

eCTD TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

This document is incorporated by reference into the following guidance document:

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

For questions regarding this technical specifications document, contact CDER at esub@fda.hhs.gov or CBER at esubprep@fda.hhs.gov

**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)**

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eCTD

TECHNICAL CONFORMANCE GUIDE

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Contents

1. Introduction.....	1
1.1. Background	1
1.2. Purpose	1
1.3. Document Revision and Control	2
1.4. Relationship to Other Documents	2
2. General Considerations.....	3
2.1. eCTD Publishing.....	3
2.2. eCTD Samples.....	3
2.3. Transitioning to eCTD Format and Resubmission of Documents	3
2.4. eCTD Leaf Titles.....	4
2.5. eCTD Life Cycle	4
2.6. Presubmissions.....	4
2.7. Rolling Submissions.....	4
2.8. Study Tagging Files.....	5
3. Organization of the eCTD.....	6
3.1. Module 1 – Administrative Information and Prescribing Information	6
3.2. Module 2 – Summaries	9
3.3. Module 3 – Quality.....	9
3.4. Module 4 – Nonclinical	11
3.5. Module 5 – Clinical.....	12
4. Issues and Solutions.....	15
4.1. Issue: Combining Multiple 3.2.S or 3.2.P Sections With Similar Metadata	15
4.2. Issue: Clinical Study Report Submitted in Incorrect Section.....	15
4.3. Issue: Not Applicable (N/A) or Unassigned Folders in Module 4 or 5	15
4.4. Issue: Multiple Similar STF Structures Displaying in Module 4 or 5.....	16
References.....	17
Related References.....	19

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This technical specifications document, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for implementing this specifications document by email at esub@fda.hhs.gov or esubprep@fda.hhs.gov.

1. Introduction

1.1. Background

This eCTD Technical Conformance Guide (Guide) provides specifications, recommendations, and general considerations on how to submit electronic Common Technical Document (eCTD)-based electronic submissions to the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). The Guide supplements the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (eCTD Guidance). The eCTD Guidance implements the electronic submission requirements of section 745A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) with respect to electronic submissions for certain investigational new drug applications (INDs); new drug applications (NDAs); abbreviated new drug applications (ANDAs); certain biologics license applications (BLAs); and master files submitted to CDER or CBER. These submissions may apply to combination products with CDER or CBER as the lead center.¹

1.2. Purpose

This Guide provides technical recommendations to sponsors and applicants for the standardized electronic submission format of INDs, NDAs, ANDAs, BLAs, and master files. The Guide is intended to complement and promote interactions between sponsors and applicants and FDA's electronic submission support staff. However, it is not intended to replace the need for sponsors and applicants to communicate directly with support staff regarding implementation approaches or issues relating to electronic submissions.

Because of the inherent variability across studies and applications, it is difficult to identify all issues that may occur related to the preparation and transmission of electronic submissions. Therefore, prior to submission, sponsors and applicants should discuss questions with the appropriate center's electronic submission support staff within the appropriate center — CDER: esub@fda.hhs.gov or CBER: esubprep@fda.hhs.gov.

¹ See 21 CFR Part 3. Combination products are comprised of any combination of a drug and a medical device; a medical device and a biological product; a biological product and a drug; or a drug, a medical device, and a biological product. Combination products are assigned to a lead center for review; see 21 CFR 3.4.

1.3. Document Revision and Control

FDA intends to issue an initial *Federal Register* notice announcing availability of this Guide and seeking public comment on its contents. Future revisions will be posted directly on the eCTD Web page² and the revision history page of this document will contain sufficient information to indicate which sections of the Guide have been revised.

1.4. Relationship to Other Documents

This Guide integrates and updates information discussed previously in the eCTD Guidance and other specifications documents (including Agency presentations). The examples of issues and concerns discussed in the Guide are intended as examples only of common issues, not an inclusive list of all possible issues.

This Guide should be considered a companion document to the following:

- Guidance to Industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*
- FDA eCTD Web page
- FDA Data Standards Catalog

² The eCTD Web page can be accessed at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>

2. General Considerations

2.1. eCTD Publishing

Submissions in the eCTD format should be created following all applicable guidances and specifications available on our eCTD Web page:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>.

