ICH eCTD Specification

Introduction

The ICH M4 Expert Working Group (EWG) has defined the Common Technical Document (CTD). The ICH M2 EWG has defined, in the current document, the specification for the Electronic Common Technical Document (eCTD). The eCTD is defined as an interface for industry to agency transfer of regulatory information while at the same time taking into consideration the facilitation of the creation, review, life cycle management and archiving of the electronic submission. The eCTD specification lists the criteria that will make an electronic submission technically valid. The focus of the specification is to provide the ability to transfer the registration application electronically from industry to a regulatory authority. Industry to industry and agency to agency transfer is not addressed.

Background

The specification for the eCTD is based upon content defined within the CTD issued by the ICH M4 EWG. The CTD describes the organization of modules, sections and documents. The structure and level of detail specified in the CTD have been used as the basis for defining the eCTD structure and content but, where appropriate, additional details have been developed within the eCTD specification.

The philosophy of the eCTD is to use open standards. Open standards, including proprietary standards which through their widespread use can be considered *de facto* standards, are deemed to be appropriate in general.

Scope

The CTD as defined by the M4 EWG does not cover the full submission that is to be made in a region. It describes only modules 2 to 5, which are common across all regions. The CTD does not describe the content of module 1, the Regional Administrative Information and Prescribing Information, nor does it describe documents that can be submitted as amendments or variations to the initial application.

The value of producing a specification for the creation of an electronic submission based only upon the modules described in the CTD would be limited. Therefore, the M2 EWG has produced a specification for the eCTD that is applicable to all modules of initial registration applications and for other submissions of information throughout the life cycle of the product, such as variations and amendments.

This document describes the parts of the registration application that are common to all regions and some of the life cycle requirements for products. The parts of the registration application that are specific to a region will be covered by regional guidance. However, this backbone has been developed to handle both the regional and common parts of submissions.

Technical Requirements

The specification is designed to support high-level functional requirements such as the following:

- Copy and paste
- Viewing and printing of documents
- Annotation of documentation
- Facilitate the exporting of information to databases
- Searching within and across applications
- Navigation throughout the eCTD and its subsequent amendments/variations

Change Control

The specification for the eCTD is likely to change with time. Factors that could affect the content of the specification include, but are not limited to:

	Title	Pharmacokinetics Written Summary
	Element	m2-6-4-pharmacokinetics-written-summary
	File	m2/26-nonclin-sum/pharmkin-written-summary.pdf
	Comment	Typically, this document should consist of a single file. The CTD defines further heading levels and navigation should be provided within the document to these sub-headings.
26	Number	2.6.5
	Title	Pharmacokinetics Tabulated Summary
	Element	m2-6-5-pharmacokinetics-tabulated-summary
	File	m2/26-nonclin-sum/pharmkin-tabulated-summary.pdf
	Comment	Should have further navigation via bookmarks
27	Number	2.6.6
	Title	Toxicology Written Summary
	Element	m2-6-6-toxicology-written-summary
	File	m2/26-nonclin-sum/toxicology-written-summary.pdf
	Comment	Typically, this document should consist of a single file. The CTD defines further heading levels and navigation should be provided within the document to these sub-headings.
28	Number	2.6.7
	Title	Toxicology Tabulated Summary
	Element	m2-6-7-toxicology-tabulated-summary
	File	m2/26-nonclin-sum/toxicology-tabulated-summary.pdf
	Comment	Should have further navigation via bookmarks
29	Number	2.7
	Title	Clinical Summary
	Element	m2-7-clinical-summary
	Directory	m2/27-clin-sum
	Comment	
30	Number	2.7.1
	Title	Summary of Biopharmaceutic Studies and Associated Analytical Methods
	Element	m2-7-1-summary-of-biopharmaceutic-studies-and-associated-analytical-methods
	File	m2/27-clin-sum/summary-biopharm.pdf
	Comment	Typically, this document should consist of a single file. The CTD defines further heading levels and navigation should be provided within the document to these sub-headings.
31	Number	2.7.2
	Title	Summary of Clinical Pharmacology Studies

	Element	m2-7-2-summary-of-clinical-pharmacology-studies
	File	m2/27-clin-sum/summary-clin-pharm.pdf
	Comment	Typically, this document should consist of a single file. The CTD defines further heading levels and navigation should be provided within the document to these sub-headings.
32	Number	2.7.3
	Title	Summary of Clinical Efficacy – *Indication*
	Element	m2-7-3-summary-of-clinical-efficacy
	File	m2/27-clin-sum/summary-clin-efficacy-*indication.pdf*
	Comment	The file name should always include the indication being claimed (abbreviated if appropriate) e.g., 'summary-clin-efficacy-asthma.pdf'. Where there is more than one indication (e.g., asthma & migraine) then the first indication has a file name 'summary-clin-efficacy-asthma.pdf' and the second 'summary-clin-efficacy-migraine.pdf'. Typically, this document should consist of a single file. The CTD defines further heading levels and navigation should be provided within the document to these sub-headings. The 'indication' attribute in the backbone should be consistent with that used in the filename but can be different. For example, an 'indication' attribute value of 'Non-Small Cell Lung Cancer' could be expressed as 'NSCLC' in the filename for that document (i.e., summclineff-nsclc.pdf). There is currently no standard terminology list for 'indication' and applicants should choose these attributes carefully as they can not be easily changed during the life cycle of the application. The only way this can be accomplished currently is to delete all the leaf elements with the incorrect attribute value and provide new leaf elements for those files with the modified attribute value. Applicants should consult with the regional authority before attempting to modify these attributes to discuss the appropriateness of, and approach to be taken for, this type of change.
33	Number	2.7.4
	Title	Summary of Clinical Safety
	Element	m2-7-4-summary-of-clinical-safety
	File	m2/27-clin-sum/summary-clin-safety.pdf
	Comment	Typically, this document should consist of a single file. The CTD defines further heading levels and navigation should be provided within the document to these sub-headings.
34	Number	2.7.5
	Title	Literature References
	Element	m2-7-5-literature-references
	File	m2/27-clin-sum/literature-references.pdf
	Comment	
35	Number	2.7.6
	Title	Synopses of Individual Studies
	Element	m2-7-6-synopses-of-individual-studies

	File	m2/27-clin-sum/synopses-indiv-studies.pdf
	Comment	These synopses should already be located in the Clinical Study Reports in Module 5 and should not, therefore, be repeated in Module 2. It is considered sufficient to provide hyperlinks from the listing of the studies, located here, to the locations of the synopses in Module 5.

36	Number	3
	Title	Quality
	Element	m3-quality
	Directory	m3
	Comment	Refer to the Granularity Annex of the M4 Organisation Document for guidance on the flexibility of multiple documents for Module 3
37	Number	3.2
	Title	Body of Data
	Element	m3-2-body-of-data
	Directory	m3/32-body-data
	Comment	
38	Number	3.2.S
	Title	Drug Substance
	Element	m3-2-s-drug-substance
	Directory	m3/32-body-data/32s-drug-sub
	Comment	
39	Number	3.2.S
	Title	Drug Substance - *Drug Substance Name - Manufacturer*
	Element	m3-2-s-drug-substance
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*
	Comment	In this section, it can be helpful if the folder name includes the name of the drug substance and manufacturer. This applies particularly when there are multiple drug substances and/or manufacturers. When naming folders, attention should be paid to the length of the name of the folder on the overall length of the full path. Abbreviations can help control the length of the path. The 'substance' and 'manufacturer' attribute values in the backbone should be consistent with that used in the folder name but can be different. For example, a 'manufacturer' attribute value of 'Company XXX, City Name, Country Name' could be expressed as 'xxx' in the folder name. There is currently no standard terminology list for these attributes and applicants should choose these attributes carefully as they can not be easily changed during the life cycle of the application. The only way this can be accomplished currently is to delete all the leaf elements with the incorrect attribute value and provide new leaf elements for those files with the modified attribute value. Applicants should consult with the regional authority before attempting to modify these attributes to discuss the appropriateness of, and approach to be taken for, this type of change.
40	Number	3.2.S.1
	Title	General Information (name, manufacturer)

	Element	m3-2-s-1-general-information
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s1-gen-info
	Comment	
41	Number	3.2.S.1.1
	Title	Nomenclature (name, manufacturer)
	Element	m3-2-s-1-1-nomenclature
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s1-gen-info/nomenclature.pdf
	Comment	
42	Number	3.2.S.1.2
	Title	Structure (name, manufacturer)
	Element	m3-2-s-1-2-structure
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s1-gen-info/structure.pdf
	Comment	
43	Number	3.2.S.1.3
	Title	General Properties (name, manufacturer)
	Element	m3-2-s-1-3-general-properties
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s1-gen-info/general-properties.pdf
	Comment	
44	Number	3.2.S.2
	Title	Manufacture (name, manufacturer)
	Element	m3-2-s-2-manufacture
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s2-manuf
	Comment	
45	Number	3.2.S.2.1
	Title	Manufacturer(s) (name, manufacturer)
	Element	m3-2-s-2-1-manufacturer
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s2-manuf/manufacturer.pdf
	Comment	For this document there should be only information regarding one manufacturer
46	Number	3.2.S.2.2
	Title	Description of Manufacturing Process and Process Controls (name, manufacturer)
	Element	m3-2-s-2-2-description-of-manufacturing-process-and-process-controls
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s2-manuf/manuf-process-and-controls.pdf
	Comment	

47	Number	3.2.S.2.3
	Title	Control of Materials (name, manufacturer)
	Element	m3-2-s-2-3-control-of-materials
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s2-manuf/control-of-materials.pdf
	Comment	
48	Number	3.2.S.2.4
	Title	Controls of Critical Steps and Intermediates (name, manufacturer)
	Element	m3-2-s-2-4-controls-of-critical-steps-and-intermediates
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s2-manuf/control-critical-steps.pdf
	Comment	
49	Number	3.2.S.2.5
	Title	Process Validation and/or Evaluation (name, manufacturer)
	Element	m3-2-s-2-5-process-validation-and-or-evaluation
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s2-manuf/process-validation.pdf
	Comment	
50	Number	3.2.S.2.6
	Title	Manufacturing Process Development (name, manufacturer)
	Element	m3-2-s-2-6-manufacturing-process-development
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s2-manuf/manuf-process-development.pdf
	Comment	
51	Number	3.2.S.3
	Title	Characterisation (name, manufacturer)
	Element	m3-2-s-3-characterisation
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s3-charac
	Comment	
52	Number	3.2.S.3.1
	Title	Elucidation of Structure and Other Characteristics (name, manufacturer)
	Element	m3-2-s-3-1-elucidation-of-structure-and-other-characteristics
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s3-charac/elucidation-of-structure.pdf
	Comment	
53	Number	3.2.S.3.2
	Title	Impurities (name, manufacturer)
	Element	m3-2-s-3-2-impurities

	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s3-charac/impurities.pdf
	Comment	
54	Number	3.2.S.4
	Title	Control of Drug Substance (name, manufacturer)
	Element	m3-2-s-4-control-of-drug-substance
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub
	Comment	
55	Number	3.2.S.4.1
	Title	Specification (name, manufacturer)
	Element	m3-2-s-4-1-specification
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s41-spec
	Comment	
56	Number	3.2.S.4.1
	Title	Specification (name, manufacturer)
	Element	m3-2-s-4-1-specification
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s41-spec/specification.pdf
	Comment	
57	Number	3.2.S.4.2
	Title	Analytical Procedures (name, manufacturer)
	Element	m3-2-s-4-2-analytical-procedures
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s42-analyt-proc
	Comment	The example below shows how a multiple file approach, where a separate file is provided for each analytical procedure, can be organized. CTD numbering is not defined below this level (e.g., 3.2.S.4.2.1).
58	Number	
	Title	*Analytical Procedure-1*
	Element	m3-2-s-4-2-analytical-procedures
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s42-analyt-proc/*analytical-procedure-1.pdf*
	Comment	
59	Number	
	Title	*Analytical Procedure-2*
	Element	m3-2-s-4-2-analytical-procedures
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s42-analyt-proc/*analytical-procedure-2.pdf*
	Comment	

60	Number	
	Title	*Analytical Procedure-3*
	Element	m3-2-s-4-2-analytical-procedures
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s42-analyt-proc/*analytical-procedure-3.pdf*
	Comment	
61	Number	3.2.S.4.3
	Title	Validation of Analytical Procedures
	Element	m3-2-s-4-3-validation-of-analytical-procedures (name, manufacturer)
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s43-val-analyt-proc
	Comment	The example below shows how a multiple file approach, where a separate file is provided for each analytical procedure, can be organized. CTD numbering is not defined below this level (e.g., 3.2.S.4.3.1).
62	Number	
	Title	*Validation of Analytical Procedure-1*
	Element	m3-2-s-4-3-validation-of-analytical-procedures
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s43-val-analyt-proc/*validation-analyt-procedure-1.pdf*
	Comment	
63	Number	
	Title	*Validation of Analytical Procedure-2*
	Element	m3-2-s-4-3-validation-of-analytical-procedures
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s43-val-analyt-proc/*validation-analyt-procedure-2.pdf*
	Comment	
64	Number	
	Title	*Validation of Analytical Procedure-3*
	Element	m3-2-s-4-3-validation-of-analytical-procedures
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s43-val-analyt-proc/*validation-analyt-procedure-3.pdf*
	Comment	
65	Number	3.2.S.4.4
	Title	Batch Analyses (name, manufacturer)
	Element	m3-2-s-4-4-batch-analyses
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s44-batch-analys
	Comment	
66	Number	3.2.S.4.4

