Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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 comments to Dockets Management Branch (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) Randy Levin 301-594-5411, or (CBER) Robert Yetter at 301-827-0373.

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)

August 2003
Electronic Submissions

Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions

Additional copies are available from:

Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane,
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(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

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Office of Communication, Training and
Manufacturers Assistance, HFM-40
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Food and Drug Administration
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(Tel) Voice Information System at 800-835-4709 or 301-827-1800
http://www.fda.gov/cber/guidelines.htm

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The following specifications will be provided with this guidance 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 or go to http://www.fda.gov/cder/oim.

- FDA Comprehensive eCTD Table of Contents Headings and Hierarchy
- FDA Module 1 Specification
- FDA Modules 2-5 Specification
- Study Tagging Files Specification

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

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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. This guidance discusses issues related to the electronic submission of applications for human pharmaceutical products and related submissions, including abbreviated new drug applications (ANDAs), biologics licensing application (BLAs), investigational new drug applications (INDs), new drug application (NDAs), master files, advertising material, and promotional labeling.[2]

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 *eCTD document information backbone files* to facilitate efficient submission handling. In addition, the guidance provides more specificity than in previous guidances with regard to the organization of individual submissions. Finally, the guidance harmonizes the organization and formatting of multiple submission types.

We recommend that users continue to refer to the guidance for industry *Regulatory Submissions in Electronic Format — General Considerations* for discussion of issues common to multiple submission types, such as acceptable file formats and submission media.

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

[2] 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.

This guidance has a series of attachments. They are being provided as stand alone documents to make them more accessible to the user. Attachments include:

- A Comprehensive Table of Contents Headings and Hierarchy for a complete submission
- The eCTD Document Information Backbone Files Specification for Module 1
- The eCTD Document Information Backbone Files Specification for Modules 2 through 5
- Study Tagging Files Specification

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. 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 is 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, and amendments to these applications and related submissions.

B. Guidance on Applications and Related Submissions

This document provides general guidance on how to organize application information for electronic submission to the Agency. More specific 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*; *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 apply

equally to other submission types, including INDs, master files, advertising material, and promotional labeling. 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 that include forms, reports, and datasets. When making an electronic submission, ***each document should be provided as a separate file.***[3] The documents, whether for a marketing application, an investigational application, or 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.

Each module has a table of contents defined by headings arranged in a hierarchical fashion. We have provided a comprehensive listing of headings and hierarchy with this guidance as a stand-alone attachment (see the Comprehensive Table of Content Headings and Hierarchy). You should contact our electronic submission coordinator prior to using any other headings. Reviewers will not be able to access documents associated with headings not listed in this attachment. Unless otherwise specified, generally, documents should be organized so that the subject matter covered by a document is specifically associated with the lowest heading in the hierarchy. For example, if you look at the attachment Comprehensive Table of Content Headings and Hierarchy, "Meeting request" and "Meeting background material " are the lowest headings in the "Meeting" hierarchy. Therefore, the meeting request and meeting background material should ***not*** be contained in one document. The meeting request would be in one document, and the meeting background material would be in another document.

A document can be associated with more than one heading while the actual electronic file is only provided once.

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 – NDA*, *Providing Regulatory Submissions in Electronic Format – ANDA*, and *Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic format – Biologics Marketing Applications.* These guidances do not recommend using the eCTD backbone files described in this guidance. 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. Once low-cost, readily available tools are developed that allow virtually all sponsors and applicants to

[3] Some documents are provided in more than one file because a file containing everything would be too large.

easily generate the eCTD backbone files and once this guidance is final, it will replace those earlier guidances. We recommend that users continue to refer to the guidance for industry *Regulatory Submissions in Electronic Format — General Considerations* for discussion of issues common to multiple submission types, such as acceptable file formats and submission media.

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, all subsequent submissions to the application including all 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.

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 document information for all documents in the eCTD backbone files following the ICH eCTD specifications and the Comprehensive Table of Contents Headings and Hierarchy.

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 XML document information files, you do not have to go back and submit the document information for the files submitted in 2001.

G. Referencing Previously Submitted Documents[4]

You do not have to submit additional copies when referencing a previously submitted document, provided the document was submitted in electronic format with the proper electronic document information included in the eCTD backbone files. 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

[4] This includes previously submitted information by reference for master files, market applications, and investigational applications is discussed under 21 CFR 312.23(a)(11)(b), 21 CFR 314.50(g)(1), 21 CFR 314.420(b), 21 CFR 314(a) and 21 CFR 601.51(a).

referenced document. The details on how to include this information in the eCTD backbone file is provided in the eCTD Backbone Files Specification.

If a document was previously submitted in either electronic format or paper without electronic document information in 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.

