Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Division of Drug Information at 301-796-3400, or (CBER) Manufacturers Assistance Branch at 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2013
Electronic Submissions

Revision 3

Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
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Center for Biologics Evaluation and Research (CBER)

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Technical specifications associated with this guidance are provided as separate, stand alone documents and are updated periodically. To make sure you have the most recent versions, check the appropriate center's eCTD web page.

For eCTD and related technical specifications (CBER and CDER):
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

For specific documents referenced in this guidance, see the References section at the end of this document.

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Guidance for Industry[1]
Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

I. INTRODUCTION

Section 745A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), added by section 1136 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144), requires 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 submitted in electronic format specified by the Food and Drug Administration (FDA or the Agency), beginning no earlier than 24 months after this guidance is finalized. Accordingly, this guidance describes how FDA plans to implement section 745A(a) of the FD&C Act for the electronic submission of applications for human pharmaceutical products[2] – including new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologics license applications (BLAs), and investigational new drug applications (INDs) – to the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER).

This guidance provides, among other things, the requirements for a valid electronic submission under section 745A(a) of the FD&C Act. In accordance with section 745A(a), following the issuance of a final guidance on this topic, submission types identified in this draft guidance must be submitted electronically (except for submissions that are exempted), in a format that FDA can process, review and archive. Currently, the Agency can process, review and archive electronic submissions made using the electronic common technical document (eCTD) specifications.[3] Submissions that are not submitted electronically and electronic submissions that are not in a format that FDA can process, review and archive will not be filed, unless exempted from the electronic submission requirement.

In Section 745A(a), Congress granted explicit authorization to FDA to implement the statutory electronic submission requirements by specifying the format for such submissions in guidance. Accordingly, to the extent that this document provides such requirements under section 745A(a) of the FD&C Act, indicated by the use of the words *must* or *required*, this document is not

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. For the most recent version of a guidance, see the FDA's website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[2] The term "human pharmaceutical products," as used in this guidance, includes those products intended for human use that meet the definition of *drug* and do not also meet the definition of *device* under the FD&C Act, including both drugs approved under the FD&C Act and biological products approved under the Public Health Service Act.

[3] To reflect the evolving nature of the technology and the experience of those using this technology, the eCTD technical specifications are being provided as separate, stand-alone documents. These associated specifications will be updated periodically. To make sure you have the most recent version of related technical specifications (CDER and CBER), check the eCTD Web page at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

subject to the usual restrictions in FDA's good guidance practice (GGP) regulations, such as the requirement that guidances not establish legally enforceable responsibilities. See 21 CFR 10.115(d).

At the same time, this document also provides guidance on FDA's interpretation of the statutory electronic submission requirement and the Agency's current thinking on the best means for implementing other aspects of the electronic submission program. For example, this document strongly recommends the electronic submission of master files (e.g., drug master files) and advertising and promotional labeling materials using the format specified herein. Therefore, to the extent that this document includes provisions that are not part of the requirements under section 745A(a), this document does not create or confer any rights for or on any person and does not operate to bind FDA or the public, but does represent the Agency's current thinking on this topic. The use of the word *should* in such parts of this guidance means that something is suggested or recommended, but not required. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

To comply with the GGP regulations and make sure that regulated entities and the public understand that guidance documents are nonbinding, FDA guidances ordinarily contain standard language explaining that guidances should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. FDA is not including this standard language in this guidance because it is not an accurate description of all of the effects of this guidance. This guidance contains both binding and nonbinding provisions. Insofar as this guidance specifies the format for electronic submissions, or provides "criteria for . . . exemptions" pursuant to section 745A(a) of the FD&C Act, it will have binding effect.

In its final form, this document will also supersede the guidance titled "Guidance for Industry Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" that was issued in October 2005 and revised in April 2006 and June 2008.

II. REQUIREMENT TO SUBMIT ELECTRONICALLY

A. For what submission types is an electronic submission required?

Section 745A(a) of the FD&C Act applies to "submissions" under sections 505(b), (i), or (j) of the FD&C Act, and under section 351(a) or (k) of the PHS Act. This includes the following submission types:

- Certain investigational new drug applications (INDs);[4]
- New drug applications (NDAs);
- Abbreviated new drug applications (ANDAs); and
- Certain biologics license applications (BLAs)[5]

This also includes all subsequent submissions, including amendments, supplements, and reports, to one of the submission types identified above. Amendments, supplements and reports must be submitted electronically even if the original was submitted to FDA prior to the implementation of the electronic submission requirements.