	Title	Batch Analyses (name, manufacturer)
	Element	m3-2-s-4-4-batch-analyses
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s44-batch-analys/batch-analyses.pdf
	Comment	
67	Number	3.2.S.4.5
	Title	Justification of Specification (name, manufacturer)
	Element	m3-2-s-4-5-justification-of-specification
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s45-justif-spec
	Comment	
68	Number	3.2.S.4.5
	Title	Justification of Specification (name, manufacturer)
	Element	m3-2-s-4-5-justification-of-specification
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s4-contr-drug-sub/32s45-justif-spec/justification-of-specification.pdf
	Comment	
69	Number	3.2.S.5
	Title	Reference Standards or Materials (name, manufacturer)
	Element	m3-2-s-5-reference-standards-or-materials
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s5-ref-stand
	Comment	
70	Number	3.2.S.5
	Title	Reference Standards or Materials (name, manufacturer)
	Element	m3-2-s-5-reference-standards-or-materials
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s5-ref-stand/reference-standards.pdf
	Comment	Where a multiple file approach is taken for this section, the file names should indicate which reference standard is covered in the document.
71	Number	3.2.S.6
	Title	Container Closure System (name, manufacturer)
	Element	m3-2-s-6-container-closure-system
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s6-cont-closure-sys
	Comment	
72	Number	3.2.S.6
	Title	Container Closure System (name, manufacturer)
	Element	m3-2-s-6-container-closure-system
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s6-cont-closure-sys/container-closure-system.pdf

	Comment	
73	Number	3.2.S.7
	Title	Stability (name, manufacturer)
	Element	m3-2-s-7-stability
	Directory	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s7-stab
	Comment	
74	Number	3.2.S.7.1
	Title	Stability Summary and Conclusions (name, manufacturer)
	Element	m3-2-s-7-1-stability-summary-and-conclusions
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s7-stab/stability-summary.pdf
	Comment	
75	Number	3.2.S.7.2
	Title	Post-approval Stability Protocol and Stability Commitment (name, manufacturer)
	Element	m3-2-s-7-2-post-approval-stability-protocol-and-stability-commitment
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s7-stab/postapproval-stability.pdf
	Comment	
76	Number	3.2.S.7.3
	Title	Stability Data (name, manufacturer)
	Element	m3-2-s-7-3-stability-data
	File	m3/32-body-data/32s-drug-sub/*substance-1-manufacturer-1*/32s7-stab/stability-data.pdf
	Comment	
77	Number	3.2.P
	Title	Drug Product (name, dosage form)
	Element	m3-2-p-drug-product
	Directory	m3/32-body-data/32p-drug-prod
	Comment	
78	Number	3.2.P
	Title	Drug Product (name, dosage form) – *Name*
	Element	m3-2-p-drug-product
	Directory	m3/32-body-data/32p-drug-prod/*product-1*

	Comment	In this section, it can be helpful if the folder name includes the name of the drug product. This applies particularly where there is more than one drug product (e.g., powder for reconstitution and diluent); the first drug product would have a folder 'powder-for-reconstitution' and the second, 'diluent'. Refer to regional guidance for definition of what constitutes a drug product and the acceptability of more than one drug product in an application. The 'product-name' attribute value in the backbone should be consistent with that used in the folder name but can be different. For example, a 'product-name' attribute value of 'Lyophilized Powder for Reconstitution' could be expressed as 'powder' in the folder name. There is currently no standard terminology list for these attributes and applicants should choose these attributes carefully as they can not be easily changed during the life cycle of the application. The only way this can be accomplished currently is to delete all the leaf elements with the incorrect attribute value and provide new leaf elements for those files with the modified attribute value. Applicants should consult with the regional authority before attempting to modify these attributes to discuss the appropriateness of, and approach to be taken for, this type of change.
79	Number	3.2.P.1
	Title	Description and Composition of the Drug Product (name, dosage form)
	Element	m3-2-p-1-description-and-composition-of-the-drug-product
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p1-desc-comp
	Comment	
80	Number	3.2.P.1
	Title	Description and Composition of the Drug Product (name, dosage form)
	Element	m3-2-p-1-description-and-composition-of-the-drug-product
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p1-desc-comp/description-and-composition.pdf
	Comment	
81	Number	3.2.P.2
	Title	Pharmaceutical Development (name, dosage form)
	Element	m3-2-p-2-pharmaceutical-development
	Directory	m3/32-body-data/32p-drug-prod*/product-1*/32p2-pharm-dev
	Comment	Refer to the M4 Organisation Document: Granularity Annex for guidance on the flexibility of multiple documents for the Pharmaceutical Development section.
82	Number	3.2.P.2
	Title	Pharmaceutical Development (name, dosage form)
	Element	m3-2-p-2-pharmaceutical-development
	File	m3/32-body-data/32p-drug-prod*/product-1*/32p2-pharm-dev/pharmaceutical-development.pdf

	Comment	Refer to the M4 Organisation Document: Granularity Annex for guidance on the flexibility of multiple documents for the Pharmaceutical Development section.
83	Number	3.2.P.3
	Title	Manufacture (name, dosage form)
	Element	m3-2-p-3-manufacture
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p3-manuf
	Comment	
84	Number	3.2.P.3.1
	Title	Manufacturer(s) (name, dosage form)
	Element	m3-2-p-3-1-manufacturers
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p3-manuf/manufacturers.pdf
	Comment	
85	Number	3.2.P.3.2
	Title	Batch Formula (name, dosage form)
	Element	m3-2-p-3-2-batch-formula
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p3-manuf/batch-formula.pdf
	Comment	
86	Number	3.2.P.3.3
	Title	Description of Manufacturing Process and Process Controls (name, dosage form)
	Element	m3-2-p-3-3-description-of-manufacturing-process-and-process-controls
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p3-manuf/manuf-process-and-controls.pdf
	Comment	
87	Number	3.2.P.3.4
	Title	Controls of Critical Steps and Intermediates (name, dosage form)
	Element	m3-2-p-3-4-controls-of-critical-steps-and-intermediates
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p3-manuf/control-critical-steps.pdf
	Comment	
88	Number	3.2.P.3.5
	Title	Process Validation and/or Evaluation (name, dosage form)
	Element	m3-2-p-3-5-process-validation-and-or-evaluation
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p3-manuf/process-validation.pdf
	Comment	The applicant has the option to submit one or multiple files, one for each validation or evaluation.

89	Number	3.2.P.4
	Title	Control of Excipients (name, dosage form)
	Element	m3-2-p-4-control-of-excipients
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p4-contr-excip
	Comment	
90	Number	3.2.P.4
	Title	Control of Excipients (name, dosage form) – *Excipient*
	Element	m3-2-p-4-control-of-excipients
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p4-contr-excip/*excipient-1*
	Comment	For a drug product containing more than one excipient, the information requested for sections 3.2.P.4.1 – 3.2.P.4.4 should be provided in its entirety for each excipient. Refer to the ICH eCTD QA and Change Requests document, Q&A No.4 for additional suggestions on structuring this section. For compendial excipient(s) without additional specification tests, it is appropriate to have all information in one file, making sure to introduce a folder for each of new documents to avoid mixing files and folders at the same level. Non-compendial excipients should follow the structure outlined below. The 'excipient' attribute value in the backbone should be consistent with that used in the folder name but can be different. There is currently no standard terminology list for these attributes and applicants should choose these attributes carefully as they can not be easily changed during the life cycle of the application. The only way this can be accomplished currently is to delete all the leaf elements with the incorrect attribute value and provide new leaf elements for those files with the modified attribute value. Applicants should consult with the regional authority before attempting to modify these attributes to discuss the appropriateness of, and approach to be taken for, this type of change.
91	Number	3.2.P.4.1
	Title	Specifications (name, dosage form)
	Element	m3-2-p-4-1-specifications
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p4-contr-excip/*excipient-1*/specifications.pdf
	Comment	See comment under 3.2.P.4.
92	Number	3.2.P.4.2
	Title	Analytical Procedures (name, dosage form)
	Element	m3-2-p-4-2-analytical-procedures
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p4-contr-excip/*excipient-1*/analytical-procedures.pdf
	Comment	See comment under 3.2.P.4.
93	Number	3.2.P.4.3
	Title	Validation of Analytical Procedures (name, dosage form)
	Element	m3-2-p-4-3-validation-of-analytical-procedures

	File	m3/32-body-data/32p-drug-prod/*product-1*/32p4-contr-excip/*excipient-1*/validation-analyt-procedures.pdf
	Comment	See comment under 3.2.P.4.
94	Number	3.2.P.4.4
	Title	Justification of Specifications (name, dosage form)
	Element	m3-2-p-4-4-justification-of-specifications
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p4-contr-excip/*excipient-1*/justification-of-specifications.pdf
	Comment	See comment under 3.2.P.4.
95	Number	3.2.P.4.5
	Title	Excipients of Human or Animal Origin (name, dosage form)
	Element	m3-2-p-4-5-excipients-of-human-or-animal-origin
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p4-contr-excip/excipients-human-animal.pdf
	Comment	
96	Number	3.2.P.4.6
	Title	Novel Excipients (name, dosage form)
	Element	m3-2-p-4-6-novel-excipients
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p4-contr-excip/novel-excipients.pdf
	Comment	
97	Number	3.2.P.5
	Title	Control of Drug Product (name, dosage form)
	Element	m3-2-p-5-control-of-drug-product
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod
	Comment	
98	Number	3.2.P.5.1
	Title	Specification(s) (name, dosage form)
	Element	m3-2-p-5-1-specifications
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p51-spec
	Comment	
99	Number	3.2.P.5.1
	Title	Specification(s) (name, dosage form)
	Element	m3-2-p-5-1-specifications
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p51-spec/specifications.pdf
	Comment	
100	Number	3.2.P.5.2

	Title	Analytical Procedures (name, dosage form)
	Element	m3-2-p-5-2-analytical-procedures
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p52-analyt-proc
	Comment	The example below shows how a multiple file approach, where a separate file is provided for each analytical procedure, may be organized. CTD numbering is not defined below this level (e.g., 3.2.P.5.2.1).
101	Number	
	Title	*Analytical Procedure – 1*
	Element	m3-2-p-5-2-analytical-procedures
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p52-analyt-proc/*analytical-procedure-1.pdf*
	Comment	
102	Number	
	Title	*Analytical Procedure – 2*
	Element	m3-2-p-5-2-analytical-procedures
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p52-analyt-proc/*analytical-procedure-2.pdf*
	Comment	
103	Number	
	Title	*Analytical Procedure – 3*
	Element	m3-2-p-5-2-analytical-procedures
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p52-analyt-proc/*analytical-procedure-3.pdf*
	Comment	
104	Number	3.2.P.5.3
	Title	Validation of Analytical Procedures (name, dosage form)
	Element	m3-2-p-5-3-validation-of-analytical-procedures
	Directory	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p53-val-analyt-proc
	Comment	The example below shows how a multiple file approach, where a separate file is provided for each analytical procedure, may be organized. CTD numbering is not defined below this level (e.g., 3.2.P.5.3.1).
105	Number	
	Title	*Validation of Analytical Procedures – 1*
	Element	m3-2-p-5-3-validation-of-analytical-procedures
	File	m3/32-body-data/32p-drug-prod/*product-1*/32p5-contr-drug-prod/32p53-val-analyt-proc/*validation-analytical-procedures-1.pdf*
	Comment	
106	Number	
	Title	*Validation of Analytical Procedures – 2*

Operation attribute value	Meaning	What the reviewer might see when using the Agency review software	
		This leaf	Previous leaf
	new leaf element replaces.		
Delete	There is no new file submitted in this case. Instead, the leaf element has the operation of "delete" and the "modified-file" attribute identifies the leaf element in a previous submission that is to be considered no longer relevant to the review. As there is no file being submitted, the checksum attribute value will be empty i.e., double quotation marks with no entry between ("").		No longer relevant to the review

The purpose of the modified-file attribute is to provide the location of a leaf element that is being modified (i.e. replaced, appended or deleted) by the subsequent leaf element. The modified-file attribute should have a value when the operation attribute has a value of *append*, *replace* or *delete*. The modified-file attribute points to the "index.xml" file and the leaf ID of the leaf element being altered. The modified-file attribute can only target a single leaf element. Furthermore, once a leaf element has been replaced or deleted by another leaf element, it is no longer current and can no longer be targeted by any subsequent leaf elements through the modified-file attribute.

An example of a modified-file attribute value is provided below:

modified-file="../0001/index.xml#a1234567"

This would provide the information needed to locate the file with the leaf element ID assigned as "a1234567" and provided in the sequence folder numbered "0001".

If a modified-file attribute is presented with no value (i.e. no characters or spaces between the quotation marks, modified-file="") it will be the same as not including the attribute in the leaf element.

The following case examples show the use of each of the operation attribute values. These examples do not cover all possible situations. Consult the appropriate regulatory authority if you have specific questions about the use of the operation attribute. When actually populating the XML instance, use the leaf ID to refer to files.

Case 1 – The first submission of a dossier.

