Guidance for Industry

Drug Master Files for Bulk Antibiotic Drug Substances

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
November 1999

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I. INTRODUCTION

This guidance is intended for those in industry whose approved applications for bulk antibiotic drug substances (i.e., *bulk applications*) were converted to Type II Drug Master Files (DMFs) when section 507 of the Federal Food, Drug, and Cosmetic Act was repealed as part of the enactment of section 125 of Title I of the Food and Drug Administration Modernization Act on November 21, 1997.[2] This guidance explains the purpose of DMFs, discusses the type of information expected in a Type II DMF, outlines administrative procedures governing review of DMFs, and clarifies your responsibilities as a DMF holder. The information presented in this guidance is also relevant to the submission of new DMFs for bulk antibiotic drug substances.

II. BACKGROUND

Prior to the repeal of section 507, bulk antibiotic drug substances were handled differently from other bulk drug substances. Bulk antibiotic drug substances were either batch certified or exempted from batch certification through the approval of an antibiotic drug application. Information about other bulk drug substances, drug substance intermediates, and materials used in their preparation were filed and maintained as Type II DMFs according to 21 CFR 314.420, or drug substance information could be filed as part of the marketing application for the finished dosage form of the drug. With the repeal of section 507 in the Modernization Act, bulk antibiotic drug substances are being handled in the same way as all other bulk drug substances under section 505 of the Federal Food, Drug, and Cosmetic Act.

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[1] This guidance has been prepared by the Antibiotic Working Group of the Chemistry, Manufacturing, and Controls Coordinating Committee (CMCCC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on drug master files for bulk antibiotic drug substances. 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 statute, regulations, or both.

[2] See also the guidance for industry and reviewers on *Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act* (May 1998).

With the implementation of the Modernization Act, the agency administratively converted all bulk antibiotic applications to DMFs. Following the conversion of these applications, the Agency gave each affected holder the newly assigned DMF number. Persons holding bulk applications were not required to take any action for their application to be converted to a DMF. However, following conversion, holders were expected to reference the new DMF number on all letters of authorization (LOAs) or other correspondence relating to the DMF for the bulk antibiotic drug substance and maintain the DMF in accordance with 21 CFR 314.420. Holders who did not wish to maintain a DMF were allowed to incorporate the information into one or more dosage form applications, or close their application in accordance with Agency record keeping practices. The incorporation of DMF information into a dosage form application usually applies to situations where the manufacturer of the bulk antibiotic drug substance and the dosage form applicant are the same corporate entity.

III. WHAT IS A DRUG MASTER FILE (DMF)?

A Drug Master File (DMF) is a submission to the Agency of confidential detailed information for the following purposes (21 CFR 314.420(a)):

- A DMF allows you (the holder) to incorporate information by reference when you submit an application (investigational new drug application (IND), new drug application (NDA), abbreviated new drug application (ANDA), another DMF, export application, or amendments and supplements to these).

- A DMF allows you to authorize other persons (applicants) to reference information in your DMF in support of a submission to the Agency without having to disclose the information to the applicant.

IV. WHAT IS A TYPE II DMF AND WHAT INFORMATION SHOULD BE INCLUDED IN IT?

There are multiple types of DMFs, but you should submit information pertaining to the manufacture of bulk antibiotic drug substances as Type II DMFs (21 CFR 314.420(a)(2)). A Type II DMF is used to provide information on drug substances, drug substance intermediates, and materials used in their preparation. It should include information on the following:

- physical, chemical, biological (e.g., anti-microbial), and stability characteristics of the drug substance;

- the name and location of the manufacturing site(s);

- the method of manufacture (e.g., microbial strain used, fermentation process, isolation process) and/or synthesis, and purification;

- the process controls used during manufacturing and packaging; and

- the specifications used to ensure the identity, strength and/or potency, quality, and purity of the drug substance.

For additional guidance on information that should be submitted in a Type II DMF, see 21 CFR 312.23(a)(7) and 314.50(d)(1)(i) and relevant CDER guidances such as the guidance on *Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances* (February 1987).[3] For guidance on information and data that should be submitted in support of sterility assurance for a sterile bulk antibiotic drug substance, see CDER and CVM's guidance on *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (November 1994).

In addition to providing the specific information described above, each submission to your DMF should include a transmittal letter and administrative details about the submission. For information on these additional items, as well as the format, assembly and delivery of DMF submissions, see CDER's guidance on *Drug Master Files* (September 1989).[4]

V. WHEN ARE LETTERS OF AUTHORIZATION NEEDED?

Before the Agency can review information in your DMF, you must send an LOA to the applicant who is incorporating information by reference from your DMF (21 CFR 314.420(b)). The applicant must include a copy of the LOA in their submission (21 CFR 314.50(g)(1)). The LOA permits FDA to access the information in your DMF. The LOA is required even if the applicant is also the holder of the DMF. A copy of the LOA should also be submitted to your DMF. For details on information that should be included in the LOA see CDER's guidance on *Drug Master Files*.

