eCTD
TECHNICAL CONFORMANCE GUIDE

Technical Specifications Document

This Document is incorporated by reference into the following Guidance Document(s):

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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U.S. FOOD & DRUG
ADMINISTRATION

eCTD
TECHNICAL CONFORMANCE GUIDE

December 2019

REVISION HISTORY

DATE	VERSION	SUMMARY OF REVISIONS
October 2015	1.0	Initial Version
September 2016	1.1	***Updated/Clarified following sections:*** Section 2.3 (Transitioning to eCTD Format and Resubmission of Non- eCTD Documents), and subsections 2.3.1, 2.3.2, 2.3.3, 2.3.4 Section 2.4 (eCTD Leaf Titles) Section 2.6 (Presubmissions) Section 2.7 (Rolling Submission) Section 3.1.2 (Cover Letter and Reviewer's Guide) Section 3.1.7 (Information Amendments) Section 3.1.8 (Letters of Authorization) Section 3.1.9 (Field Copy Certification) Section 3.5.2 (Study Reports) Section 4.1 (Combining Multiple 3.2.S or 3.2.P Sections with Similar Metadata) Section 5.0 (Combination Products) References ***Removed section:*** Section 3.3.4 (Datasets) ***Added sections:*** Section 2.3.4 (Resubmission of non-eCTD documents) Section 3.1.5.3 (Websites, Electronic Interactive Programs, and Electronic Detail Aids)
November 2017	1.2	***Updated/Clarified following sections:*** Section 2.3.3 (Transitioning from us-regional v2.01 to us-regional v3.3) Section 2.3.4 (Resubmission of non-eCTD documents) Section 2.5 (eCTD Life Cycle) Section 3.1.2 (Cover Letter and Reviewer's Guide) Section 3.4.3 (Datasets) Section 3.5.2 (M5 Study Reports) Section 3.5.4 (Periodic Safety Reports) Section 3.5.7 (Datasets) ***Added sections:*** Section 3.1.10 (REMS)
November 2018	1.3	***Updated/Clarified following sections:*** Section 2.5 (eCTD Submission Tracking and Lifecycle) Section 2.8 (Study Tagging Files) Section 3.1.10 (REMS) ***Added sections:*** 3.1.11 (Regenerative Medicine Advanced Therapy Designation)
December 2019	1.4	***Updated/Clarified following sections:*** Section 3.4 (Module 4 - Nonclinical) Section 3.5 (Module 5 - Clinical) ***Removed section:*** Section 3.1.8 (Letters of Authorization) ***Added sections:*** 2.9 (Master Files) 3.1.3 (Patient Experience Data)

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eCTD TECHNICAL CONFORMANCE GUIDE

This technical specifications document represents 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).[1] 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.[2]

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.

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[1] A link to this document can be found on the FDA eCTD website (https://www.fda.gov/ectd)

[2] 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 issued an initial *Federal Register* notice announcing availability of this Guide for public comment on its contents. Future revisions will be posted directly on the eCTD website[3] 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 Website
- FDA Data Standards Catalog
- eCTD Submission Standards

[3] FDA eCTD website (https://www.fda.gov/ectd)

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 website: https://www.fda.gov/ectd.

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 website located at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm330116.htm

2.3 Transitioning to eCTD Format and Resubmission of non-eCTD Documents

When transitioning to eCTD format, you are not required to resubmit documents already submitted in paper or other electronic format. Provide only new or changed information and begin with sequence number 0001. For example, if your original application was submitted in paper 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. For INDs, there is no requirement to match up the sequence number with the serial number.

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

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, master file, 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 utilizing us-regional v3.3 should be coded according to the current regulatory activity. The submission-id should match the sequence number of the transition sequence. To transition an IND, master file, or an original ANDA, BLA, NDA, the transition submission should be coded as “original application” for the submission-type and “application” for submission-subtype. 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., submission-type =

labeling supplement/ submission-subtype = application) or as a new annual report (e.g., submission-type = annual report / submission-subtype = report).

