Guidance for Industry

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

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)

June 2008
Electronic Submissions

Revision 2

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Technical specifications associated with this guidance will be provided as stand alone documents. They will be updated periodically. To ensure that you have the most recent versions, check the appropriate center's guidance Web page. For CBER, this Web site is http://www.fda.gov/cber/esub/esub.htm. For CDER, this Web site is http://www.fda.gov/cder/regulatory/ersr/ectd.htm.

Contains Nonbinding Recommendations

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

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such 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.

I. INTRODUCTION

This is one in a series of guidance documents intended to assist applicants making regulatory submissions to the FDA in electronic format using the electronic common technical document (eCTD) specifications. This guidance discusses issues related to the electronic submission of applications for human pharmaceutical products[2] and related submissions, including abbreviated new drug applications (ANDAs), biologics license applications (BLAs), investigational new drug applications (INDs), new drug application (NDAs), master files (e.g., drug master files), advertising material, and promotional labeling.[3] At this time, this does not include applications supporting combination products.

This guidance revises the guidance of the same title that was issued in October 2005 and revised in April 2006. The first revision corrected the names of the eCTD backbone and U.S. Regional

[1] This guidance has been developed by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).

[2] Human pharmaceutical products include those products that meet the definition of *drug* under the Food, Drug and Cosmetic Act, including those that are chemically synthesized and those derived from living sources (biologic products).

[3] Agency guidance documents on electronic submissions will be updated regularly to reflect the evolving nature of the technology and the experience of those using this technology.

Paperwork Reduction Act of 1995: This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in this guidance have been approved under OMB Control Nos. 0910-0014, 0910-0001, and 0910-0338.

backbone files referenced in section IV.A. This second revision provides updated information on the guidance referred to in section III.E.5.

The goals of the guidance are to enhance the receipt, processing, and review of electronic submissions to the FDA. Specifically, this guidance makes recommendations regarding the use of the *eCTD backbone files* developed through the International Conference on Harmonisation (ICH) to facilitate efficient submission handling. In addition, the guidance provides more specificity than in previous guidances for electronic submissions with regard to the organization of individual submissions. Finally, the guidance harmonizes the organization and formatting of electronic submissions for multiple submission types.

This guidance refers to a series of technical specifications associated with the guidance. They are being provided as stand alone documents to make them more accessible to the user. **The associated specifications will be updated periodically. To ensure that you have the most recent versions, check the appropriate center's guidance Web page.**

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. GENERAL ISSUES

This portion of the guidance makes recommendations on general organizational issues related to the electronic submission of applications for human pharmaceutical products using the cCTD specifications. The requirements for ***the content*** of such applications are described in our regulations in chapter 21 of the Code of Federal Regulations (CFR). Additional recommendations on the contents of applications are provided in Agency guidances, which are available on the Agency Web page.

A. Scope

This guidance applies to marketing applications (ANDAs, BLAs, NDAs), investigational applications (INDs), and related submissions (master files, advertising material, and promotional labeling). The guidance applies equally to original submissions, supplements, annual reports, and amendments to these applications and related submissions, including correspondence. This guidance does not apply to electronic submission of prelicense or preapproval inspection materials.

B. Guidance on the Content of Applications and Related Submissions

This document provides general guidance on how to organize application information for electronic submission to the Agency using the eCTD specifications. Guidance on the information to be included in the technical sections of applications and submissions is described in a series of

guidance documents based on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) common technical document (CTD): *M4: Organization of the CTD, M4Q: The CTD – Quality; M4S – The CTD Safety*; and *M4E: The CTD – Efficacy*.

