POLICY AND PROCEDURES

OFFICE OF THE CENTER DIRECTOR

Consulting the Controlled Substance Staff on Drug Abuse Potential and Labeling, 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 drug scheduling processes 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) 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 drug scheduling assessments for CDER. CSS evaluates drugs and other substances submitted under INDs, NDAs, and BLAs that have effects on the central nervous system (CNS) and need to be assessed for the extent to which the drug has a stimulant, depressant, or hallucinogenic effect. Examples include those drugs classified as known opioids, stimulants, hallucinogens, benzodiazepines, barbiturates, cannabinoids or those classified as anabolic steroids, but also includes CNS-active new molecular entities that may prove to have similar drug effects. These drugs must be evaluated for abuse potential as part of the overall assessment of the drug's safety. Contact CSS if there is uncertainty about the need for a formal consultation.
2. 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) that meet the criteria listed in item 1. Under rare circumstances, CSS evaluates abbreviated new drug applications (ANDAs), as described in item 8.
3. Consult requests are required for CSS to participate on multidisciplinary teams to evaluate new abuse- and dependence-related safety information on currently marketed drugs. Such information could be derived from a clinical trial, an adverse event report, a post-approval study, or peer-reviewed biomedical literature and data.
4. CSS is consulted to review 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 protocols and study reports, including but not limited to general behavioral, drug discrimination, and self-administration studies.
    b. Human abuse potential (also called human abuse liability) protocols and study reports.
    c. Clinical and nonclinical physical dependence studies.
5. For NDA and BLA submissions, applicants 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 the DRUG ABUSE AND DEPENDENCE section of the Prescribing Information, and on drug scheduling. A CSS consultation request from the reviewing division is required for NDA and BLA evaluations, which includes the filing review.

6. For some NDA and BLA submissions, 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 requires the preparation of a scheduling recommendation. When necessary after review of the information submitted, CSS drafts a scheduling recommendation in parallel with a CSS review of the NDA. This recommendation is transmitted to the DEA. CSS makes recommendations on labeling to the consulting Office/Division consistent with the scheduling recommendation and the drug's abuse and dependence liabilities.
7. CSS reviews products formulated to have abuse-deterrence, and should be consulted to review protocols or resulting data for studies investigating abuse-deterrent properties and proposed labeling claims.
8. Under rare circumstances, the Office of Generic Drugs (OGD) consults CSS. Instances include when an ANDA involves a drug product for which a new 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.
9. After concurrence between CSS and the consulting Division, CSS's advice and recommendations to sponsors are conveyed 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.

RESPONSIBILITIES

Preapproval Consultations with CSS

CDER Offices and Divisions:

1. Completes the general consult request form (FRM-CONSULT-01), which can be downloaded from the FDA Intranet "CDER Standard Templates Library".
2. Attaches supporting documents or includes links to the following information if applicable:

a. Links to the relevant IND/NDA/ANDA/BLA submission.

b. Email correspondence from sponsors on relevant drug abuse, scheduling and dependence issues.

c. Specific questions or review requests from the consulting division.

3. Places the consult request document in the current document archiving system at CDER linked to the submission in question, and ensures the consult is forwarded to CSS by cc:ing the CDER CSS Consults mailbox (CDERCSSConsults@fda.hhs.gov). The consultation can also be forwarded via email to the both the CDER CSS Consults mailbox and the CSS Project Manager.
4. Notifies CSS promptly when a consultation is required via submission of a consult request and cc:ing the CDER CSS Consults mailbox (CDERCSSConsults@fda.hhs.gov). Provides the desired completion date, and justification for the date in the consult, including the user fee goal date, dates of pertinent internal or industry meetings, Advisory Committee meetings, and meetings with other groups. CSS needs adequate time to review the submission. CSS generally needs 30 days to prepare for industry meetings, to perform IND reviews, and to prepare for filing meetings. CSS will endeavor to meet Division timelines by providing input in less than 30 days in necessary cases, for example IND safety review meetings. Consultations on NDAs, PMR study reports, abuse-related protocols and abuse-related risk management issues require longer preparation times. For example, for NDA submissions reviewed under PDUFA timelines, the CSS reviewer will review the NDA under the same timelines as all other subject matter disciplines.
5. Informs IND sponsors and NDA or BLA applicants that information and communication related to abuse, misuse, substance use disorder, diversion, dependence, and abuse deterrence must be submitted to the regulatory file.
6. Consults CSS for input and clearance, as appropriate, when drafting abuse potential-related advice sections of sponsor communications.
7. Sends CSS a courtesy copy of final actions or sponsor communications via an appropriate electronic method (for example, through CDER's electronic document archival system).