Table 6-4

Submission sequence #	File name	Operation	File Being Modified	Sample logical display in a review tool
0000	0000\…\structure.pdf	New		structure.pdf (current)

Case 2 – Two submissions. Submission 0000 is the first submission of a dossier. Submission 0001 is a subsequent amendment or variation in which the applicant intends to completely replace the structure.pdf file in submission 0000. The intent is to keep the original structure.pdf for historical purposes but to consider only the contents of the 0001\…\structure2.pdf as relevant to the review. These two submissions could be described as follows:

- Submission 0000 is the first submission of the file structure.pdf, and this file is the current version of this file.
- Submission 0001, which is submitted at a later time, is the submission of the file structure2.pdf, which is now current and replaces the file structure.pdf in submission 0000.

There is no requirement to preserve file names during life cycle changes; in fact, logical differences in file names can be helpful during review when both files are open simultaneously for comparative or other purposes.

Table 6-5

Submission sequence #	File name	Operation	File Being Modified	Sample logical display in a review tool
0000	0000\…\structure.pdf	New		structure.pdf (current)
0001	0001\…\structure2.pdf	Replace	0000\…\structure.pdf	*structure.pdf (replaced)* structure2.pdf (current)

Case 3 – Two submissions. Submission 0000 is the first submission of a dossier. Submission 0001 is an amendment or variation where the applicant intends to add new information to the original structure.pdf file, which was submitted in submission 0000. The intent is to have the reviewer consider the contents of both files relevant to the submission. These two submissions could be described as follows:

- Submission 0000 is the first submission of the file structure.pdf, and this file is the current version of this file.
- Submission 0001, submitted at a later time, is the submission of the file structure2.pdf, which is the current file but contains information that should be appended to file structure.pdf in submission 0000. Both files should be considered relevant to the review of the dossier.

There is no requirement to preserve file names during life cycle changes; in fact, logical differences in file names can be helpful during review when both files are open simultaneously for comparative or other purposes.

Table 6-6

Submission sequence #	File name	Operation	File Being Modified	Sample logical display in a review tool
0000	0000\…\structure.pdf	New		structure.pdf (current)
0001	0001\…\structure2.pdf	Append	0000\...\structure.pdf	structure.pdf (current - appended) structure2.pdf (current)

Case 4 – Two submissions. Submission 0000 is the first submission of a dossier. Submission 0001 is an amendment or variation where the applicant intends to delete a file in the previous submission. The intent is to have the reviewer disregard the contents of the original file, possibly because it should not have been submitted with the original dossier. These two submissions could be described as follows:

- Submission 0000 is the first submission of the file structure.pdf and this file is the current version of this file.
- Submission 0001, submitted at a later time, requests that the file structure.pdf in submission 0000 be deleted and no longer considered relevant to the review of the dossier.

Table 6-7

Submission sequence #	File name	Operation	File Being Modified	Sample logical display in a review tool
0000	0000\...\structure.pdf	New		structure.pdf (current)
0001		Delete	0000\...\structure.pdf	**structure.pdf (no longer relevant to the review)**

File Reuse

It is important to the successful utilization of the eCTD to clearly understand the differences between a file and a leaf element. When reviewing an eCTD sequence, either through the stylesheet or an eCTD viewing tool, the presentation of the organization of the content files is based on the organization of the leaf elements in the index.xml files. The underlying file and folder structure is not critical to the view of the organization of the files referenced in the XML backbone. This aspect of the eCTD provides users the ability to provide a file once and display it in multiple locations of the eCTD by providing multiple leaf

elements referencing that file. Users of the eCTD Specification are encouraged to provide files once in a sequence and provide as many leaf elements referencing that file as necessary. The location of the file is not critical and should only be included once in an appropriate place in the folder structure. Suppliers of eCTD viewing tools are encouraged to develop a visual way of displaying when this occurs so reviewers can readily identify files which are referenced multiple times.

This capability can also be extended across sequences and even applications as long as the location of the file is accurately cited in the xlink:href attribute for the leaf element referencing that file. Suppliers of eCTD viewing tools are encouraged to develop a visual way of displaying the difference between a leaf element referring to a file in the current sequence and a leaf element referring to a file in a previous sequence. In these situations, validation checks for the presence of files referenced by the XML backbone should allow for the xlink:href to refer to files in other sequences and not prevent viewing of the eCTD by another applicant/regulator. Users of the eCTD Specification should consult with the regulatory authority before referencing content across sequences and/or applications.

DTD Content Model

The content model of the eCTD is derived from the organization of the Common Technical Document. The graphic representation of a portion of the content model is shown below. The content model is hierarchical starting at the "ectd" and going down to a specific item to be included in the submission.

Figure 6-2

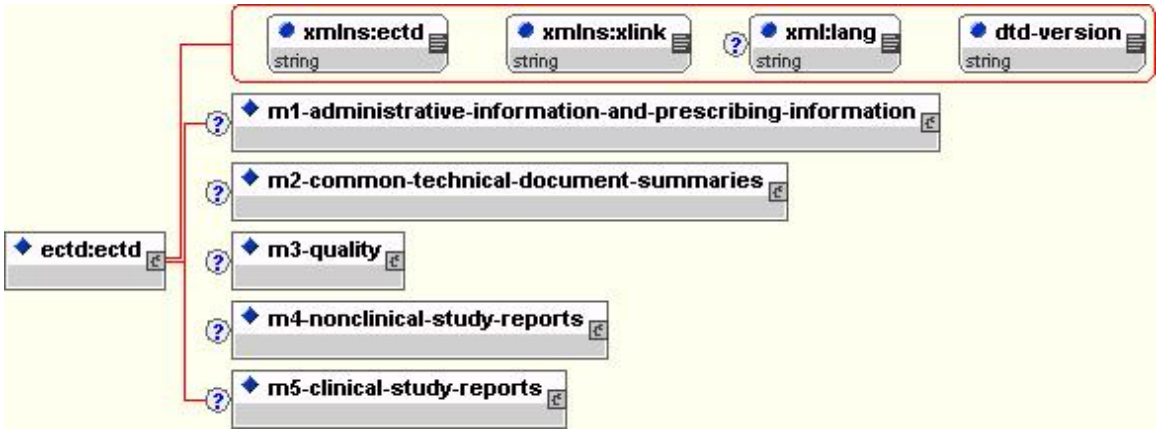
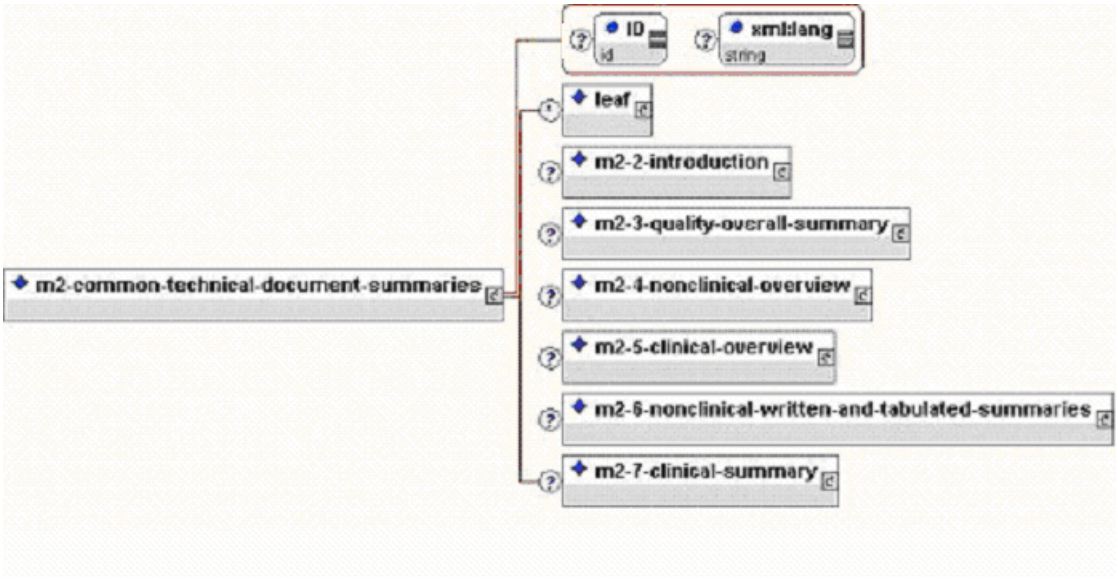


Figure 6-3 shows how the section of the CTD containing summaries is structured.

Figure 6-3



Once the appropriate element has been selected (e.g., Figure 6-4), you should use the <leaf> element and attributes (Figure 6-5) to specify a file in the submission. See "eCTD Element/Attribute Instructions" in this appendix for details.

Figure 6-4

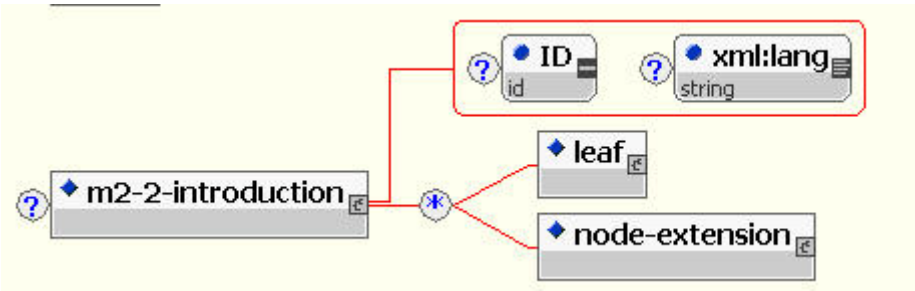
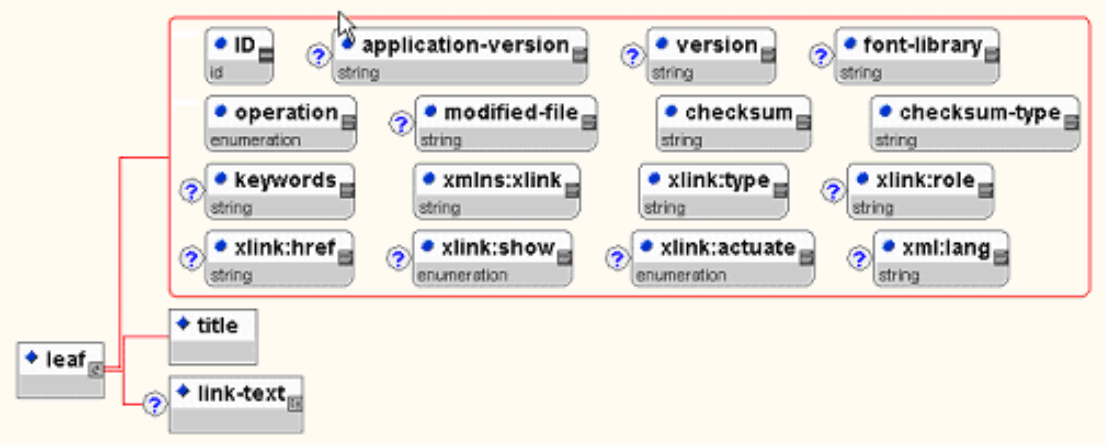


Figure 6-5



eCTD Element/Attribute Instructions

The eCTD consists of 5 primary modules:

- m1-administrative-information-and-prescribing-information
- m2-common-technical-document-summaries
- m3-quality
- m4-nonclinical-study-reports
- m5-clinical-study-reports

Each of the 5 modules is divided into one or more elements, each with a distinct element identifier that represents a CTD table of contents location. The steps should be completed as shown in the following example, where all files are submitted for modules 1 through 5:

1. Select an element that best corresponds to the CTD table of contents location for a document or file being submitted. For example, select the element <m2-7-3-summary-of-clinical-efficacy> to submit the summary of clinical efficacy document.
2. Specify any additional element attribute as appropriate; in this example, specify the 'indication' attribute to identify the subject of the efficacy summary in 2.7.3.
3. Create a child <leaf> element within the <m2-7-3-summary-of-clinical-efficacy> element.
4. Provide the relative location and file name of the actual file in the "xlink:href" attribute for the leaf element.
5. Provide a descriptive and concise title for the file in the <title> element of the leaf element.
6. Provide information for the appropriate attributes of the leaf element as described in Table 6-8.

Table 6-8 describes each of these elements and attributes in further detail.

