How To Use DMF Content To Support Your Application To The FDA

By S. D. Devendra Raj, Ph.D., Freyr

A drug master file (DMF) is a voluntary regulatory application submitted to the U.S. FDA at the discretion of the DMF holder to assist its customers. A DMF is used to provide confidential detailed information about facilities, processes, or articles used in manufacturing, processing, packaging, and storing one or more active pharmaceutical ingredients (APIs) and/or human drugs in the absence of relevant information about the drug substance, drug product, and/or container closure. A DMF is not an alternate regulatory submission for an IND, an (NDA, an ANDA, another DMF, an export application, or amendments and supplements to any of the mentioned, but can be used to support these applications.
Other countries/regions have their own versions (for example, Europe's active substance master file procedure and Japan's voluntary master file system), but this article explains DMF content requirements and how the application is prepared as a dossier and submitted to the U.S. FDA. In India, the FDA's process is generally used, unless you are a foreign manufacturer.

Each DMF submission should constitute:

- Transmittal letters – includes the type of the submission, name, address, and signature of the applicant or holder in the case of an original submission. For amendments, the DMF number, type, and updates to the original submission should be submitted.
- Administrative information contains the statement of commitment, name and address of the DMF holder or applicant and the manufacturing/processing facility, and updated sections in the case of amendments.
- Information in the DMF must be in English.

There are five types of DMFs:

- **Type I DMF (phased out since July 2000):** Manufacturing site, facilities, operating procedures, and personnel. It is generally recommended for an applicant outside the United States to aid the FDA in carrying out manufacturing site inspections. Unless the applicant is not registered or inspected properly, this type of DMF need not describe the domestic facilities. In addition, standard procedures of the equipment and process should be clearly mentioned.
- **Type II DMF:** Drug substance (APIs), drug substance intermediates and material used in their preparation, or drug product. A Type II DMF also covers dosage form for the drugs manufactured under contract for another company that would file an ANDA.
- **Type III DMF:** Packaging materials, from bottles and caps to PVC resin used in their manufacture, must be covered in a Type III DMF or other FDA document such as an NDA.
- **Type IV DMF:** Excipient, colorant, flavor, essence, or material used in their preparation. Excipients are inactive chemical substances used in the preparation of a tablet.
- **Type V DMF:** The FDA accepted reference information that is not included in the other types of DMFs.

The most common type of DMF is Type II, followed by Type III.

What Else To File Along With Your DMF Submission

Type II, III, and IV DMFs should include:

- A company commitment stating that its facilities will be operated in accordance with environmental laws.
- Information related to the stability data, study design, and interpretation.
- A letter of authorization permitting the FDA to reference the DMF before the review of DMF information in favor of an application. This letter should include the applicant's name and address, date, DMF number, products reference section, and page numbers.

The DMF holder should also send a copy of the same to the affected applicant, sponsor, or other DMF holder who is authorized to incorporate by reference the specific information contained in the DMF.

All DMF submissions since May 5, 2018, other than Type III DMFs, are being done using an electronic common technical document (eCTD). eCTD is a standard format used for submitting applications, amendments, supplements, and reports to the FDA through the Electronic Submissions Gateway (ESG) by choosing "CDER" as the center and "eCTD" as the format. For Type III DMFs, this requirement has been effective since May 5, 2020. The eCTD submissions should be in the FDA's accepted forms and must include electronic signatures to enable automated processing of the submission.

How The FDA Evaluates Your DMF Submission

A DMF goes through two stages of evaluation before it is submitted for review. First, the FDA assesses the content of DMF and whether its requirements are met. Once the FDA determines that the eDMF is acceptable, it will then undergo an administrative review as discussed above. The applicant will be informed if the DMF is not acceptable due to technical reasons. The holder must then satisfactorily respond to any deficiencies for the DMF to proceed to an administrative review, which will be conducted by the DMF staff in the Office of Pharmaceutical Quality (OPQ). If the DMF passes through the administrative review and is found to be acceptable, OPQ sends an acknowledgement letter, at which point the DMF is available for review of its technical content. At the same time, OPQ sends an Administrative Filing Issues (AFI) letter if the DMF is not accepted due to lack of administrative information. The holder must respond adequately for the DMF to be available for review of the technical content. The time frame for this could be from two to three weeks. DMF data and information availability to the public is ascertained under 21 CFR Part 20, 21 CFR 314.420(e), and 21 CFR 314.430. A DMF number will be provided only on receipt of complete and adequate administrative information of the holder or applicant.

How To Tackle The Annual Report

The status of a DMF is “active” when it is acceptable by the FDA from an administrative point of view and “inactive” when it has been closed either by the holder or by the FDA. The DMF holder should provide an annual report to the FDA on the anniversary date of the original submission. In the meantime, if there are no updates, then the holder should provide the DMF content as current in the annual report. Failure to update the DMF can cause delays in the FDA’s review of the pending NDA, IND, ANDA, or any amendment or supplement to such application; hence, the FDA can initiate procedures for closure of the DMF.

Conclusion

The drug master file is filed in support of various applications while launching drugs in the given market. The DMF provides information on chemistry, manufacturing, and controls (CMCs) on drug substance, drug product, and intermediates used in their preparations. A DMF helps the holder company shorten the IND, NDA, ANDA, or export application process by reducing the total number of review cycles and increasing the chances of approval in the first cycle. Also, the DMF supports regulatory requirements for a drug to help prove its quality, safety, and efficacy.

About The Author:

S. D. Devendra Raj, Ph.D., is senior manager at Freyr Software Solutions Private Limited. He has diverse experience in regulatory affairs, physiotherapy, and operations. He ensures adherence to guidelines and requirements of different regulatory authorities and quality systems.