C. ICH eCTD Specification

The recommendations made here on how to organize application information are based on the ICH CTD and the electronic CTD (eCTD), which was developed by the ICH M2 expert working group. Although the CTD and the eCTD were designed for marketing applications, they could apply equally to other submission types, including INDs, master files, advertising material, and promotional labeling.[4] Details on the specification for the ICH eCTD can be found in the guidance document *M2 eCTD: Electronic Common Technical Document Specification.*

D. Document Granularity and Table of Contents Headings

Submissions are a collection of documents. A document is a collection of information that includes forms, reports, and datasets. When making an electronic submission, ***each document should be provided as a separate file***.[5] The documents, whether for a marketing application, an investigational application, or a related submission, should be organized based on the five modules in the CTD: module 1 includes administrative information and prescribing information, module 2 includes CTD summary documents, module 3 includes information on quality, module 4 includes the nonclinical study reports, and module 5 includes the clinical study reports.

A table of contents is defined by headings arranged in a hierarchical fashion. See the associated specification, Comprehensive Table of Contents Headings and Hierarchy for the comprehensive listing of headings and hierarchy Because this is a comprehensive listing, not all headings are applicable to all submissions or submission types. All of the information you need to submit is covered by these headings. If you think other headings are needed, you should contact our electronic submission coordinators prior to using any other headings (see section II.S of this guidance). Reviewers will not be able to access documents associated with headings not listed in the "Comprehensive Table of Contents Headings and Hierarchy."

Unless otherwise specified, documents should be organized so that the subject matter of the document is specifically associated with the lowest heading in the table of contents hierarchy. For example, if you look at the associated document "Comprehensive Table of Contents Headings and Hierarchy," the headings "Meeting request" and "Meeting background material" are the lowest headings in the "Meeting" hierarchy. Therefore, the meeting request and meeting background material would be in two separate documents — the meeting request in one document and the meeting background material in another document.

[4] Advertising and promotional labeling provided with marketing applications.
[5] Some documents are provided in more than one file because a file containing everything would be too large. See specifications for the size limitations for a file.

A document can be associated with more than one heading. However, the actual electronic file would only be provided once. The eCTD specifications provide details on how to refer to an electronic file.

E. Electronic Submissions

Under our regulations (21 CFR 11.2(b)(2)), applicants and sponsors are expected to contact us for details on how to proceed with electronic submissions. These details are usually provided in guidance documents. For example, we are already receiving marketing application submissions for human pharmaceutical products in electronic format based on details provided in the guidances for industry *Providing Regulatory Submissions in Electronic Format – NDAs, Providing Regulatory Submissions in Electronic Format – ANDAs, Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format – Biologics Marketing Applications,* and *Providing Regulatory Submissions in Electronic Format – General Considerations.*[6] However, we recommend that you begin submitting eCTD backbone files as described in this guidance because we believe that having the information in the eCTD backbone files will result in greater efficiency in the future. In time, the other guidances may be withdrawn because they may no longer be needed.

When we are ready to receive a particular submission type in electronic format only, we usually identify it in public docket 92S-0251. Under 21 CFR part 11, you then have the option of providing that submission type in electronic format according to FDA guidance so that the Agency may adequately process, archive, and review the files.

Once you begin to submit a specific application in electronic format based on this guidance, subsequent submissions to the application, including amendments and supplements, should include eCTD backbone files. Without the eCTD backbone files, we will not be able to adequately manage, process, archive, or review the submissions. If you choose to submit an original application using the eCTD backbone files, you should obtain an application number in advance by contacting the appropriate center. You may obtain the number at any time and the numbers will not be reused.

We believe it is most beneficial to begin your eCTD-based submissions with the initial submission of an application. Contact the appropriate center first if you wish to make eCTD-based submissions to pending applications. You should avoid the submission of any paper documents when you follow the recommendations in this document. The maximum benefit will be derived once an application is in electronic format. This is particularly true for the IND, where submissions are provided over a long period of time. You should submit the electronic information for all files in the eCTD backbone files following the specifications associated with this guidance.

[6] This includes mixed electronic and paper submissions.