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., §§ 314.101 and 601.2) if the submission is illegible, uninterpretable, or otherwise clearly inadequate including having incompatible formats or inadequate organization. This applies 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 decision.[5] Following the recommendations in this guidance document will help ensure that your electronic application meets the requirements of FDA regulations and can be archived, loaded on our network drives, and reviewed within specified time frames using our tools.

I. Submission of Paper Copies

If you provide a document in electronic format, paper copies of the document, including desk copies, are not needed.

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. 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

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

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 using optical character recognition (OCR) or some other technique.

K. The Field Copy

District offices have access to documents submitted in electronic format. Therefore, when sending submissions in electronic format, you need not provide a separate copy to the field.

L. Electronic Signatures

Documents required by regulations to be submitted with an original signature (e.g., FDA form 356h, FDA form 1571) can be submitted with electronic signatures provided that you follow the controls described under 21 CFR part 11 and that our system can automatically validate the signature.

M. Number of Copies of Electronic Files

You need only provide a single copy of the electronic portions of a submission and should not send copies directly to the reviewer or review division without following procedures described in this guidance. Do not bypass the controls for electronic files described in 21 CFR 11. This will make the documents unreliable for review.

N. Naming Electronic Files

To function properly, the eCTD backbone files must have specific names (e.g., index.xml, us-regional.xml). For files without a specific 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.

O. Naming folders

The terms *folder* and *subfolder* are used in this guidance and are intended to be synonymous with *directory* and *subdirectory*. The sequence and regional administrative folders should have specific names (e.g., 0000\ml\us) for proper and efficient processing of the submission. Recommendations regarding naming the main sequence folders and regional administrative folders can be found in section III, below. You can use only letters (lower case), numbers, or hyphens in the name. The length of the folder name should not exceed 64 digits, and the length of the path should not exceed 256 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 transport files (XPT) for datasets
- ASCII text files or SAS files for statistical program controls (e.g., SAS program files, NONMEM control files) using *txt* for the file extension
- XML for document information files
- Stylesheets (XSL) and document type definition (DTD) for the XML document information files
- Microsoft Word for draft labeling (check our Web site for the current version)

The guidance for industry on *Regulatory Submissions in Electronic Format — General Considerations* provides details on submitting documents in portable document format (PDF) format and datasets in SAS transport format (XPT).

In the future, we may consider other file formats for use with electronic submissions, or we may consider the use of the current formats with other submissions. We recommend that you wait for published guidance documents regarding the submission of file formats before submitting them for review.

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 for 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.

When creating bookmarks and hyperlinks, 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 valid documents for review.

Submissions can be sent using secure email to the appropriate central document room. We are currently able to accept only submissions of less than 50 megabytes through secure email.

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. Number 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 document information for the eCTD backbone file for modules 2 to 5 for the submission in this folder (*index.xml*). You should place the checksum file in the same folder.

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.

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 attached template for the 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 are 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

We recommend that you provide the document information for the documents provided in module 1 in the *us-regional.xml* file. The details on creating these files are in the eCTD Backbone Files Specification attachments.

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. Labeling text

The labeling text is the content of labeling as defined in 21 CRF 201.57 or 201.66 and includes all text, tables, and figures. The labeling text should be formatted as follows:

- Paper size: 8.5 by 11 inches with 1-inch margins
- Page orientation: Portrait
- No columns, headers, or footers
- Pagination starting with page 1
- Text font: Times New Roman 12 point or equivalent font
- Table font: Times New Roman 10- or preferably 12-point or equivalent font

Each example of labeling text should be provided as an individual PDF file. Draft labeling text should be provided in both PDF and Word format (the Word version can be edited).

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 includes 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 or 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) related to investigational new drug applications (INDs). Also included are requests for comment on materials for the development of evidence to support future advertising or promotional labeling claims.[6] You should submit promotional material to the appropriate marketing applications. You should not mix submissions with advertising 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

[6] Under 21 CFR 99, such materials information on unapproved/new uses for drugs, biological products, and devices.

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 any additional important information to the reviewer, 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, 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, the hypertext links to references or labeling are optional. Although not required, references improve the efficiency of a review.

5. Marketing annual reports

You should provide FDA form 2252 as a single PDF file.

In the annual report, you must summarize new information that might affect the safety, effectiveness or labeling of the drug product (314.81(b)(2)(i)). Documents summarizing the following areas should be provided as separate PDF files:

- CMC changes
- Appropriate nonclinical studies
- Clinical pharmacology information
- Safety information
- Labeling changes
- Other significant new information

Reports for nonclinical (314.81(b)(v)) and clinical (314.81(b)(vi)) studies should be provided in modules 4 (Safety) and 5 (Efficacy), respectively. Information for chemistry, manufacturing, and controls (314.81(b)(iv)) should be provided in module 3 (Quality).

