IPEC-Americas Publishes Position Paper on Utility of U.S. DMFs for Excipients

IPEC-Americas Position Paper on Utility of U.S. Drug Master Files (DMFs) for Excipients

Background and Current State

A Drug Master File (DMF) is a submission of information to the U.S. FDA to permit the Agency to review information on a drug component (e.g., API, excipient and packaging material) in support of a third party's drug application. DMFs usually cover the Chemistry, Manufacturing and Controls (CMC) and where appropriate, toxicology reports/summaries for a drug substance, excipient or packaging material. The Drug Master File Guidance states "*The submission of a DMF is not required by law or FDA regulation. A DMF is submitted solely at the discretion of the holder.****[1]***" The primary purpose for establishing a DMF is to maintain confidentiality of proprietary information. Historically, excipient DMFs were submitted on paper; however, in May 2015 the U.S. FDA published a final guidance[2] which established a deadline of May 5, 2017 for DMFs (including excipients) to be submitted in the Electronic Common Technical Document (eCTD) format. There is no requirement to convert existing paper DMFs into the eCTD format. The new requirement only applies to submissions going forward. It should be noted that eCTD requirements for drug applications [(Investigational New Drugs (INDs), New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), and Biologics License Applications (BLAs)] have been in place for years, therefore, the CTD structure and electronic format is not new for drug product manufacturers. However, eCTD submission requirements for excipient DMFs place a significant burden on excipient suppliers since a majority of the excipient DMFs historically have not even followed the CTD format, and to convert the file content to CTD format could require the DMF holder to completely rewrite the file. This may require significant resource, cost and time commitment that may not be justifiable from a business standpoint. In addition, many excipient suppliers would not have the capability or information technology (IT) resources to convert the files to the necessary electronic format.

The final guidance applies the eCTD requirement to all DMFs, including excipients and packaging materials. FDA has stated in their 2015 guidance and in various webinars and public forums that eCTD requirements would be mandatory for any DMFs which will continue to be referenced after May 5, 2017 and no exemptions or waivers would be allowed.

Although the FDA has stated that there is no requirement to convert information contained in existing paper DMFs into electronic CTD format, it will be realistically impossible long-term for excipient suppliers to maintain paper DMFs since all future updates, amendments, annual reports and Letters of Authorization (LOAs) will be required to comply with eCTD format and electronic submission specifications (including XML backbone and submission through an approved FDA portal).

Based on the May 5, 2017 implementation of eCTD requirements for excipient DMFs, IPEC-Americas has developed this position paper to help industry review and reflect on the real purpose and/or utility of excipient DMFs.

IPEC-Americas Position

As a result of emerging changes in DMF requirements and misconceptions by industry stakeholders, IPEC-Americas has developed this position on when it may be prudent and beneficial to create and maintain excipient DMFs (e.g., for a novel or a non-compendial excipient) and when excipient DMFs would have limited, if any, use. In addition, alternative approaches for sharing confidential information directly with a drug product manufacturer (which can become part of the NDA, ANDA or BLA submission) are discussed. Based on the points above, IPEC-Americas is providing the following recommendations:

- Excipient suppliers should only submit or maintain a DMF if they have CONFIDENTIAL information on non-compendial, co-processed or novel excipients for which they do not want to share the CONFIDENTIAL information directly with the customer. A DMF may be submitted for a compendial excipient where proprietary toxicology information is necessary to support new routes of administration or higher levels of use than what was previously approved and the DMF holder chooses to not share the information directly with the drug product manufacturer under a confidential disclosure agreement (CDA).
- Excipient suppliers should assess and justify the rationale and expense of converting and maintaining electronic DMFs versus providing confidential information directly to customers under CDAs for submission in their regulatory filings since there is no FDA requirement to have a DMF for any type of excipient.
- Excipient suppliers should consider inactivating their DMFs for their compendial excipients and some types of non-compendial excipients (e.g., simple mixtures of common excipients) since they often do not provide added value to regulators, drug product manufacturers or companies who create and maintain the files.
- The excipient supplier and customer(s) should discuss the actual information needed to support a drug application review involving the use of the supplied excipient. They should agree on how to share the necessary information either: 1) directly with the customer, 2) through use of a DMF or 3) through a combination thereof.

- Alternative dossiers can be used to provide the non-proprietary information commonly found in some existing DMFs such as Excipient Information Packages (EIPs), Technical Documents, bridging documents, and other documentation that a supplier may have created and maintains for use by their customers.