F. Document Information for Previous Submissions

If you decide to submit a specific application in electronic format based on this guidance, you do not have to provide eCTD backbone files for the previous submissions to the application. For example, if you submitted an original application in 2001 and now submit an amendment to the application using the eCTD backbone files, you do not have to go back and submit the document information for the files submitted in 2001.

G. Referencing Previously Submitted Documents[7]

If a document was submitted in electronic format with the eCTD backbone files, you should not submit additional copies when referencing the previously submitted document. Instead, you should include the information by reference by providing in the text of the document (1) the application or master file number, (2) the date of submission (e.g., letter date), (3) the document name, and (4) the page number of the referenced document along with a hypertext link to the location of the information (see section II.Q of this guidance). If a document replaces or appends a document previously submitted with an eCTD backbone file, then you should include this information in the appropriate eCTD backbone file. The details on how to include this information in the eCTD backbone file are provided in the associated specifications for eCTD backbone files.

If a document was previously submitted in either paper or electronic format **without the proper eCTD backbone files**, you should reference the document as with any paper submission. In the text of the document, you should include (1) the application or master file number, (2) the date of submission (e.g., 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. In such cases, providing an electronic copy of the previously submitted documents can increase the utility of the submission. These documents, like all documents in the submission, should be appropriately described in the eCTD backbone files. These files are considered *new* in the eCTD backbone files.

When referring to documents that are part of other applications, please remember to include the appropriate letters of authorization with the submission (e.g., 21 CFR 314.420(d)).

H. Refuse to File

We may refuse to file an application or supplement under our regulations (e.g., 21 CFR 314.101 and 601.2) if the submission is illegible, uninterpretable, or otherwise clearly inadequate, including having incompatible formats or inadequate organization. These regulations apply to both paper and electronic submissions. The absence of electronic datasets in an acceptable format to permit review and analysis may be considered inadequate, resulting in a refuse-to-file

[7] Previously submitted documents include previously submitted information by reference for master files, market applications, and investigational applications discussed under 21 CFR 312.23(a)(11)(b), 314.50(g)(1), 314.420(b), and 601.51(a).

decision.[8] Following the recommendations in this guidance document will help ensure that your electronic application meets the requirements of FDA regulations and can be archived, processed, and reviewed within specified time frames using our tools.

I. 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, are not required and should not be sent.

J. Scanned Documents

Scanned documents submitted electronically as images are not as useful for review as documents that are text based. Image-based documents are more difficult to read and cannot be electronically searched. It takes longer to print image-based documents, and they occupy more storage space than text-based documents. For these reasons, we strongly urge that you provide text-based documents, rather than image files, whenever possible. We understand that certain documents may only be available as image files. Handwritten documents and documents that were generated independent from the company, such as journal publications, may be available only in paper. Documents that may only be available in paper can be scanned and submitted in electronic format as image-based files. However, we expect documents such as study reports recently generated by the company or recently generated as the result of the company's request to be available as text-based documents. We understand that legacy study reports, those generated years ago, may only be available in paper. For these reports, especially those for pivotal studies, you may want to consider converting these documents from image files to text-based files. Optical Character Recognition that has been validated is an option.

K. 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 documentation to the FDA Office of Regulatory Affairs District Office.

L. Electronic Signatures

Documents required by regulations to be submitted with an original signature (e.g., FDA form 356h, FDA form 1571) should be submitted with electronic signatures that follow the controls described under 21 CFR part 11.

M. Number of Copies of Electronic Files

You should send a single copy of the electronic portions of a submission to the appropriate central document room facility. Copies should not be sent directly to the reviewer or review division. Electronic documents that bypass the controls for electronic files described in 21 CFR 11 are not considered official documents for review.

[8] See more on this in CBER's SOPP 8404.

N. Naming Electronic Files

To function properly, the eCTD backbone files must have specific names (e.g., index.xml, us-regional.xml). For other files without a specified name, you should provide a name that is indicative of the contents (e.g., protocol-101). The file name should allow a reviewer to infer some concept of the file's contents relative to other files. The file name should be less than or equal to 64 characters including the appropriate file extension. You should use only letters (lower case), numbers, or hyphens in the name. You should not use blank spaces. When naming files, it is important to remember that — to avoid truncation — the length of the entire path of the file should not exceed 230 characters.

