Guidance for Industry

Submitting Type V Drug Master Files to the Center for Biologics Evaluation and Research

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance are available from the Office of Communication, Training, and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
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Table of Contents

GUIDANCE FOR INDUSTRY[1]

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This guidance document represents FDA's current thinking on submitting Type V Drug Master Files to the Center for Biologics Evaluation and Research. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION/BACKGROUND

This document discusses Type V Drug Master Files (DMF) submitted to the Center for Biologics Evaluation and Research (CBER) by a DMF holder in support of an application or supplement. The document also describes the circumstances in which we (CBER) will accept a Type V DMF without a letter of intent from you, the person who wishes to submit a DMF.

A drug master file is a submission of information to the Food and Drug Administration (FDA) that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of human drugs and biological products. We have accepted DMFs for many years in support of applications and supplements, such as investigational new drug applications (IND), biologics license applications (BLA), and new drug applications (NDA). DMFs are generally used to allow a sponsor or applicant to reference the material in the DMF without disclosing the contents of the DMF to the sponsor or applicant. FDA reviews information in a DMF only when a sponsor or applicant incorporates material in the DMF by reference.

Previously, the regulations at 21 CFR 314.420 described the following five types of DMFs:

- Type I: manufacturing site, facilities, operating procedures, and personnel
- Type II: drug substance, drug substance intermediate, and materials used in their preparation, or drug product
- Type III: packaging materials
- Type IV: excipient, colorant, flavor, essence, or materials used in their preparation
- Type V: FDA-accepted reference information.

[1] This guidance has been prepared by the Review Management Coordinating Committee of the Center for Biologics Evaluation and Research.

In the *Federal Register* of January 12, 2000 (65 FR 1776), FDA published the final rule "New Drug Applications; Drug Master Files." The final rule amended 21 CFR 314.420 by removing the provision for Type I DMFs. FDA amended the regulation to eliminate submission of information that was not necessary either to conduct inspections of manufacturing facilities or to review the chemistry, manufacturing, and controls sections of INDs, NDAs, and abbreviated applications. The regulation became effective on July 10, 2000, and the agency will no longer accept Type I DMFs as of that date.

We have historically reviewed Type I DMFs in support of certain products under an IND. Type I DMFs have also been cross-referenced in BLAs to describe proprietary information. Type I DMFs have been used to provide a list of all products manufactured in a contract facility or other general information such as floor diagrams or standard operating procedures (SOPs) that are common to multiple products or processes in the facility. DMF holders have also submitted information on contract testing facilities in Type I DMFs.

On July 10, 2000, the effective date of the final rule, we administratively recategorized current Type I DMFs to other master file types, as appropriate (i.e., Types II, III, IV, or V), with the exception of the DMFs currently listed at http://www.fda.gov/cber/rules/master.htm. We recategorized the Type I DMFs that included information described in section II of this guidance as Type V DMFs. Applicants who have current approved applications that reference Type I DMFs that were transferred to Type V DMFs should note this change in their next BLA annual report under 21 CFR 601.12(d).

We caution applicants, however, that DMFs are not generally appropriate for product-specific information and that product-specific information should be included in the applicant's submission.

II. INFORMATION THAT MAY BE SUBMITTED IN A TYPE V DMF WITHOUT SUBMITTING A LETTER OF INTENT

You may submit information on the following types of facilities in a Type V DMF without submitting a letter of intent:

A. Facilities for Production of Gene or Cell Based Therapies for Phases 1 and 2 Clinical Trials:

Information on these facilities is important so we can assess the safety of the products used in clinical trials of gene or cell based therapies. Information that may be submitted in a DMF includes:

- floor diagrams that depict the manufacturing areas
- a list of products to be manufactured and whether equipment and areas are dedicated or shared

- overview of production steps for all products manufactured in the facility
- description of the containment features and contamination precautions, such as specialized equipment, air quality classification, description of the air handling units, and pressure differentials in production areas
- screening and acceptance procedures for cell lines brought into the facility.

These facilities are often used to generate vectors or to transduce or manipulate cells which are used in a number of clinical trials under an IND. A Type V DMF will eliminate the need for you to submit the same information numerous times and will facilitate the IND review.

B. Contract Manufacturing Facilities in Support of Biologics License Applications or Biologics License Application Supplements:

1. Production Facilities

While it is the applicant's responsibility to submit product information, the information required in the chemistry, manufacturing, and controls and, when relevant, establishment description sections (Refs. 2-8) may be cross-referenced to a Type V DMF. This would allow the holder of the Type V DMF to submit proprietary information to the agency without informing the applicant. An example of proprietary information that may be submitted in a Type V DMF is a specific list of all products manufactured at a contract facility. The applicant should have enough information to determine the impact of other products handled at the facility on its product, such as the types of other product classes manufactured, but the applicant may not need to know the specific products produced. Other information, such as basic floor diagrams and SOPs, may also be cross-referenced to the Type V DMF.

2. Testing Facilities

Quality control functions, such as cell bank testing and viral clearance studies, are often performed at contract sites. The sponsor or applicant should submit the results of such tests and studies to the IND or BLA. Information on the testing facilities, SOPs, and other relevant control procedures may be submitted in a Type V DMF that may be cross-referenced by the sponsor or applicant.

III. OTHER TYPE V DMFS

If you wish to submit information and supporting data in a DMF, other than that covered under section II of this guidance or by Types II, III or IV DMFs, you should first submit a letter of intent to:

FDA/CBER
Division of Manufacturing and Product Quality (HFM-670)
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448

IV. UPDATING DMFS

You should regularly update the DMF so that it remains current. You should submit an update to the DMF when significant changes occur that may impact on products, such as the addition of a new product to a contract manufacturing facility. You should submit updates to the address listed in section III.

V. REFERENCES

1. "New Drug Applications; Drug Master Files," Final Rule, January 12, 2000 (65 FR 1776).

2. "Guidance for Industry on the Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information For an Allergenic Extract or Allergen Patch Test," April 1999.

3. "Guidance for Industry on the Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Biological In Vitro Diagnostic Product," March 1999.

4. "Guidance for Industry on the Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for Human Plasma-Derived Biological Products, Animal Plasma or Serum-Derived Products," February 1999.

5. "Guidance for Industry on the Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product," January 1999.

6. "Guidance for Industry on the Content and Format of Chemistry, Manufacturing and Controls Information for Synthetic Peptide Substances," January 1998.

7. "Guidance for Industry on the Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for Autologous Somatic Cell Therapy Products," January 1997.

8. "Guidance for Industry on the Content and Format of Chemistry, Manufacturing and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use," August 1996.

9. "Guideline for Drug Master Files, Center for Drug Evaluation and Research," September 1989.