You should provide the distribution data (314.81(b)(2)(ii)) as a single PDF file. A log of outstanding regulatory business (314.81(b)(2)(ix)) should be provided as a single PDF file. The status of postmarketing study commitments (314.81(b)(2)(vii)) should be provided as a single PDF file. In the postmarketing study commitments file, you should include a bookmark for each study described. The status of other postmarketing studies (314.81(b)(2)(viii)) should be provided as a single PDF file. You should include a bookmark for each study described.

Labeling provided with the annual report should be provided as described previously.

6. IND annual report

You should provide individual study information (312.33(a)) as a single PDF file. You should provide the summaries of the clinical studies (312.33(b)), including phase 1 changes (312.33(e), nonclinical studies (312.33(b)), microbiology (312.33(b)), and manufacturing (312.33(b)) as separate PDF files. The general investigational plan for the coming year (312.33(c)) should also be provided as a separate PDF file. The general investigational plan for the first submission should be included here. You should also include a separate PDF file for a summary of foreign marketing developments (312.33(f)) and one for a log of outstanding regulatory business (3212.33(g)).

7. 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." 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

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 example provided with this document. Each document should be provided as an individual PDF file. The subfolders described in the *Electronic Common Technical Document Specification* from the ICH M2 expert working group are optional. They 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. 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 attachment on Table of Contents Headings and Hierarchy provided with this guidance. The only exception is for pharmaceutical development information, which can be provided as a single document. Each document should be provided as an individual PDF file. The subfolders described in the *Electronic Common Technical Document Specification* from the ICH M2 expert working group are optional. They 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

The organization of the module 4 folder is the same for all applications and related submissions. 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 attachment on Table of Contents and Hierarchy provided with this guidance. 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 *Electronic Common Technical Document Specification* from the ICH M2 expert working group are optional. They 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.

- Legacy Study Report[7]
- 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 inter laboratory 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

[7] The legacy study report is included to include study reports that are already prepared as single documents.

- 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 in more than one document, you should include the Study Tagging File (STF) described in the attachment Study Tagging File Specification.

2. Literature references

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

3. Datasets

You should place all datasets and related files (e.g., data definition file, program files) for each study in a single folder incorporating the study's unique identification in the folder name. All study folders should be placed in a single folder named *datasets.* The *datasets* folder should be placed in the *m4* folder.

We plan on issuing separate guidance on organizing and submitting animal line listings. Until that guidance has been finalized, you should refer to the *g*uidance for industry *Providing Regulatory Submissions in Electronic Format – NDA* for details on the submission of animal line listings.

E. Module 5: Clinical Study Reports folder

The organization of the module 5 folder is the same for all applications and related submissions. 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 attachment on Table of Contents Headings and Hierarchy provided with this guidance. 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 *Electronic Common Technical Document Specification* from the ICH M2 expert working group are optional. They 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.[8] 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 documents that should be included in a study report are listed below:

- Legacy Study Report[9]
- Synopsis[10] (E3 2)
- Study report (E3 1, 3 to 15)
- Protocol (E3 16.1.1)
- Protocol amendment [number] (E3 16.1.2)
- 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)
- Randomisations 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 inter laboratory 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)

[8] When providing a study report in more than one document, you should include the Study Tagging File (STF) described in the attachment Study Tagging File Specification.

[9] The legacy study report is included to include study reports that are already prepared as single documents.

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

- Compliance and/or drug concentration data (E3 16.2.5)
- Individual efficacy response data (E3 16.2.6)
- 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
  - — Data listing
    - Data listing datasets
    - -Data definitions
  - — Analysis datasets
    - Analysis datasets
    - Analysis programs
    - Data definitions
  - — Subject profiles
  - — IND safety reports

3. Case report forms

You should provide each 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.

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 § 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

You should place all datasets and related files (e.g., data definition files, program files) for each study in a single folder incorporating the study's unique identification in the folder name. All study folders should be placed in a single folder named *datasets.* Programs included in your submission should be executable using PC SAS.

We plan on issuing separate guidance on organizing and submitting clinical data. Until that guidance has been finalized, you should follow the recommendations in the pre-existing

guidance for industry *Providing Regulatory Submissions in Electronic Format – NDA* regarding the submission of clinical data.

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 to each of the sections and subsections of this report. ICSR and ICSR attachments should be provided as described in the guidance for industry *Providing Regulatory Submissions in Electronic Format – Post-marketing Periodic Adverse Drug Experience Reports.*

6. Literature references

You should provide each literature references 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

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

B. Style and PDF Index 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/.