Table 6-8

Element	Attribute	Description/Instructions	Example
Any table of contents element such as <m2-4-nonclinical-overview>		A table of contents element represents a grouping of one or more files related to a specific section of the Common Technical Document. A number of TOC elements can be further defined by the use of attributes. The eCTD DTD defines the following attributes at various places in the eCTD: substance, manufacturer, product-name, indication, excipient, dosage-form (e.g., 2.3.S and 3.2.S have two 'free text' attributes: substance and manufacturer; 5.3.5 has the additional 'free text' attribute, indication). To be consistent with the CTD General Q&A, values for these attributes should be included where specified as is appropriate. There is currently no standard terminology list for any of these attributes and applicants should carefully choose the text of these attributes as they can not be easily changed during the life cycle of the application. One or more child <leaf> elements can be declared for a parent table of contents element. It is possible to extend a table of contents element by providing a <node-extension> element. Node extensions should only be added at the lowest level of the defined table of contents elements. Using node extensions is discouraged and should be done only when unavoidable. Please refer to regional guidance before using node extensions. See the section "Instructions for extending XML eCTD DTD elements" in this appendix (Example 6-5).	
	ID	A unique identifier for this location in the XML instance.	id403 (note: At this level, ID is optional)
	xml:lang	The primary language used by the files in this entire section of the submission. Use ISO-639 standard language abbreviations	en

Element	Attribute	Description/Instructions	Example
<leaf>		A leaf element is a reference to a file. One or more leaf elements can be declared for a table of contents element.	
	application-version	This is the version of the file format produced by the software application that was used to create this file.	PDF 1.4
	font-library	Reserved for Future Use	
	ID	The ID attribute is intended to be a unique reference within the submission that can be used to reference the item from another item within the XML document. An XML ID value begins with an alphabetic character or underscore. If an applicant is using an internal ID generator that uses only numbers, appending this generated number to a leading alphabetic character or underscore will create a valid ID value.	id050520 NOTE: See the XML-ID recommendations on the W3C website for info on the composition of this attribute value (http://www.w3.org/TR/xml-id/#processing)
	checksum	The checksum value for the file being submitted.	e854d3002c02a61fe5cbe926fd97b001
	checksum-type	The checksum algorithm used.	MD5
	modified-file	The purpose of the modified-file attribute is to provide the location of the leaf that is being modified (i.e. replaced, appended or deleted) by the leaf element. The modified-file attribute should have a value when the operation attribute has a value of append, replace or delete. The modified-file attribute points to the "index.xml" file and the leaf ID of the leaf being altered.	../0001/index.xml#a1234567
	operation	Indicates the action to be performed. You should select one of the following valid values: • new • replace • append • delete See the section Operation Attribute in this appendix for details on the meaning of these values.	new
	version	The file submitter's internal version number or version identification for the file.	V23.5
	xlink:actuate	Reserved for Future Use	

Element	Attribute	Description/Instructions	Example
	xlink:href	Provides the reference to the actual content file. You should use the relative path to the file and the file name. The content file does not need to be in the same sequence as the leaf element that refers to it.	0000/m2/27-clin-sum/literature-references.pdf
	xlink:role	Reserved for Future Use	
	xlink:show	Reserved for Future Use	
	xlink:type	Fixed value of "simple"	simple
	keywords	Reserved for Future Use	
<title>		As part of the leaf element, this element contains a practical name for the file being referenced by the leaf.	Study Report 1234 NOTE: Leaf titles should be concise; 1024 bytes (512 characters) are proposed as the maximum length
	ID	Unique identifier for this location in the XML instance. Leaf ID starts with an alphabetic character or underscore.	a1234567 NOTE 1: See the XML-ID recommendations on the W3C website for info on the composition of this attribute value (http://www.w3.org/TR/xml-id/#processing) NOTE 2: At this level, ID is optional
<link-text>		Reserved for Future Use	
<xref>		Reserved for Future Use	

Example 6-1: Instructions for a Simple New Submission[7]

The following XML fragment demonstrates the submission of a clinical overview of efficacy as a single PDF document.

```
<?xml version = "1.0" encoding = "UTF-8"?>
<!DOCTYPE ectd:ectd SYSTEM "util/dtd/ich-ectd-3-x.dtd">
<?xml-stylesheet type="text/xsl" href="util/style/ectd-2-1-x.xsl"?>
<ectd:ectd xmlns:ectd = "http://www.ich.org/ectd" xmlns:xlink = "http://www.w3c.org/1999/xlink">
        <m2-common-technical-document-summaries>
                <m2-5-clinical-overview xml:lang = "en">
                        <leaf ID="s123456" operation = "new" xlink:type = "simple" checksum-type="md5"
                        checksum = "e854d3002c02a61fe5cbe926fd973401" xlink:href = "m2/25-clin-
                        over/clinical-overview.pdf" application-version = "PDF 1.4">
                        <title>Clinical Overview</title>
                        </leaf>
                </m2-5-clinical-overview>
        </m2-common-technical-document-summaries>
</ectd:ectd>
```

This submission includes the file "clinical-overview.pdf" in the relative directory "m2/25-clin-over/" (i.e. the one starting below the dossier number directory). The file is "new" and has a descriptive name of "Clinical Overview"

The regional review application should treat this as a new submission to be associated with the submission identified in CTD module 1, which is region specific.

[7] Note that these XML examples are examples only and do not necessarily contain all of the elements and attributes that you should use when preparing an eCTD submission.

If this is the first submission for Dossier CTD 123456, all the files in this submission would typically be in the ctd-123456\0000 directory and below.

Example 6-2: Instructions for an Amendment, Supplement, or Variation

In the previous example, a clinical overview was submitted. In this example, it is replaced by an updated version.

To replace a file, add the replacement <leaf> element under the same element as the original file.
If this is the second submission for Dossier CTD 123456, all the files in this submission would typically be in the ctd-123456\0001 directory and below.

```
<?xml version = "1.0" encoding = "UTF-8"?>
<!DOCTYPE ectd:ectd SYSTEM "util/dtd/ich-ectd-3-x.dtd">
<?xml-stylesheet type="text/xsl" href="util/style/ectd-2-1-x.xsl"?>
<ectd:ectd xmlns:ectd = "http://www.ich.org/ectd" xmlns:xlink = "http://www.w3c.org/1999/xlink">
<m2-common-technical-document-summaries>
        <m2-5-clinical-overview xml:lang = "en">
                <leaf ID="a123457" operation = "replace"  xlink:type = "simple" checksum-type="md5" checksum =
                "502e9ab5827431f077340cea3b5e465a" xlink:href = "m2/25-clin-over/clinical-overview-revised.pdf"
                application-version = "PDF 1.4" modified-file = "../0000/index.xml#s123456">
                   <title>Clinical Overview</title>
                </leaf>
        </m2-5-clinical-overview>
</m2-common-technical-document-summaries>
</ectd:ectd>
```

Example 6-3: Instructions for Multiple Indications

Multiple therapeutic indications use an additional attribute associated with the <m2-7-3-summary-of-clinical-efficacy> and the <m5-3-5-reports-of-efficacy-and-safety-studies> elements to allow multiple indications to be submitted. There is currently no standard terminology list for 'indication'. Applicants should choose these attributes carefully as they can not be easily changed during the life cycle of the application. The only way this can be accomplished currently is to delete all the leaf elements with the incorrect attribute value and provide new leaf elements for those files with the modified attribute value. Applicants should consult with the regional authority before attempting to modify these attributes to discuss the appropriateness of, and approach to be taken for, this type of change. The following table shows the use of these attributes.

Table 6-9

Element	Attribute	Description/Instructions	Example
<m2-7-3-summary-of-clinical-efficacy>	indication	Name of the indication	Pain
<m5-3-5-reports-of-efficacy-and-safety-studies>	indication	Name of the indication.	Pain

Note that the indication attribute is used by the regulatory authority to apply to all the table of contents elements beneath the <m2-7-3-summary-of-clinical-efficacy> and <m5-3-5-reports-of-efficacy-and-safety-studies> elements. The following example expands on the instance showing the submission of information about two indications (pain and nausea).

```
<?xml version = "1.0" encoding = "UTF-8"?>
<!DOCTYPE ectd:ectd SYSTEM "util/dtd/ich-ectd-3-x.dtd">
<?xml-stylesheet type="text/xsl" href="util/style/ectd-2-1-x.xsl"?>
```

```
<ectd:ectd xmlns:ectd = "http://www.ich.org/ectd" xmlns:xlink = "http://www.w3c.org/1999/xlink">
    <m2-common-technical-document-summaries>
        <m2-7-clinical-summary>
        <m2-7-3-summary-of-clinical-efficacy indication = "pain">
            <leaf ID="s123456"operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
            "5aa5c0e630a700af869e4c72535fc922" xlink:href = "m2/27-clin-sum/summary-clin-efficacy-
            pain.pdf">
                <title>pain efficacy summary</title>
            </leaf>
        </m2-7-3-summary-of-clinical-efficacy>
        <m2-7-3-summary-of-clinical-efficacy indication = "nausea">
            <leaf ID="a123457" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
            "bde4d34dc80678a266352daf450c3962" xlink:href = "m2/27-clin-summ/summary-clin-efficacy-
            nausea.pdf">
                <title>nausea efficacy summary</title>
            </leaf>
        </m2-7-3-summary-of-clinical-efficacy>
        </m2-7-clinical-summary>
    </m2-common-technical-document-summaries>
    <m5-clinical-study-reports>
        <m5-3-clinical-study-reports>
        <m5-3-5-reports-of-efficacy-and-safety-studies indication = "pain">
            <m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
                <leaf ID="a123458" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
                    "a4529c4a257f07f8a0ec591dde854578" xlink:href = "m5/53-clin-stud-rep/535-rep-eff-safety-
                    stud/pain/pain-sr1.pdf">
                    <title>pain study report 1</title>
                </leaf>
            </m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
        </m5-3-5-reports-of-efficacy-and-safety-studies>
        <m5-3-5-reports-of-efficacy-and-safety-studies indication = "nausea">
            <m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
                <leaf ID="a123459" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
                    "c5c39f594b2070a57bea66e58860efcf" xlink:href = "m5/53-clin-stud-rep/535-rep-eff-safety-
                    stud/nausea/nausea-sr15.pdf" >
                    <title>nausea study report 15</title>
                </leaf>
                <leaf ID = "a123460" operation = "new" xlink:type = "simple" checksum-type = "md5" checksum
                    = "15faf198015f3599acabb7755c2d6b0c" xlink:href = "m5/53-clin-stud-rep/535-rep-eff-
                    safety-stud/nausea/5351-stud-rep-contr/xyz0015/nausea-sr15.pdf">
                        <title>nausea study report 15</title>
                </leaf>
            </m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication>
        </m5-3-5-reports-of-efficacy-and-safety-studies>
        </m5-3-clinical-study-reports>
    </m5-clinical-study-reports>
</ectd:ectd>
```

Example 6-4: Instructions for Multiple Drug Substances, Manufacturers, and Products

Multiple drug substances use additional attributes associated with the <m3-2-s-drug-substance> element to allow unique combinations of the drug substance name and manufacturer to be submitted. There are currently no standard terminology lists for these attributes. Applicants should choose these attributes carefully as they can not be easily changed during the life cycle of the application. The only way this can be accomplished currently is to delete all the leaf elements with the incorrect attribute value and provide new leaf elements for those files with the modified attribute value.Applicants should consult with the regional authority before attempting to modify these attributes to discuss the appropriateness of, and approach to be taken for, this type of change. The following table shows the use of these attributes in 3.2.S.

Table 6-10

Element	Attribute	Description/Instructions	Example
<m3-2-s-drug-substance>	substance	Name of one of the drug substances	Acetaminophen
	manufacturer	Name of the manufacturer of the drug substance	My Supplier

Example 6-4A:
This is an example of a section of the instance showing the submission of information about two drug substances (acetominophen and codeine), one of which is supplied by two manufacturers:

```
<m3-2-body-of-data>
        <m3-2-s-drug-substance substance = "Acetaminophen" manufacturer = "My Supplier">
                <leaf  ID="a123456" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
                "b002e4544c02361fe54be926ae777012" xlink:href = "m3/32-body-data/32s-drug-
                sub/acetaminophen-my-supplier/acetaminophen.pdf">
                        <title>Acetaminophen - My Supplier Data</title>
                </leaf>
        </m3-2-s-drug-substance>
        <m3-2-s-drug-substance substance = "Acetaminophen" manufacturer = "Bulk Company 2">
                <leaf ID="a123457" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
                "0000cdfa05b1e995f88057150414a783" xlink:href = "m3/32-body-data/32s-drug-
                sub/acetaminophen-bulk-company-2/acetaminophen2.pdf">
                        <title>Acetaminophen - bulk company 2 data</title>
                </leaf>
        </m3-2-s-drug-substance>
        <m3-2-s-drug-substance substance = "Codeine" manufacturer = "Drug company 2">
                <leaf ID="a123458" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
                "f555a3234f65623fe54be926ee435354" xlink:href = "m3/32-body-data/32s-drug-sub/codeine-
                drug-company-2/codeine-quality-data.pdf">
                        <title>codeine - drug company 2 data</title>
                </leaf>
        </m3-2-s-drug-substance>
</m3-2-body-of-data>
```

Multiple drug products use additional attributes associated with the <m3-2-p-drug-product> element to allow unique combinations of the drug product name and dosage form to be submitted. Applicants should choose these attributes carefully as they can not be easily changed during the life cycle of the application. The only way this can be accomplished currently is to delete all the leaf elements with the incorrect attribute value and provide new leaf elements for those files with the modified attribute value. Applicants should consult with the regional authority before attempting to modify these attributes to discuss the appropriateness of, and approach to be taken for, this type of change. The following table shows the use of these attributes in 3.2.P.