The FD&C Act provides that the submission types listed above shall be submitted in electronic format "beginning no earlier than 24 months after the issuance of a [final guidance specifying the format for such submissions]." Section 745A(a). Therefore, the electronic submission requirement will be phased in according to the following schedule: (1) 24 months after publication of the final version of this draft revised guidance, the requirements will apply to NDA, ANDA, and BLA submissions; (2) 36 months after publication of the final guidance, the requirements will apply to IND submissions.

Under section 745A(a)(3) of the FD&C Act, the electronic submission requirement does not apply to submissions described in section 561 of the FD&C Act. FDA will continue to accept submissions under section 561 in alternate formats.

B. Are there other submission types not subject to the electronic submission requirement for which electronic submission is recommended?

Section 745A(a) of the FD&C Act does not apply to master files and advertising and promotional labeling submissions. However, FDA accepts and strongly encourages you to submit master files and advertising and promotional labeling materials electronically in eCTD version 3.2.2 format.

C. What types of submissions are exempted from the electronic submission requirement?

[4] This guidance is not applicable to INDs for devices that are regulated by CBER as biological products under Section 351 of the Public Health Service (PHS) Act. Such devices are generally those intended for use in screening donated blood for transfusion transmissible diseases.

[5] This guidance is not applicable to those devices that are regulated by CBER as biological products under Section 351 of the PHS Act.

Above, FDA identified the submission types that are subject to the electronic submission requirements under section 745A(a) of the FD&C Act. The statute also allows for FDA to set forth criteria for exemptions from the electronic submission requirements. Accordingly, FDA will exempt INDs for products that are not intended to be distributed commercially from the electronic submission requirement. Though these submissions will be exempt, FDA also accepts and strongly encourages sponsors to submit such INDs electronically, as described in this guidance document.

D. Will FDA issue waivers of Electronic Submission Requirements?

No. The resources to enable the creation of an electronic submission that FDA can process, review and archive are widely available. FDA anticipates that all non-exempt applicants will have the ability to comply with the electronic submission requirements.

E. What are the requirements that I must follow?

1. The eCTD Specifications

Under section 745A(a), electronic submissions "shall be in such electronic format as specified by [FDA]" in the final version of this guidance. FDA has determined that electronic submissions described in section II.A must be in a format that the Agency can process, review, and archive. Currently the Agency can process, review and archive electronic submissions in the eCTD version 3.2.2 format. The eCTD version 3.2.2 format is described in the following primary documents:

- the ICH Electronic Common Technical Document Specification,
- the ICH eCTD Backbone File Specification for Study Tagging Files and
- the FDA eCTD Backbone Files Specification for Module 1.

Additional technical references are cited throughout this document and may be found on FDA's eCTD website.

2. Pre-submission Considerations

Before making the first electronic submission to an application, you must obtain a pre-assigned application number by contacting the appropriate center.

3. Files and Folders[6]

Files pertaining to each module must be placed in the appropriate folder (e.g., m1 – m5). The terms "folder" and "subfolder," as used in this draft guidance, are intended to be synonymous with "directory" and "subdirectory." The main submission, regional administrative folders, and certain subfolders must have specific names for proper and efficient processing of the submission.

[6] Sections II.E.3 and II.E.4 apply only when you have chosen to make an electronic submission using the eCTD version 3.2.2 format.

You must use only letters (lower case), numbers, or hyphens in the folder name and not blank spaces or special characters. The length of each folder name must not exceed 64 characters. When naming folders, the length of the entire path must not exceed 230 characters. Empty folders must not be included in the submission.