O. Naming Folders

The terms *folder* and *subfolder* are used in this guidance and are intended to be synonymous with *directory* and *subdirectory*. The main submission, regional administrative folders, and certain subfolders should have specific names for proper and efficient processing of the submission. Recommendations regarding naming the main submission folders and regional administrative folders can be found in section III, below. Other specific folder names can be found in the specifications associated with this guidance. You can use only letters (lower case), numbers, or hyphens in the name. You should not use blank spaces. The length of the folder name should not exceed 64 characters. When naming folders, it is important to remember that the length of the entire path should not exceed 230 characters. You should not include empty folders in the submission.

P. File Formats

We recommend that you send electronic documents in the file formats specified in this guidance. We will not be able to manage, process, archive, or review documents provided in other file formats.

The following file formats should be used:

- PDF for reports and forms
- SAS XPORT (version 5) transport files (XPT) for datasets
- ASCII text files (e.g., SAS program files, NONMEM control files) using *txt* for the file extension
- XML for documents, data, and document information files
- Stylesheets (XSL) and document type definition (DTD) for the XML document information files
- Microsoft Word for draft labeling (because Microsoft Word can change, check our Web site for the current version)

In the future, we may consider other electronic file formats for use with electronic submissions, or we may consider the use of the current formats with other electronic submissions. We intend

to publish guidance to advise on the use of file formats for specific types of submissions for use in the future.

Q. PDF Bookmarks and Hypertext Links

For documents with a table of contents, provide bookmarks and hypertext links for each item listed in the table of contents including tables, figures, publications, references, and associated appendices. These bookmarks and hypertext links are essential for efficient navigation through documents. You should make the bookmark hierarchy identical to the table of contents. Navigation efficiency is also improved by providing hypertext links throughout the body of the document to supporting annotations, related sections, references, appendices, tables, or figures that are not located on the same page.

It is possible to link to other documents in a submission using relative paths when creating hypertext linking. Absolute links that reference specific drives and root directories are not functional once the submission is loaded onto the document repository. For example, the link path ../../../123456/0001/.. will work, but the link c:\123456\0001\… will not work. However, you should keep in mind that some documents may be subsequently replaced or appended, possibly rendering the link obsolete, so linking should be used cautiously.

When creating bookmarks and hypertext links, choose the magnification setting *Inherit Zoom* so that the destination page displays at the same magnification level that the reviewer is using for the rest of the document.

R. Sending Electronic Submissions

All submissions provided in electronic format must be sent to the appropriate central document room facility for processing to maintain the integrity of the submission as required under 21 CFR part 11. Electronic documents sent directly to division document rooms or to reviewers bypass the controls established for the receipt and archiving of documents and are not considered official documents for review. See the associated specifications for more information, including electronic transmission.

S. Technical Problems or Questions

If you have any questions on technical issues related to providing electronic submissions according to the recommendations in this guidance, contact the electronic submission coordinator at esub@cder.fda.gov. Specific technical issues related to submissions to CBER should be sent to esubprep@cber.fda.gov. Specific questions pertaining to content should be directed to the appropriate review division or office.

III. ORGANIZING THE MAIN SUBMISSION FOLDER

All documents in the electronic submission should be placed in a main submission folder using a four-digit sequence number for the application with the original submission for an application

designated 0000. You should assign numbers for each submission to the same application with consecutive numbers. For example, the folder for the 3rd submission to an application, whether it is an amendment, supplement, or general correspondence is numbered 0002. The 4th submission is numbered 0003. This also applies to applications where previous submissions were not based on the ICH eCTD specifications. For example, if the submission is the 25th and the previous 24 were in paper, you would number the folder 0024. You should place the eCTD backbone file for modules 2 to 5 for the submission in this folder (*index.xml*). You should place the checksum file (e.g., index-md5.txt) in the same folder. Sequence numbers are used to differentiate between submissions for the same application and do not need to correspond to the order they are received by the Agency.

