# PROCEDURES

## OFFICE OF THE CENTER DIRECTOR

## Office of Generic Drugs (OGD) Consultation with the Controlled Substance Staff (CSS) on Subject Abbreviated New Drug Application (ANDA) Submissions

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### PURPOSE

This MAPP describes responsibilities in the Center for Drug Evaluation and Research (CDER) for the OGD to consult with the CSS regarding OGD review of ANDA submissions involving substances controlled under the Controlled Substances Act (CSA), to respond to CSS requests for information on such ANDA submissions, and to notify CSS of OGD responses to Drug Enforcement Administration (DEA) inquiries.

### BACKGROUND

The Secretary of the Department of Health and Human Services (HHS) has delegated certain functions under the Controlled Substances Act (CSA) to the Food and Drug Administration (FDA)/CDER, and the CSS performs these functions for the Agency/Center. In this regard, CSS provides expertise to FDA centers and CDER offices and divisions on the abuse liability evaluation of drugs. CSS determines whether a drug under review requires abuse potential studies, a recommendation for scheduling under the CSA, or application of other measures to reduce abuse.

The CSA, and Drug Enforcement Administration (DEA) regulations mandate special requirements for drugs and substances which are controlled in Schedule I and Schedule II of the CSA. For example, Section 303(f) of the CSA requires HHS to review the scientific merit of the studies and qualifications of the investigators conducting research with Schedule I controlled substances and to inform the DEA if the researcher is qualified and the study is

"bona fide research." In addition, HHS is responsible for providing the DEA with annual estimates of the amounts of specific Schedule I and Schedule II substances and drugs that will be needed for medical and scientific use. DEA relies on these estimates to establish annual manufacturing quotas for the substances and drugs (CSA and the Public Health Services Act (PHSA). These responsibilities have also been assigned to CSS within CDER.

OGD reviews Abbreviated New Drug Applications (ANDAs) and approves generic drugs for marketing, under 21 CFR § 314 subparts C-D. Among the ANDAs that are reviewed are numerous drug products that are controlled substances which are subject to the same provisions of the CSA as the reference listed drugs (RLD).

## RESPONSIBILITIES

### The CSS will:

- Serve as the FDA and CDER focal point for all activities related to the control and abuse potential assessment of subject ANDAs with abuse potential issues and potential need for scheduling recommendations

- Perform abuse liability evaluations

- Develop recommendations for drug scheduling under the CSA, if appropriate

- Provide to DEA necessary information on ANDA products containing controlled substances.

### The OGD will:

- Notify CSS of subject ANDAs, including the following:
  - ANDA submissions for products where the listed drugs are drugs controlled in Schedule II or where the generic drug pending approval contains a substance controlled in Schedule I and Schedule II:
    - examples include dronabinol, fentanyl, and gamma-hydroxybutyrate [GHB] and any cannabinoid (natural, synthetic, or combination of natural and synthetic origin);
  - ANDA submissions for any generic product in which the controlled substance is formulated in a transdermal, aerosol, nasal spray, transmucosal and buccal product; and

- ANDA submissions for any other generic drug product that is in a formulation that raises abuse or CSA scheduling issues that is identified by OGD staff. Some examples include, abuse deterrent products; Central Nervous System depressants that are in unique formulations, e.g. Diastat; and drugs that have chemistry extraction study information in label of the RLD (such as Concerta).

• Respond to CSS requests for information on ANDAs with Schedule I and Schedule II controlled substances and, as necessary, on abuse liability issues that involve other controlled substances

• Inform CSS of proposed OGD responses to DEA inquiries to allow CSS the opportunity to review the OGD response. This information is needed for assurance of consistency in the information provided on all controlled substances

**PROCEDURES**

OGD will notify CSS by an email when a subject ANDA has been accepted for filing by the Regulatory Support Branch of OGD, and the review team will complete a consult request form (FDA 3291) upon the completion of a comprehensive review and submit to "CDER CSS Consults" email box.

The submission to CSS will include ANDA number, name of the generic drug, reference listed drug (RLD), the ANDA Applicant, description of the formulation and identification of the Active Pharmaceutical Ingredient (controlled substance), dosage, a summary table of studies performed, summary of any issues that OGD has identified (including impurity profile if relevant to CSA control).

OGD will provide a due date for CSS response and identify an OGD contact.

OGD will, at CSS request, contact the Applicant for additional information as needed and OGD will be responsible for meeting coordination with Applicants on CSS-identified issues.

CSS will review ANDA materials related to the above issues and respond to OGD in a timely manner.

CSS will prepare responses for OGD to provide the ANDA Applicant.

CSS will alert OGD to any major issues related to the application and the drug product's abuse potential.

CSS will convey any information to DEA if needed or required.

## REFERENCES

- Controlled Substances Act (CSA) of 1970, as amended (primarily 21 U.S.C. 811, 812, 823(f), 826)
- 21 Code of Federal Regulations parts 5, 5.1100, and 1300; FDA Staff Manual Guide 1410.10 1.A
- Public Health Service Act (PHSA) (primarily Title 42 U.S.C. 242(a))
- February 16, 2000 Memorandum from Janet Woodcock, M.D., outlining CSS responsibilities

## DEFINITIONS

**Active Pharmaceutical Ingredient (API):** Any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body of humans or other animals. APIs include substances manufactured by processes such as (1) chemical synthesis; (2) fermentation; (3) recombinant DNA or other biotechnology methods; (4) isolation/recovery from natural sources; or (5) any combination of these processes.

**Reference Listed Drug (RLD):** The listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application. (21 CFR 314.3)

**Schedule I Substances:** Substances with high abuse potential and no accepted medical use in the United States. Examples of Schedule I substances are heroin, marijuana, dronabinol, lysergic acid diethylamide (LSD), gamma-hydroxybutyrate (GHB) and methaqualone. A complete list of current Schedule I substances maintained by the DEA can be found on the Internet at: http://www.deadiversion.usdoj.gov/21cfr/cfr/1308/1308_11.htm

**Schedule II Substances:** Substances with high abuse potential, an accepted medical use in the United States, and abuse of the substance may lead to severe psychological or physical dependence. Examples of Schedule II drugs include morphine, methadone, oxycodone, hydrocodone, fentanyl, amphetamine, methylphenidate, tapentadol, and phenobarbital. A complete list of current Schedule II drugs maintained by the DEA can be found on the Internet at: http://www.deadiversion.usdoj.gov/21cfr/cfr/1308/1308_12.htm

## EFFECTIVE DATE

This MAPP is effective upon date of publication.