All documents in the electronic submission must be placed in a main submission folder named using a four-digit sequence number (specified by the submitter) that is unique within the application, with the original submission for an application designated 0001. The eCTD backbone file for modules 2 to 5 (*index.xml*) for the submission must be placed in this folder along with the checksum file for the eCTD backbone file (*index-md5.txt*). Numbering for each subsequent submission to the same application is described in the associated FDA technical specification *eCTD Backbone Files Specification for Module 1*. Sequence numbers are used to differentiate between submissions within the same application and need not correspond to the order in which they are received by FDA. It is not necessary for sequence numbers and IND Serial Numbers to match for submissions to an IND.

We require the use of subfolders within each module to organize files in a submission. These subfolders must be placed in the sequence number folder (e.g., folder named *0001* for the initial submission to an application). Empty subfolders must not be included. The *util* subfolder is required in order to organize supporting eCTD technical files in the submission, as described in the ICH M2 technical specification *Electronic Common Technical Document Specification.* Other specific folder names that are compliant with the eCTD version 3.2.2 format can be found in the same document.

4. Study Reports and Data

When providing study information in either module 4 or 5, you must include the Study Tagging File (STF) described in the associated ICH M2 technical specification the *eCTD Backbone File Specification for Study Tagging Files*. Individual study files must be referenced in a STF using the appropriate STF ‘file-tag’ describing the document’s contents.

Study data must be provided only in modules 3 – 5. Refer to the FDA technical specification *Study Data Specifications* for further information on how to submit this data.

III. GENERAL CONSIDERATIONS

This section of the draft guidance describes general considerations related to electronic submissions that are made using the eCTD version 3.2.2 format.

A. Document Granularity and Table of Contents Headings

Submissions are defined as a collection of documents and data files. A document is a collection of information that includes forms, reports, tables, and datasets. When making an electronic submission, document granularity, or the level for which the submissions content is broken out into separate documents, should follow the FDA guidance for industry *M4 Granularity Annex*.

With a few exceptions,[7] the eCTD specification maps CTD headings to XML elements. The specification indicates that each element (heading) is optional, and that multiple document references (eCTD leaf elements) can be created under each heading. The "Granularity Annex" provides recommendations on where it is appropriate to submit combined documents at higher heading levels and where it is appropriate to submit multiple documents as leaf elements under the same heading.

A table of contents is defined by headings arranged in hierarchical fashion. See the associated FDA technical specification *Comprehensive Table of Contents Headings and Hierarchy* for the comprehensive listing of headings and hierarchy and a section mapping the headings to their respective regulations. Because this is a comprehensive listing, not all headings are applicable to all submissions or submission types. All of the submission information is covered by these headings.

Unless otherwise specified in the FDA guidance for industry *M4 Granularity Annex* or ICH M2 technical specification *eCTD IWG Question and Answer and Specification Change Request Document (eCTD Q&As)*, documents should be organized such that the subject matter of the document is specifically associated with the lowest heading in the table of contents hierarchy. For example, in the associated FDA technical specification *Comprehensive Table of Contents Headings and Hierarchy*, the headings "Summary of safety information" and "Summary of nonclinical studies" are the lowest headings in the "Annual Report" hierarchy. Therefore, the summary of safety information and summary of nonclinical studies would be in two separate documents referenced under their respective heading elements—the summary of safety information and the summary of nonclinical studies, respectively.

A document can be associated with more than one heading. However, the actual electronic file should only be provided once. The ICH M2 technical specification *Electronic Common Technical Document Specification* provides details on how to refer to an electronic file that has already been submitted.

[7] For example, in Module 3, lower level headings subordinate to 3.2.P.2 (i.e., 3.2.P.2.1, 3.2.P.2.1.1, etc.) are not mapped to an XML element. Consequently, leaf element files relating to 3.2.P.2.1, 3.2.P.2.1.1, etc. should be submitted as multiple leafs under the parent 3.2.P.2 element (heading). The contents of these files can also be combined into larger files and submitted at the 3.2.P.2 heading level.

B. Resubmission of Previous Submissions

To transition an existing application to eCTD format, you should provide electronic files and eCTD backbone files for new and changed information only. It is not necessary to provide eCTD backbone files for the previous submissions to the application. For example, if the original application was submitted in paper in 2010, and now a supplement will be submitted to the application using the eCTD backbone files, you do not have to submit electronic copies of files and the eCTD backbone files for the previously submitted paper files.

