(vii)).

Drug Addiction: A cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than any other activities and obligations), and possible tolerance or physical dependence..

Drug Scheduling: Drugs and other substances that are considered controlled substances under the CSA are divided into five schedules (CI – CV). Substances are placed in their respective schedules based on whether they have a currently accepted medical use in treatment in the United States, their relative abuse potential, and likelihood of causing dependence when abused. An updated and complete list of the schedules is published annually in 21 CFR 1308.11- 1308.15.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
5/08/03	Initial	n/a
	1	<ol style="list-style-type: none"> 1. The inclusion of a <i>Policy</i> section, describing CSS’s general role within CDER, CSS’s role in the 21st Century review process and the abuse-related information reviewed by CSS. 2. The inclusion of a <i>Definitions</i> section, which lists abuse-related terms.