VI. WHAT ARE THE POLICIES RELATED TO PROCESSING AND REVIEWING DMFS?

Ordinarily, the information in your DMF is reviewed only in conjunction with an application that references the information through an LOA. The Agency neither approves or disapproves your DMF, but makes a judgment on the adequacy of the referenced information in support of the application that references it (21 CFR 314.420(a)). If upon review, the information provided in your DMF is determined to be inadequate, you will receive a letter from the Agency describing the deficiencies. At the same time, the Agency will notify the applicant who relies on information in your DMF

[3] For relevant CDER guidances see http://www.fda.gov/cder/guidance/index.htm

[4] CDER's guidance on *Drug Master Files* (September 1989) is currently being revised. Applicants should refer to the updated guidance when it is finalized.

of the inadequate status, but details of the deficiencies are not disclosed to the applicant. When you submit the requested information to your DMF in response to the Agency's letter, a copy of the transmittal letter should be sent to the FDA review division issuing the letter, and the affected applicant should be notified that the response was submitted. This provides notice to the applicant and review division that the DMF has been amended and the deficiencies have been addressed.

VII. WHAT ARE MY RESPONSIBILITIES AS A DMF HOLDER ?

As a DMF holder you have a number of obligations. Failure to meet these obligations may delay approval of applications that rely on the information in your DMF or result in the Agency closing your DMF. The following discusses your responsibilities.

A. Changes to your DMF

Any addition, deletion, or change to information in your DMF is required to be submitted to the Agency in duplicate (21 CFR 314.420(c)). This includes changes you formerly reported to the Agency under 21 CFR 314.70 when the information was part of an approved bulk application. The submission describing the change should include appropriate cross-references to the affected information in previous submissions, including the date(s), volume(s), section(s), and/or page number(s). Additionally, you must notify each person (applicant) authorized to reference information in your DMF of pertinent changes (21 CFR 314.420(c)). Notification should be provided well in advance to give the affected persons (applicants) ample time to amend or supplement their applications as necessary under 21 CFR 314.70.

B. Annual Update

You should update your DMF on an annual basis. The update should identify all changes and additional information incorporated into your DMF since the previous update. If no changes were made to your DMF, you should provide a statement that the information remains current. For more information on annual updates see CDER's guidance on *Drug Master Files*.

C. Listing of Persons Authorized to Reference your DMF

Your DMF must contain a complete list of persons currently authorized to reference information in your DMF (21 CFR 314.420(d)). For more information on this topic see CDER's guidance on *Drug Master Files*.

D. Appointment of an Agent

If you have an appointed agent for your DMF, you should include a signed letter of appointment in your DMF that includes the agent's name, address, and scope of responsibility (administrative and/or scientific).

E. Transfer of Ownership

If you intend to transfer ownership of your DMF to another party, you should notify the Agency and persons authorized to reference the DMF (applicants) in writing. Details regarding information to be included in the letter are provided in CDER's guidance on *Drug Master Files*.

F. Incorporation of Information into a Dosage Form Application

If you do not wish to maintain a DMF, the information may be filed as part of one or more dosage form applications (IND, NDA, or ANDA). The dosage form applicant is then responsible for ensuring this information meets regulatory requirements. If the information is certified as being current and there have been no changes, it may be submitted to the dosage form application(s) as an annual report. If the information is not current or changes have been made, the DMF information should be filed as (1) a prior approval supplement, changes being effected supplement, or annual report for an NDA or ANDA or (2) an information amendment or annual report for an IND. The reporting category would depend on the nature of the change.

GLOSSARY

Agency: The Food and Drug Administration.

Agent: Any person who is appointed by a DMF holder to serve as the contact for the holder.

Applicant: Any person who submits an application or abbreviated application or an amendment or supplement to them to obtain FDA approval of a new drug or an antibiotic drug (21 CFR 314.3(b)).

Application: The investigational new drug application (IND), new drug application (NDA), abbreviated new drug application (ANDA), other DMF or export application that references the DMF.

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)).

Export Application: An application submitted under section 802 of the Federal Food, Drug, and Cosmetic Act to export a drug that is not approved for marketing in the United States.

Holder: Any person who submits a DMF.

Letter of Authorization: A written statement by the holder or designated agent permitting other persons to refer to information in a DMF in support of applications.

Person: Includes individual, partnership, corporation, and association (Section 201(e) of the Federal Food, Drug, and Cosmetic Act).