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. If the submission is updating a regulatory activity started in us-regional v2.01, the submission-id in us-regional v3.3 should match the sequence number of the initial eCTD submission to that regulatory activity. If the submission using us-regional v3.3 is creating a new regulatory activity, the submission-id should match the sequence number. If the v3.3 submission is amending a regulatory activity where that submission type does not exist in v2.01 but does exist in v3.3, set the submission id equal to the sequence number and use a submission subtype which starts the regulatory activity (e.g., submission-type = IND safety report / submission–subtype = report).

2.3.4 Resubmission of non-eCTD documents

In general, resubmission of previously submitted content is neither necessary nor encouraged. However, there are occasional circumstances in which a "baseline" submission is helpful to the reviewer. One example is CMC information contained in module 3. In a circumstance such as this, the FDA will accept the resubmission of non-eCTD content (e.g., paper, eNDA) but the previously submitted content should be submitted as a separate submission, as opposed to being included in a supplement or an amendment to a regulatory activity. The cover letter should state that the submission contains only previously submitted content and certify that the sequence does not include any changes or updates to the application. For marketing applications, the certification should include a table with a listing of approvals that relate to the content being resubmitted. For INDs and master files, the list should include amendments that relate to the content being resubmitted.

In most cases, the submission of a "baseline" or other previously submitted content will require that the previous content be reorganized to meet the eCTD format requirements. You should not resubmit the previous content "as-is", unless the content was in the CTD format but you did not use the eCTD backbone when content was originally submitted.

If the previous content will be submitted using us-regional v2.01, the submission-type should be coded as "other". If the submission will be submitted using us-regional v3.3, the submission-type should be coded as "product correspondence". On the 356h form, you should select "Product Correspondence" for the Submission type and enter "Submission of previous non-eCTD content in the eCTD format".

Prior to resubmitting content, you should contact the responsible review division to determine if resubmission is acceptable.

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. 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 or sequence number (e.g., cover-letter-2015-12-31 or cover-letter-0001). 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 to quickly identify which software applications are necessary to open the files.

Per eCTD Guidance (*Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications)*, when naming folders and files, the length of the entire path must not exceed 150 characters. The character limit on the leaf title field is 512 characters.

2.5 eCTD Submission Tracking and Life Cycle

The rules for submission tracking information (i.e., the allowable submission types for the application) can be found in the Module 1 specification.[4]

Refer to published specifications for descriptions and details regarding life cycle operation attributes.[5] For life cycle of STF (Study Tagging File), please reference the STF specification.[6]

Please note: The use of "append" is not common. 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. However, it may be appropriate if, for example, you are adding a single page of information to a lengthy document. Updated datasets should "replace" the old dataset. Do not use "append" when updating datasets.

2.6 Presubmissions

Any information submitted in eCTD format utilizing us-regional DTD v2.01 or v3.3 before the "original-application" should be coded as "presubmission" and should start with sequence 0001. A high submission sequence series (e.g., 9000) should not be used. If utilizing DTD v3.3, code as submission-type "original application" and submission-

[4] The eCTD Backbone Files Specification for Module 1 can be accessed through the eCTD Submission Standards catalog. The catalog is located on the FDA eCTD website (https://www.fda.gov/ectd)
[5] The ICH Electronic Common Technical Document Specifications v3.2.2 can be accessed at:https://www.ich.org/page/ich-electronic-common-technical-document-ectd-v322-specification-and-related-files

[6] The ICH Electronic Common Technical Document Study Tagging File Specification v2.6.1 can be accessed through the eCTD Submission Standards catalog. The catalog is located on the FDA eCTD website (https://www.fda.gov/ectd)

subtype "presubmission". The original application will use the next available sequence number depending on the number of submitted "presubmissions".

2.7 Rolling Submissions

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

If utilizing us-regional DTD v3.3, the rolling submission should be coded as submission-type "original application" with submission-subtype "presubmission". The final submission completing the application should be coded as submission-type "original-application" with submission-subtype "application".