The CSS Project Manager:

1. Serves 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. This responsibility includes monitoring the CDER CSS Consults mailbox (CDERCSSConsults@fda.hhs.gov) for incoming consults.
2. Keeps accurate records of pending consult review projects.

3. Ensures the CSS reviewer enters completed consultations into CDER's electronic document archival system.
4. Notifies the DEA if a new drug submitted under a marketing application appears to have abuse potential.
5. Notifies the DEA of a new drug approval if that approved drug will require scheduling in accordance with statutory timelines for DEA action (e.g., within 90 days of new drug approval).

The CSS Reviewer:

1. Reviews submitted documents. Responds to the consultation requests under the supervision of their Team Leader or the CSS Director, or designated individual.
2. Attends meetings, as requested by the consulting offices or divisions, the CSS Team Leaders, CSS Director, or other designees.
3. Contacts other Offices or Divisions for additional support in clarifying consultation questions. If necessary, coordinates with the other Offices or Divisions to develop the final work product.
4. Assesses the need for additional information on abuse and dependence. Communicates the need for additional information from sponsors with the appropriate project manager in the review division. Participates in the review and discussions pertaining to proposed labeling.
5. Advises CDER Offices and Divisions on drug scheduling, proposed labeling, and proposed postmarketing studies or clinical trials.
6. Assesses NDA and BLA applications for the need for a scheduling recommendation as soon as possible. If a scheduling recommendation is necessary, notifies the CSS Project Manager so prompt due dates for the scheduling recommendation and review can be established. Prepares scheduling recommendations.
7. Enters consultation reviews into CDER's electronic document archival system.

Postapproval Consultations with CSS

The CDER Offices and Divisions:

1. Consults CSS if abuse, dependence or related events are reported as postmarketing adverse events.
2. Includes CSS in meetings on abuse, dependence, REMS related to abuse and dependence risks, and on products that have or could have abuse-deterrent properties.

3. Consults CSS on labeling revisions for drugs when abuse, dependence, and abuse deterrence topics are concerned.
4. Consults CSS when drafting risk communications to the public about abuse, diversion, and dependence.

PROCEDURES

1. CDER office or division completes the general consult request form (FRM-CONSULT-01).
    a. A consult request for NDA or BLA evaluations should occur promptly upon receipt of the NDA or BLA, as the CSS reviewer will review the NDA under the same timelines as all other subject matter disciplines and participates in the filing review.
    b. All other consult requests should be submitted as soon as possible and by a date that allows adequate time for the requested review. CSS needs 30 days to prepare for industry meetings and to perform IND reviews. Consultations on NDAs or BLAs, PMR study reports, abuse-related protocols and abuse-related risk management issues require longer preparation times.
2. CDER Office or Division submits the consult form to CSS through CDER's electronic document archival system and to the CSS consults mailbox (CDERCSSConsults@fda.hhs.gov).
3. CSS reviews the consult request form and assigns a reviewer.
4. CSS contacts the party requesting the consult as soon as possible once assigned, and provides the name of the assigned reviewer and other relevant information.
5. CSS participates in both internal and external meetings related to the consult request.
6. CSS completes the requested review within the agreed upon timelines.
7. CSS enters consultation review into CDER's electronic document archival system linked to the consultation request.

REFERENCES

1. Controlled Substances Act of 1970, as amended.
2. 21 Code of Federal Regulations (CFR) parts 5.10, 200, and 314.
3. 21 Code of Federal Regulations (CFR), Section 312.23(a)(10)(i).
4. 21 Code of Federal Regulations (CFR), Section 1300 and 1308.11 – 1308.15.
5. 21 U.S.C. §811(b) and (f).
6. 21 U.S.C. §802(6).

7. FDA *Guidance for Industry: Assessment of Abuse Potential of Drugs*, 01/2017.
8. FDA *Guidance for Industry: Abuse-Deterrent Opioids - Evaluation and Labeling,* 04/2015.
9. FDA *Guidance for Industry: General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Product*, 11/2017.
10. FDA, 2013, CDER MAPP 6030.9, *Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review.*
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 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 (abbreviated CI - CV) (21CFR 1308.11 – 1308.15). 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 nonclinical, clinical, and 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 dependence (sometimes called "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 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
3/6/17	Rev. 1	1. The inclusion of a *Policy* 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 *Definitions* section, which lists abuse-related terms.
10/26/22	Rev. 2	1. Revised to reflect current processes. 2. Removes processes unrelated to this consultation MAPP.