Submitting Master Files in eCTD Format: How and When to Comply

Companies filing master files have one extra year to comply with electronic submission requirements. The FDA has extended the deadline for filing master files and all documents submitted to existing master files, in the electronic Common Technical Data (eCTD) format from May 5, 2017 to **May 5, 2018.** The compliance date for electronically submitting new drug applications (NDAs), biologics license applications (BLAs), and abbreviated new drug applications (ANDAs) remains unchanged.

- FDA considers master files to be submissions to an NDA, ANDA, BLA, or investigational new drug application (IND). These include new drug master files (DMFs), new biological product files (BPFs), and any amendments to or annual reports on previously submitted DMFs or BPFs.

- A DMF 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.

- The eCTD is the standard format for submitting applications, amendments, supplements, and reports to FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER).

The requirement to submit DMFs using the eCTD format is part of FDA's overall effort to review drug applications more efficiently. eCTD standardizes how industry submits applications, amendments, supplements, and reports.

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Implementing electronic DMFs will improve the standardization of the DMF review process. After May 5, 2018, there will be no waivers or exemptions for DMFs that are not submitted in eCTD format.

Why the change? In response to industry comments and internal review, FDA has determined that it is appropriate to extend the required date to submit master files in eCTD format to May 5, 2018. Among other factors, FDA recognizes that industry has had challenges with submitting master files in eCTD format. In particular, data has suggested that adhering to the May 5, 2017 date could have led to high rejection rates of master
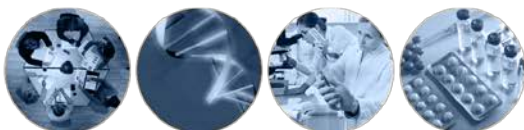
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files. This would have slowed FDA review processes and led to unnecessary delay in the review of some drug applications.

Submitting DMFs in eCTD format – After the May 5, 2018 deadline, all documents submitted to the DMF (e.g., amendment, annual report, letter of authorization) must be in eCTD format. If you are updating just part of a DMF, you only need to provide the new information in the eCTD format. DMF holders must submit all subsequent submissions electronically after the initial electronic submission. More information is found in FDA's Guidance for Industry: Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.

Below, we have outlined the steps involved in the electronic submission process:

- *Obtain a Pre-Assigned Application Number:*

Before submitting an electronic DMF, you must obtain a pre-assigned number in order to populate the US Regional.xml. Though this may appear minor, a small error such as a wrong digit in your application number can have big implications.

- *Convert DMF to eCTD Format:*

The eCTD format is composed of five modules. The modules provide structure for the submission and guide submitters where to place information. For new electronic DMFs, all sections within modules 1, 2 and 3 should be submitted. However, it is not necessary to submit modules that are not applicable to the subject of the DMF. For example, it is not necessary to submit module 4 and 5 for a Type II DMF for a drug substance. DMFs should adhere to the CTD format as outlined in:
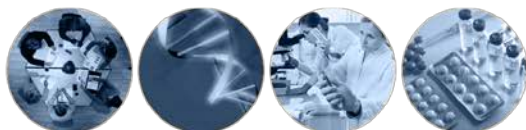
- o Draft Guidance for Industry Submitting Marketing Applications According to the ICH-CTD Format — General Considerations

- o Guidance for Industry M4Q: The CTD –Quality

- o Guidance for Industry Granularity Document Annex to M4: Organization of the CTD

- o The Comprehensive Table of Contents Headings and Hierarchy

- o eCTD Technical Conformance Guide

You must submit electronic submissions using the Data Standards Catalog, which is the version of eCTD currently supported by FDA. Additional resources are listed on our eCTD and eCTD Resources webpages.

Generally, there are no forms required for DMFs. The exception is the Generic Drug User Fee Cover Sheet (Form 3794), which applies to Type II API DMFs that support ANDAs under GDUFA. Note that scanned images of FDA forms will not be accepted.

- *Set up Electronic Submissions Gateway (ESG) account:*

The ESG is the central transmission point for sending information electronically to FDA. The first step to submitting DMFs electronically through the ESG is to request an ESG test account. The account creation process includes a testing phase designed to ensure that the FDA ESG can successfully receive your electronic submission and that the electronic submission is prepared according to published guidelines. Once the submitter's test submission has passed the testing phase, an account will be set up to allow submissions through the FDA ESG production system.

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Setting up an ESG account is a multi-step process and can take several weeks, so you should start the process well before you intend to make your first electronic submission. The process includes a testing phase designed to ensure that the FDA ESG can successfully receive your electronic submission and that the electronic submission is prepared according to published guidelines. Choose the appropriate center (e.g., "CDER") and "eCTD" as the submission type, when transmitting via ESG. For complete instructions, refer to the ESG User Guide.

Most submitters use the "WebTrader Hosted Solution." Note that there is no cost for an ESG account, but you must obtain a digital certificate for each person in your organization who will be sending files through the ESG.

- *Send a sample submission to FDA*

Submitting a sample eCTD or standardized data sample is optional, but doing so can provide valuable feedback. Refer to the Sample Submission Process for details. Be sure to submit the sample early to allow time to make adjustments prior to final submission.

- *Submit via ESG*

Submissions of 10 GB or smaller must be submitted through the ESG. Most submissions fall within these limits. Submissions that are **more** than 10 GB may be submitted through ESG or on physical media (e.g., DVD/USB drive). Details are outlined in the document *Transmitting Electronic Submissions Using eCTD Specifications.*

Do not submit paper copies of the application when submitting in eCTD format. This includes review and desk copies. And be sure to review and validate your eCTD submission prior to submitting to avoid submission errors.

- *Converting a paper DMF to eCTD:*

If you currently hold a DMF in paper form, you are not required to resubmit previous content in eCTD format. However, you may convert an existing paper DMF into eCTD format if you wish. If you are converting a paper DMF to eCTD, use the same DMF application number. If your existing number is four digits (e.g., 1234), you will need to add two zeroes to the beginning of the number to convert it to a six-digit format (e.g., 001234 when you convert your DMF to electronic format). This process is detailed in the eCTD Technical Conformance Guide.

How is FDA helping industry meet the requirement? In addition to extending the deadline, FDA has provided DMF holders with a number of resources to explain the eCTD format and submission process. These resources are listed in the left-hand column of the first page of this issue.

Don't procrastinate! Take advantage of all the FDA resources to learn about eCTD submission requirements and how to beat the deadline! If you have questions, contact SBIA at cdersbia@fda.hhs.gov.
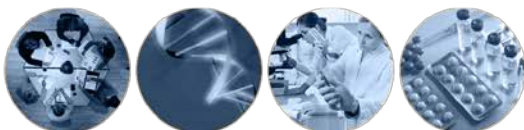
Cheers,
Renu Lal, Pharm.D.
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