If utilizing us-regional DTD v2.01, the rolling submission should be coded as submission-type "presubmission". The final submission completing the application should be coded as submission-type "original-application".

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.[7] STFs are not required for 4.3 Literature references, 5.2 Tabular listings, 5.3.6 Postmarketing reports and, 5.4 Literature references. These documents may be submitted as single separate files without an STF.

2.9 Master Files

For information on Drug Master File submissions, including Letters of Authorization, please refer to the Drug Master File website (https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs).

[7] This requirement is discussed in the eCTD Guidance available on FDA eCTD website. (https://www.fda.gov/ectd)

3. Organization of the eCTD

3.1 Module 1 – Administrative Information and Prescribing Information

Module 1 contains administrative, labeling, and promotional material 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 website.[8] (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 version 3.3. *Please note*: Once transitioning an application to version 3.3, you cannot submit a subsequent submission to that application using version 2.01.

3.1.2 Cover Letter and Reviewers Guide

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)
- 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

Reviewers Guide

A reviewers guide[9] is beneficial when accompanying an original NDA, BLA, or combination product[10] application. The reviewers guide should include a high-level overview of the submission with hyperlinks to submitted information. The reviewers 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 reviewers 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.

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[8] Comprehensive Table of Contents Headings and Hierarchy may be found in the eCTD Submissions Standards catalog. The catalog is located on the FDA eCTD website (https://www.fda.gov/ectd)

[9] This is different than a Study Data Reviewers Guide (SDRG). Additional information on the SDRG can be found in the Study Data Technical Conformance Guide located at: https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

[10] See additional recommendation for combination products in section 5 of this document

3.1.3 Patient Experience Data

If submitting patient experience data as part of an application for marketing approval, the following table should be populated and included in the Reviewer's Guide (section 1.2). Patient experience data (e.g., clinical outcome assessments) collected as part of a clinical trial should be submitted as part of the relevant clinical trial data. Other patient experience data that is separate from clinical trials should be submitted to section 5.3.5.4.

								Section(s) and if applicable, file names where data are located and discussed in the application
□	The patient experience data that was submitted as part of the application, include:							
	□	Clinical outcome assessment (COA) data, such as						
			□	Patient reported outcome (PRO)				
			□	Observer reported outcome (ObsRO)				
			□	Clinician reported outcome (ClinRO)				
			□	Performance outcome (PerfO)				
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)						
	□	Patient-focused drug development or other stakeholder meeting summary reports						
	□	Observational surveys studies designed to capture patient experience data						
	□	Natural history studies						
	□	Patient preference studies (e.g., submitted studies or scientific publications)						
	□	Other: (Please specify)						

3.1.4 Cross Referencing Previously Submitted Information that is not in eCTD Format

If reference to a non-eCTD submission is needed, place a cross reference document (e.g., table showing where to find non-eCTD documents) in section 1.4.4. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name (if applicable), (4) the page number (if necessary), and (5) the submission identification (e.g., submission number, volume number if paper, electronic folder if applicable) of the referenced document.

3.1.5 Labeling

This section describes how to provide specific labeling documents:

Labeling History

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

- 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

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.

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

3.1.6 Advertisements and Promotional Labeling Material

3.1.6.1 Advertisements and Promotional Labeling to CDER

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

Advertisements and promotional labeling materials must be submitted using version 3.3 of the us-regional.xml backbone file and 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.*

3.1.6.2 Advertisements and Promotional Labeling to CBER

3.1.6.2.1 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 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.

3.1.6.2.2 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.*

3.1.6.3 Websites, Electronic Interactive Programs, and Electronic Detail Aids

Refer to the guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*, for CDER and CBER preference and requirements with submission of electronic promotional materials.

While HTML (a commonly used file type for websites) is an acceptable file format type to use for eCTD Module 1 submissions, submission of HTML files that depend on JavaScript, PHP or server-side scripts that generate dynamic content should not be submitted in eCTD Module 1 because these dependent files are not on the list of acceptable file format types. An acceptable alternative for these types of HTML files is to utilize PDF. Please refer to the *PDF Specifications* for details.[11]

3.1.7 Marketing Annual Reports

You 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 (e.g. Status of Postmarketing Study Commitments - MMDDYY-MMDDYY).

