FDA/CDER SBIA CHRONICLES
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DMF 101

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Find answers at

FDA's DMF Webpage

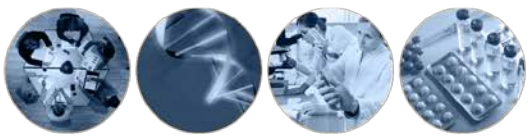
It is possible for a firm submitting an application to FDA to incorporate confidential information submitted by another firm. This is done via a Drug Master File (DMF). The DMF is a submission to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. DMFs are generally created to allow a party other than the DMF holder to reference material without disclosing to that party the contents of the file.

There are four types of DMFs that correspond to the type of information being submitted (Note that Type I DMFs - Manufacturing Site, Facilities, Operating Procedures, and Personnel - were eliminated in 2000 and are no longer applicable):

- Type II: Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product
- Type III: Packaging Material
- Type IV: Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation
- Type V: FDA Accepted Reference Information

A company may submit a DMF to FDA to support various applications, such as an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), another DMF, an Export Application, or amendments and supplements to any of these. There is no requirement for a company to submit a DMF to FDA. FDA ordinarily does not review DMFs independently of an application that references the DMF. DMFs are neither approved nor disapproved. Rather, the agency will review information in a DMF only when an IND sponsor, an applicant for an NDA, ANDA, or Export Application, or another DMF holder incorporates material in the DMF by reference. If FDA reviewers find deficiencies in the information provided in a DMF, a letter describing the deficiencies is sent to the DMF holder. FDA will notify the person who relies on the information in the deficient DMF that additional information is needed in the supporting DMF.

Letter of Authorization (LOA): Before FDA can review DMF information in support of an application, the DMF holder must submit (in duplicate if the DMF is in paper) to the DMF a letter of authorization (LOA) permitting FDA to reference the DMF. The DMF holder should also send a copy of the LOA to the affected applicant, sponsor, or other holder who is authorized (authorized party) to incorporate by reference the specific information contained in the DMF, and they in turn are required to include a copy of the LOA in their application. The LOA should contain the name of the item being referenced and the date of submission. Note that a DMF is required to contain a complete list of persons authorized to incorporate information in the DMF by reference. If the holder restricts the authorization to particular drug products, the list is should include the name of each drug product and the application number, if known, to which the authorization applies. The DMF holder should update the list in an Annual Report.



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DMF Review: FDA reviews the DMF for Administrative content when it is received, which may take 2-3 weeks. If the DMF is acceptable from an administrative point of view, FDA will issue an Acknowledgement Letter, notifying the holder of the DMF number. At this point the DMF is "ACTIVE." If it is not acceptable from an administrative point of view, FDA will notify the holder of what deficiencies need to be corrected and the DMF remains "PENDING." All DMFs are subject to a complete review for technical information only under the following circumstances:

1. The DMF is ACTIVE
2. The DMF holder submits an LOA in two copies (if a paper submission) to the DMF. This LOA should contain the DMF number.
3. The holder sends a copy of the LOA to the authorized party.
4. The authorized party submits an application to the FDA that contains a copy of the LOA.

GDUFA and Type II API DMFs: The Generics Drug User Fee Act (GDUFA) section of the Food and Drug Administration Safety and Innovation Act" (S.3187) includes provisions for fees for DMFs, an initial completeness assessment, and communications with DMF holders. GDUFA applies only to Type II DMFs for drug substances (Active Pharmaceutical Ingredients (APIs)) used to support Abbreviated New Drug Applications (ANDAs). Type II DMFs to support ANDAs under GDUFA are subject to an initial "Completeness Assessment" under the conditions specified in the Draft Guidance for Industry Initial Completeness Assessments for Type II API DMFs Under GDUFA. GDUFA does NOT apply to DMFs for Type III, IV or V DMFs, or to Type II DMFs used to support only NDAs or INDs; API intermediates; material used in the preparation of APIs drug product manufacturing intermediates; or drug products. FDA has also posted the list of DMFs that have passed the Completeness Assessment and are available for reference by ANDAs under GDUFA. This list is updated weekly.

Format: FDA has prepared a Guideline for Drug Master Files that provides information about how to prepare a well-organized DMF. Different approaches may be followed, but the applicant is encouraged to discuss significant variations in advance with FDA reviewers to preclude spending time and effort in preparing a submission that FDA may later determine to be unacceptable. Some key points for submission include:

- The DMF Holder should submit the DMF to FDA in duplicate if in paper
- DMFs must be current at the time of review
- The DMF Guidance recommends that DMF holders update their DMFs annually by submission of an Annual Report
- Each DMF should contain only one type of information and all supporting data. Supporting information and data in a DMF can be cross referenced to any other DMF
- Each DMF submission should contain a transmittal letter, administrative information about the submission, and the specific information to be included in the DMF as described in the guidance document.
- The DMF must be in the English language. Whenever a submission contains information in another language, an accurate English translation must also be included.
- Each page of each copy of the DMF should be dated and consecutively numbered. An updated table of contents should be included with each submission
- To request a DMF Pre-Assigned Number, see "Requesting a Pre-Assigned Application number." It is not necessary to have a pre-assigned DMF number for a new paper DMF submission. However, it is necessary to have a DMF number, whether pre-existing or pre-assigned, to pay the User Fee, whether the DMF is in paper or electronic.

Currently, there is no requirement to file DMFs in electronic format. Paper DMFs will continue to be accepted until further notice. DMF holders are encouraged to submit their DMFs in electronic form, including updating current paper DMFs. Electronic DMFs must be in Electronic Common Technical Document (eCTD) format.

FDA has posted DMF lists along with a great deal of information on the DMF webpage. This webpage also lists contact information for questions relating to DMFs.

Cheers,
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CDER Small Business and Industry Assistance

Issues of this newsletter are archived at http://www.fda.gov/cdersmallbusinesschronicles

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