Table 6-11

Element	Attribute	Description/Instructions	Example
<m3-2-p-drug-product>	product-name	Name of one of the drug products	Wonder drug
	dosageform	Dosage form	Capsule
	manufacturer	Manufacturer of the drug product	Company A

Example 6-4B
This is an example of a section of the instance showing the submission of information about two drug products (a capsule and a tablet):

```
<m3-2-body-of-data>
        <m3-2-p-drug-product product-name = "Wonder drug" dosageform="Capsule" manufacturer="Company
        A">
```

```
                <leaf ID="a123456" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
                "f27cd9e659d8acf7baab10cc753d733c" xlink:href = "m3/32-body-data/32p-drug-prod/capsule-
                5mg/32p1-desc-comp/description-and-composition.pdf">
                        <title>Wonder drug capsule product information</title>
                </leaf>
        </m3-2-p-drug-product>
        <m3-2-p-drug-product product-name = "Wonder drug" dosageform="Tablet" manufacturer="Company A">
                <leaf ID="a123457" operation = "new" xlink:type = "simple" checksum-type="md5" checksum =
                "7490d74c3d5e442ad57daa155253eb16" xlink:href = "m3/32-body-data/32p-drug-prod/tablet-
                5mg/32p1-desc-comp/description-and-composition.pdf">
                        <title>Wonder drug tablet product data</title>
                </leaf>
        </m3-2-p-drug-product>
</m3-2-body-of-data>
```

Example 6-5: Instructions for Extending XML eCTD DTD Elements

An applicant can extend the definition of an element by creating node extensions beneath a defined table of contents element. Using node extensions is discouraged and should be done only when unavoidable. Please refer to regional guidance before using node extensions. The child element <node-extension> should be used for each new table of contents node created. The <title> element value is inherited from the parent element. You should only extend the lowest level of defined elements. For example you can extend the <m2-3-r-regional-information> element but not the <m2-3-quality-overall-summary> element since the latter is not the lowest element defined in the table of contents.

The following is an example of a section of an eCTD instance in which the applicant extends the <m2-3-r-regional-information> to provide specific regional information as requested by a regulatory authority. The title element associated with the <node-extension> describes the extension. Alternatively, the regional information in this example could have been provided as a <leaf> element under the <m2-3-r-regional-information> element without the use of a "node extension".

```
<m2-common-technical-document-summaries>
        <m2-3-quality-overall-summary>
        <m2-3-r-regional-information>
        <node-extension>
                <title>special-summary</title>
                <leaf ID="a123456" operation = "new" xlink:type = "simple" xlink:href = "m2/23-qos/extra-
                quality-sum.pdf" checksum-type="md5" checksum = "7490d74c3d5e442ad57daa155253eb16">
                        <title>Extra Quality Summary </title>
                </leaf>
        </node-extension>
        </m2-3-r-regional-information>
        </m2-3-quality-overall-summary>
</m2-common-technical-document-summaries>
```

To update a file that has been submitted as an extended node, you should submit the replacement file using exactly the same element and "node extension" information, including the <title> element for the <node-extension>. This makes it possible for the regulatory authority to locate the original file and update its status.

Example 6-6: Instructions for Submitting Sections as Paper

During the transition to fully electronic submissions of the CTD, some regions will accept that some sections can be submitted as paper only. Please refer to regional guidance. These sections should be identified in the XML eCTD instance by including a PDF file in the instance that describes the content and location of the paper section. For example, the PDF file might consist of only one page with the name of the CTD document and the physical volume number and tab identifier. The <title> element in the XML eCTD instance could indicate that this is a paper submission.

This is an example of the instance showing the submission of a paper efficacy overview document.

```
<m2-common-technical-document-summaries>
        <m2-5-clinical-overview xml:lang = "en">
        <leaf ID=“a123456” operation = "new" xlink:type = "simple" checksum-type=“md5” checksum =
        "e854d3002c02a61fe5cbe926fd973401" xlink:href = "m2/25-clin-over/clinical-overview.pdf" application-
        version = "PDF 1.4">
                <title>Paper Submission </title>
        </leaf>
        </m2-5-clinical-overview>
</m2-common-technical-document-summaries>
```

Appendix 7: Specification for Submission Formats

Introduction

This appendix describes the way files should be constructed for inclusion in the eCTD. This section includes file formats that are commonly used in electronic submissions. Other formats can be used according to guidance published in each region.

PDF

Adobe Portable Document Format (PDF) is a published format created by Adobe Systems Incorporated (http://www.adobe.com). It is not necessary to use a product from Adobe or from any specific company to produce PDF documents. PDF is accepted as a standard for documents defined in this specification. The following recommendations support the creation of PDF files that agencies can review effectively. For any specification of the Japanese version of Adobe Acrobat, or where Japanese characters will be in the file, please refer to the regional guidance.

To ensure that PDF files can be accessed efficiently, PDF files should be no larger than 100 megabytes. Optimize PDF files for fast web view.

Version

All ICH Regional Health Authorities are able to read and have agreed to accept PDF files saved as PDF version 1.4. Agencies should not need any additional software to read and navigate the PDF files. PDF/A-1 (an ISO standard - ISO 19005-1:2005) is an archive format and does not meet the ICH review needs for use with an eCTD. Please consult regional guidance to submit other versions of PDF.

Fonts

PDF viewing software automatically substitutes a font to display text if the font used to create the text is unavailable on the reviewer's computer. Font substitution can affect a document's appearance and structure, and, in some cases, the information conveyed by a document. Agencies cannot guarantee the availability of any fonts except Times New Roman, Arial, and Courier and fonts supported in the Acrobat product set itself. Therefore, all additional fonts used in the PDF files should be embedded to ensure that those fonts would always be available to the reviewer. When embedding fonts, all characters for the font should be embedded, not just a subset of the fonts being used in the document

Embedding fonts requires additional computer storage space. Three techniques to help limit the storage space taken by embedding fonts include:

- Limiting the number of fonts used in each document
- Using only True Type or Adobe Type 1 fonts
- Avoiding customized fonts

Japanese fonts (2-byte fonts) are larger than Roman fonts (1-byte fonts), therefore, the specification allows a subset to be embedded for all Japanese fonts. The purpose of embedding fonts to is to enable the receiver of the document to use a personal computer to display and print the document correctly without having the same fonts installed in the computer. Therefore, it is not necessary to embed all Japanese fonts. Embedding a subset of Japanese fonts should work satisfactorily.

Definition of Subset

A subset means to embed only those characters used in the document. Embedding a full-set means all characters that comprise the font are embedded, even characters that are not used in the document. All two-byte fonts such as Japanese should be embedded as a sub-set.

Notes on Embedding Japanese Fonts:
The following should be considered when embedding fonts:

Advantages:
- Embedding fonts allows the PDF file to be correctly displayed and printed on any receiving PC environment.
- The computer does not need the original fonts installed.

Disadvantages:
- The file size increases when fonts are embedded.
- When document contains many pages, this can make the document slower to print.
- Many eCTD documents contain a large number of pages. Printing time in such cases becomes a concern.
- When using Japanese fonts, rules of operation should be established between the sender and receiver. (See regional guidance)
- The use of popular fonts only would allow the sender and receiver to view and print the document correctly without embedding fonts.

Font Size
Resizing a document because the contents are too small to read is inefficient. Times New Roman, 12-point font, the font used for this document, is adequate in size for narrative text and should be used whenever possible. It is sometimes tempting to use fonts which are smaller than 12 point in tables and charts but this should be avoided whenever possible. When choosing a font size for tables, a balance should be sought between providing sufficient information on a single page to facilitate data comparisons for the reviewer while maintaining a font size that remains legible. The corollary of this is that in using larger font size, more tables might be necessary, which can complicate data comparisons since data might now be included in separate tables. Generally, Times New Roman font sizes 9-10 or an equivalent size of other recommended fonts are considered acceptable in tables but smaller font sizes should be avoided.

Use of Color Fonts
The use of a black font color is recommended. Blue can be used for hypertext links. Light colors that do not print well on grayscale printers should be avoided. Color reproduction can be tested prior to submission by printing sample pages from the document using a gray scale printer. The use of background shadowing should be avoided.

Page Orientation
Pages should be properly oriented so that all portrait pages are presented in portrait and all landscape pages are presented in landscape. To achieve this, the page orientation of landscape pages should be set to landscape prior to saving the PDF document in final form.

Page Size and Margins
The print area for pages should fit on a sheet of A4 (210 x 297 mm) and Letter (8.5” x 11”) paper. A sufficient margin (at least 2.5 cm) on the left side of each page should be provided to avoid obscuring information if the reviewer subsequently prints and binds the pages for temporary use. For pages in landscape orientation (typically tables and publications), smaller margins (at least 2.0 cm at the top and 0.8 cm left and right) allow more information to be displayed legibly on the page (see Fonts). Header and footer information can appear within these margins but should not appear so close to the page edge to risk being lost upon printing.

Headers and Footers
The M4 Granularity document specifies that all pages of a document should include a unique header or footer that briefly identifies its subject matter. With the eCTD there is a significant amount of metadata

available to the reviewer to allow easy identification of the document but it is still appropriate to have a unique identifier on each page (header or footer) of the document (e.g., when the document is printed or multiple documents are viewed on screen at the same time). The unique identifier does not necessarily have to contain the CTD section identifier or other metadata. It should be sufficient to identify the general subject matter of the document (e.g., study identifier, batch number).

Source of Electronic Document

PDF documents produced by scanning paper documents are usually inferior to those produced from an electronic source document. Scanned documents saved as image files are more difficult to read and do not allow reviewers to search or copy and paste text for editing. Scanning should be avoided where possible.

Methods for Creating PDF Documents and Images

The method used for creating PDF documents should produce the best replication of a paper document. To ensure that the paper and PDF version of the document are the same, the document should be printed from the PDF version. Documents that are available only in paper should be scanned at resolutions that will ensure the pages are legible both on the computer screen and when printed. At the same time, the file size should be limited. It is recommended that scanning be undertaken at a resolution of 300 dots per inch (dpi) to balance legibility and file size. The use of grayscale or color is discouraged because of file size. After scanning, resampling to a lower resolution should be avoided.

When creating PDF files containing images, the images should not be downsampled. Downsampling does not preserve all of the pixels in the original. For PDF images, one of the following lossless compression techniques should be used:

- For lossless compression of color and grayscale images, use Zip/Flate (one technique with two names). This is specified in Internet RFC 1950 and RFC 1951 (http://www.ietf.org/rfc/rfc1950.txt).
- For lossless compression of black and white images, use the CCITT Group 4 Fax compression technique. It is specified as CCITT recommendations T.6 (1988) - *Facsimile coding schemes and coding control functions for Group 4 facsimile apparatus*.

Paper documents containing hand-written notes should be scanned at a resolution of at least 300 dpi. Hand-written notes should be done in black ink for clarity. Higher resolution is specifically requested when scanning documents containing non-Western characters (e.g. Kanji); 600 dpi is recommended.

For photographs, the image should be obtained with a resolution of 600 dpi. If black and white photos are submitted, 8-bit grayscale images should be considered. If color photos are submitted, 24-bit RGB images should be considered. A captured image should not be subjected to non-uniform scaling (i.e., sizing).

Gels and karyotypes should be scanned directly, rather than from photographs. Scanning should be at 600 dpi and 8-bit grayscale depth.

Plotter output graphics should be scanned or captured digitally at 300 dpi.

High-pressure liquid chromatography or similar images should be scanned at 300 dpi.
Applicants should validate the quality of the renditions.

Hypertext Linking and Bookmarks

Hypertext links and bookmarks improve navigation through PDF documents. Hypertext links can be designated by rectangles using thin lines or by blue text as appropriate.

In general, for documents with a table of contents, bookmarks for each item listed in the table of contents should be provided including all tables, figures, publications, other references, and appendices. Bookmarks should follow hierarchical level and order of table of contents. These bookmarks are essential for the efficient navigation through documents. The bookmark hierarchy should be identical to the table of contents with no additional bookmark levels beyond those present in the table of contents. Each additional

level increases the need for space to read the bookmarks. The use of no more than 4 levels in the hierarchy is recommended.

Hypertext links throughout the document to support annotations, related sections, references, appendices, tables, or figures that are not located on the same page are helpful and improve navigation efficiency. Relative paths should be used when creating hypertext links to minimize the loss of hyperlink functionality when folders are moved between disk drives. Absolute links that reference specific drives and root directories will no longer work once the submission is loaded onto the Agency's network servers.

When creating bookmarks and hyperlinks, the magnification setting *Inherit Zoom* should be used so that the destination page displays at the same magnification level that the reviewer is using for the rest of the document.

Insufficient experience is available across agencies to provide any formal guidance on whether bookmarks should be presented expanded or collapsed. It might not be considered appropriate to have all the bookmarks open since, in some instances, these can be so numerous that they are not useful to the review and can affect 'refresh' time in a web-browser. Equally, it is probably not useful to have the bookmarks fully closed, since the reviewer would always have to open them. It is recommended, therefore, that the applicant consider the usefulness to the reviewers of how to present bookmarks and have some level of consistency across similar document types within the submission.

Page Numbering

Only the internal page numbers of the document are expected (1-n). No additional page/volume numbers running across documents are expected. It is easier to navigate through an electronic document if the page numbers for the document and the PDF file are the same. To accomplish this, the first page of the document should be numbered page 1, and all subsequent pages (including appendices and attachments) should be numbered consecutively with Arabic numerals. Roman numerals should not be used to number pages (e.g., title pages, tables of contents) and pages should not be left unnumbered (e.g., title page.) Numbering in this manner keeps the Acrobat numbering in synchrony with the internal document page numbers.

The only exception should be where a document is split because of its size (e.g., >100 MB); the second or subsequent file should be numbered consecutively to that of the first or preceding file.

Document Information Fields

Recommendations for the document information fields will be provided in the regional guidance for the specific submission type.

Open Dialog Box

The open dialog box sets the document view when the file is opened. The initial view of the PDF files should be set as *Bookmarks* and *Page*. If there are no bookmarks, the initial view as *Page* only should be set. The *Magnification* and *Page Layout* should be set as default.

Security

No security settings or password protection for PDF files should be included. Security fields should be set to allow printing, changes to the document, selecting text and graphics, and adding or changing notes and form fields.