2.2. eCTD Samples

Samples of eCTDs can be submitted for feedback on document placement, navigation, and effective use of metadata and Study Tagging Files (STFs). For eCTD samples and instructions, please refer to our eCTD Basics and Getting Started Web site located at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm330116.htm>

2.3. Transitioning to eCTD Format and Resubmission of Documents

When transitioning to eCTD format, do not resubmit documents already submitted in paper or other electronic format. Provide only new or changed information. For example, if your original application was submitted in paper in 2010 and now a supplement will be submitted to the application in eCTD format, you should not resubmit electronic copies of documents and eCTD backbone files for the previously submitted paper files.

2.3.1 Transitioning from Paper to eCTD using us-regional v2.01


Transition sequences from paper can use any eCTD sequence number including the correlating current IND serial number, but there is no requirement for the eCTD sequence number and the IND serial number to match.

When transitioning to eCTD format from paper or a non-eCTD format, the initial eCTD submission should be coded according to the current regulatory activity. To transition an IND or an original ANDA, BLA, NDA, the transition submission should be coded as "original-application" for the submission-type. If the original application has been approved and a supplement or annual report is the current regulatory activity, code the transition sequence as the appropriate supplement type or as annual report. To transition with the submission of a new supplement or annual report, the submission type should be coded with the appropriate supplement type (e.g., labeling supplement) or as annual report.

2.3.2 Transitioning from Paper to eCTD using us-regional v3.3

The initial eCTD submission should be coded according to the current regulatory activity. The submission-id should match the sequence number of the transition sequence.

2.3.3 Transitioning from us-regional v2.01 to us-regional v3.3

The initial eCTD submission should be coded according to the current regulatory activity. The submission-id should match the sequence number of the initial eCTD submission to that regulatory activity. It is important to use a value for the submission-id that exists as a us-regional v2.01 sequence that has already been processed in the application. 


2.4. eCTD Leaf Titles

Leaf titles for eCTDs 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 (because the document file name is not the primary field 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., 2015-12-31). 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.

2.5. eCTD Life Cycle

Refer to published specifications for descriptions and details regarding lifecycle operation attributes.³

Note, the use of "append" is not common yet may be appropriate if you have a large document and need to add a single page of information. You should avoid appending multiple documents to a single leaf and consider consolidating the information and using the "replace" life cycle attribute to update the original file. 

2.6. Presubmissions

Any information submitted in eCTD format before the "original-application" should be coded as "presubmission" and should use sequence 0001.   The original application will use the next available sequence number depending on the number of submitted "presubmissions." Signed FDA forms are not required for presubmissions. If you are going to submit using the Electronic Submission Gateway (ESG),⁴ include a completed fillable form without a signature. Fillable forms aid automated processing. You should use the ESG if the submission is 10  gigabytes or less. For INDs, the serial number field can be left blank for presubmissions and should be used only starting with the original application. There is no requirement for the IND serial number and the eCTD sequence number to match.  

2.7. Rolling Submissions

Rolling submissions are treated the same as presubmissions to the application until the application is complete and ready for review. The cover letter and form should state


³ The ICH Electronic Common Technical Document Specifications v3.2.2 can be accessed at: <http://estri.ich.org/eCTD/index.htm>.

⁴ The ESG Web page can be accessed at: <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/>.

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“presubmission to rolling submission – part 1 of XXX” (depending on how many parts before the final submission). The final submission completing the application should be coded as “original-application” to start the respective review clock. The cover letter and form of the final submission should state "original application – part XXX of XXX of rolling submission."

2.8. Study Tagging Files

Study Tagging Files (STFs) are required for all files in section 4.2.x and 5.3.1.x – 5.3.5.x.⁵ STFs are not required for 5.2 Tabular listings, 5.4 Literature references and 5.3.6 Postmarketing  reports. These documents are submitted as single separate files without an STF.

⁵ This requirement is discussed in the eCTD Guidance available on CDER’s guidance Web page under Electronic Submissions:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064994.htm>

3. Organization of the eCTD

3.1. Module 1 – Administrative Information and Prescribing Information

Module 1 contains administrative and labeling documents. The subject matter for each document should be assigned to the lowest level of the hierarchy outlined in the associated FDA technical specification *Comprehensive Table of Contents Headings and Hierarchy* available on our eCTD Web page. (Note that some headings apply only to specific applications or specific submissions.)