C. Referencing Previously Submitted Documents[8]

If a document was previously submitted in either paper or non-eCTD electronic format, it should be referenced as with any paper submission. A document detailing previously submitted information that is referenced by the current application can be submitted in section 1.4.4 of the eCTD. In the text of the document, you should include (1) the application or master file number, (2) the date of submission (e.g., cover letter date), (3) the document name, (4) the page number, and (5) the submission identification (e.g., submission serial number, volume number, electronic folder, and file name) of the referenced document.

If a document was previously submitted in eCTD format, you should not resubmit the electronic files when referencing that document. Instead, you should submit a document in section 1.4.4 of the eCTD with reference details, including: (1) the application or master file number, (2) the eCTD sequence number, (3) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (4) the document leaf title, and (5) the page number of the referenced document along with a hypertext link to the location of the information.

If a document replaces a document previously submitted with an eCTD backbone file within the same application, you should use the eCTD "replace" operation to indicate this, rather than submitting the file as "new". The details on how to include this information in the eCTD backbone file are provided in the ICH M2 technical specification *Electronic Common Technical Document Specification*.

When referring to documents within another application, include the appropriate letters of authorization for cross-reference in Module 1, if applicable (e.g., letters required by 21 CFR 314.420(d)).

D. File Formats and Versions

You should send electronic documents in the file formats and versions specified by the FDA on the appropriate center's eCTD web page. For details on producing PDF documents, refer to the FDA technical specification *Portable Document Format (PDF) Specifications*. For details on submitting data files, refer to the FDA technical specification *Study Data Specifications*.

[8] Previously submitted documents include previously submitted information by reference for master files, marketing applications, and investigational applications discussed under 21 CFR 312.23(b), 21 CFR 314.50(g)(1), 21 CFR 314.420(b), and 21 CFR 601.51(a).

E. Leaf Titles

eCTD leaf titles are displayed to the reviewer when viewing an eCTD application. Although some eCTD tools generate leaf titles that are similar to file names, the two are not related. All modules of the eCTD should contain descriptive eCTD leaf titles that are short, meaningful, and indicative of each document's content (as the document file name is not displayed to reviewers). You should not include the eCTD section number in the leaf title.

For documents of the same type (such as the cover letter, Form FDA 356h, and annual report documents), you should provide additional information in the eCTD leaf title so reviewers can distinguish documents submitted in different sequences. For example, the leaf title for a cover letter should also include the date (e.g., 2012-12-31). Additionally, if documents of the same type are being provided in different file formats, a file format (e.g., "MS Word") should be included at the end of the leaf title. This helps reviewers quickly identify which software applications are necessary to open the files.

F. Transmission of Electronic Submissions

The FDA Electronic Submissions Gateway[9] enables the secure submission of regulatory information for review and is our preferred method of transmission.

Additional information on the transmission of electronic submissions is available in the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*.

G. Receipt Date of Electronic Submissions

The receipt date for an electronic submission will be determined only after the submission has passed a technical validation check to ensure that it can be opened, processed, and archived. Additional information on the validation of electronic submissions is available in the FDA technical specification *Specifications for eCTD Validation Criteria*.

Additional information on receipt dates for electronic submissions is available in the FDA draft guidance for industry *Providing Regulatory Submissions in Electronic Format — Receipt Date.*

H. Submission of Paper Copies

When providing applications in electronic format using the eCTD backbone files, paper copies of the application, including review copies and desk copies, should not be sent. An exception to this is the submission of paper copies of meeting briefing materials, as described in the FDA guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants.*

[9] Additional information concerning the FDA ESG is available on the Internet at http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm

I. The FDA District Office Copy

FDA District offices have access to documents submitted in electronic format. Therefore, when sending submissions in electronic format, you need not provide any duplicate documentation to the FDA Office of Regulatory Affairs District Office.

A Field Copy Certification, which is required by regulation,[10] should be included with the electronic submission in section 1.3.2 of the eCTD.

A letter certifying that the electronic CMC section has been submitted should also be provided to the Office of Regulatory Affairs District Office.

[10] 21 CFR 314.50(d)(1)(v) ("The applicant shall include a statement certifying that the field copy of the application has been provided to the applicant's home FDA district office.").