We recommend that you use subfolders to organize files in a submission, including for each module *m1*, *m2*, *m3*, *m4*, and *m5*, respectively. There is a subfolder *util* to organize eCTD technical files in the submission. Place these subfolders in the sequence number folder (e.g., folder named 0000 for the initial submission to an application). Do not include empty subfolders.

The following sections provide guidance for organizing the folders and files in the *m1*, *m2*, *m3*, *m4*, *m5,* and *util* folders. In addition, you can find instructions on preparing the submission of an electronic application to CBER at http://www.fda.gov/cber/esub/esub.htm.

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. The subject matter for each document should be assigned to the lowest level of the hierarchy outlined in the associated document "Comprehensive Table of Contents Headings and Hierarchy." Note that some headings apply only to specific applications or specific submissions. You should create a folder named *us* and place it in the folder named *m1*. The documents for module 1 should be placed in the *us* folder including the *us-regional.xml* file pertaining to the eCTD backbone files for module 1. Below are some additional details on providing specific types of documents.

1. eCTD backbone document information files

The details on creating this file are in the associated document "eCTD Backbone Files Specification for Module 1."

2. Cover letter (optional)

If you decide to include a cover letter, we recommend you include the following information:

- Description of the submission including appropriate regulatory information
- Description of the submission including the approximate size of the submission (e.g., 2 gigabytes), the format used for DLT tapes, and the type and number of electronic media used (e.g., three CDROMs), 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
- Regulatory and technical point of contact for the submission

3. Labeling

The following section describes how to provide specific labeling documents.

a. Labeling history

You can provide a history summarizing labeling changes 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, you should 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

See the guidance for industry on *Providing Regulatory Submissions in Electronic Format — Content of Labeling* for 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 individual PDF files. 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.

4. Advertisements and promotional material

Advertisements and promotional labeling include material submitted under 21 CFR 314.81(b)(3)(i) or 601.12(f)(4) as part of the postmarketing reporting regulations for approved applications, submitted under the requirements of 21 CFR 314.550 and 601.45 (part of the accelerated approval requirements and restricted distribution for drug and biological products), or voluntarily submitted to INDs. You should submit promotional material to the appropriate application. You should 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 when promotional writing or images cover more than one page (e.g., a brochure spread), the reviewer 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, can also be submitted.

If you choose to include cover letters with your submissions of advertising and promotional material, they should be provided as individual PDF files and indicate for the reviewer any additional important information, such as which materials need priority reviews.

If references are provided, each reference should be submitted as an individual PDF file and placed in the appropriate module based on subject matter. If possible, you should highlight the sections of the full reference that you refer to in the promotional materials. 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.

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.

5. Marketing annual reports

In the postmarketing study commitments files, you should include a bookmark for each study described.

6. Information amendments

You should include documents that are provided in information amendments in the appropriate module using the appropriate headings to describe the subject matter. In the unusual case when information amendments do not fit appropriately under any heading in the CTD, you should place the documents in module 1 under the heading "information amendment: Information not covered under modules 2 to 5." You should provide a separate PDF file for each subject covered. Documents that apply to more than one module should be placed under the heading "Multiple module information amendments."

B. Module 2 Summary Folder

You should place the documents for module 2 in the *m2* folder. The subject matter for each document should be specific for the lowest level of the hierarchy outlined in the associated document "Comprehensive Table of Contents Headings and Hierarchy." Each document should be provided as an individual PDF file. The subfolders described in the *M2 eCTD: Electronic Common Technical Document Specification* are not necessary for the review of the submission.

If you choose to use the additional subfolder, we will maintain the subfolder structure so links will function properly.