3.1.8 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.

Section 1.11 may be used for submission of responses to Information Requests (IR), where the information being submitted does not fit under any heading in Module 2, 3, 4 or 5. The IR response should be submitted under the appropriate subheading 1.11.1 – 1.11.3 within section 1.11, for quality, nonclinical, or clinical information, respectively. The subheading 1.11.4 for multiple module information should be used if the IR response covers multiple subject areas.

If the IR response impacts documents submitted in Modules 2 – 5, the new or replacement documents should be submitted to the appropriate location in Module 2 – 5 and referenced from Section 1.11.

[11] See "Special Considerations for Promotional, Labeling, and Advertising Material" in the Portable Document Format (PDF) Specifications located in the eCTD Submission Standards catalog. The catalog is located on the FDA eCTD website (https://www.fda.gov/ectd)

3.1.9 Field Copy Certification

For marketing applications, the Field Copy Certification (copy of communication described below) should be included with the electronic application in section 1.3.2 of the eCTD. You should notify the District office by letter that your 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
- FDA center and division
- Application is in eCTD format

3.1.10 Risk Evaluation and Mitigation Strategy (REMS)

A REMS supplement is a supplemental application proposing a new REMS or modifications (major and/or minor) to an approved REMS.

Currently there is no eCTD submission type of REMS supplement. Therefore, generally we recommend coding the submission as a labeling supplement in the us-regional.xml and selecting REMS supplement on the 356h form.

If new proposed REMS or modifications to an approved REMS is submitted as part of an efficacy, CMC, or labeling supplement, the submission type should be coded with the appropriate supplement type (e.g., either efficacy, CMC, or labeling). On the 356h form, you should select both supplements for the submission type.

REMS assessments, REMS revisions, and REMS correspondences are not supplements. If the submission will be submitted using us-regional v3.3, the submission type should be coded as "product correspondence". On the 356h form, you should select "other" for the submission type.

The following table is provided to assist applicants on placing documents under the eCTD Module 1 REMS 1.16 sub-headings using DTD v3.3 of the us-regional.xml file.

eCTD Section: 1.16 Risk Management	
eCTD Section Heading	**Description**
1.16.1 Risk Management (Non-REMS)	Applicants should place risk management plans (RMP), risk minimization action plans (RiskMAPs), and RiskMAP reports under this heading. Submission of a Risk Evaluation and Mitigation Strategy (REMS) should ***not*** be placed under this heading as REMS are to be included under heading 1.16.2. However, if the applicant is submitting a rationale for not submitting a proposed REMS, it should be placed here.
1.16.2 Risk Evaluation and Mitigation Strategy (REMS)	Do not include any files under this heading. The files should be specific for the lowest level of the hierarchy outlined in the FDA technical specification *Comprehensive Table of Contents Headings and Hierarchy* available on our eCTD website [12]and provided below for sub-heading 1.16.2.

[12] Comprehensive Table of Contents Headings and Hierarchy may be found in the eCTD Submissions Standards catalog. The catalog is located on the FDA eCTD website (https://www.fda.gov/ectd)