IV. ORGANIZATION OF THE eCTD

This section of the guidance contains recommendations on the organization of an electronic submission made using the eCTD version 3.2.2 format.

A. Module 1 Administrative Information and Prescribing Information Folder

Module 1 contains administrative and labeling documents. The organization of the documents in Module 1 is the same for all applications and related submissions.

1. FDA regional eCTD backbone files

Details regarding these files are contained in the associated FDA technical specification *eCTD Backbone Files Specification for Module 1*.

2. FDA forms

Electronic submissions should include an FDA fillable form (e.g. 1571 or 356h) and electronic signatures to enable automated processing of the submission.

If electronic signatures cannot be applied and you are submitting a scanned form, you should also include an unsigned fillable form using the form name in the filename (e.g., 1571.pdf or 356h.pdf). The scanned version of the form should not include the specific form name anywhere in the file name (e.g., signed-form.pdf).

3. Cover letter

We recommend that your cover letter include the following information:

- Regulatory description of the submission, including appropriate regulatory information, the eCTD locations of submitted information, and hyperlinks to submitted information (for NDA supplements, all proposed changes should be summarized)
- Technical description of the submission, including the approximate size of the submission (e.g., 2 gigabytes), the format used for transmission (ESG or physical electronic media), and the type and number of electronic media used (e.g., USB drive or two DVDs), if applicable
- Statement that the submission is virus free, with a description of the software (name, version, and company) used to check the files for viruses
- A regulatory and technical point of contact for the submission

4. Reviewer's guide (optional)

The reviewer's guide can be helpful when submitted with large applications, such as original applications and efficacy supplements. If providing a reviewer's guide, you should include a high-level overview of the submission with hyperlinks to submitted information. The reviewer's guide should not be an exact copy of the eCTD table of contents. An outline format describing

the submission's content is preferred and it should include tables or lists as opposed to a lengthy description of the application's content.

A reviewer's guide should be placed in section 1.2 of the eCTD and provided as a separate document from the cover letter, with a descriptive leaf title.

5. Labeling

The following describes how to provide specific labeling documents:

a. Labeling history

A history summarizing labeling changes can be provided as a single PDF file. The following information will help us confirm changes made to the labeling:

- complete list of the labeling changes being proposed in the current submission and the explanation for the changes
- date of the last approved labeling
- history of all changes since the last approved labeling. With each change, note the submission that originally described the change and the explanation for the change.
- list of supplements pending approval that may affect the review of the labeling in the current submission

b. Content of labeling

The FDA guidance for industry *Providing Regulatory Submissions in Electronic Format — Content of Labeling* gives details on providing the content of labeling files.

c. Labeling samples

Each labeling sample (e.g., carton labels, container labels, package inserts) should be provided as an individual PDF file. The samples should (1) include all panels, if applicable; (2) be provided in their actual size; and (3) reflect the actual color proposed for use.

6. Advertisements and promotional labeling material

Form FDA 2253 submissions for advertisements and promotional labeling materials to CDER should be submitted according to the FDA draft guidance for industry *Providing Regulatory Submissions in Electronic Form —Prescription Drug Advertising and Promotional Labeling.* Other submissions of advertising and promotional labeling materials to CDER should be made in paper or electronically in non-eCTD electronic format prior to the implementation of version 3.x of the *us-regional.xml* backbone file.

Following the implementation of version 3.x of the *us-regional.xml* backbone file, advertisements and promotional labeling materials should be submitted to CDER in eCTD format.

Advertisements and promotional labeling materials should be submitted to CBER in eCTD format using version 2.01 of the *us-regional.xml* backbone file and the following instructions:

You should submit promotional material to the appropriate application and not mix submissions of advertisements and promotional labeling with submissions containing other types of information.

Each promotional piece should be provided as an individual PDF file. In cases in which promotional writing or images cover more than one page (e.g., a brochure spread), we should be able to view the entire layout at one time. For three-dimensional objects, you should provide a digital image of the object in sufficient detail to allow us to review the promotional material. In addition, you should provide information adequate to determine the size of the object (e.g., point size, dimensions). A dimensional piece shown flat, such as a flattened carton, also can be submitted.