3.1.1. FDA Regional eCTD Backbone Files

Submissions to CDER and CBER can be made using either version 2.01 of the us-regional.xml backbone file or, the newer and preferred version 3.3. Note that once transitioning an application to v. 3.3, you cannot submit a subsequent submission to that application using version 2.01.

3.1.2. Cover Letter

Cover letters contain pertinent information which aid communication within the review process. It is recommended that the cover letter include the following information:

- Regulatory description of the submission, including appropriate regulatory information, and any desired hyperlinks to submitted information
- 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
- Certifying statement that the submission is virus free, with a description of the software (name, version, and company) that was used to check the files for viruses
- A regulatory and technical point of contact for the submission, including email address

3.1.3. Reviewer's Guide

A reviewer's guide is beneficial when accompanying large applications, such as original applications or efficacy supplements. The reviewer's guide should include a high-level overview of the submission with hyperlinks to submitted information. The reviewer's guide should not contain a copy of the eCTD backbone table of contents. Rather, an outline format describing the submission's content is preferred, including tables or lists and avoiding a continuous narrative description of the application's content.

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

3.1.4. Labeling

This section describes how to provide specific labeling documents:

1. Labeling History

A history that summarizes labeling changes should be provided as a single PDF file. The history summary should include the following information:

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- 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

2. 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.

3. Labeling Samples

Each labeling sample (e.g., carton labels, container labels, package inserts) should be provided as an individual PDF file. The samples should:

- Include all panels, if applicable
- Be provided in their actual size, and
- Reflect the actual color proposed for use

3.1.5. Advertisements and Promotional Labeling Material

3.1.5.1. Advertisements and Promotional Labeling to CDER

3.1.5.1.1 Using version 2.01 of the us-regional.xml file

CDER does not accept advertisements and promotional labeling materials in eCTD format using version 2.01 of the us-regional.xml backbone file.

3.1.5.1.2 Using version 3.3 of the us-regional.xml file

Advertisements and promotional labeling materials submitted using version 3.3 of the us-regional.xml backbone file should be submitted according to the guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.

3.1.5.2. Advertisements and Promotional Labeling to CBER

3.1.5.2.1 Using version 2.01 of the us-regional.xml file

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

Applicants should submit promotional material to the appropriate application and 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. Promotional writing or images that cover more than one page (e.g., a brochure layout) should allow the entire layout

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to be viewed together. For three-dimensional objects, a digital image of the object should be provided in sufficient detail to allow review of the promotional material. In addition, information should be provided 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.

Promotional materials submitted as part of the postmarketing reporting requirements should be provided as hypertext links to references or labeling. 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.

3.1.5.2.2 Using version 3.3 of the us-regional.xml file

Advertisements and promotional labeling materials submitted using version 3.3 of the us-regional.xml backbone file should be submitted according to the guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.

3.1.6. Marketing Annual Reports



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

3.1.7. Information Amendments

Documents for information amendments should be included in the applicable eCTD module using the appropriate eCTD heading to describe 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 section 1.11, "Information amendment: Information not covered under Modules 2 to 5." A separate PDF file should be provided for each subject area covered.

If you are providing a combined response to an IR letter in section 1.11 you should also provide revised documents in the applicable eCTD module using the appropriate eCTD heading to describe the document's subject matter.

3.1.8. Letters of Authorization (LOAs)




For information on LOAs and other references submitted to the eCTD (generally for master files), refer to the Drug Master File Web page:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/UCM2007046>

3.1.9. Field Copy Certification

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

Sponsors and applicants should notify the District office by letter that their eCTD submission will be submitted to FDA, and because the field offices have access to the complete submission on the FDA network, an individual field copy is no longer required. The letter should include:

- Drug and application number, and
- FDA center and division

A copy of the letter should be placed in eCTD section 1.3.2.

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

3.2. Module 2 – Summaries

3.2.1. 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 available on the ANDA Forms and Submission Requirements Web page located at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120955.htm>.