1.16.2.1 Final REMS	The final REMS document, all REMS materials in their final format, and the REMS supporting document (for original REMS, REMS modifications, and REMS revisions)[13] should be submitted in Microsoft Word and PDF format. FDA can also accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the approval, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST). For more information on submitting REMS in SPL format, please email REMS_Website@fda.hhs.gov.
1.16.2.2 Draft REMS	The proposed REMS document, all REMS materials, and the REMS supporting document in clean and track changes (for original REMS, REMS modifications, and REMS revisions) should be submitted in Microsoft Word format as individual files. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format. Applicants can also submit the proposed REMS document in SPL format. If you intend to submit the proposed REMS document in SPL format, include the SPL file with your proposed REMS submission. The REMS SPL file should be referenced in the eCTD xml backbone under section 1.16.2.2. The REMS SPL file should be placed in a folder named "spl", along with copies of any REMS materials referenced in the REMS SPL file.
1.16.2.3 REMS Assessment	Applicants REMS assessment report, abbreviated REMS assessment for an efficacy supplement, and responses to FDA "Requests for Information or Comments" that are associated with an assessment should be placed here.
1.16.2.4 REMS Assessment Methodology	Any survey or other methodology used to assess the REMS should be placed here.
1.16.2.5 REMS Correspondence	Official REMS related correspondence to the FDA that is not associated with a submission under review should be placed here. Applicants responses to FDA "Requests for Information or Comments" that are associated with a REMS supplement or an assessment that is under review should be included under applicable sub-headings.
1.16.2.6 REMS Modification History	It is recommended that applicants submit a REMS history that summarizes all type of changes (revisions, minor modifications, and major modifications) made to the REMS since its approval.[14] The REMS history should be in tabular format similar to the history of labeling changes and submitted as a single PDF file.

[13] See Guidance for Industry *Risk Evaluation and Mitigation Strategies: Modifications and Revisions*, available at*:* https://www.fda.gov/Drugs/GuidancecomplianceRegulatoryInformation/Guidances/default.htm

[14] See Guidance for Industry *Risk Evaluation and Mitigation Strategies: Modifications and Revisions*, available at*:* https://www.fda.gov/Drugs/GuidancecomplianceRegulatoryInformation/Guidances/default.htm for a more detailed description of the REMS history

3.1.11 Regenerative Medicine Advanced Therapy (RMAT) Designation

Currently there is no Module 1 section for RMAT designation requests. Therefore, please place the RMAT designation request in section 1.12.4 and provide a hyperlink in the cover letter to the request. For additional information on the RMAT designation requirements please refer to https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm.

3.2 Module 2 – Summaries

3.2.1 Bioequivalence Summary Tables

For ANDAs, 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 Website located at: https://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 for BLAs according to the guidance for industry *Electronic Submission of Lot Distribution Reports* available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM412006.pdf

3.3.2 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).

3.4 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. Please refer to the *Study Data Technical Conformance Guide* for additional requirements.

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 you are 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), 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 specifications document *Study Data Technical Conformance Guide* provides details on the submission of datasets and related files (e.g., data definition file, program files).[15] Datasets should be provided only in modules 3 – 5 of the eCTD. Updated datasets should "replace" the old dataset. Do not use "append" when updating datasets.

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. Please refer to the *Study Data Technical Conformance Guide* for additional requirements.

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.

[15] Study Data Resources page is located at: https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm.

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.[16] Individual study documents should be referenced in an STF using the appropriate STF 'file-tag' describing the document's contents. In the case where no other file tag is appropriate, you may use "study report body".

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*.

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. The file tag "legacy-clinical-study-report" should be used for the study report.

Human Factors submissions should be in Module 5.3.5.4 Other Study Reports and Related Information and should include the appropriate human factors file tag (e.g., HF-validation protocol, HF-validation report, HF-validation other) to describe the document's contents.

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

[16] Available via eCTD Submissions Standards catalog. The catalog is located on the FDA eCTD website (https://www.fda.gov/ectd)

corrected page or addendum. Bookmarks for these items should be displayed at the bottom of the hierarchy.

3.5.4 Periodic Safety Reports

Periodic safety reports[17] consist of two parts: a descriptive portion and the individual case safety reports (ICSR). Only the descriptive portion of the periodic report may be submitted to the eCTD.

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.

Do not submit ICSR E2B formatted XML files in eCTD.

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, as per eCTD Specifications 3.2.2. 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 specifications document *Study Data Technical Conformance Guide* provides details on the submission of datasets and related files (e.g., data definition file, program files).[18] Datasets should be provided only in modules 3 – 5 of the eCTD. Updated datasets should "replace" the old dataset. Do not use "append" when updating datasets.