C. Module 3 Quality Folder

The organization of the module 3 folder is the same for all applications and related submissions. You should place the documents for module 3 in the *m3* folder. The subject matter for each document should be specific for the lowest level of the hierarchy outlined in the associated document "Comprehensive Table of Contents Headings and Hierarchy." Each document should be provided as an individual PDF file. The subfolders described in the *M2 eCTD: Electronic Common Technical Document Specification* are not necessary for the review of the submission. If you choose to use the additional subfolder, we will maintain the subfolder structure used so links will function properly.

You should provide the files pertaining to Key Literature References (CTD section 3.3) as individual PDF files. The filenames should be short and meaningful.

D. Module 4 Safety Folder

The organization of the module 4 folder is the same for all applications and related submissions. You should place the documents for module 4 in the *m4* folder. The subject matter for each document should be specific for the lowest level of the hierarchy outlined in the associated document "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 *M2 eCTD: Electronic Common Technical Document Specification* are not necessary for the review of the submission. If you choose to use the additional subfolder, we will maintain the subfolder structure 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 you provide the study reports as multiple documents, you should confine the subject matter of each document to a single item in the following list.

- Synopsis
- Study report body
- Protocol and amendments
- Signatures of principal or coordinating investigator(s)
- Audit certificates and reports
- Documentation of statistical methods and interim analysis plans
- Documentation of interlaboratory standardization methods of quality assurance procedures if used
- Publications based on the study
- Important publications referenced in the report
- Compliance and/or drug concentration data

- Individual subject data listings
  — Data tabulations
    - Data tabulations datasets
    - Data definitions
  — Data listing
    - Data listing datasets
    - Data definitions
  — Analysis datasets
    - Analysis datasets
    - Analysis programs
    - Data definitions
  — IND safety reports

In the following examples, you should provide the study reports as separate documents

- Documents previously submitted. If you have provided a document in a previous submission (e.g., protocol), you should provide a reference to the protocol, not resubmit the protocol.
- Additional information added. If you think you will want to add information to the study report over time (e.g., audit information, publication based on the study), you should provide the study reports as separate documents and then the new information can be provided as a separate file, rather than replacing the entire study report.
- Different file formats. If you submit the individual animal data listings as datasets (e.g., SAS transport files), you should provide these as separate files from the study reports (e.g., submitted as PDF files).

When providing a study report, you should include the study tagging file (STF) described in the associated document "The eCTD Backbone File Specifcation for Study Tagging Files."

2. Literature references

You should provide each literature reference as an individual PDF file. The filenames should be short and meaningful.

3. Datasets

See the associated document "Study Data Specifications" for details on providing datasets and related files (e.g., data definition file, program files)

E. Module 5 Clinical Study Reports Folder

The organization of the module 5 folder is the same for all applications and related submissions. You should place the documents for module 5 in the *m5* folder. The subject matter for each document should be specific for the lowest level of the hierarchy outlined in the associated document "Comprehensive Table of Contents Headings and Hierarchy." One exception is that legacy study reports can be provided as a single document. Each document should be provided as

an individual PDF file. The subfolders described in the guidance *M2 eCTD: Electronic Common Technical Document Specification* are not necessary for the review of the submission. If you choose to use the additional subfolder, we will maintain the subfolder structure so links will function properly.

1. Tabular listing of all clinical studies

You should provide the tabular listing of all clinical studies as a single PDF file.