3.3. Module 3 – Quality

3.3.1. Lot Distribution Data

Lot distribution data should be submitted according to the guidance for industry *Electronic Submission of Lot Distribution Reports* available at:

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM412006.pdf>

3.3.2. Combination Products⁷

Generally, the combination drug and device product information (including an autoinjector or similar delivery) and related engineering and manufacturing information should be located in the same eCTD module that would provide similar information for the drug or biological product. The following recommendations should be followed by sponsors and applicants for combination products:

1. Adhere to eCTD headings as defined in the FDA technical specification

⁶ 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”).

⁷ As set forth in 21 CFR part 3, a combination product is a product composed of any combination of a drug, device, or biological product.

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Comprehensive Table of Contents Headings and Hierarchy. Specifically, any title that is associated with a numerical item should not change (i.e., Section 3.2.P.7 should say “Container Closure System”).

2. Do not use "node extensions" to create new elements. Although this is described in the ICH eCTD specification, and may be acceptable in some regions, it is not acceptable in submissions to FDA.
3. Including and referencing device information
 - Reference under section 3.2.P.7 files that are not currently listed as numerical items in ICH and FDA specifications and guidance
 - Include, in section 3.2.P.7, a leaf title, for example “Table of Contents for Drug-Device Descriptor/Name. This leaf/document should provide reference links to the other files in section 3.2.P.7. Obtaining concurrence from the review division on the proposed outline is recommended.
 - Leaf titles should be clear, concise and indicative of the document's content
4. Provide references including copies of an application’s table of contents, reference tables, or other similar documents in Module 1.4.4 when cross referencing to other applications. If cross referencing another company's application or master file, you should include the appropriate letters of authorization from the other companies in sections 1.4.1 – 1.4.3 (1.4.1 contains the letter of authorization, 1.4.2 contains the statement of right of reference, and 1.4.3 contains the list of authorized persons to incorporate by reference). If there are standards you will reference in the Performance Specifications that also meet these criteria, put them in section 1.4.4. The Performance Specifications section should link to this information.
5. Include all device information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with 21 CFR part 4 and the applicable 21 CFR part 820 regulations should be located in section 3.2.P.3. This includes the list of manufacturing facilities provided on the Form FDA 356h, or as an attachment to the form, should explicitly describe the manufacturing, assembly, or testing processes taking place at each site with regards to the device constituent part
 - In this section, as applicable, identify whether facilities subject to 21 CFR part 4⁸ follow the combination product streamlined manufacturing approach and identify the base set of regulations (i.e., 21 CFR 211 or 820).
 - Suggestions on the types of documents that you submit for review of required sections of 21 CFR part 820 should be placed in this section.

⁸ 21 CFR Part 4 “Current Good Manufacturing Practice Requirements for Combination Products” is accessible at <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>


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6. A reviewer's guide should be provided in section 1.2 Cover letters (as described in section 3.1.3). The reviewer's guide is separate from the cover letter and referenced after the cover letter. It should provide a high-level overview (with reference links) of the submission's content and should list the location of information in the eCTD. For example, it should identify where drug, device, and combination product information is located.
7. Human Factors Validation Study results should be located in eCTD section 5.3.5.4 Other Study reports and related information. Do not place these data in Module 3. However, you may cross reference from Module 5 to Module 3.

3.3.3. Literature References

The files pertaining to key literature references should be provided as individual PDF files 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).

3.3.4. Datasets

When providing standardized stability data or other quality related data, 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). 

3.4. Module 4 – Nonclinical


The organization of Module 4 is the same for all applications and related submissions. The documents for Module 4 should be placed in the m4 folder. The subject matter for each document should be specific for the lowest level of the hierarchy outlined in the 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.

3.4.1. Study Reports

When providing a study report, you should include the Study Tagging File (STF) described in the associated ICH M2 technical specification *The eCTD Backbone File Specification for Study Tagging Files* and required by the eCTD Guidance. Individual study documents should be referenced in an STF using the appropriate STF 'file-tag' describing the document's contents.

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:



1. **Documents previously submitted within an application:** If a document has been provided in a previous submission (e.g., referencing a previously provided protocol), 

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the applicant should provide only an eCTD leaf reference to the protocol and not resubmit the protocol file.

2. **Inclusion of additional information:** Study reports should be provided as separate documents. Additional information (e.g., audit information or a publication based on the study) should be provided as a separate file, rather than replacing the entire study report.