Indexing PDF Documents

There are no current plans in the ICH regions to use full text indexes.

Use of Acrobat Plug-Ins

It is appropriate to use plug-ins to assist in the creation of a submission. However, the review of the submission should not call for the use of any plug-ins in addition to those provided with Adobe Acrobat because agencies will not necessarily have access to the additional plug-in functionality.

XML Files

A working group at the World Wide Web Consortium (W3C) developed XML. It is a nonproprietary language developed to improve on previous markup languages including standard generalized markup language (SGML) and hypertext markup language (HTML).

Information in an XML file is divided into specific pieces. These pieces are called objects or element types. The element type identifies the piece of information. For example, the name of the company submitting a registration application in eCTD format for review is identified with the element type <applicant>. All element type names are bracketed using the special characters <>. Inside the XML document, the element type name is placed just prior to the piece of information and after the information. This is called tagging. So, in the XML file, the applicant could be tagged as follows: <applicant>Worldwide Pharmaceuticals Inc.</applicant>. The "/" prior to the element type denotes that this is the end of the information about the applicant.

It is recognized that there is a general trend towards describing the contents of documents with XML. However, the current specification supports only the use of XML for structured information. It can be interpreted from this that the submission of summaries, reports and other narrative documents in XML format is not currently supported by the specification. Regulatory authorities and applicants could agree to use other formats regionally (including uses of the common formats in a different way from the above). Thus, if an applicant wishes to use XML for narrative documents, the applicant should contact the applicant's own regional regulatory authority, understanding that other regulatory authorities may not accept these XML files.

By using a hierarchical structure, XML allows you to relate two or more elements. This is accomplished by nesting one element within another.

Additional information about the element type is provided by attributes. Attributes are placed within the element types and are surrounded by quotation marks (" ".) For example, if you wanted to show that the applicant name is presented in the English language, you could add this piece of information as an attribute. This could be represented in the XML file as <applicant XML:LANG="EN"> Worldwide Pharmaceuticals Inc.</applicant>.

XML files are read by a parser found in Internet browsers. Stylesheets provide the browser with the information to create tables, fonts, and colors for display.

The specific names of the element types and attributes as well as the valid syntax, structure and format for defining the XML elements are included in a file called document type definition (DTD). If the XML document does not follow the DTD, then the file will not be able to be used properly.

The top three lines of the XML file should include the XML version, the stylesheet type and address, and the DTD name and address.

Additional information about the XML standard can be found at the W3C Web site at www.w3.org.

SVG Files

SVG is a language for describing two-dimensional graphics in XML. SVG allows for three types of graphic objects: vector graphic shapes (e.g., paths consisting of straight lines and curves), images, and text. Graphical objects can be grouped, styled, transformed and composited into previously rendered objects. Text can be in any XML namespace suitable to the application, which enhances searchability

and accessibility of the SVG graphics. The feature set includes nested transformations, clipping paths, alpha masks, filter effects, template objects, and extensibility.

SVG drawings can be dynamic and interactive. The Document Object Model (DOM) for SVG, which includes the full XML DOM, allows for straightforward and efficient vector graphics animation via scripting. A rich set of event handlers such as onmouseover and onclick can be assigned to any SVG graphical object. Because of its compatibility and leveraging of other Web standards, features like scripting can be done on SVG elements and other XML elements from different namespaces simultaneously within the same Web page. [8]

The specific use of SVG in a submission should be discussed with the regulatory authority.