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

[18] Available at https://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.
- Reference the 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 place 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.

5. Combination Products

Combination Products[19]

Generally, drug or biological product information for combination drug and device product information and related engineering and manufacturing information should be located in the same eCTD sections that would provide similar information for the drug or biological product alone. This particularly applies to device constituent parts that also serve as the drug container closure system. For example, the M3 quality module should contain information on such devices constituents in section 3.2.P.7. Supportive files for container closure device constituents should be located in section 3.2.R. For other types of device constituent parts that do not have a logical location within 3.2.P, the information should be placed in 3.2.R. For example, quality data for a free standing laser would be in 3.2.R. Quality information on the combination product as a whole (not the separate constituent parts) should be located in 3.2.P with appropriate hyperlinks to 3.2.R. The following recommendations should be followed by sponsors and applicants for combination products:[20]

1. General format comments
    a. Use of eCTD headings: Adhere to eCTD headings as defined in the FDA technical specification *Comprehensive Table of Contents Headings and Hierarchy*.
    b. Node extensions: 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 any submissions to FDA.
    c. Leaf titles: As there are no-sub elements permitted under 3.2.R, when placing combination product files in this section, prefix the leaf title with "DEVICE" as this will help the reviewer differentiate between combination and other categories of files.

2. Module 1, Section 1.2
    To facilitate the review, a reviewer's guide should be provided in section 1.2 cover letters. 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. [21] For example, it should identify where drug, device,

[19] 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.

[20] FDA recognizes the breadth of combination product designs. The information in this guide is to promote consistency and facilitate timely review. The agency recommends that applicants, who wish to provide data in a different location, should contact the review division for discussion. Applicants that wish to continue to use a location based on legacy submissions for the same application may continue to use that location.

[21] If referencing previously submitted information not in the eCTD format, see section 3.1.3 of this guide- "Cross Referencing Previously Submitted Information that is not in eCTD Format"

and combination product information is located. Additionally, the reviewers guide should identify the location of information that cannot be further identified within the electronic format. This particularly applies to the following:

- Files that are not currently listed as numerical items in ICH and FDA specifications and guidance documents (e.g., *Comprehensive Table of Contents Headings and Hierarchy*[22]). For example, the reviewer's guide should provide reference links to each file in section 3.2.R.
- Sections which are repeated through the use of different XML attributes (e.g. <m3-2-p-drug-product product-name = "Albuterol">; <m3-2-p-drug-product product-name = "Dry Powder Inhaler">)

3. Module 1.1. Forms
   Form 356h should identify all facilities involved in the manufacture and testing of the combination product (drug, device, drug-device combination). Also see item 4.a below for additional information in Section 3.2.P.3 Manufacture

4. Module 3
   a. Section 3.2.P.3 Manufacture
   Combination product manufacturing applies to the entire combination product (e.g., drug –device combination) in accordance with 21 CFR Part 4. [23] In Section 3.2.P.3 include applicable device information pertaining to manufacturing or assembly of the finished combination product as a whole. As applicable, this section may hyperlink to unique device constituent manufacturing information in 3.2.R.
      i. Section 3.2.P.3.1 Manufacturer(s)

      - For each facility identify the type of manufacturing and testing activities that occur
      - For each facility that is subject to 21 CFR part 4, identity whether it follows the combination product streamlined manufacturing approach and identify the base set of regulations (i.e., 21 CFR 211 or 820).
      - Provide a detailed list of all manufacturing facilities; what activities occur at the site (e.g., assembly, filling, sterilization, testing, other); what constituents are at the site (e.g., drug only, device only, both drug and device). For the facilities that have both the drug and device, identify which combination product operating system is used at the site.

      ii. Section 3.2.P.3.2 Batch Formula (nm, df)

[22] Available via eCTD Submissions Standards catalog. The catalog is located on the FDA eCTD website (https://www.fda.gov/ectd)
[23] 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

Use this section to describe only the drug components and composition.

iii. Section 3.2.P.3.3 Description of Manufacturing Process and Process Controls (nm, df)

This section would contain any submitted general descriptions/summaries. It may cross reference to section 3.2.R to support the manufacturing process.