For promotional materials submitted as part of the postmarketing reporting requirements, you may choose to provide hypertext links to references or labeling. References improve the efficiency of a review. References should be submitted as individual PDF files. If possible, the sections of the full reference that is referred to in the promotional materials should be highlighted. When a reference is used to support a claim in proposed promotional materials voluntarily submitted for advisory opinion or Agency comment, you should provide a hypertext link to the page of the reference or labeling that contains the supporting information.

7. Marketing annual reports

You should include a bookmark for each study or trial described in the postmarketing requirement/commitments files. The eCTD leaf title should include the reporting period covered by the annual report.

8. Information amendments

Documents for information amendments should be included in the appropriate eCTD module using the appropriate eCTD heading describing the document's subject matter. In the unusual case when information amendments do not fit appropriately under any heading in the eCTD, you should provide the documents in the appropriate subheading within 1.11, "Information amendment: Information not covered under Modules 2 to 5." You should provide a separate PDF file for each subject covered.

B. Module 2 Summary Folder

The subject matter for each document in Module 2 should be appropriate for each heading in accordance with the "Granularity Annex" and the associated FDA technical specification

Comprehensive Table of Contents Headings and Hierarchy. Each document should be provided as an individual PDF file. The subfolders described in the ICH M2 technical specification *Electronic Common Technical Document Specification* are not necessary for the review of the submission. If additional subfolders are used, the subfolder structure will be maintained so links will function properly.

1. Bioequivalence Summary Tables

For ANDA submissions, Bioequivalence Summary Tables should be provided in section 2.7.1 of the eCTD. Additional information about ANDA submissions is provided in the FDA technical specification *ANDA Filing Checklist for Completeness and Acceptability of an Application*.

2. Summary of Clinical Efficacy and Summary of Clinical Safety

Additional information on sections 2.7.3 Summary of Clinical Efficacy and 2.7.4 Summary of Clinical Safety is provided in the FDA guidance for industry *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document.*

C. Module 3 Quality Folder

The organization of the Module 3 folder is the same for all applications and related submissions. The subject matter for each document submitted should be appropriate for each heading in accordance with the "Granularity Annex" and the associated FDA technical specification *Comprehensive Table of Contents Headings and Hierarchy*. Each document should be provided as an individual PDF file, and files should not be combined using "Adobe PDF Packages," "Portfolios," or "PDF Binders." The subfolders described in the ICH M2 technical specification *Electronic Common Technical Document Specification* are not necessary for the review of the submission, and do not affect the view as displayed in eCTD viewing tools. If additional subfolders are used, the subfolder structure will be maintained so links will function properly, but the view as displayed in eCTD viewing tools will be unaffected. An application should maintain the same file and folder structure through the life of the application.

1. Granularity

Document granularity should generally be consistent with the FDA guidance for industry *M4 Granularity Annex* considering business needs and ease of review.

There are some exceptions to granularity, however. For INDs in the eCTD format, following the recommendations of the "Granularity Annex" may result in many small files with little content. Consequently, it is appropriate to submit single files submitted at higher levels of the eCTD hierarchy. For example, you may choose to submit a single leaf for 3.2.S Drug Substance or 3.2.P Drug Product. Note also that the submission of high-level leaf elements is compliant with the current ICH M2 technical specification *Electronic Common Technical Document Specification*. For example, if there is little excipient information to submit, you may choose to submit this single leaf under the section 3.2.P.4 Control of Excipients heading. Additional considerations for granularity in Module 3 of the eCTD are available in the ICH M2 technical

specification *eCTD IWG Question and Answer and Specification Change Request Document (eCTD Q&As).*

2. Lot Distribution Data

For BLA submissions, you should provide Lot Distribution Data in section 3.2.R of the eCTD. For ANDA and NDA submissions, you should provide Lot Distribution Data in section 1.13.11 of the eCTD.

3. Literature References

The files pertaining to Key Literature References should be provided as individual PDF files and referenced in section 3.3 of the eCTD. The file names and eCTD leaf titles should be short and meaningful (e.g., eCTD leaf title: SmithJA 2002 Impurities).

4. Datasets

When providing standardized stability data or other Quality related data, you should create a directory named "datasets" in the *m3* folder and reference the individual data files in the eCTD backbone file under their appropriate eCTD heading element(s).