2. Study reports

Typically, clinical study reports are provided as more than one document based on the ICH E3 guidance document when providing a study.[9] In addition, if you have provided a document in a previous submission (e.g., protocol), you should provide a reference to the protocol rather than resubmitting the protocol. In cases when a legacy report has already been prepared as a single electronic document, you can provide the entire study report, other than the case report forms (CRFs) and individual data listings, as a single document. The individual documents that should be included in a study report are listed below:

- Synopsis[10] (E3 2)
- Study report (E3 1, 3 to 15)
- Protocol and amendments (E3 16.1.1)
- Sample case report forms (E3 16.1.2)
- List of IECs or IRBs (E3 16.1.3) and consent forms
- List and description of investigators (E3 16.1.4) and sites
- Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer (E3 16.1.5)
- Listing of patients receiving test drug(s) from specified batch (E3 16.1.6)
- Randomizations scheme (E3 16.1.7)
- Audit certificates (E3 16.1.8) and reports
- Documentation of statistical methods (E3 16.1.9) and interim analysis plans
- Documentation of interlaboratory standardization methods of quality assurance procedures if used (E3 16.1.10)
- Publications based on the study (E3 16.1.11)
- Important publications referenced in the report (E3 16.1.12)
- Discontinued patients (E3 16.2.1)
- Protocol deviations (E3 16.2.2)
- Patients excluded from the efficacy studies (E3 16.2.3)
- Demographic data (E3 16.2.4)
- Compliance and/or drug concentration data (E3 16.2.5)
- Individual efficacy response data (E3 16.2.6)

[9] When providing a study report, you should include the study tagging file (STF) described in the associated document "The eCTD Backbone File Specification for Study Tagging Files."

[10] The synopsis should be provided as a document separate from the study report.

- Adverse event listings (E3 16.2.7)
- Listing of individual laboratory measurements by patient (E3 16.2.8)
- Case report forms (E3 16.3)
- Individual patient data listings (CRTs) (E3 16.4)
  - — Data tabulations
    - Data tabulations datasets
    - Data definitions
    - Annotated case report form
  - — Data listing
    - Data listing datasets
    - Data definitions
    - Annotated case report form
  - — Analysis datasets
    - Analysis datasets
    - Analysis programs
    - Data definitions
    - Annotated case report form
  - — Subject profiles
  - — IND safety reports

3. Case report forms

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, you should submit a PDF-generated form or other PDF representation of the information (e.g., subject profile).

You should use the subject's unique identifier 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 must 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. Datasets

See the associated document "Study Data Specifications" for details on providing datasets and related files (e.g., data definition files, program files). For subject profiles, you should use the subject's unique identifier in the title of the document and the file name.

5. Periodic safety update reports

To facilitate electronic submissions, we have divided the postmarketing periodic adverse drug experience report into three parts: (1) individual case safety reports (ICSRs), (2) ICSR attachments, if applicable, and (3) descriptive information. The descriptive information includes the narrative summary and analysis of the information in the report (i.e., periodic ICSRs and ICSR attachments), an analysis of the 15-day alert reports submitted during the reporting interval (i.e., expedited ICSRs and ICSR attachments), and the history of actions taken since the last report because of adverse drug experiences (e.g., labeling changes, studies initiated) as described in 21 CFR 314.80(c)(2)(ii)(a) and (c) and 600.80(c)(2)(ii)(A) and (C)). You should supply the descriptive information as an individual PDF file. You should provide bookmarks for each of the sections and subsections of this report. ICSR and ICSR attachments should be provided as described in FDA's guidance for industry on electronic submission of postmarketing ICSRs (Available under the topic "Electronic Submission" on CDER and CBER's guidance Web pages).

6. Literature references

You should provide each literature reference as an individual PDF file. The filenames should be short and meaningful.

IV. UTILITY FOLDER

You should create two folders, *dtd* and *style* and place them in the *util* folder.

A. Document Type Definition Folder

You should place the document type definition (DTD) that you used to create the eCTD backbone file (index.xml), the DTD you used to create the FDA Regional eCTD backbone file (us-regional.xml), and the DTD used for the STF in the folder named *dtd*. You should use the most recent DTD.[11]

B. Style Folder

You should use the most recent stylesheet. See the guidance for industry *M2 eCTD: Electronic Common Technical Document Specification.*

[11] See the FDA Web site at http://www.fda.gov/cder/regulatory/ersr/.