- Management Controls
- Design Control, General
- Purchasing Controls
- Corrective Action

b. Section 3.2.P.5 Drug Product

Section 3.2.P.5, should usually be an element of a repeated section, as appropriate. The first 3.2.P Drug Product section would be for the drug product (e.g., <m3-2-p-drug-product product-name = "midazolam injection">. The second 3.2.P Drug Product section might be for the final combination product lot release specifications that include the specification requirements for the device constituent (e.g. <m3-2-p-drug-product product-name = "midazolam pre-filled syringe">). These specifications should rely on the device design transfer data (see design control information) and should link to the supporting eCTD data section; e.g., in section 3.2.R.

c. Section 3.2.P.7 Container Closure System

Continue to use this section for devices that serve as primary or secondary container closure. Please refer to FDA guidance on Container Closure for additional information.[24] This section may link to section 3.2.R as appropriate for device constituent testing.

d. Section 3.2.R Regional Information

This section may be used for device engineering design documentation and narrative explanations that are not otherwise provided in Section 3.2.P.7. Examples of the information include the following:

A. Design Input Requirements
B. Design Output Specifications (e.g., device description, drawings, specifications, bill of materials, etc.)
C. Design Verification Plan/Summary Report and supporting data (e.g., software, electromechanical conformance, bench testing, biocompatibility)

[24] Guidance to Industry: Container Closure Systems for Packaging Human Drugs and Biologics; https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070551.pdf

D. Design Validation Plan/Summary Report and supporting data (e.g., performance testing, narrative discussion of the applicability of data provided in Module 5).
E. Risk Management File
F. Traceability Matrix

Note: Section 3.2 R does not provide for subordinate sections. Every file is listed under a common heading. Leaf titles should be clear, concise and indicative of the document's content. Please refer to section 2.4 of this guide for additional information on leaf titles. In this section, for device related files, each leaf title should be prefixed with "DEVICE:"

5. Module 5
Human Factors submissions for the combination product should be located in eCTD section 5.3.5.4 Other Study Reports with links from appropriate Module 3 files, and should include the appropriate human factors file tag (e.g., HF-validation protocol, HF-validation report, HF-validation other) to describe the document's contents. Additionally, you may cross reference from Module 5 to Module 3 as applicable.

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*. These documents are located on the FDA eCTD website at: https://www.fda.gov/ectd.

1. ICH technical specification, *Electronic Common Technical Document Specification v3.2.2* (also accessible at https://www.ich.org/page/ich-electronic-common-technical-document-ectd-v322-specification-and-related-files)

2. ICH M2 technical specification, *The eCTD Backbone File Specification for Study Tagging Files*

3. FDA technical specification, *eCTD Backbone Files Specification for Module 1*

4. FDA guidance for industry, *M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use*

5. ICH M2 technical specification, *eCTD IWG Question and Answer and Specification Change Request Document*

6. FDA technical specification, FDA eCTD *Table of Contents Headings and Hierarchy*

7. FDA technical specification, *Specifications for File Format Types Using eCTD Specifications*

8. FDA technical specification, *FDA Portable Document Format (PDF) Specifications*

9. FDA guidance for industry, *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*

10. FDA technical specification, Transmission Specifications, *Specification for Transmitting Electronic Submissions Using eCTD Specifications*

11. FDA technical specification, eCTD Validation Specifications Website, *Specifications for eCTD Validation Criteria*

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 https://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 https://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 of PDUFA Products* (accessible at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm under Procedural)

4. FDA guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products* (accessible at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm under Procedural)

5. FDA guidance for industry, *Providing Regulatory Submissions in Electronic Format — Receipt Dates* (accessible at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm under Electronic Submissions)

6. FDA guidance for industry, M4: The CTD – Quality, Questions and Answers/Location Issues *(accessible at* https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm under International Conference on Harmonisation - Joint Safety/Efficacy (Multidisciplinary))