[8] This description of SVG is from w3c Web page http://www.w3.org/graphics/svg

Appendix 8: XML eCTD DTD

```
<?xml version="1.0" encoding="UTF-8"?>
<!-- Changes prior to Version 1.00 captured in file
      "Historical Changes.txt

    ICH eCTD DTD
    Version 1.0 - March 6, 2002
    Version 3.0 - Sept 11, 2002
    Version 3.0 - Oct 1, 2002
    Version 3.0 - Oct 8, 2002
    Version 3.1 - Nov 11, 2003
          Version 3.2 - Nov 21, 2003

Changes in version 3.1
-         ID was changed to REQUIRED in the following four locations:
                  <!ENTITY % att " ID      ID     #REQUIRED
          xml:lang CDATA  #IMPLIED">

        <!ELEMENT leaf (title, link-text?)>
                        <!ATTLIST leaf
                                ID ID #REQUIRED  <attlist continues>

                  <!ELEMENT xref EMPTY>
                        <!ATTLIST xref
                                ID ID #REQUIRED  <attlist continues>

                  <!ELEMENT node-extension (title, (leaf | node-extension)+)>
                        <!ATTLIST node-extension
                                ID ID #REQUIRED
                                xml:lang CDATA #IMPLIED>


Changes in version 3.2

-         Indication attribute was changed to REQUIRED in the following two locations:
                  <!ATTLIST m2-7-3-summary-of-clinical-efficacy
                  %att;
                  indication CDATA #REQUIRED

                  <!ATTLIST m5-3-5-reports-of-efficacy-and-safety-studies
                  %att;
                  indication CDATA #REQUIRED

-         Since ID is only needed for files referenced in a LEAF, changed ID back to IMPLIED for:
                  <!ENTITY % att " ID      ID     #REQUIRED
                        xml:lang CDATA  #IMPLIED">

                  <!ELEMENT node-extension (title, (leaf | node-extension)+)>
                  <!ATTLIST node-extension
                        ID ID #REQUIRED
                        xml:lang CDATA #IMPLIED>


End of changes
-->
<!ENTITY % att " ID      ID     #IMPLIED
  xml:lang CDATA  #IMPLIED">
<!-- ========================================================== -->
<!-- Top-level element -->
```

```
<!-- ============================================================= -->
<!ELEMENT ectd:ectd (m1-administrative-information-and-prescribing-information?, m2-common-technical-
document-summaries?, m3-quality?, m4-nonclinical-study-reports?, m5-clinical-study-reports?)>
<!ATTLIST ectd:ectd
        xmlns:ectd CDATA #FIXED "http://www.ich.org/ectd"
        xmlns:xlink CDATA #FIXED "http://www.w3c.org/1999/xlink"
        xml:lang CDATA #IMPLIED
        dtd-version CDATA #FIXED "3.2"
>
<!-- ============================================================= -->
<!-- Leaf content -->
<!-- ============================================================= -->
<!ELEMENT leaf (title, link-text?)>
<!ATTLIST leaf
        ID ID #REQUIRED
        application-version CDATA #IMPLIED
        version CDATA #IMPLIED
        font-library CDATA #IMPLIED
        operation (new | append | replace | delete) #REQUIRED
        modified-file CDATA #IMPLIED
        checksum CDATA #REQUIRED
        checksum-type CDATA #REQUIRED
        keywords CDATA #IMPLIED
        xmlns:xlink CDATA #FIXED "http://www.w3c.org/1999/xlink"
        xlink:type CDATA #FIXED "simple"
        xlink:role CDATA #IMPLIED
        xlink:href CDATA #IMPLIED
        xlink:show (new | replace | embed | other | none) #IMPLIED
        xlink:actuate (onLoad | onRequest | other | none) #IMPLIED
        xml:lang CDATA #IMPLIED
>
<!ELEMENT title (#PCDATA)>
<!ATTLIST title
        ID ID #IMPLIED
>
<!ELEMENT link-text (#PCDATA | xref)*>
<!ATTLIST link-text
        ID ID #IMPLIED
>
<!ELEMENT xref EMPTY>
<!ATTLIST xref
        ID ID #REQUIRED
        xmlns:xlink CDATA #FIXED "http://www.w3c.org/1999/xlink"
        xlink:type CDATA #FIXED "simple"
        xlink:role CDATA #IMPLIED
        xlink:title CDATA #REQUIRED
        xlink:href CDATA #REQUIRED
        xlink:show (new | replace | embed | other | none) #IMPLIED
        xlink:actuate (onLoad | onRequest | other | none) #IMPLIED
>
<!ELEMENT node-extension (title, (leaf | node-extension)+)>
<!ATTLIST node-extension
        ID ID #IMPLIED
        xml:lang CDATA #IMPLIED
>
<!-- ============================================================= -->
<!-- CTD Backbone structures -->
<!-- ============================================================= -->
<!ELEMENT m1-administrative-information-and-prescribing-information (leaf*)>
<!ATTLIST m1-administrative-information-and-prescribing-information
        %att;
>
```

```
<!ELEMENT m2-common-technical-document-summaries (leaf*, m2-2-introduction?, m2-3-quality-overall-summary?, m2-4-nonclinical-overview?, m2-5-clinical-overview?, m2-6-nonclinical-written-and-tabulated-summaries?, m2-7-clinical-summary?)>
<!ATTLIST m2-common-technical-document-summaries
        %att;
>
<!ELEMENT m2-2-introduction ((leaf | node-extension)*)>
<!ATTLIST m2-2-introduction
        %att;
>
<!ELEMENT m2-3-quality-overall-summary (leaf*, m2-3-introduction?, m2-3-s-drug-substance*, m2-3-p-drug-product*, m2-3-a-appendices?, m2-3-r-regional-information?)>
<!ATTLIST m2-3-quality-overall-summary
        %att;
>
<!ELEMENT m2-3-introduction ((leaf | node-extension)*)>
<!ATTLIST m2-3-introduction
        %att;
>
<!ELEMENT m2-3-s-drug-substance ((leaf | node-extension)*)>
<!ATTLIST m2-3-s-drug-substance
        %att;
        substance CDATA #REQUIRED
        manufacturer CDATA #REQUIRED
>
<!ELEMENT m2-3-p-drug-product ((leaf | node-extension)*)>
<!ATTLIST m2-3-p-drug-product
        %att;
        product-name CDATA #IMPLIED
        dosageform CDATA #IMPLIED
        manufacturer CDATA #IMPLIED
>
<!ELEMENT m2-3-a-appendices ((leaf | node-extension)*)>
<!ATTLIST m2-3-a-appendices
        %att;
>
<!ELEMENT m2-3-r-regional-information ((leaf | node-extension)*)>
<!ATTLIST m2-3-r-regional-information
        %att;
>
<!ELEMENT m2-4-nonclinical-overview ((leaf | node-extension)*)>
<!ATTLIST m2-4-nonclinical-overview
        %att;
>
<!ELEMENT m2-5-clinical-overview ((leaf | node-extension)*)>
<!ATTLIST m2-5-clinical-overview
        %att;
>
<!ELEMENT m2-6-nonclinical-written-and-tabulated-summaries (leaf*, m2-6-1-introduction?, m2-6-2-pharmacology-written-summary?, m2-6-3-pharmacology-tabulated-summary?, m2-6-4-pharmacokinetics-written-summary?, m2-6-5-pharmacokinetics-tabulated-summary?, m2-6-6-toxicology-written-summary?, m2-6-7-toxicology-tabulated-summary?)>
<!ATTLIST m2-6-nonclinical-written-and-tabulated-summaries
        %att;
>
<!ELEMENT m2-6-1-introduction ((leaf | node-extension)*)>
<!ATTLIST m2-6-1-introduction
        %att;
>
<!ELEMENT m2-6-2-pharmacology-written-summary ((leaf | node-extension)*)>
<!ATTLIST m2-6-2-pharmacology-written-summary
        %att;
```

```
>
<!ELEMENT m2-6-3-pharmacology-tabulated-summary ((leaf | node-extension)*)>
<!ATTLIST m2-6-3-pharmacology-tabulated-summary
        %att;
>
<!ELEMENT m2-6-4-pharmacokinetics-written-summary ((leaf | node-extension)*)>
<!ATTLIST m2-6-4-pharmacokinetics-written-summary
        %att;
>
<!ELEMENT m2-6-5-pharmacokinetics-tabulated-summary ((leaf | node-extension)*)>
<!ATTLIST m2-6-5-pharmacokinetics-tabulated-summary
        %att;
>
<!ELEMENT m2-6-6-toxicology-written-summary ((leaf | node-extension)*)>
<!ATTLIST m2-6-6-toxicology-written-summary
        %att;
>
<!ELEMENT m2-6-7-toxicology-tabulated-summary ((leaf | node-extension)*)>
<!ATTLIST m2-6-7-toxicology-tabulated-summary
        %att;
>
<!ELEMENT m2-7-clinical-summary (leaf*, m2-7-1-summary-of-biopharmaceutic-studies-and-associated-analytical-
methods?, m2-7-2-summary-of-clinical-pharmacology-studies?, m2-7-3-summary-of-clinical-efficacy*, m2-7-4-
summary-of-clinical-safety?, m2-7-5-literature-references?, m2-7-6-synopses-of-individual-studies?)>
<!ATTLIST m2-7-clinical-summary
        %att;
>
<!ELEMENT m2-7-1-summary-of-biopharmaceutic-studies-and-associated-analytical-methods ((leaf | node-
extension)*)>
<!ATTLIST m2-7-1-summary-of-biopharmaceutic-studies-and-associated-analytical-methods
        %att;
>
<!ELEMENT m2-7-2-summary-of-clinical-pharmacology-studies ((leaf | node-extension)*)>
<!ATTLIST m2-7-2-summary-of-clinical-pharmacology-studies
        %att;
>
<!ELEMENT m2-7-3-summary-of-clinical-efficacy ((leaf | node-extension)*)>
<!ATTLIST m2-7-3-summary-of-clinical-efficacy
        %att;
        indication CDATA #REQUIRED
>
<!ELEMENT m2-7-4-summary-of-clinical-safety ((leaf | node-extension)*)>
<!ATTLIST m2-7-4-summary-of-clinical-safety
        %att;
>
<!ELEMENT m2-7-5-literature-references ((leaf | node-extension)*)>
<!ATTLIST m2-7-5-literature-references
        %att;
>
<!ELEMENT m2-7-6-synopses-of-individual-studies ((leaf | node-extension)*)>
<!ATTLIST m2-7-6-synopses-of-individual-studies
        %att;
>
<!ELEMENT m3-quality (leaf*, m3-2-body-of-data?, m3-3-literature-references?)>
<!ATTLIST m3-quality
        %att;
>
<!ELEMENT m3-2-body-of-data (leaf*, m3-2-s-drug-substance*, m3-2-p-drug-product*, m3-2-a-appendices?, m3-2-r-
regional-information?)>
<!ATTLIST m3-2-body-of-data
        %att;
>
```

```
<!ELEMENT m3-2-s-drug-substance (leaf*, m3-2-s-1-general-information?, m3-2-s-2-manufacture?, m3-2-s-3-characterisation?, m3-2-s-4-control-of-drug-substance?, m3-2-s-5-reference-standards-or-materials?, m3-2-s-6-container-closure-system?, m3-2-s-7-stability?)>
<!ATTLIST m3-2-s-drug-substance
        %att;
        substance CDATA #REQUIRED
        manufacturer CDATA #REQUIRED
>
<!ELEMENT m3-2-s-1-general-information (leaf*, m3-2-s-1-1-nomenclature?, m3-2-s-1-2-structure?, m3-2-s-1-3-general-properties?)>
<!ATTLIST m3-2-s-1-general-information
        %att;
>
<!ELEMENT m3-2-s-1-1-nomenclature ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-1-1-nomenclature
        %att;
>
<!ELEMENT m3-2-s-1-2-structure ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-1-2-structure
        %att;
>
<!ELEMENT m3-2-s-1-3-general-properties ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-1-3-general-properties
        %att;
>
<!ELEMENT m3-2-s-2-manufacture (leaf*, m3-2-s-2-1-manufacturer?, m3-2-s-2-2-description-of-manufacturing-process-and-process-controls?, m3-2-s-2-3-control-of-materials?, m3-2-s-2-4-controls-of-critical-steps-and-intermediates?, m3-2-s-2-5-process-validation-and-or-evaluation?, m3-2-s-2-6-manufacturing-process-development?)>
<!ATTLIST m3-2-s-2-manufacture
        %att;
>
<!ELEMENT m3-2-s-2-1-manufacturer ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-2-1-manufacturer
        %att;
>
<!ELEMENT m3-2-s-2-2-description-of-manufacturing-process-and-process-controls ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-2-2-description-of-manufacturing-process-and-process-controls
        %att;
>
<!ELEMENT m3-2-s-2-3-control-of-materials ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-2-3-control-of-materials
        %att;
>
<!ELEMENT m3-2-s-2-4-controls-of-critical-steps-and-intermediates ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-2-4-controls-of-critical-steps-and-intermediates
        %att;
>
<!ELEMENT m3-2-s-2-5-process-validation-and-or-evaluation ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-2-5-process-validation-and-or-evaluation
        %att;
>
<!ELEMENT m3-2-s-2-6-manufacturing-process-development ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-2-6-manufacturing-process-development
        %att;
>
<!ELEMENT m3-2-s-3-characterisation (leaf*, m3-2-s-3-1-elucidation-of-structure-and-other-characteristics?, m3-2-s-3-2-impurities?)>
<!ATTLIST m3-2-s-3-characterisation
        %att;
>
<!ELEMENT m3-2-s-3-1-elucidation-of-structure-and-other-characteristics ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-3-1-elucidation-of-structure-and-other-characteristics
```

```
        %att;
>
<!ELEMENT m3-2-s-3-2-impurities ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-3-2-impurities
        %att;
>
<!ELEMENT m3-2-s-4-control-of-drug-substance (leaf*, m3-2-s-4-1-specification?, m3-2-s-4-2-analytical-procedures?, m3-2-s-4-3-validation-of-analytical-procedures?, m3-2-s-4-4-batch-analyses?, m3-2-s-4-5-justification-of-specification?)>
<!ATTLIST m3-2-s-4-control-of-drug-substance
        %att;
>
<!ELEMENT m3-2-s-4-1-specification ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-4-1-specification
        %att;
>
<!ELEMENT m3-2-s-4-2-analytical-procedures ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-4-2-analytical-procedures
        %att;
>
<!ELEMENT m3-2-s-4-3-validation-of-analytical-procedures ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-4-3-validation-of-analytical-procedures
        %att;
>
<!ELEMENT m3-2-s-4-4-batch-analyses ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-4-4-batch-analyses
        %att;
>
<!ELEMENT m3-2-s-4-5-justification-of-specification ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-4-5-justification-of-specification
        %att;
>
<!ELEMENT m3-2-s-5-reference-standards-or-materials ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-5-reference-standards-or-materials
        %att;
>
<!ELEMENT m3-2-s-6-container-closure-system ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-6-container-closure-system
        %att;
>
<!ELEMENT m3-2-s-7-stability (leaf*, m3-2-s-7-1-stability-summary-and-conclusions?, m3-2-s-7-2-post-approval-stability-protocol-and-stability-commitment?, m3-2-s-7-3-stability-data?)>
<!ATTLIST m3-2-s-7-stability
        %att;
>
<!ELEMENT m3-2-s-7-1-stability-summary-and-conclusions ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-7-1-stability-summary-and-conclusions
        %att;
>
<!ELEMENT m3-2-s-7-2-post-approval-stability-protocol-and-stability-commitment ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-7-2-post-approval-stability-protocol-and-stability-commitment
        %att;
>
<!ELEMENT m3-2-s-7-3-stability-data ((leaf | node-extension)*)>
<!ATTLIST m3-2-s-7-3-stability-data
        %att;
>
<!ELEMENT m3-2-p-drug-product (leaf*, m3-2-p-1-description-and-composition-of-the-drug-product?, m3-2-p-2-pharmaceutical-development?, m3-2-p-3-manufacture?, m3-2-p-4-control-of-excipients*, m3-2-p-5-control-of-drug-product?, m3-2-p-6-reference-standards-or-materials?, m3-2-p-7-container-closure-system?, m3-2-p-8-stability?)>
<!ATTLIST m3-2-p-drug-product
        %att;
```

```
        product-name CDATA #IMPLIED
        dosageform CDATA #IMPLIED
        manufacturer CDATA #IMPLIED
>
<!ELEMENT m3-2-p-1-description-and-composition-of-the-drug-product ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-1-description-and-composition-of-the-drug-product
        %att;
>
<!ELEMENT m3-2-p-2-pharmaceutical-development ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-2-pharmaceutical-development
        %att;
>
<!ELEMENT m3-2-p-3-manufacture (leaf*, m3-2-p-3-1-manufacturers?, m3-2-p-3-2-batch-formula?, m3-2-p-3-3-
description-of-manufacturing-process-and-process-controls?, m3-2-p-3-4-controls-of-critical-steps-and-intermediates?,
m3-2-p-3-5-process-validation-and-or-evaluation?)>
<!ATTLIST m3-2-p-3-manufacture
        %att;
>
<!ELEMENT m3-2-p-3-1-manufacturers ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-3-1-manufacturers
        %att;
>
<!ELEMENT m3-2-p-3-2-batch-formula ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-3-2-batch-formula
        %att;
>
<!ELEMENT m3-2-p-3-3-description-of-manufacturing-process-and-process-controls ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-3-3-description-of-manufacturing-process-and-process-controls
        %att;
>
<!ELEMENT m3-2-p-3-4-controls-of-critical-steps-and-intermediates ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-3-4-controls-of-critical-steps-and-intermediates
        %att;
>
<!ELEMENT m3-2-p-3-5-process-validation-and-or-evaluation ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-3-5-process-validation-and-or-evaluation
        %att;
>
<!ELEMENT m3-2-p-4-control-of-excipients (leaf*, m3-2-p-4-1-specifications?, m3-2-p-4-2-analytical-procedures?,
m3-2-p-4-3-validation-of-analytical-procedures?, m3-2-p-4-4-justification-of-specifications?, m3-2-p-4-5-excipients-
of-human-or-animal-origin?, m3-2-p-4-6-novel-excipients?)>
<!ATTLIST m3-2-p-4-control-of-excipients
        %att;
        excipient CDATA #IMPLIED
>
<!ELEMENT m3-2-p-4-1-specifications ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-4-1-specifications
        %att;
>