3.4.2. 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).  

3.4.3. Datasets

The FDA technical specification *Study Data Technical Conformance Guide* provides details on the submission of datasets and related files (e.g., data definition file, program files).⁹

3.5. Module 5 – Clinical

The organization of Module 5 is the same for all applications and related submissions. The documents for Module 5 should be placed in the m5 folder, and the subject matter for each document should be specific for the lowest level of the hierarchy outlined in the 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.

3.5.1. 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. For ease of review, hyperlinks to the referenced studies in m5 should be provided. A study tagging file (STF) is not necessary for the tabular listing of clinical studies.

3.5.2. Study Reports

When providing a study report, you should include the STF described in the associated ICH M2 technical specification *The eCTD Backbone File Specification for Study Tagging Files* and required by the eCTD Guidance.¹⁰ Individual study documents should be referenced in an STF using the appropriate STF ‘file-tag’ describing the document’s contents. For reports without a file tag, “study-report-body” can be applied as the file tag, with clear leaf title

⁹ This requirement is discussed in the eCTD Guidance. Guidances are periodically updated. To make sure you have the most recent version of a guidance, see the FDA webpage: <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>. CDER’s electronic submissions guidances are located at: <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>.

¹⁰ Available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>.

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indicating content of the document.

Typically, study reports should be provided according to the FDA guidance for industry *ICH E3 Structure and Content of Clinical Study Reports*. 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.

Study reports should be provided as separate documents. Additional information (e.g., audit information or a publication based on the study) should be provided as a separate file, rather than replacing the entire study report.

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.

Combination Product Human Factors Study reports should be in Module 5.3.5.4 Other Study Reports and Related Information.

3.5.3. Case Report Forms (CRFs)

An individual subject's complete CRF should be provided 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, therefore do not place files under this heading.

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 must have bookmarks as part of the comprehensive table of contents required under 21 CFR 314.50(b). Each CRF domain and study visit should be bookmarked to assist reviewers in their review of CRFs. For addenda and corrections, avoid confusion by making a hypertext link from the amended item to the corrected page or addendum. Bookmarks for these items should be displayed at the bottom of the hierarchy.

3.5.4. Periodic Safety Reports¹¹


Periodic safety reports consist of two parts: a descriptive portion and the individual case safety reports (ICSRs). Only the descriptive portion of the periodic report may be submitted to the eCTD.

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


The descriptive portion of the report may be sent as either the periodic adverse (drug) experience report (PADER) or the ICH-E2C periodic safety update report (PSUR) (allowed with approved waiver). Either format may be submitted to the eCTD in section 5.3.6 as an individual PDF file without an STF. Include the reporting period in the document's leaf title.

Non-expedited ICSRs reports must be submitted in electronic E2B (R2) formatted XML files through ESG. They are not submitted in eCTD format. The format of non-expedited reports are the same as expedited ICSR submissions, except the <fulfillexpeditecriteria> tag code value must be set to "2" for non-expedited reporting. Do not submit the expedited ICSRs that have been previously submitted.

3.5.5. IND Safety Reports

Each individual IND safety report with its associated study should be provided 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. Each IND safety report should be submitted as "new" without replacing any previously submitted information. Leaf titles that clearly relate to the individual cases should be used. For additional details on providing IND safety reports, refer to the FDA guidance for industry *Safety Reporting Requirements for INDs and BA/BE Studies*. 

3.5.6. Literature References

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 2002 Impurities) 

3.5.7 Datasets

The FDA technical specification *Study Data Technical Conformance Guide* provides details on the submission of datasets and related files (e.g., data definition file, program files).¹² Datasets should be provided only in modules 3 – 5 of the eCTD.

¹² Available at <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>.

4. Issues and Solutions

4.1. Issue: Combining Multiple 3.2.S or 3.2.P Sections With Similar Metadata

This issue is caused by leafs being submitted with incorrect metadata ('name', 'manufacturer', and/or 'dosage form' which are not an exact match to what was submitted previously).

To resolve:

- Use the eCTD "delete" operator to delete all the leaf IDs that were referenced in the section to be deleted. Deleting all leafs will remove the entire section from our review tool.
- Re-reference the existing files using new leaf IDs, ensuring that the 'name', 'manufacturer', and/or 'dosage form' metadata is an exact match to the section where you want to re-add the leafs.