Rationale for IPEC-Americas Position

There is concern that drug product manufacturers may expect their suppliers to have eCTD compliant DMFs by May of 2017. As noted above this is not a requirement for existing excipient DMFs. This would place significant burden on excipient suppliers in terms of resources, cost and time. A number of excipient suppliers have decided to no longer maintain excipient DMFs, especially for compendial products. According to Dr. Arthur Shaw[3],[4] (an FDA DMF Expert Review Chemist), there is no regulatory requirement to establish or maintain a DMF for excipients and the U.S. FDA does not approve or disapprove excipient DMFs. In addition, the U.S. FDA has openly stated[5] *"Since CMC for compendial excipients (covered by the USP/NF) is generally not reviewed, DMFs for compendial excipients are generally not reviewed."* Therefore, DMFs for compendial excipients are typically not needed. Unfortunately, some drug product manufacturers have the misconception that a DMF is required for review of a drug application. However, the real purpose of a DMF is for the supplier to provide CONFIDENTIAL information directly to the REGULATORS. Non-proprietary information is not needed in a DMF and can be provided directly to the drug product manufacturer for inclusion in their drug application (e.g., IND, NDA, ANDA or BLA). For confidential information that a supplier is willing to share directly with customers, providing the information directly under CDA should be considered instead of a DMF.

In the above referenced webinars and at other public events, the U.S. FDA has repeatedly stated:

- There is NO regulatory requirement for DMFs
- The Agency does not generally review COMPENDIAL DMFs
- The Agency does not review DMFs until they are reviewing a drug application
- The Agency never APPROVES a DMF

Another misconception is that a regulatory agency in one region can share DMF information with regulatory authorities in another region. Currently there are only three countries (U.S., Japan and Canada) that have a system for excipient DMFs and information from a DMF filed in one country cannot be shared with any 3rd party, including regulators in other countries.

Historically, excipient manufacturers established excipient DMFs as paper files. The content and format of these excipient DMFs often varied significantly since no specific requirements, format and/or suggested content was provided by FDA. In many cases, an entire excipient family (e.g., multiple grades or products) was included in a single DMF since much of the information was the same for the various grades within the family.

Updating historical paper DMF files to CTD format, converting them to the eCTD structure and submitting these files through an electronic FDA electronic gateway places a significant burden on excipient suppliers. The cost of generating eCTD compliant documentation, including

acquiring the necessary software (meeting FDA specified standards) for eCTD publishing (conversion), is significant and often prohibitive to excipient suppliers.

Electronic requirements for U.S. DMFs are specified in the FDA Data Standards Catalog and include technical and portable document format justification and validation of the submission package. Since submissions will need to be prepared using the established FDA Data Standards, published into an acceptable electronic format, validated and submitted through an FDA electronic gateway, companies who elect to maintain a DMF will need to either acquire the software necessary for publishing and establish a client gateway with the FDA in order to make new submissions and maintain DMFs, or they will need to work with a third party provider to publish and submit their documents.

Currently, many excipient suppliers do not have the software required for eCTD publishing, nor do they have systems that can communicate directly with the FDA computer systems; therefore, updating Excipient DMFs to eCTD format would require significant resources (investment in human and information technology resources for both implementation and maintenance) that would need to be justified, especially if the sales of the excipients are only a small portion of their business.

Establishing a DMF may be advantageous for:

- Novel (new chemistry), co-processed or non-compendial excipients with limited precedence of use in drug products.
- Providing “safety/toxicology” information for excipients used in a new (higher) level of use or route of administration where proprietary toxicology and other information may be relevant for regulatory review.

- Maintaining confidentiality of proprietary information (e.g., manufacturing procedure) for the DMF holder, assuming the information would be of value to an FDA reviewer and the DMF holder does not want to supply the information under a CDA directly to the drug product sponsor.
- Permitting FDA reviewers’ access to proprietary information needed to support multiple applications submitted by one or more applicants. The same DMF could be accessed to support an IND, NDA, ANDA and BLA, thus minimizing submission of detailed information to multiple customers under CDAs.

Summary

Excipient manufacturers should proactively evaluate any existing DMFs and determine if there is any value to their customers by maintaining these DMFs. It may be better to simply provide certain confidential information to their customers under a CDA so that their customer can simply include the information directly into their regulatory filing documentation. There is no significant impact on the customer regardless of which pathway is used to supply the information as long as the information is available to the FDA during the drug review. Based on this assessment, the excipient manufacturer should determine which approach makes the most sense for them, their customers and the FDA.

Excipient manufacturers should complete these evaluations before May 5, 2017 and notify their customers of their plans to either close or inactivate any existing DMFs they may have, or convert them to an eDMF in eCTD format in a timely fashion.

[1] [1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122886.htm [1]

[2] Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications. Guidance for Industry. FDA, CDER CBER. May 2015. Revision 3. [2]

[3] CDER Small Business and Industry Assistance (CDER SBIA) Webinar - New Requirement for Electronic Submission of Drug Master Files (DMFs): What You Need to Know - February 4, 2016 [3]

[4] CDER Small Business and Industry Assistance > CDER Small Business and Industry Assistance (CDER SBIA) Webinar: Stay Compliant! Electronic Submission of Drug Master Files (DMFs) is MANDATORY starting May 5, 2017: What You Need to Know - August 4, 2016 [4]

[5] Slide 35 of CDER SBIA February 4, 2016 Webinar

Links
[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122886.htm
[2] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf

[3] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm481089.htm
[4] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm511254.htm