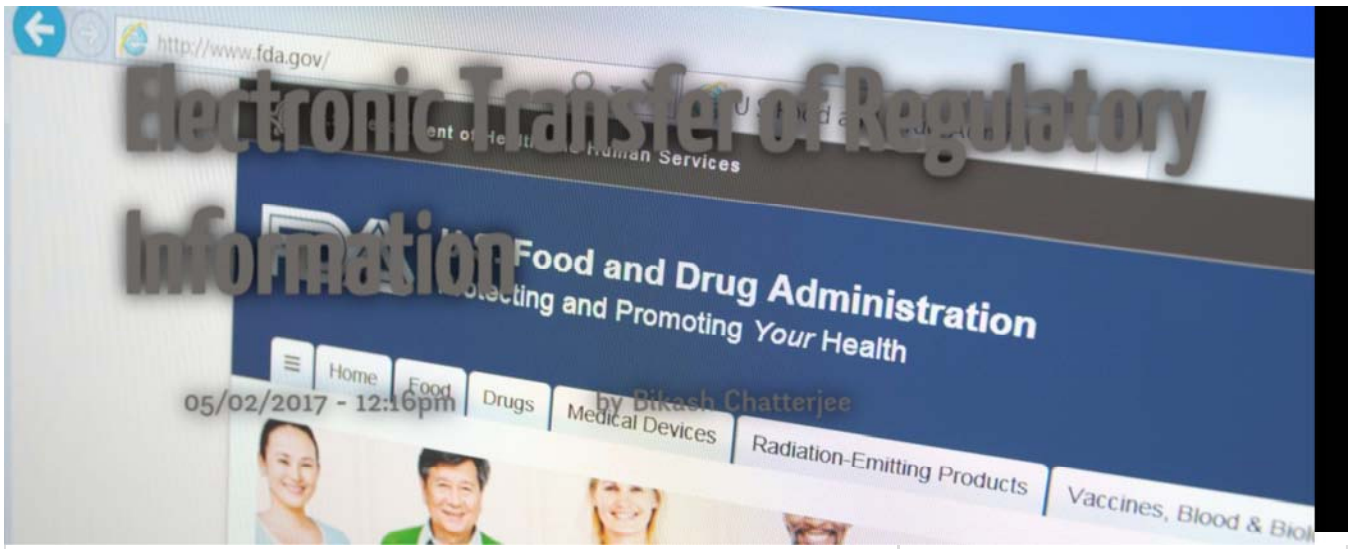

Regulations/Standards

A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that is 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 typically contain critical details required in support of the Chemistry, Manufacturing, and Controls (CMC) elements within a regulatory filing. They can also be used to provide non-CMC details such as toxicology information in support of a third-party regulatory submission. There is no regulatory requirement to file a DMF. However, detailed information required to support a regulatory filing (IND, NDA, BLA, etc.) can be included directly into the regulatory document if acceptable to all parties involved in providing the information.

The FDA is moving toward electronic filing because electronic documents greatly simplify the update,

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receipt, processing, and evaluation process within the agency. In 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) included a section (745A(a)) requiring that submissions under section 505 (b), (i), or (j) of the FD&C Act and submissions under section 351(a) or (k) of the Public Health Service Act (PHS Act), be presented in electronic format specified by the FDA beginning May 5, 2017. Any DMF submissions that are not in electronic format and are not compliant with the FDA's standards will be rejected. There are no waivers or exemptions as part of the new requirement. The FDA issued its guidance for electronic submission of DMFs in May of 2015.[1] The submissions must use a version of the Electronic Common Technical Document (eCTD) that is specified in the FDA's Data Standards Catalogue.[2] As a common technical document, there are harmonized standards available through ICH and FDA that capture the structural components of the document. Relevant key standards include:

- ICH eCTD Specifications Version 3.2.2 published by the ICH M2 Expert working group
- ICH eCTD Backbone File Specification for Study Tagging Files
- FDA eCTD Backbone File Specification for Module 1
- FDA eCTD Comprehensive Table of Contents and Hierarchy

There is no requirement to resubmit an electronic DMF if a paper DMF has already been submitted, although there no regulation that precludes a DMF holder from doing so. To be successful after May 5, 2017, the key will be to closely follow the process for filing an eDMF document.

eCTD process

Four electronic submissions the numbering was kept the same for the four types of DMFS: Type II — Drug Substance; Type III — Packaging; Type IV —

Excipients; Type V — Other (requires FDA pre-clearance).

There are no new forms for filing an eDMF. The only form that is required is the User Fee form. All eDMF will require a pre-assigned eDMF number. A step-by-step description of the process is provided on the FDA's website.[3]

The complete list application information can be found on in the FDA eCTD document 1. However, the basic elements include:

a. Transmittal (cover) letter, including pre-assigned number, where applicable
b. Administrative information including:
▸ Telephone number, fax number, and e-mail address for the responsible individual (contact person)
▸ A Statement of Commitment (Recommended in the DMF Guideline: "A signed statement by the holder certifying that the DMF is current and that the DMF holder will comply with the statements made in it.")
▸ A List of Referenced applications e.g. DMF for intermediates. Include in Section 1.4.2 "Right of Reference."

eDMF processing

A DMF undergoes two reviews before being accepted as complete and compliant and can be made available for review of technical content. The first stage is a structural review of the electronic format. If the DMF is acceptable from an "electronic technical" point of view as defined by the harmonized standards for electronic submission, then it is released for the Administrative Review. If the DMF is found to be unacceptable from an "electronic technical" point of view, the holder will be informed. Then the holder must respond adequately to the deficiencies for the DMF to proceed to the Administrative Review.

The second stage Administrative Review is performed by DMF staff in the Office of Pharmaceutical Quality (OPQ). If it is found to be complete and compliant then the OPQ sends an Acknowledgement Letter. The DMF is now available for review of the technical content. The Acknowledgement Letter notifies the holder of the DMF number and type and reminds the holder of the exact wording of the Title (Subject) and holder of DMF as they will appear in the cover letter of the original DMF when it becomes publicly available. It also reminds the DMF holder of its obligations to submit all changes as amendments, submit annual reports, and to submit a letter of authorization (LOA).

A DMF will only be reviewed when it is referenced in an Application or in another DMF. It cannot be reviewed without a LOA. The LOA will grant the FDA the authorization to review the information in the DMF and it grants authorization to incorporate the information in the DMF by reference. The authorized party must include a copy of the LOA in their regulatory submission. This is the only mechanism to trigger a review of the DMF.

If the DMF is not acceptable from an administrative point of view, OPQ sends an Administrative Filing Issues (AFI) letter. The holder must then respond adequately for the DMF to be available for a review of the technical content.

The deadline looms for submitting electronic DMFs. Given the complexity of today's global pharmaceutical supply chains, the move to eCTD submissions should simplify the overall management and update of documentation. However, as with all eCTD format documents, it will be essential to strictly adhere to the technical and administrative components to ensure your DMF is accepted.

References

1. Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, May 2015
2. FDA Data Standards Catalogue. http://bit.ly/2okrdi1
3. Requesting a Pre-Assigned Application Number. http://bit.ly/2opPd2g

Bikash Chatterjee is President and Chief Science Officer of Pharmatech Associates, a Hayward, Calif.-based company that provides consulting and services to the regulated life science industry. Bikash has been involved in the biopharmaceutical, pharmaceutical, medical device, and diagnostics industry for over 30 years. His expertise includes site selection, project management, design, and validation of facilities for U.S. and European regulatory requirements. He can be reached by email at bchatterjee@pharmatechassociates.com

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