This issue is also caused when multiple 3.2.P sections were submitted for multiple strengths of the same drug product.

In general, when a single application for multiple strengths can be submitted, information for each of the product presentations and manufacturing schemes should be combined and presented together in one Drug Product section, with information for each of the product presentations and manufacturing schemes provided in the Appendices and Regional Information sections, as warranted. See FDA guidance for industry, *M4: The CTD – Quality, Questions and Answers/Location Issues* for more information.

4.2. Issue: Clinical Study Report Submitted in Incorrect Section

To resolve:

Use the eCTD "delete" operator to delete all the leaf IDs that were referenced in the STF under the wrong heading element. This action deletes the STF itself from our review tool.

- Create a new STF referencing all the same files, but use new leaf IDs.
- Submit the updated STF in a new submission sequence.
- Resubmission of files should not be necessary. Create the new leafs with file references to the documents submitted in the original sequence.

4.3. Issue: Not Applicable (N/A) or Unassigned Folders in Module 4 or 5

This issue is caused by leafs submitted without an STF in a section that requires STFs.

To resolve:

- Use the eCTD "delete" operator to delete all the leaf IDs that were not referenced by an STF.
- Create a new STF referencing all the same files, but use new leaf IDs.
- Submit the STF in a new submission sequence.
- Resubmission of files should not be necessary. Create the new leafs with file references to the documents submitted in the original sequence.

4.4. Issue: Multiple Similar STF Structures Displaying in Module 4 or 5

This issue is caused by an updated STF being submitted with incorrect metadata (study-id and study title not an exact match).

To resolve:

- Use the eCTD “delete” operator to delete all the leaf IDs that were referenced in the STF with incorrect study-id or study title metadata. This action deletes the STF itself from our review tool.
- Create a new STF referencing all the same files, but use new leaf IDs. Ensure that the study-id and study title are an exact match to the original STF.
- Submit the updated STF in a new submission sequence.
- Resubmission of files should not be necessary. Create the new leafs with file references to the documents submitted in the original sequence.

References

The following are technical specifications documents incorporated by reference into the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

For a complete listing of technical supportive files that you will need in order to submit in eCTD format, refer to the eCTD Web page at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>.

1. ICH technical specification, *Electronic Common Technical Document Specification* v3.2.2 (accessible at <http://estri.ich.org/eCTD/index.htm>)
2. ICH M2 technical specification, *The eCTD Backbone File Specification for Study Tagging Files* (accessible at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)
3. FDA technical specification, *eCTD Backbone Files Specification for Module 1* (accessible at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)
4. FDA guidance for industry, ICH M4 Granularity Annex, *Granularity Document — Annex to M4: Organization of the CTD* (accessible at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)
5. ICH M2 technical specification, *eCTD IWG Question and Answer and Specification Change Request Document* (accessible at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)
6. FDA technical specification, *FDA eCTD Table of Contents Headings and Hierarchy* (accessible at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)
7. FDA technical specification, *Specifications for File Format Types Using eCTD Specifications* (accessible at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

Contains Nonbinding Recommendations

8. FDA technical specification, *FDA Portable Document Format (PDF) Specifications* (accessible at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)
9. FDA guidance for industry, *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document* (accessible at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)
10. FDA technical specification, *Transmission Specifications, Specification for Transmitting Electronic Submissions Using eCTD Specifications* (accessible at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)
11. FDA technical specification, *eCTD Validation Specifications Web page, Specifications for eCTD Validation Criteria* (accessible at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

Related References

1. FDA guidance for industry, *Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act* (accessible at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> under Electronic Submissions)
2. FDA guidance for industry, *Providing Regulatory Submissions in Electronic Format — Standardized Study Data* (accessible at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> under Electronic Submissions)
3. FDA guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants* (accessible at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> under Procedural)
4. FDA guidance for industry, *Providing Regulatory Submissions in Electronic Format — Receipt Dates* (accessible at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> under Electronic Submissions)
5. FDA guidance for industry, M4: The CTD – Quality, Questions and Answers/Location Issues (accessible at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> under International Conference on Harmonisation - Joint Safety/Efficacy (Multidisciplinary))