D. Module 4 Nonclinical Folder

The organization of the Module 4 folder is the same for all applications and related submissions. The subject matter for each document should be specific for the lowest level of the hierarchy outlined in the associated FDA technical specification *Comprehensive Table of Contents Headings and Hierarchy*. The headings for study reports should also be specific for the lowest level of the hierarchy. Each document should be provided as an individual PDF file. The subfolders described in the ICH M2 technical specification *Electronic Common Technical Document Specification* are not necessary for the review of the submission. If additional subfolders are used, the subfolder structure will be maintained so links will function properly.

1. Study reports

Typically, a single document should be provided for each study report included in this module. However, if providing the study reports as multiple documents, the subject matter of each document should be confined to a single item from the list provided in the FDA technical specification *Comprehensive Table of Contents Headings and Hierarchy*.

In the following examples, study reports should be provided as separate (granular) documents:

- Documents previously submitted. If a document has been provided in a previous submission (e.g., referencing a previously provided protocol), the applicant should provide only an eCTD leaf reference to the protocol and not resubmit the protocol file.
- Additional information added. If it is possible that information will be added to the study report over time (e.g., audit information or a publication based on the study), you

should provide the study reports as separate documents; then the new information can be provided as a separate file, rather than replacing the entire study report.

- Different file formats. If submitting the individual animal data listings as datasets (e.g., SAS transport files), these should be provided as separate files from the study reports (e.g., submitted as PDF files).

2. Literature references

Each literature reference should be provided as an individual PDF file (not referenced by a STF) in section 4.3 of the eCTD. The file names and eCTD leaf titles should be short and meaningful (e.g., eCTD leaf title: SmithJA 2002 Impurities).

3. Datasets

See the associated FDA technical specification *Study Data Specification*s for details on providing datasets and related files.

E. Module 5 Clinical Folder

The organization of the Module 5 folder is the same for all applications and related submissions. The subject matter for each document should be specific for the lowest level of the hierarchy outlined in the associated FDA technical specification *Comprehensive Table of Contents Headings and Hierarchy*. The headings for study reports should also be specific for the lowest level of the hierarchy. Each document should be provided as an individual PDF file. The subfolders described in the ICH M2 technical specification *Electronic Common Technical Document Specification* are not necessary for the review of the submission. If additional subfolders are used, the subfolder structure will be maintained so links will function properly.

1. Tabular listing of all clinical studies

The tabular listing of all clinical studies should be provided as a single PDF file in section 5.2 of the eCTD. A study tagging file (STF) is not necessary for the tabular listing of clinical studies.

2. Study reports

Typically, clinical study reports are provided as more than one document based on the FDA guidance for industry *E3 Structure and Content of Clinical Study Reports*. In cases when a legacy report has already been prepared as a single electronic document, you should provide the entire study report as a single document, not including the case report forms (CRFs) and individual data listings. The individual documents that should be included in a study report are listed in the FDA technical specification *Comprehensive Table of Contents Headings and Hierarchy*. If a document has been provided in a previous submission (e.g., protocol), provide only an eCTD leaf reference to the protocol in the eCTD backbone file, rather than resubmitting the protocol file.

3. Case report forms (CRFs)

You should provide an individual subject's complete CRF as a single PDF file. If a paper CRF was used in the clinical trial, the electronic CRF should be a scanned image of the paper CRF including all original entries with all modifications, addenda, corrections, comments, annotations, and any extemporaneous additions. If electronic data capture was used in the clinical trial, a PDF-generated form or other PDF representation of the information (e.g., subject profile) should be submitted. Each CRF should be included with its corresponding clinical study report, and should be referenced by the report's STF, individually tagged as 'case-report-forms.' FDA does not use the eCTD heading 5.3.7 for CRFs.

The subject's unique identifier should be used as the title of the document and the file name. These names are used to assist reviewers in finding the CRF for an individual subject. Each CRF should have bookmarks as part of the comprehensive table of contents required under 21 CFR 314.50(b). We recommend bookmarks for each CRF domain and study visit to help the reviewer navigate the CRFs. For addenda and corrections, making a hypertext link from the amended item to the corrected page or addendum is a useful way to avoid confusion. Bookmarks for these items should be displayed at the bottom of the hierarchy.