<!ELEMENT m3-2-p-4-2-analytical-procedures ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-4-2-analytical-procedures
        %att;
>
<!ELEMENT m3-2-p-4-3-validation-of-analytical-procedures ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-4-3-validation-of-analytical-procedures
        %att;
>
<!ELEMENT m3-2-p-4-4-justification-of-specifications ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-4-4-justification-of-specifications
        %att;
>
<!ELEMENT m3-2-p-4-5-excipients-of-human-or-animal-origin ((leaf | node-extension)*)>
```

```
<!ATTLIST m3-2-p-4-5-excipients-of-human-or-animal-origin
	%att;
>
<!ELEMENT m3-2-p-4-6-novel-excipients ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-4-6-novel-excipients
	%att;
>
<!ELEMENT m3-2-p-5-control-of-drug-product (leaf*, m3-2-p-5-1-specifications?, m3-2-p-5-2-analytical-
procedures?, m3-2-p-5-3-validation-of-analytical-procedures?, m3-2-p-5-4-batch-analyses?, m3-2-p-5-5-
characterisation-of-impurities?, m3-2-p-5-6-justification-of-specifications?)>
<!ATTLIST m3-2-p-5-control-of-drug-product
	%att;
>
<!ELEMENT m3-2-p-5-1-specifications ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-5-1-specifications
	%att;
>
<!ELEMENT m3-2-p-5-2-analytical-procedures ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-5-2-analytical-procedures
	%att;
>
<!ELEMENT m3-2-p-5-3-validation-of-analytical-procedures ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-5-3-validation-of-analytical-procedures
	%att;
>
<!ELEMENT m3-2-p-5-4-batch-analyses ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-5-4-batch-analyses
	%att;
>
<!ELEMENT m3-2-p-5-5-characterisation-of-impurities ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-5-5-characterisation-of-impurities
	%att;
>
<!ELEMENT m3-2-p-5-6-justification-of-specifications ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-5-6-justification-of-specifications
	%att;
>
<!ELEMENT m3-2-p-6-reference-standards-or-materials ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-6-reference-standards-or-materials
	%att;
>
<!ELEMENT m3-2-p-7-container-closure-system ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-7-container-closure-system
	%att;
>
<!ELEMENT m3-2-p-8-stability (leaf*, m3-2-p-8-1-stability-summary-and-conclusion?, m3-2-p-8-2-post-approval-
stability-protocol-and-stability-commitment?, m3-2-p-8-3-stability-data?)>
<!ATTLIST m3-2-p-8-stability
	%att;
>
<!ELEMENT m3-2-p-8-1-stability-summary-and-conclusion ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-8-1-stability-summary-and-conclusion
	%att;
>
<!ELEMENT m3-2-p-8-2-post-approval-stability-protocol-and-stability-commitment ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-8-2-post-approval-stability-protocol-and-stability-commitment
	%att;
>
<!ELEMENT m3-2-p-8-3-stability-data ((leaf | node-extension)*)>
<!ATTLIST m3-2-p-8-3-stability-data
	%att;
>
```

```
<!ELEMENT m3-2-a-appendices (leaf*, m3-2-a-1-facilities-and-equipment*, m3-2-a-2-adventitious-agents-safety-evaluation*, m3-2-a-3-excipients?)>
<!ATTLIST m3-2-a-appendices
        %att;
>
<!ELEMENT m3-2-a-1-facilities-and-equipment ((leaf | node-extension)*)>
<!ATTLIST m3-2-a-1-facilities-and-equipment
        %att;
        manufacturer CDATA #IMPLIED
        substance CDATA #IMPLIED
        dosageform CDATA #IMPLIED
        product-name CDATA #IMPLIED
>
<!ELEMENT m3-2-a-2-adventitious-agents-safety-evaluation ((leaf | node-extension)*)>
<!ATTLIST m3-2-a-2-adventitious-agents-safety-evaluation
        %att;
        manufacturer CDATA #IMPLIED
        substance CDATA #IMPLIED
        dosageform CDATA #IMPLIED
        product-name CDATA #IMPLIED
>
<!ELEMENT m3-2-a-3-excipients ((leaf | node-extension)*)>
<!ATTLIST m3-2-a-3-excipients
        %att;
>
<!ELEMENT m3-2-r-regional-information ((leaf | node-extension)*)>
<!ATTLIST m3-2-r-regional-information
        %att;
>
<!ELEMENT m3-3-literature-references ((leaf | node-extension)*)>
<!ATTLIST m3-3-literature-references
        %att;
>
<!ELEMENT m4-nonclinical-study-reports (leaf*, m4-2-study-reports?, m4-3-literature-references?)>
<!ATTLIST m4-nonclinical-study-reports
        %att;
>
<!ELEMENT m4-2-study-reports (leaf*, m4-2-1-pharmacology?, m4-2-2-pharmacokinetics?, m4-2-3-toxicology?)>
<!ATTLIST m4-2-study-reports
        %att;
>
<!ELEMENT m4-2-1-pharmacology (leaf*, m4-2-1-1-primary-pharmacodynamics?, m4-2-1-2-secondary-pharmacodynamics?, m4-2-1-3-safety-pharmacology?, m4-2-1-4-pharmacodynamic-drug-interactions?)>
<!ATTLIST m4-2-1-pharmacology
        %att;
>
<!ELEMENT m4-2-1-1-primary-pharmacodynamics ((leaf | node-extension)*)>
<!ATTLIST m4-2-1-1-primary-pharmacodynamics
        %att;
>
<!ELEMENT m4-2-1-2-secondary-pharmacodynamics ((leaf | node-extension)*)>
<!ATTLIST m4-2-1-2-secondary-pharmacodynamics
        %att;
>
<!ELEMENT m4-2-1-3-safety-pharmacology ((leaf | node-extension)*)>
<!ATTLIST m4-2-1-3-safety-pharmacology
        %att;
>
<!ELEMENT m4-2-1-4-pharmacodynamic-drug-interactions ((leaf | node-extension)*)>
<!ATTLIST m4-2-1-4-pharmacodynamic-drug-interactions
        %att;
>
```

```
<!ELEMENT m4-2-2-pharmacokinetics (leaf*, m4-2-2-1-analytical-methods-and-validation-reports?, m4-2-2-2-absorption?, m4-2-2-3-distribution?, m4-2-2-4-metabolism?, m4-2-2-5-excretion?, m4-2-2-6-pharmacokinetic-drug-interactions?, m4-2-2-7-other-pharmacokinetic-studies?)>
<!ATTLIST m4-2-2-pharmacokinetics
        %att;
>
<!ELEMENT m4-2-2-1-analytical-methods-and-validation-reports ((leaf | node-extension)*)>
<!ATTLIST m4-2-2-1-analytical-methods-and-validation-reports
        %att;
>
<!ELEMENT m4-2-2-2-absorption ((leaf | node-extension)*)>
<!ATTLIST m4-2-2-2-absorption
        %att;
>
<!ELEMENT m4-2-2-3-distribution ((leaf | node-extension)*)>
<!ATTLIST m4-2-2-3-distribution
        %att;
>
<!ELEMENT m4-2-2-4-metabolism ((leaf | node-extension)*)>
<!ATTLIST m4-2-2-4-metabolism
        %att;
>
<!ELEMENT m4-2-2-5-excretion ((leaf | node-extension)*)>
<!ATTLIST m4-2-2-5-excretion
        %att;
>
<!ELEMENT m4-2-2-6-pharmacokinetic-drug-interactions ((leaf | node-extension)*)>
<!ATTLIST m4-2-2-6-pharmacokinetic-drug-interactions
        %att;
>
<!ELEMENT m4-2-2-7-other-pharmacokinetic-studies ((leaf | node-extension)*)>
<!ATTLIST m4-2-2-7-other-pharmacokinetic-studies
        %att;
>
<!ELEMENT m4-2-3-toxicology (leaf*, m4-2-3-1-single-dose-toxicity?, m4-2-3-2-repeat-dose-toxicity?, m4-2-3-3-genotoxicity?, m4-2-3-4-carcinogenicity?, m4-2-3-5-reproductive-and-developmental-toxicity?, m4-2-3-6-local-tolerance?, m4-2-3-7-other-toxicity-studies?)>
<!ATTLIST m4-2-3-toxicology
        %att;
>
<!ELEMENT m4-2-3-1-single-dose-toxicity ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-1-single-dose-toxicity
        %att;
>
<!ELEMENT m4-2-3-2-repeat-dose-toxicity ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-2-repeat-dose-toxicity
        %att;
>
<!ELEMENT m4-2-3-3-genotoxicity (leaf*, m4-2-3-3-1-in-vitro?, m4-2-3-3-2-in-vivo?)>
<!ATTLIST m4-2-3-3-genotoxicity
        %att;
>
<!ELEMENT m4-2-3-3-1-in-vitro ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-3-1-in-vitro
        %att;
>
<!ELEMENT m4-2-3-3-2-in-vivo ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-3-2-in-vivo
        %att;
>
<!ELEMENT m4-2-3-4-carcinogenicity (leaf*, m4-2-3-4-1-long-term-studies?, m4-2-3-4-2-short-or-medium-term-studies?, m4-2-3-4-3-other-studies?)>
```

```
<!ATTLIST m4-2-3-4-carcinogenicity
	%att;
>
<!ELEMENT m4-2-3-4-1-long-term-studies ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-4-1-long-term-studies
	%att;
>
<!ELEMENT m4-2-3-4-2-short-or-medium-term-studies ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-4-2-short-or-medium-term-studies
	%att;
>
<!ELEMENT m4-2-3-4-3-other-studies ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-4-3-other-studies
	%att;
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<!ELEMENT m4-2-3-5-reproductive-and-developmental-toxicity (leaf*, m4-2-3-5-1-fertility-and-early-embryonic-development?, m4-2-3-5-2-embryo-fetal-development?, m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function?, m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated?)>
<!ATTLIST m4-2-3-5-reproductive-and-developmental-toxicity
	%att;
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<!ELEMENT m4-2-3-5-1-fertility-and-early-embryonic-development ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-5-1-fertility-and-early-embryonic-development
	%att;
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<!ELEMENT m4-2-3-5-2-embryo-fetal-development ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-5-2-embryo-fetal-development
	%att;
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<!ELEMENT m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function
	%att;
>
<!ELEMENT m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated
	%att;
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<!ELEMENT m4-2-3-6-local-tolerance ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-6-local-tolerance
	%att;
>
<!ELEMENT m4-2-3-7-other-toxicity-studies (leaf*, m4-2-3-7-1-antigenicity?, m4-2-3-7-2-immunotoxicity?, m4-2-3-7-3-mechanistic-studies?, m4-2-3-7-4-dependence?, m4-2-3-7-5-metabolites?, m4-2-3-7-6-impurities?, m4-2-3-7-7-other?)>
<!ATTLIST m4-2-3-7-other-toxicity-studies
	%att;
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<!ELEMENT m4-2-3-7-1-antigenicity ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-7-1-antigenicity
	%att;
>
<!ELEMENT m4-2-3-7-2-immunotoxicity ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-7-2-immunotoxicity
	%att;
>
<!ELEMENT m4-2-3-7-3-mechanistic-studies ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-7-3-mechanistic-studies
	%att;
>
<!ELEMENT m4-2-3-7-4-dependence ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-7-4-dependence
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        %att;
>
<!ELEMENT m4-2-3-7-5-metabolites ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-7-5-metabolites
        %att;
>
<!ELEMENT m4-2-3-7-6-impurities ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-7-6-impurities
        %att;
>
<!ELEMENT m4-2-3-7-7-other ((leaf | node-extension)*)>
<!ATTLIST m4-2-3-7-7-other
        %att;
>
<!ELEMENT m4-3-literature-references ((leaf | node-extension)*)>
<!ATTLIST m4-3-literature-references
        %att;
>
<!ELEMENT m5-clinical-study-reports (leaf*, m5-2-tabular-listing-of-all-clinical-studies?, m5-3-clinical-study-
reports?, m5-4-literature-references?)>
<!ATTLIST m5-clinical-study-reports
        %att;
>
<!ELEMENT m5-2-tabular-listing-of-all-clinical-studies ((leaf | node-extension)*)>
<!ATTLIST m5-2-tabular-listing-of-all-clinical-studies
        %att;
>
<!ELEMENT m5-3-clinical-study-reports (leaf*, m5-3-1-reports-of-biopharmaceutic-studies?, m5-3-2-reports-of-
studies-pertinent-to-pharmacokinetics-using-human-biomaterials?, m5-3-3-reports-of-human-pharmacokinetics-pk-
studies?, m5-3-4-reports-of-human-pharmacodynamics-pd-studies?, m5-3-5-reports-of-efficacy-and-safety-studies*,
m5-3-6-reports-of-postmarketing-experience?, m5-3-7-case-report-forms-and-individual-patient-listings?)>
<!ATTLIST m5-3-clinical-study-reports
        %att;
>
<!ELEMENT m5-3-1-reports-of-biopharmaceutic-studies (leaf*, m5-3-1-1-bioavailability-study-reports?, m5-3-1-2-
comparative-ba-and-bioequivalence-study-reports?, m5-3-1-3-in-vitro-in-vivo-correlation-study-reports?, m5-3-1-4-
reports-of-bioanalytical-and-analytical-methods-for-human-studies?)>
<!ATTLIST m5-3-1-reports-of-biopharmaceutic-studies
        %att;
>
<!ELEMENT m5-3-1-1-bioavailability-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-1-1-bioavailability-study-reports
        %att;
>
<!ELEMENT m5-3-1-2-comparative-ba-and-bioequivalence-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-1-2-comparative-ba-and-bioequivalence-study-reports
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>
<!ELEMENT m5-3-1-3-in-vitro-in-vivo-correlation-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-1-3-in-vitro-in-vivo-correlation-study-reports
        %att;
>
<!ELEMENT m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies ((leaf | node-extension)*)>
<!ATTLIST m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies
        %att;
>
<!ELEMENT m5-3-2-reports-of-studies-pertinent-to-pharmacokinetics-using-human-biomaterials (leaf*, m5-3-2-1-
plasma-protein-binding-study-reports?, m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies?, m5-3-
2-3-reports-of-studies-using-other-human-biomaterials?)>
<!ATTLIST m5-3-2-reports-of-studies-pertinent-to-pharmacokinetics-using-human-biomaterials
        %att;
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<!ELEMENT m5-3-2-1-plasma-protein-binding-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-2-1-plasma-protein-binding-study-reports
        %att;
>
<!ELEMENT m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies ((leaf | node-extension)*)>
<!ATTLIST m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies
        %att;
>
<!ELEMENT m5-3-2-3-reports-of-studies-using-other-human-biomaterials ((leaf | node-extension)*)>
<!ATTLIST m5-3-2-3-reports-of-studies-using-other-human-biomaterials
        %att;
>
<!ELEMENT m5-3-3-reports-of-human-pharmacokinetics-pk-studies (leaf*, m5-3-3-1-healthy-subject-pk-and-initial-
tolerability-study-reports?, m5-3-3-2-patient-pk-and-initial-tolerability-study-reports?, m5-3-3-3-intrinsic-factor-pk-
study-reports?, m5-3-3-4-extrinsic-factor-pk-study-reports?, m5-3-3-5-population-pk-study-reports?)>
<!ATTLIST m5-3-3-reports-of-human-pharmacokinetics-pk-studies
        %att;
>
<!ELEMENT m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports
        %att;
>
<!ELEMENT m5-3-3-2-patient-pk-and-initial-tolerability-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-3-2-patient-pk-and-initial-tolerability-study-reports
        %att;
>
<!ELEMENT m5-3-3-3-intrinsic-factor-pk-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-3-3-intrinsic-factor-pk-study-reports
        %att;
>
<!ELEMENT m5-3-3-4-extrinsic-factor-pk-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-3-4-extrinsic-factor-pk-study-reports
        %att;
>
<!ELEMENT m5-3-3-5-population-pk-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-3-5-population-pk-study-reports
        %att;
>
<!ELEMENT m5-3-4-reports-of-human-pharmacodynamics-pd-studies (leaf*, m5-3-4-1-healthy-subject-pd-and-pk-
pd-study-reports?, m5-3-4-2-patient-pd-and-pk-pd-study-reports?)>
<!ATTLIST m5-3-4-reports-of-human-pharmacodynamics-pd-studies
        %att;
>
<!ELEMENT m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports
        %att;
>
<!ELEMENT m5-3-4-2-patient-pd-and-pk-pd-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-4-2-patient-pd-and-pk-pd-study-reports
        %att;
>
<!ELEMENT m5-3-5-reports-of-efficacy-and-safety-studies (leaf*, m5-3-5-1-study-reports-of-controlled-clinical-
studies-pertinent-to-the-claimed-indication?, m5-3-5-2-study-reports-of-uncontrolled-clinical-studies?, m5-3-5-3-
reports-of-analyses-of-data-from-more-than-one-study?, m5-3-5-4-other-study-reports?)>
<!ATTLIST m5-3-5-reports-of-efficacy-and-safety-studies
        %att;
        indication CDATA #REQUIRED
>
<!ELEMENT m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication ((leaf | node-
extension)*)>
<!ATTLIST m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication
        %att;
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<!ELEMENT m5-3-5-2-study-reports-of-uncontrolled-clinical-studies ((leaf | node-extension)*)>
<!ATTLIST m5-3-5-2-study-reports-of-uncontrolled-clinical-studies
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>
<!ELEMENT m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study ((leaf | node-extension)*)>
<!ATTLIST m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study
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>
<!ELEMENT m5-3-5-4-other-study-reports ((leaf | node-extension)*)>
<!ATTLIST m5-3-5-4-other-study-reports
        %att;
>
<!ELEMENT m5-3-6-reports-of-postmarketing-experience ((leaf | node-extension)*)>
<!ATTLIST m5-3-6-reports-of-postmarketing-experience
        %att;
>
<!ELEMENT m5-3-7-case-report-forms-and-individual-patient-listings ((leaf | node-extension)*)>
<!ATTLIST m5-3-7-case-report-forms-and-individual-patient-listings
        %att;
>
<!ELEMENT m5-4-literature-references ((leaf | node-extension)*)>
<!ATTLIST m5-4-literature-references
        %att;
>
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