4. Periodic safety reports[11]

Periodic reports consist of two parts: a descriptive portion and the Individual Case Safety Reports (ICSRs). Only the descriptive portion of the periodic report should be submitted to the eCTD. For more information on the submission of ICSRs, please see the draft guidance for industry *Providing Regulatory Submissions in Electronic Format — Postmarketing Individual Case Safety Reports*.

The descriptive portion of the report (e.g., the Periodic Adverse (Drug) Experience Report (PADER) or the ICH-E2C Periodic Safety Update Report (PSUR)) should be submitted to the eCTD in section 5.3.6 as an individual PDF file. Firms should indicate, in the body of the descriptive portion, the transmission method of related ICSRs, i.e., whether submitted electronically as XML files to the FDA Electronic Submissions Gateway or the forms (e.g., FDA 3500A or VAERS-1) mailed to the appropriate Center's Document Control Room. The appropriate reporting period should be indicated in the eCTD leaf title for the descriptive portion.

5. IND safety reports

You should provide each individual IND safety report with its associated study in section 5.3 of the eCTD. Each safety report should be referenced in the study's STF using the 'safety-report' file tag, with "Safety Report" in the eCTD leaf title along with "initial" or "follow-up," depending on the content of the individual safety report.

Refer to the FDA guidance for industry *Safety Reporting Requirements for INDs and BA/BE Studies* for additional details on providing IND safety reports.

[11] Periodic adverse drug experience reports or Periodic adverse experience reports, as described in 21 CFR 314.80 and 600.80, respectively.

6. Literature references

You should provide each literature reference as an individual PDF file (not referenced by a STF) in section 5.4 of the eCTD. The file names and eCTD leaf titles should be short and meaningful (e.g., eCTD leaf title: SmithJA 2010 Impurities).

7. Datasets

The associated FDA technical specification *Study Data Specifications* gives details on providing datasets and related files.

CONTACT INFORMATION

For questions related to providing electronic submissions according to the recommendations in this guidance, you should contact the center electronic submission coordinator at esub@fda.hhs.gov for submissions to CDER and esubprep@fda.hhs.gov for submissions to CBER. Specific questions pertaining to the content of applications should be directed to the appropriate review division or office.

REFERENCE LIST

References provided in order of first appearance in text

ICH M2 technical specification, Electronic Common Technical Document Specification (accessible at http://estri.ich.org/eCTD/)

ICH M2 technical specification, The eCTD Backbone File Specification for Study Tagging Files (accessible at http://estri.ich.org/STF/)

FDA technical specification, eCTD Backbone Files Specification for Module 1 (accessible at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

FDA technical specification, Study Data Specifications (accessible at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

FDA guidance for industry, M4 Granularity Annex (accessible at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)

FDA technical specification, Comprehensive Table of Contents Headings and Hierarchy (accessible at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

ICH M2 technical specification, eCTD IWG Question and Answer and Specification Change Request Document (accessible at http://estri.ich.org/eCTD/)

FDA technical specification, FDA Portable Document Format (PDF) Specifications (accessible at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

FDA technical specification, Specification for Transmitting Electronic Submissions using eCTD Specifications (accessible at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

FDA technical specification, Specifications for eCTD Validation Criteria (accessible at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

FDA draft guidance for industry, Providing Regulatory Submissions in Electronic Format — Receipt Date (accessible at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)

FDA guidance for industry, Formal Meetings Between the FDA and Sponsors or Applicants (accessible at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)

FDA guidance for industry, Providing Regulatory Submissions in Electronic Format — Content of Labeling (accessible at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)

FDA draft guidance for industry, Providing Regulatory Submissions in Electronic Form — Prescription Drug Advertising and Promotional Labeling (accessible at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090181.htm)

FDA technical specification, ANDA Filing Checklist for Completeness and Acceptability of an Application (accessible at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/)

FDA guidance for industry, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (accessible at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)

FDA guidance for industry, E3 Structure and Content of Clinical Study Reports (accessible at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)

FDA guidance for industry, Safety Reporting Requirements for INDs and BA/BE Studies (accessible at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm)