INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH M2 EWG

Electronic Common Technical Document Specification

This specification has been developed by the ICH M2 Expert Working Group in accordance with the ICH Process as pertains to the M2 EWG.

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, lifecycle management and archival 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.

The specification is divided into a series of main sections followed by a number of appendices in which detailed technical specifications are given. It will provide a mechanism whereby parts of the specification will be updated or adjusted to agreed new technologies or standards on an independent basis without the necessity of updating it all. This aspect will be covered in the chapter Change Control.

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 has 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 utilize open standards. Open standards, including proprietary standards, which through their widespread usage 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. It 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 production of 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 lifecycle 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 lifecycle requirements for products. The parts of the registration

application that are specific to a region will be covered by regional guidance. However, the backbone has been developed to handle both the regional and common parts of submissions.

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

Introduction

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:

- Change in the content of the CTD, either through the amendment of information, at the same level of detail, or by provision of more detailed definition of content and structure
- Change to the regional requirements for applications that are outside the scope of the CTD
- Updating of standards that are already in use within the eCTD
- Identification of new standards that provide additional value for the creation and/or usage of the eCTD
- Identification of new functional requirements
- Experience of use of the eCTD by all parties

The first specification for an eCTD is an ICH M2 Step 4 document. The Specification includes an appendix for the modules of the CTD. Each appendix consists of (or includes) detailed information for the structure and format to be used in preparing a CTD module.

It is understood that technology will continue to evolve at a rapid pace. There could also be changes to the CTD. Information technology capabilities and requirements will also evolve in the pharmaceutical industry and in the regulatory authorities. The change control process described in this section allows the eCTD Specification to be updated to meet new requirements and to take advantage of technology improvements. Each appendix should be updated as needed, independent of the remainder of the document.

Process

The eCTD Specification Change Control Board (CCB) is authorized by the ICH Steering Committee to make changes to the eCTD Specification to keep pace with advancing technology. Since the issuance of guidelines is the responsibility of the regulatory authorities, in line with the standards ICH process, the regulatory authorities are the voting members of the CCB. Industry representatives from each of the three regions, and Health Canada as observer, are non-voting members of the CCB. The position of chair of the CCB rotates on an annual basis among the regulatory authority members.

The three regulatory authorities represented in the ICH M2 Expert Working Group are responsible for initiating changes to the eCTD Specification, based on industry or regulatory input. A change can be proposed by any of the regulatory authorities. A group or individual, not a member of an ICH regulatory authority, can propose a change to the specification, including recommendation for experts to be invited, by submitting the proposal to one of the regional regulatory authorities.

The CCB meets on a regular schedule to discuss, evaluate and agree on proposed changes to the specification. During these meetings the members of the CCB and other invited parties evaluate the proposed changes. The decision to accept a change to the eCTD Specification is made by a unanimous vote of the regulatory authority representatives.

The agreed changes to the specification will be published for public comment in each region. Comments are collected and considered by the CCB and will be adopted in modified or unmodified form or rejected. The updated part of the eCTD Specification will be agreed upon and signed by the three regional regulatory authorities, and will be published as required in each region. The planned implementation date and transition period for each change in each region is included in the published description of the change. Adopted changes will normally be published on an annual basis except for emergency changes, e.g. an error in critical meta-data, as defined by the CCB which will be published immediately upon adoption. The CCB will provide guidance that will indicate how existing submissions and those currently undergoing late stage-compilation should be updated.

Regulatory authorities will support submissions described by at least two consecutive versions of the eCTD Specification. The regulatory authority intends to keep all versions of the specification as long as needed to process eCTD submissions that are on file with a regulatory authority.

The CCB will establish its meeting schedule at the first meeting of the CCB. The first meeting will be at the same time as the ICH Steering Committee.

Procedure

Change requests should be submitted to a regulatory authority. Change requests received at least 30 days before a scheduled CCB meeting will be placed on the agenda for that

meeting. Change requests received less than 30 days before a CCB meeting will be placed on the agenda for the following meeting.

Change requests should contain as much of the following information as possible:

- A description of the problem that the change is intended to solve.
- The proposed solution(s) – this consists of a description of the solution(s) and the text of the changes to affected documents.
- A detailed description of any testing or research that was done to support the solution(s) being proposed.
- Advice on backward compatibility issues, if any.

The CCB will maintain a public list of requests and the status of each request. New change requests will be posted to the list within 30 days of their receipt.

Approach to Documentation and Use of the eCTD Specification

The approach to the management of the specification for the eCTD is to divide the documentation into a series of independent but related appendices. This will facilitate the maintenance of the specification, as it will not require that all documentation be updated even for a small change to one part of the specification. Each appendix can be updated independently as and when required, thus being able to more readily support the currency of the specification as a whole.

Appendix 1 Overall Architecture

Guiding Design Principles

This appendix defines the basic principles that drove the design and architecture of the eCTD. Detailed specifications are defined in appendices 2 and 6.

Business Model

The business process to be supported can be described as follow:

Industry <-----> Message <------> Agency

The business process defines specific requirements for the message.

The primary focus of the eCTD is to provide a data interchange message between the industry and agencies. The industry initiates the process by creating the initial submission in terms of an electronic CTD. Throughout the lifecycle of this process, additional information will be submitted to update or modify the information contained in the initial submission e.g. supplement, amendment, variation etc. The agency can submit acknowledgements, queries and requests to the industry. These are considered simple messages utilizing electronic mail or other transport formats. The overall architecture of the eCTD is designed to provide a commonly agreed upon submission and submission structure that imposes minimal restriction to the industry and agencies.

Modular Structure of the eCTD

The structure of the electronic submission in terms of organization and navigation should be consistent with the modular structure of the Common Technical Document. The goal of this design principle is to standardize the electronic format of the common parts of the eCTD.

XML Based eCTD

The XML eCTD DTD (Document Type Definition) defines the overall structure of the submission. The purpose of the XML backbone is two-fold: (1) to manage meta-data for the entire submission and each document within the submission and (2) to constitute a comprehensive table of contents and provide corresponding navigation aids. Meta-data on submission level includes information about submitting and receiving organization, manufacturer, publisher, ID and kind of the submission, and related data items. Examples for meta-data on document level are versioning information, language, descriptive information such as document names, checksums, etc. Details are defined in appendix 6.

The XML instance of any submission should be created and validated according to the XML eCTD DTD as defined in appendix 8.

The XML eCTD DTD describes the hierarchical structure according to the CTD as defined by the ICH M4 expert working group. It includes multiple hierarchical levels depending on the specific module as defined in the CTD. The actual submission can

include more hierarchical levels below those defined in the CTD. The XML eCTD instance covers the entire submission including all hierarchical levels and includes references to each individual file.

The submission should include a style sheet that supports presentation of the XML instance, navigation according to the table of contents and provides access to all documents within the submission. A standard style sheet is defined and provided by the ICH M2 EWG. Presentation and navigation via other style sheets on the receiving side should be possible.

The XML eCTD DTD includes a reference for each document to the physical file within the folder structure. The XML eCTD DTD includes attributes for descriptive names of folders and documents.

Multiple Region Support

The scope of each submission is global according to the Common Technical Document, meaning that modules 2 through 5 of a submission are intended for all regions with the exception of selected documents (e.g. in the quality module), which have a regional scope. Module 1 of a submission is regional in nature.

The DTD as defined by the ICH M2 expert working group specifies the structure of the common parts of the eCTD primarily focusing in module 2 through 5. It allows linking to regional DTDs for module 1 which will be defined by the authorities in each region.

Lifecycle Management

The applicant creates a submission that is stored in a local repository. The applicant submits the initial submission to the agency, which imports the submission into another local repository. The nature and kind of the local repositories is not within the scope of the eCTD. The initial submission should be self-contained meaning that it includes all documents and no references to other submissions. Regional guidance should be consulted if references to other submissions are needed.

Following the initial submission, the applicant can submit incremental updates such as amendments and variations. Updates can refer to documents in the previous submissions. Updates should be designed in a way that they can be loaded into the repository by fully preserving the initial or previous submission via version control. The XML backbone should include meta-data identifying the update and providing navigation aids to filter for different submission types.

It is preferred that when a Common Technical Document is submitted electronically, the entire submission should be in electronic form with the exception of certain regional forms that currently require written signatures. See appendix 5 for regional requirements. See appendix 6 for a description of how to submit a CTD containing both paper and electronic components.

Appendix 2 The eCTD Submission

Introduction

This appendix specifies the Information Technology aspect of the eCTD Submission. Informally, the eCTD Submission is a directory structure with files including the XML eCTD instance, reports, data and other submission information. The eCTD Submission supports multilingual and multi-region aspects.

The eCTD Submission

An eCTD Submission is a collection of data objects that follows the eCTD Specification. The main function of the eCTD Submission is data exchange. Information systems would have to be created to process the eCTD Submission. The biggest benefits are expected when the eCTD Submission is loaded into an information system that supports the review process. However, one can view an eCTD Submission with a web browser as it is web ready. In the web environment, the eCTD Submission should be usable without processing in at least in the following ways:

- Standalone: Viewable with a web browser.
- Network: Loadable into a web server.

The eCTD Submission is composed of the following:

- Directory Structure
- XML eCTD instance
- Content files

Directory Structure

The directory structure is a structure of directories and files. There should be a reasonable maximum number of entries (directories and files) per directory. The directory structure should follow the rules below. The files could be in several formats as specified of below.

The name of the files and directories are identifiers. They should be short. The file names are not intended to convey meta-data, though some meaning in the names helps; i.e., no random names.

Names for directories and files are recommended in Appendix 4. Any directory names and file names that are added to the eCTD submission by the applicant should be descriptive and logical.

XML eCTD Instance

The instance is in the submission sequence number directory (see appendix 6). The submission sequence number directory should contain at least two files and one or more directories. One of the files in the submission sequence directory is the instance and the other is the MD5 checksum of the instance. The instance is the starting file for the processing by an XML processor.

The intention is to have links from the instance to leaf files in the eCTD submission as opposed to creating a single XML document that contains the entire eCTD submission. The instance should contain mostly linking facilities to the leaf files. The instance also contains meta-data at the leaf level.

eCTD Template

The ICH web site includes an eCTD Template that is an empty directory structure with a recommended style sheet. It is an illustration of an eCTD Submission and it is ready to be populated with the applicant data. Appendix 4 defines the directories used to create this template.

Logical Documents and Files

A logical document is comprised of one or more CTD table of contents sections that together contain the minimum amount of information to be exchanged. In general, the XML eCTD DTD maps explicitly to the CTD table of contents, but there are exceptions where the XML eCTD DTD maps to the level of use designated by the appropriate ICH CTD Implementation Working Group (IWG) instead. Ideally, a logical document consists of a single physical file. In the event the physical file exceeds the recommended maximum file size due to graphics, data content, scanned images, or other large format content, additional files may make up the logical document. Furthermore, if the logical document consists of multiple file formats, then more than one physical file would be needed. An example of such a case would be PDF and XML data that together represent the logical document.

Formats

Formats should be readable at least for as long as it is needed for the regulatory process. This process could be very long; e.g. 50 years. This points to neutral formats: formal standard, industrial standard, vendor independent, text-like, etc. The format should be adapted to the type of data. Appendix 7 describes the way in which these files should be constructed.

The list of agreed formats will be updated as technology evolves and new requirements arise. XML will be the preferred format for all types of data.

Common Formats

The common formats that can be included in an eCTD Submission are:

- Narrative: Portable Document Format (PDF)
- Structured: Extensible Markup Language (XML)
- Graphic: Whenever possible, use PDF. When appropriate or when PDF is not possible, use Joint Photographic Experts Group (JPEG), Portable Network Graphics (PNG), Scalable Vector Graphics (SVG) and Graphics Interchange Format (GIF). Special formats for very high resolutions may be appropriate on a case-by-case basis.

Regional Use of Other Formats

Regulatory authorities and applicants could agree to use other formats regionally; i.e.,

non-common formats or uses of the common formats in a different way from above. The use of other formats is discouraged and the intention is to use as much as possible the common formats. The intention of the use of other formats is for transition.

There are two classes of transitions:

- Legacy Transition: from the past to the present; i.e., old formats to present formats.
- Future Transition: from the present to the future; i.e., from present formats to new formats. The new formats would normally be candidates for common formats.

Links

Links among objects in the eCTD Submission should be relative. The intention is to make the eCTD submission self-contained. All literature references introduced by the applicant should be included in the submission, for secondary references (references to a reference), absolute links to external objects can be used.

One can always point to a file. The capacity to point to a specific location within a file depends on the linking technology. Different formats allow for the use of different linking technology. See Appendix 7.

Presentation

Presentation is closely associated with formats. To associate a style sheet with a file usually one has to use a linking technology. The linking between style sheet (that could be in a separate file) and a data file should be relative. In addition, there is the dimension of media. One file could have several style sheets; the one used depends on the media. For example, there could be one presentation for the screen and another for paper.

Checksums

The eCTD Submission should contain checksums for each individual file including a checksum file for the eCTD XML instance. Initially, the MD5 Message-Digest Algorithm (MD5) should be used for this purpose. Including a checksum for each individual file provides a number of benefits including:

- The integrity of each file can be verified by comparing the checksum submitted with the file and the computed checksum.
- The checksum can be used to verify that the file has not been altered in the historical archive of the regulatory authority. This is especially useful as the files are migrated from one storage medium to another, as in the case of backup to magnetic tape storage.

Element to file directory mapping

Follow these rules:

- The rules below for the file and directories take precedence.
- Add the corresponding extension to the file.
- If needed, use a reasonable abbreviation.

File extension

All files should have one and only one file extension. The file extension should be used to indicate the format of the file. For example:

hello.pdf	PDF
hello.rtf	RTF

The mapping between formats and extensions are:

IANA nomenclature	
text/css	css
text/html	html or htm
text/xml	xml
application/pdf	pdf
application/rtf	rtf
application/vnd.ms-excel	xls
image/jpeg	jpg
image/png	png
image/gif	gif

Non IANA nomenclature	
DTD	dtd
XPT (SAS)	xpt
XSL	xsl

The eCTD Submission could use formats not registered with the Internet Assigned Numbers Authority (IANA).

The presence of a format in this list does not imply that it would be considered an acceptable format. For formats absent from this list, widely used mapping between the formats and the extensions should be used.

Future direction: if a mechanism (e.g., standard) becomes available that associate the formats with file extension, it should be considered for this specification.

Name

Name is a token composed of the following characters:

- Letters "a" to "z [U+0061 to U+007A].
- Digits "0" to "9" [U+0030 to U+0039].
- "-" [HYPHEN-MINUS, U+002D].

The notation "U+" refers to the Unicode [UNICODE] notation.

Correct Names (only the name without the extension):

part-b
myfile

hello

Incorrect names (only the name without the extension):

part a	(' ' ; SPACE is not allowed)
myfile.xml	('.' ; FULL STOP is not allowed)
hello:pdf	(':' ; COLON is not allowed)
part_a	('_', LOW LINE is not allowed)

Directory name is a name.

File name is one name followed by one name separated by a '.' (FULL STOP, U+002E).

Correct file names (with the extension):

myfile.pdf
hello.cml

Incorrect file names (with the extension)::

a part.pdf	(' ' ; SPACE is not allowed)
hello	(missing extension)
hello:xml	(':' ; COLON is not allowed)

The maximum length of a directory name or a file name is 64 characters. Only lower case letters should be used in all file and directory names. The maximum length of a path is 256 characters. For example, "data/module_1/introduction.html" is the path; "introduction.html" is a File Name.

Document Name is the first Name in the File Name. For example, "docname" in the file name "docname.ext".

Character encoding

The character encoding (charset) in order of preference is:

- Unicode UTF-8, Unicode 16 bits [ISO-10646].
- ISO-8859-1 (Latin-1) or appropriate ISO-8859-x; e.g., ISO-8859-7 for Greek.
- The appropriate SHIFT_JIS.
- Other character encoding agreed upon regionally by the regulatory authority and applicant.

References

[CML] *Chemical Markup Language*
http://www.xml-cml.org

[CSS2] *Cascading Style Sheets, level 2*
http://www.w3.org/TR/REC-CSS2

[ECMAScript] *ECMAScript Language Specification*, 3rd edition. ECMA- 262
http://www.ecma.ch/ecma1/STAND/ECMA-262.HTM

[EXCEL] Microsoft Excel
http://www.microsoft.com/office/excel/default.htm

[GIF] *Graphics Interchange Format*
http://tronche.com/computer-graphics/gif/gif89a.html

[HTML] *HTML 4.01 Specification*
http://www.w3.org/TR/html4

[IANA] Internet Assigned Numbers Authority
http://www.iana.org

[IMT] Internet Media Types
http://www.isi.edu/in-notes/iana/assignments/media-types/media-types

[ISO-10646] Information Technology -- Universal Multiple-Octet Coded Character Set (UCS) -- Part 1: Architecture and Basic Multilingual Plane, ISO/IEC 10646-1:1993

[ISO-639] *Codes for the representation of names of languages*
ISO 639:1988.
http://www.iso.ch/cate/d4766.html
http://www.oasis-open.org/cover/iso639a.html.

[JPEG] Joint Photographic Experts Group
http://www.jpeg.org/public/wg1n1807.txt

[MD5] *The MD5 Message-Digest Algorithm*
http://ietf.org/rfc/rfc1321.txt

[PDF] *Portable Document Format*
http://partners.adobe.com/asn/developer/technotes.html#pdfspec

[PNG] *PNG (Portable Network Graphics) Specification Version 1.0*
http://www.w3.org/TR/REC-png.html

[RTF] *Rich Text Format (RTF) Specification, version 1.6*
http://msdn.microsoft.com/library/specs/rtfspec.htm

[SVG] *Scalable Vector Graphics (SVG) 1.0 Specificatio*n (work in progress)
http://www.w3.org/TR/1999/WD-SVG-19991203

[UNICODE] Unicode Consortium
http://www.unicode.org

[XHTML] *XHTML 1.0: The Extensible HyperText Markup Language*
http://www.w3.org/TR/WD-html-in-xml

[XML] *Extensible Markup Language (XML) 1.0 (Second Edition)*
http://www.w3.org/TR/REC-xml.html

[XSL] *Extensible Stylesheet Language (XSL)*
W3C Candidate Recommendation 21 November 2000 (work in progress)
http://www.w3.org/TR/WD-xsl

[XSLT] *XSL Transformations*
http://www.w3.org/TR/xslt.html

Appendix 3 General Considerations for the CTD Modules

Introduction

Documents that are provided in the different modules should be formatted as defined by the ICH Common Technical Document. There should also be consistency in the way navigation aids are provided. Within each document, bookmarks and hypertext links from the table of contents should be provided to all tables, figures, publications, and appendices.

Hypertext links should be provided throughout the body of these documents to aid efficient navigation to annotations, related sections, publications, appendices, tables, and figures that are not located on the same page. If a list of references is included at the end of a document, there should be hypertext links to the appropriate publication.

Documents should be generated from electronic source documents and not from scanned material, except where access to the source electronic file is not available or where a signature is required.

Folder and File Naming Conventions

A folder and file organization is presented in this specification. This could be used in most cases, however applicants may modify this specification where appropriate.[1] For example, to include an additional folder for information where an appropriate folder name is not available in the eCTD specification. It is recommended that applicants maintain folder names listed in this specification. This should not be interpreted to mean that the actual eCTD XML DTD should be changed or altered in any way.

The maximum length of a folder or file name is 64 characters including the extension. Folder or file names should be written in lower case only. All files should have one and only one file extension. The file extension should be used to indicate the format of the file. More details on the naming conventions are given in appendix 2, and examples in appendix 4.

Typically, the file name would be the applicant's internal numbering or naming convention for the studies. The following table gives an example how files could be named.

[1] Regulatory authorities should be notified of additions and changes to the folder structure according to regional guidance.

Table 3-1

Description	File Name
Study Report 1	*study-report-1.pdf*
Study Report 2	*study-report-2.pdf*
…	…
Study Report n	*study-report-n.pdf*

Data listings can be included as part of a study report document or as a separate appendix. An example of such file names follows.

Table 3-2

Description	File Name
Study Report 1	*study-report-1.pdf*
Study Report 1 Data	*study-report-1-data.pdf*
Study Report 2	*study-report-2.pdf*
Study Report 2 Data	*study-report-2-data.pdf*
…	…
Study Report n	*study-report-n.pdf*
Study Report n Data	*study-report-n-data.pdf*

Regional requirements can provide for the submission of the data listings as a data file. Reference should be made to regional guidances.

Screenshots and folder hierarchy

Screenshots are provided in the following chapters for all modules down to the level of hierarchy as described in this appendix. The representations are in alphabetical order due to the nature of the computer operating system and are therefore not entirely consistent with the sequence of the CTD. In a web browser the content will appear in the order of the CTD table of contents.

Detailed options on the folders and files are provided in appendix 4 in case the applicant chooses to submit more granular documents. It is not mandatory to use the full folder hierarchy. Empty directories can be omitted.

Module 1 Administrative Information and Prescribing Information

The name of the folder for module 1 should be *module-1*.

This module contains administrative information that is unique for each region. Regional guidance will provide the specific instructions on how to provide the administrative forms and detailed prescribing information. Please refer to appendix 5 when preparing module 1.

Module 2 Summaries

The files in this module should be provided as PDF text with the exception of a few embedded images, when needed. The name of the folder for module 2 should be *module-2*. The folders in module 2 should be named as follows.

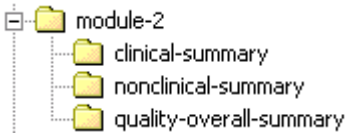
Table 3-3

Section in CTD	Description	Folder Name
2.3	Quality Overall Summary	*quality- overall-summary*
2.6	Nonclinical Written and Tabulated Summary	*nonclinical-summary*
2.7	Clinical Summary	*clinical-summary*

Other sections at this level not listed above can typically be submitted as individual files.

The folder hierarchy for module 2 is presented in the screenshot in figure 3-1.

Figure 3-1 Screenshot of the folder structure of module 2



Module 3 Quality

The name of the folder for module 3 should be *module-3*. The folders in module 3 should be named as follows.

Table 3-4

Section in CTD	Description	Folder Name
3.2	Body of Data	*body-of-data*
3.2.S	Drug Substance	*drug-substance*

Section in CTD	Description	Folder Name
3.2.S	Drug Substance [Drug Substance Name] [Manufacturer][2]	*substance-1-manufacturer-1*
3.2.S.1	General Information	*general-information*
3.2.S.2	Manufacture	*manufacture*
3.2.S.3	Characterisation	*characterisation*
3.2.S.4	Control of Drug Substance	*control-drug-substance*
3.2.S.4.1	Analytical Procedures	*analytical-procedures*
3.2.S.4.2	Validation Analytical Procedures	*validation-analyt-procedures*
3.2.S.7	Stability	*stability*
3.2.P	Drug Product[3]	*drug-product*
3.2.P	Product 1	*product-1*
3.2.P.3	Manufacture	*manufacture*
3.2.P.4	Control of Excipients	*control-excipients*
3.2.P.4	Excipient 1	*excipient-1*
3.2.P.5	Control of Drug Product	*control-drug-product*
3.2.P.5.1	Analytical Procedures	*analytical-procedures*
3.2.P.5.2	Validation Analytical Procedures	*validation-analyt-procedures*
3.2.P.8	Stability	*stability*
3.2.A	Appendices	*appendices*
3.2.A.1	Facilities and Equipment	*facilities-and-equipment*
3.2.A.2	Adventitious Agents Safety Evaluation	*adventitious-agents*
3.2.A.3	Novel Excipient 1 [4]	*novel-excipient-name-1*
3.2.R	Regional Information[5]	*regional-information*

[2]Each drug substance-manufacturer should be placed in a separate subordinate folder. Folders and files should be created for each drug substance-manufacturer section included in the submission in accordance with the hierarchy identified in the following chapters.

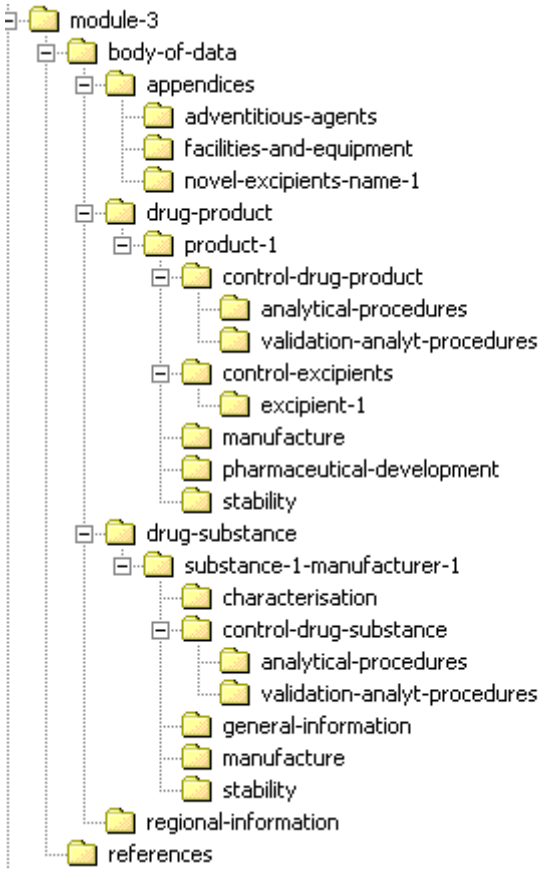
[3] Each drug product should be placed in a separate subordinate folder. Folders and files should be created for each drug product section included in the submission in accordance with the hierarchy identified in the following chapters. Reference should be made to regional guidance to determine whether the inclusion of multiple products within a single application is considered appropriate.

[4] The folder name should include the name of the novel excipient, abbreviated as necessary to remain within the 64 character limit.

Section in CTD	Description	Folder Name
3.3	Literature References	*references*

The folder hierarchy for module 3 is presented in the screenshot in figure 3-2.

Figure 3-2 Screenshot of the folder structure of module 3



Module 4 Nonclinical Study Reports

The name of the folder for module 4 should be *module-4.* The folders in module 4 should be named as follows.

Table 3-5

Section in CTD	**Description**	**Folder Name**

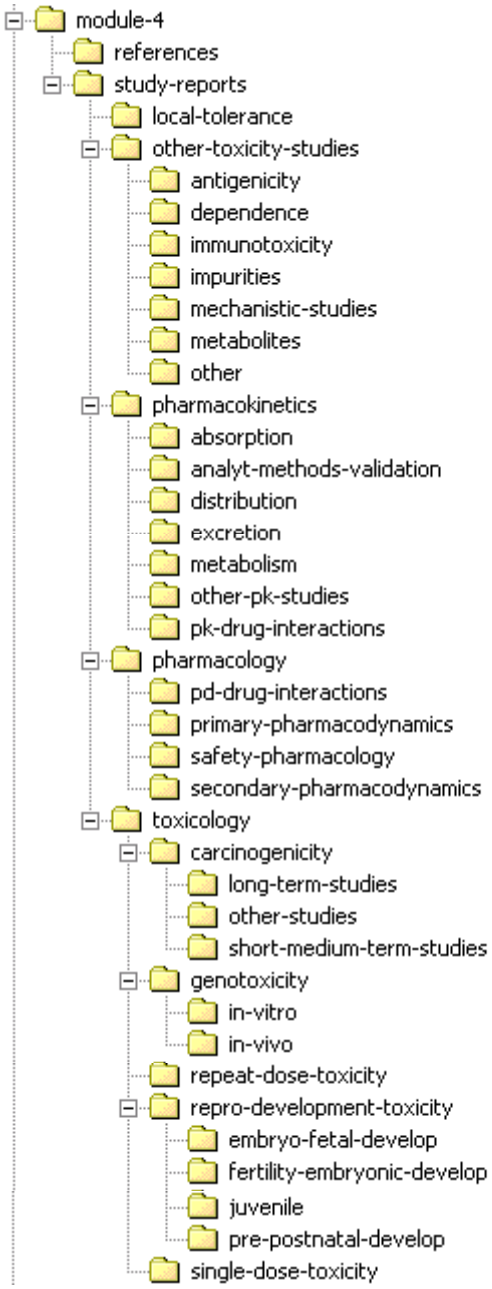
[5] This folder should be included where regional information is appropriate. Reference should be made to regional guidance for the types of information to be included in this section.

Section in CTD	Description	Folder Name
4.2	Study Reports	*study-reports*
4.2.1	Pharmacology	*pharmacology*
4.2.1.1	Primary Pharmacodynamics	*Primary-pharmacodynamics*
4.2.1.2	Secondary Pharmacodynamics	*secondary-pharmacodynamics*
4.2.1.3	Safety Pharmacology	*safety-pharmacology*
4.2.1.4	Pharmacodynamic Drug Interactions	*pd-drug-interactions*
4.2.2	Pharmacokinetics	*pharmacokinetics*
4.2.2.1	Analytical Methods and Validation Reports (if separate reports are available)	*analyt-methods-validation*
4.2.2.2	Absorption	*absorption*
4.2.2.3	Distribution	*distribution*
4.2.2.4	Metabolism	*metabolism*
4.2.2.5	Excretion	*excretion*
4.2.2.6	Pharmacokinetic Drug Interactions (nonclinical)	*pk-drug-interactions*
4.2.2.7	Other Pharmacokinetic Studies	*other-pk-studies*
4.2.3	Toxicology	*toxicology*
4.2.3.1	Single-Dose Toxicity (in order by species, by route)	*single-dose-toxicity*
4.2.3.2	Repeat-Dose Toxicity (in order by species, by route, by duration, including supportive toxicokinetic evaluations)	*repeat-dose-toxicity*
4.2.3.3	Genotoxicity	*genotoxicity*
4.2.3.3.1	In vitro	*in-vitro*
4.2.3.3.2	In vivo (including supportive toxicokinetics evaluations)	*in-vivo*
4.2.3.4	Carcinogenicity (including supportive toxicokinetics evaluations)	*carcinogenicity*
4.2.3.4.1	Long-term studies (in order by species, including range-finding studies that cannot be appropriately include under	*long-term-studies*

Section in CTD	Description	Folder Name
	repeat-dose toxicity or pharmacokinetics)	
4.2.3.4.2	Short-or medium-term studies (including range-finding studies that cannot be appropriately include under repeat-dose toxicity or pharmacokinetics)	*short-medium-term-studies*
4.2.3.4.3	Other studies	*other-studies*
4.2.3.5	Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations)	*repro-development-toxicity*
4.2.3.5.1	Fertility and early embryonic development	*fertility-embryonic-develop*
4.2.3.5.2	Embryo-fetal development	*embryo-fetal-develop*
4.2.3.5.3	Prenatal and postnatal development, including maternal function	*pre-postnatal-develop*
4.2.3.5.4	Studies in which the offspring (juvenile animals) are dosed and/or further evaluated	*juvenile*
4.2.4	Local Tolerance	*local-tolerance*
4.2.5	Other Toxicity Studies (if available)	*other-toxicity-studies*
4.2.5.1	Antigenicity	*antigenicity*
4.2.5.2	Immunotoxicity	*immunotoxicity*
4.2.5.3	Mechanistic studies (if not included elsewhere)	*mechanistic-studies*
4.2.5.4	Dependence	*dependence*
4.2.5.5	Metabolites	*metabolites*
4.2.5.6	Impurities	*impurities*
4.2.5.7	Other	*other*
4.3	Literature References	*references*

The folder hierarchy for module 4 is presented in the screenshot in figure 3-3.

Figure 3-3 Screenshot of the folder structure of module 4



Module 5 Clinical Study Reports

The name of the folder for module 5 should be *module-5.* The folders in module 5 should be named as follows.

Table 3-6

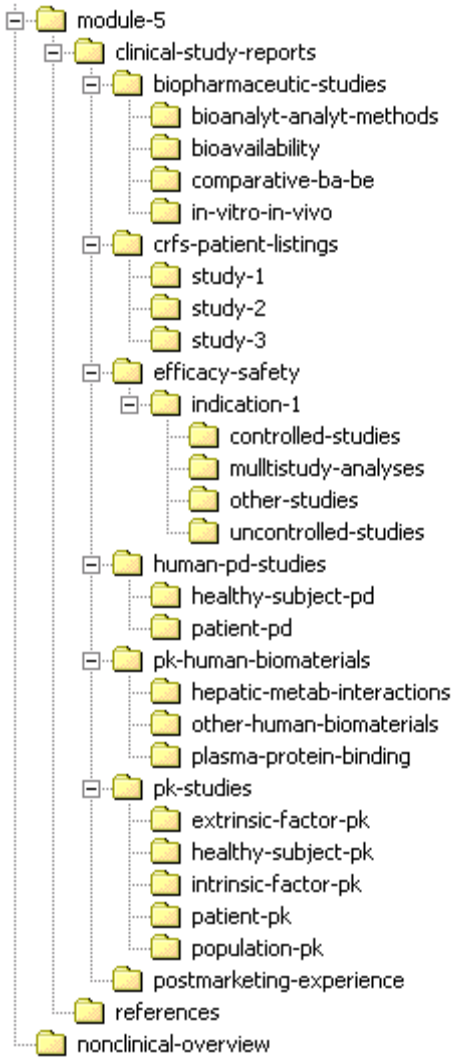
Section in CTD	Description	Folder Name
5.3	Clinical Study Reports	*clinical-study-reports*
5.3.1	Reports of Biopharmaceutic Studies	*biopharmaceutic-studies*
5.3.1.1	Bioavailaility (BA) Study Reports	*bioavailability*
5.3.1.2	Comparative BA and Bioequivalence (BE) Study Reports	*comparative-ba-be*
5.3.1.3	In vitro – In vivo Correlation Study Reports	*in-vitro-in-vivo*
5.3.1.4	Reports of Bioanalytical and Analytical Methods for Human Studies	*bioanalyt-analyt-methods*
5.3.2	Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials	*pk-human-biomaterials*
5.3.2.1	Plasma Protein Binding Study Reports	*plasma-protein-binding*
5.3.2.2	Reports of Hepatic Metabolism and Interaction Studies	*hepatic-metab-interactions*
5.3.2.3	Reports of Studies Using Other Human Biomaterials	*other-human-biomaterials*
5.3.3	Reports of Human Pharmacokinetic (PK) Studies	*pk-studies*
5.3.3.1	Healthy Subject PK and Initial Tolerability Study Reports	*healthy-subject-pk*
5.3.3.2	Patient PK and Initial Tolerability Study Reports	*patient-pk*
5.3.3.3	Intrinsic Factor PK Study Reports	*intrinsic-factor-pk*
5.3.3.4	Extrinsic Factor PK Study Reports	*extrinsic-factor-pk*
5.3.3.5	Population PK Study Reports	*population-pk*
5.3.4	Reports of Human Pharmacodynamic (PD) Studies	*human-pd-studies*
5.3.4.1	Healthy Subject PD and PK/PD Study Reports	*healthy-subject-pd*
5.3.4.2	Patient PD and PK/PD Study Reports	*patient-pd*
5.3.5	Reports of Efficacy and Safety Studies	*efficacy-safety*

Section in CTD	Description	Folder Name
	"Indication 1"	*indication*-1
	"Indication 2"	*indication*-2
	"Indication 3"	*indication*-3
5.3.5.1	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication	*controlled-studies*
5.3.5.2	Study Reports of Uncontrolled Clinical Studies	*uncontrolled-studies*
5.3.5.3	Reports of Analyses of Data from More than One Study	*multistudy-analyses*
5.3.5.4	Other Study Reports	*other-studies*
5.3.6	Reports of Postmarketing Experience	*postmarketing-experience*
5.3.7	Case Report Forms and Individual Patient Listings[6]	*crfs-patient-listings*
	"Study 1"	*study-1*
	"Study 2"	*study-2*
	"Study n"	*study-n*
5.4	References	*references*

[6] This folder contains as many folders as studies are included. The folders should be named as indicated. The content of the folders should follow regional guidance.

The folder hierarchy for module 5 is presented in the screenshot in figure 3-4.

Figure 3-4 Screenshot of the folder structure of module 5



Appendix 4 File Organization for the eCTD

Each item in the file organization table that is included in this appendix includes the following information: The table below covers files that constitute the backbone itself plus necessary additional files to make the submission complete, readable and processable.

Where file names are presented in italics typically applicants would substitute these with file names in accordance with their own naming conventions.

Sequential number		Each item in the table has a unique sequentially assigned reference number. These reference numbers can change with each version of this appendix.
	Number	CTD section number
	Title	CTD title
	Element	Element name in the Backbone
	File/Directory	Full path of the File/Directory. The file extension corresponds to the file type; i.e., the "pdf" extension is only illustrative. Refer to Table 6.1, Appendix 6 for details for the head of the path name
	Comment	Comments

1	Number	
	Title	
	Element	
	File	index.xml
	Comment	This is Backbone
2	Number	
	Title	
	Element	
	File	index-md5.txt
	Comment	The MD5 of the Backbone

3	Number	1
	Title	Administrative Information and Prescribing Information
	Element	m1-administrative-information-and-prescribing-information
	Directory	module-1
	Comment	Only one of the regional directory is needed
4	Number	
	Title	
	Element	
	Directory	module-1/eu
	Comment	EU directory : In addition to the appropriate regional documents, the regional xml instance should be located in this folder. Refer to regional guidance for details
5	Number	
	Title	
	Element	
	Directory	module-1/jp
	Comment	Japan directory : In addition to the appropriate regional documents, the regional xml instance should be located in this folder. Refer to regional guidance for details
6	Number	
	Title	
	Element	
	Directory	module-1/us
	Comment	US directory : In addition to the appropriate regional documents, the regional xml instance should be located in this folder. Refer to regional guidance for details
7	Number	
	Title	
	Element	
	Directory	module-1/xx

	Comment	xx directory; where xx is a two character country code from ISO-3166-1. : In addition to the appropriate regional documents, the regional xml instance should be located in this folder. Refer to regional guidance for details

8	Number	2
	Title	Common Technical Document Summaries
	Element	m2-common-technical-document-summaries
	Directory	module-2
	Comment	
9	Number	2.2
	Title	Introduction
	Element	m2-2-introduction
	File	module-2/introduction.pdf
	Comment	
10	Number	2.3
	Title	Quality Overall Summary
	Element	m2-3-quality-overall-summary
	Directory	module-2/quality-overall-summary
	Comment	
11	Number	2.3
	Title	Introduction
	Element	m2-3-introduction
	File	module-2/quality-overall-summary/introduction.pdf
	Comment	
12	Number	2.3.S
	Title	Drug Substance
	Element	m2-3-s-drug-substance
	File	module-2/quality-overall-summary/drug-substance.pdf
	Comment	Typically, this logical 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.
13	Number	2.3.P
	Title	Drug Product

	Element	m2-3-p-drug-product
	File	module-2/quality-overall-summary/drug-product.pdf
	Comment	Typically, this logical 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.
14	Number	2.3.A
	Title	Appendices
	Element	m2-3-a-appendices
	File	module-2/quality-overall-summary/appendices.pdf
	Comment	Typically, this logical 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.
15	Number	2.3.R
	Title	Regional Information
	Element	m2-3-r-regional-information
	File	module-2/quality-overall-summary/regional-information.pdf
	Comment	
16	Number	2.4
	Title	Nonclinical Overview
	Element	m2-4-nonclinical-overview
	File	module-2/nonclinical-overview.pdf
	Comment	Typically, this logical 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.
17	Number	2.5
	Title	Clinical Overview
	Element	m2-5-clinical-overview
	File	module-2/clinical-overview.pdf
	Comment	Typically, this logical 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.
18	Number	2.6
	Title	Nonclinical Written and Tabulated Summary

	Element	m2-6-nonclinical-written-and-tabulated-summary
	Directory	module-2/nonclinical-summary
	Comment	
19	Number	2.6.1
	Title	Introduction
	Element	m2-6-1-introduction
	File	module-2/nonclinical-summary/introduction.pdf
	Comment	
20	Number	2.6.2
	Title	Pharmacology Written Summary
	Element	m2-6-2-pharmacology-written-summary
	File	module-2/nonclinical-summary/pharmacol-written-summary.pdf
	Comment	Typically, this logical 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.
21	Number	2.6.3
	Title	Pharmacology Tabulated Summary
	Element	m2-6-3-pharmacology-tabulated-summary
	File	module-2/nonclinical-summary/phamacol-tabulated-summary.pdf
	Comment	Should have further navigation via bookmarks
22	Number	2.6.4
	Title	Pharmacokinetics Written Summary
	Element	m2-6-4-pharmacokinetics-written-summary
	File	module-2/nonclinical-summary/pharmkin-written-summary.pdf
	Comment	Typically, this logical 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.
23	Number	2.6.5
	Title	Pharmacokinetics Tabulated Summary
	Element	m2-6-5-pharmacokinetics-tabulated-summary
	File	module-2/nonclinical-summary/pharmkin-tabulated-summary.pdf

	Comment	Should have further navigation via bookmarks
24	Number	2.6.6
	Title	Toxicology Written Summary
	Element	m2-6-6-toxicology-written-summary
	File	module-2/nonclinical-summary/toxicology-written-summary.pdf
	Comment	Typically, this logical 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.
25	Number	2.6.7
	Title	Toxicology Tabulated Summary
	Element	m2-6-7-toxicology-tabulated-summary
	File	module-2/nonclinical-summary/toxicology-tabulated-summary.pdf
	Comment	Should have further navigation via bookmarks
26	Number	2.7
	Title	Clinical Summary
	Element	m2-7-clinical-summary
	Directory	module-2/clinical-summary
	Comment	
27	Number	2.7.1
	Title	Summary of Biopharmaceutic and Associated Analytical Methods
	Element	m2-7-1-summary-of-biopharmaceutic-and-associated-analytical-methods
	File	module-2/clinical-summary/summary-biopharm.pdf
	Comment	Typically, this logical 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	2.7.2
	Title	Summary of Clinical Pharmacology Studies
	Element	m2-7-2-summary-of-clinical-pharmacology-studies
	File	module-2/clinical-summary/summary-clin-pharm.pdf
	Comment	Typically, this logical 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.

29	Number	2.7.3
	Title	Summary of Clinical Efficacy - *Indication*
	Element	m2-7-3-summary-of-clinical-efficacy
	File	module-2/clinical-summary/summary-clin-efficacy-*indication.pdf*
	Comment	The folder name should always include the indication being claimed (abbreviated if appropriate) eg. 'summary-clin-efficacy-asthma'. Where there is more than one indication (eg asthma & migraine) then the first indication has a folder 'summary-clin-efficacy-asthma' and the second 'summary-clin-efficacy-migraine'. Typically, this logical 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.
30	Number	2.7.4
	Title	Summary of Clinical Safety
	Element	m2-7-4-summary-of-clinical-safety
	File	module-2/clinical-summary/summary-clin-safety.pdf
	Comment	Typically, this logical 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	2.7.5
	Title	References
	Element	m2-7-5-references
	File	module-2/clinical-summary/references.pdf
	Comment	
32	Number	2.7.6
	Title	Synopses of Individual Studies
	Element	m2-7-6-synopses-of-individual-studies
	File	module-2/clinical-summary/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 to the locations in Module 5.

33	Number	3
	Title	Quality
	Element	m3-quality
	Directory	module-3
	Comment	
34	Number	3.2
	Title	Body of Data
	Element	m3-2-body-of-data
	Directory	module-3/body-of-data
	Comment	
35	Number	3.2.S
	Title	Drug Substance
	Element	m3-2-s-drug-substance
	Directory	module-3/body-of-data/drug-substance
	Comment	
36	Number	3.2.S
	Title	Drug Substance - *Drug Substance Name - Manufacturer*
	Element	m3-2-s-drug-substance
	Directory	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*

	Comment	The folder name should always include the name of the drug substance eg. ranitidine through inclusion of the International Non-proprietary Name to give 'ranitidine-hydrochloride'. Similarly, for manufacturer, the folder name should always include the name of the manufacturer eg. *ranitidine-manufacturer-1*. Where there is more than one manufacturer, the drug substance folder should be repeated but with an indication of each manufacturer concerned included in the folder name, the first instance eg. *'drug-substance-1- manufacturer-1'* and the second *'drug-substance-1-manufacturer-2'*. Where there is more than one drug substance (eg ranitidine hydrochloride and cimetidine) then the first drug substance has a folder 'ranitidine-hydrochloride' and the second 'cimetidine'. In this example a set of folders can include: *ranitidine-manufacturer-1* *ranitidine-manufacturer-2* *cimetidine-manufacturer-1* *cimetidine-manufacturer-2* Typically the applicant would include the specific manufacturer(s) (and/or site) in the folder name
37	Number	3.2.S.1
	Title	General Information
	Element	m3-2-s-1-general-information
	Directory	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/general-information
	Comment	
38	Number	3.2.S.1.1
	Title	Nomenclature
	Element	m3-2-s-1-1-nomenclature
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/general-information/nomenclature.pdf
	Comment	
39	Number	3.2.S.1.2
	Title	Structure

	Element	m3-2-s-1-2-structure
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/general-information/structure.pdf
	Comment	
40	Number	3.2.S.1.3
	Title	General Properties
	Element	m3-2-s-1-3-general-properties
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/general-information/general-properties.pdf
	Comment	
41	Number	3.2.S.2
	Title	Manufacture
	Element	m3-2-s-2-manufacture
	Directory	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/manufacture
	Comment	
42	Number	3.2.S.2.1
	Title	Manufacturer(s)
	Element	m3-2-s-2-1-manufacturers
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/manufacture/manufacturer.pdf
	Comment	For this document there should be only information regarding one manufacturer
43	Number	3.2.S.2.2
	Title	Description of Manufacturing Process and Process Controls
	Element	m3-2-s-2-2-description-of-manufacturing-process-and-process-controls
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/manufacture/manuf-process-and-controls.pdf
	Comment	
44	Number	3.2.S.2.3
	Title	Control of Materials
	Element	m3-2-s-2-3-control-of-materials
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/manufacture/control-of-materials.pdf
	Comment	
45	Number	3.2.S.2.4

	Title	Controls of Critical Steps and Intermediates
	Element	m3-2-s-2-4-controls-of-critical-steps-and-intermediates
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/manufacture/control-critical-steps.pdf
	Comment	
46	Number	3.2.S.2.5
	Title	Process Validation and/or Evaluation
	Element	m3-2-s-2-5-process-validation-and-or-evaluation
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/manufacture/process-validation.pdf
	Comment	
47	Number	3.2.S.2.6
	Title	Manufacturing Process Development
	Element	m3-2-s-2-6-manufacturing-process-development
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/manufacture/manuf-process-development.pdf
	Comment	
48	Number	3.2.S.3
	Title	Characterisation
	Element	m3-2-s-3-characterisation
	Directory	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/characterisation
	Comment	
49	Number	3.2.S.3.1
	Title	Elucidation of Structure and Other Characteristics
	Element	m3-2-s-3-1-elucidation-of-structure-and-other-characteristics
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/characterisation/elucidation-of-structure.pdf
	Comment	
50	Number	3.2.S.3.2
	Title	Impurities
	Element	m3-2-s-3-2-impurities
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/characterisation/impurities.pdf
	Comment	

51	Number	3.2.S.4
	Title	Control of Drug Substance
	Element	m3-2-s-4-control-of-drug-substance
	Directory	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/control-drug-substance
	Comment	
52	Number	3.2.S.4.1
	Title	Specification
	Element	m3-2-s-4-1-specification
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/control-drug-substance/specification.pdf
	Comment	
53	Number	3.2.S.4.2
	Title	Analytical Procedures
	Element	m3-2-s-4-2-analytical-procedures
	Directory	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/control-drug-substance/analytical-procedures
	Comment	For each analytical procedure a separate file should be provided
54	Number	3.2.S.4.2.1
	Title	*Analytical Procedure-1*
	Element	m3-2-s-4-2-analytical-procedures
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/control-drug-substance/analytical-procedures/*analytical-procedure-1.pdf*
	Comment	
55	Number	3.2.S.4.2.2
	Title	*Analytical Procedure-2*
	Element	m3-2-s-4-2-analytical-procedures
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/control-drug-substance/analytical-procedures/*analytical-procedure-2.pdf*
	Comment	
56	Number	3.2.S.4.2.3
	Title	*Analytical Procedure-3*

	Element	m3-2-s-4-2-analytical-procedures
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/control-drug-substance/analytical-procedures/*analytical-procedure-3.pdf*
	Comment	
57	Number	3.2.S.4.3
	Title	Validation of Analytical Procedures
	Element	m3-2-s-4-3-validation-of-analytical-procedures
	Directory	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/control-drug-substance/validation-analyt-procedures
	Comment	For each validation of an analytical procedure a separate file should be provided
58	Number	3.2.S.4.3.1
	Title	Validation of Analytical Procedures
	Element	m3-2-s-4-3-validation-of-analytical-procedures
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/control-drug-substance/validation-analyt-procedures/*validation-analyt-procedure-1.pdf*
	Comment	
59	Number	3.2.S.4.3.2
	Title	Validation of Analytical Procedures
	Element	m3-2-s-4-3-validation-of-analytical-procedures
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/control-drug-substance/validation-analyt-procedures/*validation-analyt-procedure-2.pdf*
	Comment	
60	Number	3.2.S.4.3.3
	Title	Validation of Analytical Procedures
	Element	m3-2-s-4-3-validation-of-analytical-procedures
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/control-drug-substance/validation-analyt-procedures/*validation-analyt-procedure-3.pdf*
	Comment	
61	Number	3.2.S.4.4

	Title	Batch Analyses
	Element	m3-2-s-4-4-batch-analyses
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/control-drug-substance/batch-analyses.pdf
	Comment	
62	Number	3.2.S.4.5
	Title	Justification of Specification
	Element	m3-2-s-4-5-justification-of-specification
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/control-drug-substance/justification-of-specification.pdf
	Comment	
63	Number	3.2.S.5
	Title	Reference Standards or Materials
	Element	m3-2-s-5-reference-standards-or-materials
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/reference-standards.pdf
	Comment	The applicant can decide whether one file is provided that covers all reference standards or individual files are provided for each reference standard. In deciding whether one or more files are appropriate, it should be considered that once a particular approach has been adopted, this should be maintained throughout the life of the dossier.
64	Number	3.2.S.6
	Title	Container Closure System
	Element	m3-2-s-6-container-closure-system
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/container-closure-system.pdf
	Comment	
65	Number	3.2.S.7
	Title	Stability
	Element	m3-2-s-7-stability
	Directory	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/stability
	Comment	
66	Number	3.2.S.7.1
	Title	Stability Summary and Conclusions

	Element	m3-2-s-7-1-stability-summary-and-conclusions
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/stability/stability-summary.pdf
	Comment	
67	Number	3.2.S.7.2
	Title	Post-approval Stability Protocol and Stability Commitment
	Element	m3-2-s-7-2-post-approval-stability-protocol-and-stability-commitment
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/stability/postapproval-stability.pdf
	Comment	
68	Number	3.2.S.7.3
	Title	Stability Data
	Element	m3-2-s-7-3-stability-data
	File	module-3/body-of-data/drug-substance/*substance-1-manufacturer-1*/stability/stability-data.pdf
	Comment	
69	Number	3.2.P
	Title	Drug Product
	Element	m3-2-p-drug-product
	Directory	module-3/body-of-data/drug-product
	Comment	
70	Number	3.2.P
	Title	Drug Product - *Name*
	Element	m3-2-p-drug-product
	Directory	module-3/body-of-data/drug-product/*product-1*
	Comment	The folder name should always include the name of the drug product through inclusion of the name of the form/strength to give eg. 'tablet 5mg'. Where there is more than one drug product (eg powder for reconstitution and diluent) then the first drug product has 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.
71	Number	3.2.P.1
	Title	Description and Composition of the Drug Product

	Element	m3-2-p-1-description-and-composition-of-the-drug-product
	File	module-3/body-of-data/drug-product/*product-1*/description-and-composition.pdf
	Comment	
72	Number	3.2.P.2
	Title	Pharmaceutical Development
	Element	m3-2-p-2-pharmaceutical-development
	Directory	module-3/body-of-data/drug-product/*product-1*/pharmaceutical-development
	Comment	
73	Number	3.2.P.2
	Title	Pharmaceutical Development
	Element	m3-2-p-2-pharmaceutical-development
	File	module-3/body-of-data/drug-product/*product-1*/pharmaceutical-development/pharmaceutical-development.pdf
	Comment	A single pdf file covering all sub-sections can be provided. If the applicant wishes to subdivide the document into its constituent parts as defined in the CTD, they can choose to do so and should utilize the following file names. • module-3/body-of-data/drug-product/*product-1*/pharmaceutical-development/components-drug-product.pdf • module-3/body-of-data/drug-product/*product-1*/pharmaceutical-development/drug-product.pdf • module-3/body-of-data/drug-product/*product-1*/pharmaceutical-development/manuf-process-development.pdf • module-3/body-of-data/drug-product/*product-1*/pharmaceutical-development/container-closure-system.pdf • module-3/body-of-data/drug-product/*product-1*/pharmaceutical-development/microbiological-attributes.pdf • module-3/body-of-data/drug-product/*product-1*/pharmaceutical-development/compatibility.pdf In deciding whether one or more files are appropriate, it should be considered that once a particular approach has been adopted, this should be maintained throughout the life of the dossier.
74	Number	3.2.P.3
	Title	Manufacture
	Element	m3-2-p-3-manufacture
	Directory	module-3/body-of-data/drug-product/*product-1*/manufacture
	Comment	

75	Number	3.2.P.3.1
	Title	Manufacturer(s)
	Element	m3-2-p-3-1-manufacturers
	File	module-3/body-of-data/drug-product/*product-1*/manufacture/manufacturers.pdf
	Comment	
76	Number	3.2.P.3.2
	Title	Batch Formula
	Element	m3-2-p-3-2-batch-formula
	File	module-3/body-of-data/drug-product/*product-1*/manufacture/batch-formula.pdf
	Comment	
77	Number	3.2.P.3.3
	Title	Description of Manufacturing Process and Process Controls
	Element	m3-2-p-3-3-description-of-manufacturing-process-and-process-controls
	File	module-3/body-of-data/drug-product/*product-1*/manufacture/manuf-process-and-controls.pdf
	Comment	
78	Number	3.2.P.3.4
	Title	Controls of Critical Steps and Intermediates
	Element	m3-2-p-3-4-controls-of-critical-steps-and-intermediates
	File	module-3/body-of-data/drug-product/*product-1*/manufacture/control-critical-steps.pdf
	Comment	
79	Number	3.2.P.3.5
	Title	Process Validation and/or Evaluation
	Element	m3-2-p-3-5-process-validation-and-or-evaluation
	File	module-3/body-of-data/drug-product/*product-1*/manufacture/process-validation.pdf
	Comment	
80	Number	3.2.P.4
	Title	Control of Excipients
	Element	m3-2-p-4-control-of-excipients
	Directory	module-3/body-of-data/drug-product/*product-1*/control-excipients

	Comment	
81	Number	3.2.P.4
	Title	Control of Excipients - *Excipient*
	Element	m3-2-p-4-control-of-excipients
	Directory	module-3/body-of-data/drug-product/*product-1*/control-excipients/*excipient-1*
	Comment	For a drug product containing more than one excipient, the information requested for sections P4.1 – P4.4 should be provided in its entirety for each excipient
82	Number	3.2.P.4.1
	Title	Specifications
	Element	m3-2-p-4-1-specifications
	File	module-3/body-of-data/drug-product/*product-1*/control-excipients/*excipient-1*/specifications.pdf
	Comment	
83	Number	3.2.P.4.2
	Title	Analytical Procedures
	Element	m3-2-p-4-2-analytical-procedures
	File	module-3/body-of-data/drug-product/*product-1*/control-excipients/*excipient-1*/analytical-procedures.pdf
	Comment	
84	Number	3.2.P.4.3
	Title	Validation of Analytical Procedures
	Element	m3-2-p-4-3-validation-of-analytical-procedures
	File	module-3/body-of-data/drug-product/*product-1*/control-excipients/*excipient-1*/validation-analyt-procedures.pdf
	Comment	
85	Number	3.2.P.4.4
	Title	Justification of Specifications
	Element	m3-2-p-4-4-justification-of-specifications
	File	module-3/body-of-data/drug-product/*product-1*/control-excipients/*excipient-1*/justification-of-specification.pdf
	Comment	
86	Number	3.2.P.4.5
	Title	Excipients of Human or Animal Origin

	Element	m3-2-p-4-5-excipients-of-human-or-animal-origin
	File	module-3/body-of-data/drug-product/*product-1*/control-excipients/excipients-human-animal.pdf
	Comment	
87	Number	3.2.P.4.6
	Title	Novel Excipients
	Element	m3-2-p-4-6-novel-excipients
	File	module-3/body-of-data/drug-product/*product-1*/control-excipients/novel-excipients.pdf
	Comment	
88	Number	3.2.P.5
	Title	Control of Drug Product
	Element	m3-2-p-5-control-of-drug-product
	Directory	module-3/body-of-data/drug-product/*product-1*/control-drug-product
	Comment	
89	Number	3.2.P.5.1
	Title	Specification(s)
	Element	m3-2-p-5-1-specifications
	File	module-3/body-of-data/drug-product/*product-1*/control-drug-product/specifications.pdf
	Comment	
90	Number	3.2.P.5.2
	Title	Analytical Procedures
	Element	m3-2-p-5-2-analytical-procedures
	Directory	module-3/body-of-data/drug-product/*product-1*/control-drug-product/analytical-procedures
	Comment	For each analytical procedure a separate file should be provided
91	Number	3.2.P.5.2.1
	Title	*Analytical Procedure - 1*
	Element	m3-2-p-5-2-analytical-procedures
	File	module-3/body-of-data/drug-product/*product-1*/control-drug-product/analytical-procedures/*analytical-procedure-1.pdf*
	Comment	

92	Number	3.2.P.5.2.2
	Title	*Analytical Procedure – 2*
	Element	m3-2-p-5-2-analytical-procedures
	File	module-3/body-of-data/drug-product/*product-1*/control-drug-product/analytical-procedures/*analytical-procedure-2.pdf*
	Comment	
93	Number	3.2.P.5.2.3
	Title	*Analytical Procedure - 3*
	Element	m3-2-p-5-2-analytical-procedures
	File	module-3/body-of-data/drug-product/*product-1*/control-drug-product/analytical-procedures/*analytical-procedure-3.pdf*
	Comment	
94	Number	3.2.P.5.3
	Title	Validation of Analytical Procedures
	Element	m3-2-p-5-3-validation-of-analytical-procedures
	Directory	module-3/body-of-data/drug-product/*product-1*/control-drug-product/validation-analyt-procedures
	Comment	For each validation of an analytical procedure, a separate file should be provided
95	Number	3.2.P.5.3.1
	Title	*Validation of Analytical Procedures - 1*
	Element	m3-2-p-5-3-validation-of-analytical-procedures
	File	module-3/body-of-data/drug-product/*product-1*/control-drug-product/validation-analyt-procedures/*validation-analytical-procedures-1.pdf*
	Comment	
96	Number	3.2.P.5.3.2
	Title	*Validation of Analytical Procedures - 2*
	Element	m3-2-p-5-3-validation-of-analytical-procedures
	File	module-3/body-of-data/drug-product/*product-1*/control-drug-product/validation-analyt-procedures/*validation-analytical-procedures-2.pdf*
	Comment	

97	Number	3.2.P.5.3.3
	Title	*Validation of Analytical Procedures - 3*
	Element	m3-2-p-5-3-validation-of-analytical-procedures
	File	module-3/body-of-data/drug-product/*product-1*/control-drug-product/validation-analyt-procedures/*validation-analytical-procedures-3.pdf*
	Comment	
98	Number	3.2.P.5.4
	Title	Batch Analyses
	Element	m3-2-p-5-4-batch-analyses
	File	module-3/body-of-data/drug-product/*product-1*/control-drug-product/batch-analyses.pdf
	Comment	
99	Number	3.2.P.5.5
	Title	Characterisation of Impurities
	Element	m3-2-p-5-5-characterisation-of-impurities
	File	module-3/body-of-data/drug-product/*product-1*/control-drug-product/characterisation-impurities.pdf
	Comment	
100	Number	3.2.P.5.6
	Title	Justification of Specifications
	Element	m3-2-p-5-6-justification-of-specifications
	File	module-3/body-of-data/drug-product/*product-1*/control-drug-product/justification-of-specification.pdf
	Comment	
101	Number	3.2.P.6
	Title	Reference Standards or Materials
	Element	m3-2-p-6-reference-standards-or-materials
	File	module-3/body-of-data/drug-product/*product-1*/reference-standards.pdf
	Comment	The applicant can decide whether one file is provided that covers all reference standards or individual files are provided for each reference standard. In deciding whether one or more files are appropriate, it should be considered that once a particular approach has been adopted, this should be maintained throughout the life of the dossier.
102	Number	3.2.P.7

	Title	Container Closure System
	Element	m3-2-p-7-container-closure-system
	File	module-3/body-of-data/drug-product/*product-1*/container-closure-system.pdf
	Comment	
	Number	3.2.P.8
	Title	Stability
103	Element	m3-2-p-8-stability
	Directory	module-3/body-of-data/drug-product/*product-1*/stability
	Comment	
	Number	3.2.P.8.1
	Title	Stability Summary and Conclusion
104	Element	m3-2-p-8-1-stability-summary-and-conclusion
	File	module-3/body-of-data/drug-product/*product-1*/stability/stability-summary.pdf
	Comment	
	Number	3.2.P.8.2
	Title	Post-approval Stability Protocol and Stability Commitment
105	Element	m3-2-p-8-2-post-approval-stability-protocol-and-stability-commitment
	File	module-3/body-of-data/drug-product/*product-1*/stability/postapproval-stability.pdf
	Comment	
	Number	3.2.P.8.3
	Title	Stability Data
106	Element	m3-2-p-8-3-stability-data
	File	module-3/body-of-data/drug-product/*product-1*/stability/stability-data.pdf
	Comment	
	Number	3.2.A
	Title	Appendices
107	Element	m3-2-a-appendices
	Directory	module-3/body-of-data/appendices
	Comment	

108	Number	3.2.A.1
	Title	Facilities and Equipment
	Element	m3-2-a-1-facilities-and-equipment
	Directory	module-3/body-of-data/appendices/facilities-and-equipment
	Comment	Several reports are likely to be included in this appendix. The organisation is left to the applicant to define
109	Number	3.2.A.1.1
	Title	*Facilities and Equipment Report 1*
	Element	m3-2-a-1-facilities-and-equipment
	File	module-3/body-of-data/appendices/facilities-and-equipment/*facilities-and-equipment-report-1.pdf*
	Comment	
110	Number	3.2.A.1.2
	Title	*Facilities and Equipment Report 2*
	Element	m3-2-a-1-facilities-and-equipment
	File	module-3/body-of-data/appendices/facilities-and-equipment/*facilities-and-equipment-report-2.pdf*
	Comment	
111	Number	3.2.A.1.3
	Title	*Facilities and Equipment Report 3*
	Element	m3-2-a-1-facilities-and-equipment
	File	module-3/body-of-data/appendices/facilities-and-equipment/*facilities-and-equipment-report-3.pdf*
	Comment	
112	Number	3.2.A.2
	Title	Adventitious Agents Safety Evaluation
	Element	m3-2-a-2-adventitious-agents-safety-evaluation
	Directory	module-3/body-of-data/appendices/adventitious-agents
	Comment	For nonviral adventitious agents reports should be placed in this folder. For viral adventitious agents the following sub-folder structure should be used. An example of the file naming convention is given for each folder
113	Number	3.2.A.2.1
	Title	*Adventitious Agents Safety Evaluation Report 1*
	Element	m3-2-a-2-adventitious-agents-safety-evaluation

	File	module-3/body-of-data/appendices/adventitious-agents/*adventitious-agents-report-1.pdf*
	Comment	
114	Number	3.2.A.2.2
	Title	*Adventitious Agents Safety Evaluation Report 2*
	Element	m3-2-a-2-adventitious-agents-safety-evaluation
	File	module-3/body-of-data/appendices/adventitious-agents/*adventitious-agents-report-2.pdf*
	Comment	
115	Number	3.2.A.2.3
	Title	*Adventitious Agents Safety Evaluation Report 3*
	Element	m3-2-a-2-adventitious-agents-safety-evaluation
	File	module-3/body-of-data/appendices/adventitious-agents/*adventitious-agents-report-3.pdf*
	Comment	
116	Number	3.2.A.3
	Title	Novel Excipients - *Name*
	Element	m3-2-a-3-novel-excipients
	Directory	module-3/body-of-data/appendices/novel-excipients-*name-1*
	Comment	The name of any novel excipient should be included in the folder name. If there is more than one novel excipient then each folder should have unique identification through the use of different names eg. 'novel-excipient-*name-1'* and 'novel-excipient-*name-2*. The directory/file structure would typically follow that of the drug substance section in Module 3. Refer to Regional guidances for the need for such information to be included in the submission directly as opposed to its inclusion in a Drug Master File.
117	Number	3.2.R
	Title	Regional Information
	Element	m3-2-r-regional-information
	Directory	module-3/body-of-data/regional-information
	Comment	
118	Number	3.3

	Title	Literature References
	Element	m3-3-literature-references
	Directory	module-3/references
	Comment	
119	Number	3.3.1
	Title	*Reference 1*
	Element	m3-3-literature-references
	File	module-3/references/*reference-1.pdf*
	Comment	An alternative approach is allowable whereby a single PDF file includes all references with bookmarks to each individual reference. However, this would mean that the whole file would need to be replaced if any update is made to its components
120	Number	3.3.2
	Title	*Reference 2*
	Element	m3-3-literature-references
	File	module-3/references/*reference-2.pdf*
	Comment	
121	Number	3.3.3
	Title	*Reference 3*
	Element	m3-3-literature-references
	File	module-3/references/*reference-3.pdf*
	Comment	

122	Number	4
	Title	Nonclinical Study Reports
	Element	m4-nonclinical-study-reports
	Directory	module-4
	Comment	
123	Number	4.2
	Title	Study Reports
	Element	m4-2-study-reports
	Directory	module-4/study-reports
	Comment	
124	Number	4.2.1
	Title	Pharmacology
	Element	m4-2-1-pharmacology
	Directory	module-4/study-reports/pharmacology
	Comment	
125	Number	4.2.1.1
	Title	Primary Pharmacodynamics
	Element	m4-2-1-1-primary-pharmacodynamics
	Directory	module-4/study-reports/pharmacology/primary-pharmacodynamics
	Comment	
126	Number	4.2.1.1.1
	Title	*Study Report 1*
	Element	m4-2-1-1-primary-pharmacodynamics
	File	module-4/study-reports/pharmacology/primary-pharmacodynamics/*study-report-1.pdf*
	Comment	It is possible to have the additional graphic file(s) inserted directly into the PDF file, thus making management of the file easier. Alternatively, the applicant can choose to manage these independently. This comment is applicable to all study reports in Module 4
127	Number	4.2.1.1.2

	Title	*Study Report 1 Data*
	Element	m4-2-1-1-primary-pharmacodynamics
	File	module-4/study-reports/pharmacology/primary-pharmacodynamics/*study-report-1-data.pdf*
	Comment	The data listings can be included as part of the study report document or as a separate appendix. This is relevant to all study reports in Module 4. Regional requirements can allow the submission of the data listings as a data file. Refer to regional guidances.
128	Number	4.2.1.1.3
	Title	*Study Report 2*
	Element	m4-2-1-1-primary-pharmacodynamics
	File	module-4/study-reports/pharmacology/primary-pharmacodynamics/*study-report-2.pdf*
	Comment	
129	Number	4.2.1.1.4
	Title	*Study Report 2 Data*
	Element	m4-2-1-1-primary-pharmacodynamics
	File	module-4/study-reports/pharmacology/primary-pharmacodynamics/*study-report-2-data.pdf*
	Comment	
130	Number	4.2.1.1.5
	Title	*Study Report 3*
	Element	m4-2-1-1-primary-pharmacodynamics
	File	module-4/study-reports/pharmacology/primary-pharmacodynamics/*study-report-3.pdf*
	Comment	
131	Number	4.2.1.1.6
	Title	*Study Report 3 Data*
	Element	m4-2-1-1-primary-pharmacodynamics
	File	module-4/study-reports/pharmacology/primary-pharmacodynamics/*study-report-3-data.pdf*
	Comment	
132	Number	4.2.1.2
	Title	Secondary Pharmacodynamics
	Element	m4-2-1-2-secondary-pharmacodynamics

	Directory	module-4/study-reports/pharmacology/secondary-pharmacodynamics
	Comment	
133	Number	4.2.1.2.1
	Title	*Study Report 1*
	Element	m4-2-1-2-secondary-pharmacodynamics
	File	module-4/study-reports/pharmacology/secondary-pharmacodynamics/*study-report-1.pdf*
	Comment	
134	Number	4.2.1.2.2
	Title	*Study Report 1 Data*
	Element	m4-2-1-2-secondary-pharmacodynamics
	File	module-4/study-reports/pharmacology/secondary-pharmacodynamics/*study-report-1-data.pdf*
	Comment	
135	Number	4.2.1.2.3
	Title	*Study Report 2*
	Element	m4-2-1-2-secondary-pharmacodynamics
	File	module-4/study-reports/pharmacology/secondary-pharmacodynamics/*study-report-2.pdf*
	Comment	
136	Number	4.2.1.2.4
	Title	*Study Report 2 Data*
	Element	m4-2-1-2-secondary-pharmacodynamics
	File	module-4/study-reports/pharmacology/secondary-pharmacodynamics/*study-report-2-data.pdf*
	Comment	
137	Number	4.2.1.2.5
	Title	*Study Report 3*
	Element	m4-2-1-2-secondary-pharmacodynamics
	File	module-4/study-reports/pharmacology/secondary-pharmacodynamics/*study-report-3.pdf*
	Comment	
138	Number	4.2.1.2.6
	Title	*Study Report 3 Data*

	Element	m4-2-1-2-secondary-pharmacodynamics
	File	module-4/study-reports/pharmacology/secondary-pharmacodynamics/*study-report-3-data.pdf*
	Comment	
	Number	4.2.1.3
	Title	Safety Pharmacology
139	Element	m4-2-1-3-safety-pharmacology
	Directory	module-4/study-reports/pharmacology/safety-pharmacology
	Comment	
	Number	4.2.1.3.1
	Title	*Study Report 1*
140	Element	m4-2-1-3-safety-pharmacology
	File	module-4/study-reports/pharmacology/safety-pharmacology/*study-report-1.pdf*
	Comment	
	Number	4.2.1.3.2
	Title	Study Report 1 Data
141	Element	m4-2-1-3-safety-pharmacology
	File	module-4/study-reports/pharmacology/safety-pharmacology/*study-report-1-data.pdf*
	Comment	
	Number	4.2.1.3.3
	Title	*Study Report 2*
142	Element	m4-2-1-3-safety-pharmacology
	File	module-4/study-reports/pharmacology/safety-pharmacology/*study-report-2.pdf*
	Comment	
	Number	4.2.1.3.4
	Title	*Study Report 2 Data*
143	Element	m4-2-1-3-safety-pharmacology
	File	module-4/study-reports/pharmacology/safety-pharmacology/*study-report-2-data.pdf*
	Comment	
144	Number	4.2.1.3.5

	Title	*Study Report 3*
	Element	m4-2-1-3-safety-pharmacology
	File	module-4/study-reports/pharmacology/safety-pharmacology/*study-report-3.pdf*
	Comment	
145	Number	4.2.1.3.6
	Title	*Study Report 3 Data*
	Element	m4-2-1-3-safety-pharmacology
	File	module-4/study-reports/pharmacology/safety-pharmacology/*study-report-3-data.pdf*
	Comment	
146	Number	4.2.1.4
	Title	Pharmacodynamic Drug Interactions
	Element	m4-2-1-4-pharmacodynamic-drug-interactions
	Directory	module-4/study-reports/pharmacology/pd-drug-interactions
	Comment	
147	Number	4.2.1.4.1
	Title	*Study Report 1*
	Element	m4-2-1-4-pharmacodynamic-drug-interactions
	File	module-4/study-reports/pharmacology/pd-drug-interactions/*study-report-1.pdf*
	Comment	
148	Number	4.2.1.4.2
	Title	*Study Report 1 Data*
	Element	m4-2-1-4-pharmacodynamic-drug-interactions
	File	module-4/study-reports/pharmacology/pd-drug-interactions/*study-report-1-data.pdf*
	Comment	
149	Number	4.2.1.4.3
	Title	*Study Report 2*
	Element	m4-2-1-4-pharmacodynamic-drug-interactions
	File	module-4/study-reports/pharmacology/pd-drug-interactions/*study-report-2.pdf*
	Comment	

150	Number	4.2.1.4.4
	Title	*Study Report 2 Data*
	Element	m4-2-1-4-pharmacodynamic-drug-interactions
	File	module-4/study-reports/pharmacology/pd-drug-interactions/*study-report-2-data.pdf*
	Comment	
151	Number	4.2.1.4.5
	Title	*Study Report 3*
	Element	m4-2-1-4-pharmacodynamic-drug-interactions
	File	module-4/study-reports/pharmacology/pd-drug-interactions/*study-report-3.pdf*
	Comment	
152	Number	4.2.1.4.6
	Title	*Study Report 3 Data*
	Element	m4-2-1-4-pharmacodynamic-drug-interactions
	File	module-4/study-reports/pharmacology/pd-drug-interactions/*study-report-3-data.pdf*
	Comment	
153	Number	4.2.2
	Title	Pharmacokinetics
	Element	m4-2-2-pharmacokinetics
	Directory	module-4/study-reports/pharmacokinetics
	Comment	
154	Number	4.2.2.1
	Title	Analytical Methods and Validation Reports (if separate reports are available)
	Element	m4-2-2-1-analytical-methods-and-validation-reports
	Directory	module-4/study-reports/pharmacokinetics/analyt-methods-validation
	Comment	
155	Number	4.2.2.1.1
	Title	*Study Report 1*
	Element	m4-2-2-1-analytical-methods-and-validation-reports
	File	module-4/study-reports/pharmacokinetics/analyt-methods-validation/*study-report-1.pdf*

	Comment	
156	Number	4.2.2.1.2
	Title	*Study Report 1 Data*
	Element	m4-2-2-1-analytical-methods-and-validation-reports
	File	module-4/study-reports/pharmacokinetics/analyt-methods-validation/*study-report-1-data.pdf*
	Comment	
157	Number	4.2.2.1.3
	Title	*Study Report 2*
	Element	m4-2-2-1-analytical-methods-and-validation-reports
	File	module-4/study-reports/pharmacokinetics/analyt-methods-validation/*study-report-2.pdf*
	Comment	
158	Number	4.2.2.1.4
	Title	*Study Report 2 Data*
	Element	m4-2-2-1-analytical-methods-and-validation-reports
	File	module-4/study-reports/pharmacokinetics/analyt-methods-validation/*study-report-2-data.pdf*
	Comment	
159	Number	4.2.2.1.5
	Title	*Study Report 3*
	Element	m4-2-2-1-analytical-methods-and-validation-reports
	File	module-4/study-reports/pharmacokinetics/analyt-methods-validation/*study-report-3.pdf*
	Comment	
160	Number	4.2.2.1.6
	Title	*Study Report 3 Data*
	Element	m4-2-2-1-analytical-methods-and-validation-reports
	File	module-4/study-reports/pharmacokinetics/analyt-methods-validation/*study-report-3-data.pdf*
	Comment	
161	Number	4.2.2.2
	Title	Absorption
	Element	m4-2-2-2-absorption

	Directory	module-4/study-reports/pharmacokinetics/absorption
	Comment	
162	Number	4.2.2.2.1
	Title	*Study Report 1*
	Element	m4-2-2-2-absorption
	File	module-4/study-reports/pharmacokinetics/absorption/*study-report-1.pdf*
	Comment	
163	Number	4.2.2.2.2
	Title	*Study Report 1 Data*
	Element	m4-2-2-2-absorption
	File	module-4/study-reports/pharmacokinetics/absorption/*study-report-1-data.pdf*
	Comment	
164	Number	4.2.2.2.3
	Title	*Study Report 2*
	Element	m4-2-2-2-absorption
	File	module-4/study-reports/pharmacokinetics/absorption/*study-report-2.pdf*
	Comment	
165	Number	4.2.2.2.4
	Title	*Study Report 2 Data*
	Element	m4-2-2-2-absorption
	File	module-4/study-reports/pharmacokinetics/absorption/*study-report-2-data.pdf*
	Comment	
166	Number	4.2.2.2.5
	Title	*Study Report 3*
	Element	m4-2-2-2-absorption
	File	module-4/study-reports/pharmacokinetics/absorption/*study-report-3.pdf*
	Comment	
167	Number	4.2.2.2.6
	Title	*Study Report 3 Data*

	Element	m4-2-2-2-absorption
	File	module-4/study-reports/pharmacokinetics/absorption/*study-report-3-data.pdf*
	Comment	
	Number	4.2.2.3
	Title	Distribution
168	Element	m4-2-2-3-distribution
	Directory	module-4/study-reports/pharmacokinetics/distribution
	Comment	
	Number	4.2.2.3.1
	Title	*Study Report 1*
169	Element	m4-2-2-3-distribution
	File	module-4/study-reports/pharmacokinetics/distribution/*study-report-1.pdf*
	Comment	
	Number	4.2.2.3.2
	Title	*Study Report 1 Data*
170	Element	m4-2-2-3-distribution
	File	module-4/study-reports/pharmacokinetics/distribution/*study-report-1-data.pdf*
	Comment	
	Number	4.2.2.3.3
	Title	*Study Report 2*
171	Element	m4-2-2-3-distribution
	File	module-4/study-reports/pharmacokinetics/distribution/*study-report-2.pdf*
	Comment	
	Number	4.2.2.3.4
	Title	*Study Report 2 Data*
172	Element	m4-2-2-3-distribution
	File	module-4/study-reports/pharmacokinetics/distribution/*study-report-2-data.pdf*
	Comment	
173	Number	4.2.2.3.5

	Title	*Study Report 3*
	Element	m4-2-2-3-distribution
	File	module-4/study-reports/pharmacokinetics/distribution/*study-report-3.pdf*
	Comment	
	Number	4.2.2.3.6
	Title	*Study Report 3 Data*
174	Element	m4-2-2-3-distribution
	File	module-4/study-reports/pharmacokinetics/distribution/*study-report-3-data.pdf*
	Comment	
	Number	4.2.2.4
	Title	Metabolism
175	Element	m4-2-2-4-metabolism
	Directory	module-4/study-reports/pharmacokinetics/metabolism
	Comment	
	Number	4.2.2.4.1
	Title	*Study Report 1*
176	Element	m4-2-2-4-metabolism
	File	module-4/study-reports/pharmacokinetics/metabolism/*study-report-1.pdf*
	Comment	
	Number	4.2.2.4.2
	Title	*Study Report 1 Data*
177	Element	m4-2-2-4-metabolism
	File	module-4/study-reports/pharmacokinetics/metabolism/*study-report-1-data.pdf*
	Comment	
	Number	4.2.2.4.3
	Title	*Study Report 2*
178	Element	m4-2-2-4-metabolism
	File	module-4/study-reports/pharmacokinetics/metabolism/*study-report-2.pdf*
	Comment	

	Number	4.2.2.4.4
	Title	*Study Report 2 Data*
179	Element	m4-2-2-4-metabolism
	File	module-4/study-reports/pharmacokinetics/metabolism/*study-report-2-data.pdf*
	Comment	
	Number	4.2.2.4.5
	Title	*Study Report 3*
180	Element	m4-2-2-4-metabolism
	File	module-4/study-reports/pharmacokinetics/metabolism/*study-report-3.pdf*
	Comment	
	Number	4.2.2.4.6
	Title	*Study Report 3 Data*
181	Element	m4-2-2-4-metabolism
	File	module-4/study-reports/pharmacokinetics/metabolism/*study-report-3-data.pdf*
	Comment	
	Number	4.2.2.5
	Title	Excretion
182	Element	m4-2-2-5-excretion
	Directory	module-4/study-reports/pharmacokinetics/excretion
	Comment	
	Number	4.2.2.5.1
	Title	*Study Report 1*
183	Element	m4-2-2-5-excretion
	File	module-4/study-reports/pharmacokinetics/excretion/*study-report-1.pdf*
	Comment	
184	Number	4.2.2.5.2
	Title	*Study Report 1 Data*
	Element	m4-2-2-5-excretion
	File	module-4/study-reports/pharmacokinetics/excretion/*study-report-1-data.pdf*

	Comment	
185	Number	4.2.2.5.3
	Title	*Study Report 2*
	Element	m4-2-2-5-excretion
	File	module-4/study-reports/pharmacokinetics/excretion/*study-report-2.pdf*
	Comment	
186	Number	4.2.2.5.4
	Title	*Study Report 2 Data*
	Element	m4-2-2-5-excretion
	File	module-4/study-reports/pharmacokinetics/excretion/*study-report-2-data.pdf*
	Comment	
187	Number	4.2.2.5.5
	Title	*Study Report 3*
	Element	m4-2-2-5-excretion
	File	module-4/study-reports/pharmacokinetics/excretion/*study-report-3.pdf*
	Comment	
188	Number	4.2.2.5.6
	Title	*Study Report 3 Data*
	Element	m4-2-2-5-excretion
	File	module-4/study-reports/pharmacokinetics/excretion/*study-report-3-data.pdf*
	Comment	
189	Number	4.2.2.6
	Title	Pharmacokinetic Drug Interactions (nonclinical)
	Element	m4-2-2-6-pharmacokinetic-drug-interactions
	Directory	module-4/study-reports/pharmacokinetics/pk-drug-interactions
	Comment	
190	Number	4.2.2.6.1
	Title	*Study Report 1*
	Element	m4-2-2-6-pharmacokinetic-drug-interactions

	File	module-4/study-reports/pharmacokinetics/pk-drug-interactions/*study-report-1.pdf*
	Comment	
	Number	4.2.2.6.2
	Title	*Study Report 1 Data*
191	Element	m4-2-2-6-pharmacokinetic-drug-interactions
	File	module-4/study-reports/pharmacokinetics/pk-drug-interactions/*study-report-1-data.pdf*
	Comment	
	Number	4.2.2.6.3
	Title	*Study Report 2*
192	Element	m4-2-2-6-pharmacokinetic-drug-interactions
	File	module-4/study-reports/pharmacokinetics/pk-drug-interactions/*study-report-2.pdf*
	Comment	
	Number	4.2.2.6.4
	Title	*Study Report 2 Data*
193	Element	m4-2-2-6-pharmacokinetic-drug-interactions
	File	module-4/study-reports/pharmacokinetics/pk-drug-interactions/*study-report-2-data.pdf*
	Comment	
	Number	4.2.2.6.5
	Title	*Study Report 3*
194	Element	m4-2-2-6-pharmacokinetic-drug-interactions
	File	module-4/study-reports/pharmacokinetics/pk-drug-interactions/*study-report-3.pdf*
	Comment	
	Number	4.2.2.6.6
	Title	*Study Report 3 Data*
195	Element	m4-2-2-6-pharmacokinetic-drug-interactions
	File	module-4/study-reports/pharmacokinetics/pk-drug-interactions/*study-report-3-data.pdf*
	Comment	
196	Number	4.2.2.7
	Title	Other Pharmacokinetic Studies

	Element	m4-2-2-7-other-pharmacokinetic-studies
	Directory	module-4/study-reports/pharmacokinetics/other-pk-studies
	Comment	
197	Number	4.2.2.7.1
	Title	*Study Report 1*
	Element	m4-2-2-7-other-pharmacokinetic-studies
	File	module-4/study-reports/pharmacokinetics/other-pk-studies/*study-report-1.pdf*
	Comment	
198	Number	4.2.2.7.2
	Title	*Study Report 1 Data*
	Element	m4-2-2-7-other-pharmacokinetic-studies
	File	module-4/study-reports/pharmacokinetics/other-pk-studies/*study-report-1-data.pdf*
	Comment	
199	Number	4.2.2.7.3
	Title	*Study Report 2*
	Element	m4-2-2-7-other-pharmacokinetic-studies
	File	module-4/study-reports/pharmacokinetics/other-pk-studies/*study-report-2.pdf*
	Comment	
200	Number	4.2.2.7.4
	Title	*Study Report 2 Data*
	Element	m4-2-2-7-other-pharmacokinetic-studies
	File	module-4/study-reports/pharmacokinetics/other-pk-studies/*study-report-2-data.pdf*
	Comment	
201	Number	4.2.2.7.5
	Title	*Study Report 3*
	Element	m4-2-2-7-other-pharmacokinetic-studies
	File	module-4/study-reports/pharmacokinetics/other-pk-studies/*study-report-3.pdf*
	Comment	
202	Number	4.2.2.7.6

	Title	*Study Report 3 Data*
	Element	m4-2-2-7-other-pharmacokinetic-studies
	File	module-4/study-reports/pharmacokinetics/other-pk-studies/*study-report-3-data.pdf*
	Comment	
203	Number	4.2.3
	Title	Toxicology
	Element	m4-2-3-toxicology
	Directory	module-4/study-reports/toxicology
	Comment	
204	Number	4.2.3.1
	Title	Single-Dose Toxicity (in order by species, by route)
	Element	m4-2-3-1-single-dose-toxicity
	Directory	module-4/study-reports/toxicology/single-dose-toxicity
	Comment	
205	Number	4.2.3.1.1
	Title	*Study Report 1*
	Element	m4-2-3-1-single-dose-toxicity
	File	module-4/study-reports/toxicology/single-dose-toxicity/*study-report-1.pdf*
	Comment	
206	Number	4.2.3.1.2
	Title	*Study Report 1 Data*
	Element	m4-2-3-1-single-dose-toxicity
	File	module-4/study-reports/toxicology/single-dose-toxicity/*study-report-1-data.pdf*
	Comment	
207	Number	4.2.3.1.3
	Title	*Study Report 2*
	Element	m4-2-3-1-single-dose-toxicity
	File	module-4/study-reports/toxicology/single-dose-toxicity/*study-report-2.pdf*
	Comment	

208	Number	4.2.3.1.4
	Title	*Study Report 2 Data*
	Element	m4-2-3-1-single-dose-toxicity
	File	module-4/study-reports/toxicology/single-dose-toxicity/*study-report-2-data.pdf*
	Comment	
209	Number	4.2.3.1.5
	Title	*Study Report 3*
	Element	m4-2-3-1-single-dose-toxicity
	File	module-4/study-reports/toxicology/single-dose-toxicity/*study-report-3.pdf*
	Comment	
210	Number	4.2.3.1.6
	Title	*Study Report 3 Data*
	Element	m4-2-3-1-single-dose-toxicity
	File	module-4/study-reports/toxicology/single-dose-toxicity/*study-report-3-data.pdf*
	Comment	
211	Number	4.2.3.2
	Title	Repeat-Dose Toxicity (in order by species, by route, by duration, including supportive toxicokinetics evaluations)
	Element	m4-2-3-2-repeat-dose-toxicity
	Directory	module-4/study-reports/toxicology/repeat-dose-toxicity
	Comment	
212	Number	4.2.3.2.1
	Title	*Study Report 1*
	Element	m4-2-3-2-repeat-dose-toxicity
	File	module-4/study-reports/toxicology/repeat-dose-toxicity/*study-report-1.pdf*
	Comment	
213	Number	4.2.3.2.2
	Title	*Study Report 1 Data*
	Element	m4-2-3-2-repeat-dose-toxicity
	File	module-4/study-reports/toxicology/repeat-dose-toxicity/*study-report-1-data.pdf*

	Comment	
214	Number	4.2.3.2.3
	Title	*Study Report 2*
	Element	m4-2-3-2-repeat-dose-toxicity
	File	module-4/study-reports/toxicology/repeat-dose-toxicity/*study-report-2.pdf*
	Comment	
215	Number	4.2.3.2.4
	Title	*Study Report 2 Data*
	Element	m4-2-3-2-repeat-dose-toxicity
	File	module-4/study-reports/toxicology/repeat-dose-toxicity/*study-report-2-data.pdf*
	Comment	
216	Number	4.2.3.2.5
	Title	*Study Report 3*
	Element	m4-2-3-2-repeat-dose-toxicity
	File	module-4/study-reports/toxicology/repeat-dose-toxicity/*study-report-3.pdf*
	Comment	
217	Number	4.2.3.2.6
	Title	*Study Report 3 Data*
	Element	m4-2-3-2-repeat-dose-toxicity
	File	module-4/study-reports/toxicology/repeat-dose-toxicity/*study-report-3-data.pdf*
	Comment	
218	Number	4.2.3.3
	Title	Genotoxicity
	Element	m4-2-3-3-genotoxicity
	Directory	module-4/study-reports/toxicology/genotoxicity
	Comment	
219	Number	4.2.3.3.1
	Title	In vitro
	Element	m4-2-3-3-1-in-vitro

	Directory	module-4/study-reports/toxicology/genotoxicity/in-vitro
	Comment	
220	Number	4.2.3.3.1.1
	Title	*Study Report 1*
	Element	m4-2-3-3-1-in-vitro
	File	module-4/study-reports/toxicology/genotoxicity/in-vitro/*study-report-1.pdf*
	Comment	
221	Number	4.2.3.3.1.2
	Title	*Study Report 1 Data*
	Element	m4-2-3-3-1-in-vitro
	File	module-4/study-reports/toxicology/genotoxicity/in-vitro/*study-report-1-data.pdf*
	Comment	
222	Number	4.2.3.3.1.3
	Title	*Study Report 2*
	Element	m4-2-3-3-1-in-vitro
	File	module-4/study-reports/toxicology/genotoxicity/in-vitro/*study-report-2.pdf*
	Comment	
223	Number	4.2.3.3.1.4
	Title	*Study Report 2 Data*
	Element	m4-2-3-3-1-in-vitro
	File	module-4/study-reports/toxicology/genotoxicity/in-vitro/*study-report-2-data.pdf*
	Comment	
224	Number	4.2.3.3.1.5
	Title	*Study Report 3*
	Element	m4-2-3-3-1-in-vitro
	File	module-4/study-reports/toxicology/genotoxicity/in-vitro/*study-report-3.pdf*
	Comment	
225	Number	4.2.3.3.1.6
	Title	*Study Report 3 Data*

	Element	m4-2-3-3-1-in-vitro
	File	module-4/study-reports/toxicology/genotoxicity/in-vitro/*study-report-3-data.pdf*
	Comment	
	Number	4.2.3.3.2
	Title	In vivo (including supportive toxicokinetics evaluations)
226	Element	m4-2-3-3-2-in-vivo
	Directory	module-4/study-reports/toxicology/genotoxicity/in-vivo
	Comment	
	Number	4.2.3.3.2.1
	Title	*Study Report 1*
227	Element	m4-2-3-3-2-in-vivo
	File	module-4/study-reports/toxicology/genotoxicity/in-vivo/*study-report-1.pdf*
	Comment	
	Number	4.2.3.3.2.2
	Title	*Study Report 1 Data*
228	Element	m4-2-3-3-2-in-vivo
	File	module-4/study-reports/toxicology/genotoxicity/in-vivo/*study-report-1-data.pdf*
	Comment	
	Number	4.2.3.3.2.3
	Title	*Study Report 2*
229	Element	m4-2-3-3-2-in-vivo
	File	module-4/study-reports/toxicology/genotoxicity/in-vivo/*study-report-2.pdf*
	Comment	
	Number	4.2.3.3.2.4
	Title	*Study Report 2 Data*
230	Element	m4-2-3-3-2-in-vivo
	File	module-4/study-reports/toxicology/genotoxicity/in-vivo/*study-report-2-data.pdf*
	Comment	
231	Number	4.2.3.3.2.5

	Title	*Study Report 3*
	Element	m4-2-3-3-2-in-vivo
	File	module-4/study-reports/toxicology/genotoxicity/in-vivo/*study-report-3.pdf*
	Comment	
232	Number	4.2.3.3.2.6
	Title	*Study Report 3 Data*
	Element	m4-2-3-3-2-in-vivo
	File	module-4/study-reports/toxicology/genotoxicity/in-vivo/*study-report-3-data.pdf*
	Comment	
233	Number	4.2.3.4
	Title	Carcinogenicity (including supportive toxicokinetics evaluations)
	Element	m4-2-3-4-carcinogenicity
	Directory	module-4/study-reports/toxicology/carcinogenicity
	Comment	
234	Number	4.2.3.4.1
	Title	Long-term studies (in order by species, including range-finding studies that cannot be appropriately included under repeat-dose toxicity or pharmacokinetics)
	Element	m4-2-3-4-1-long-term-studies
	Directory	module-4/study-reports/toxicology/carcinogenicity/long-term-studies
	Comment	
235	Number	4.2.3.4.1.1
	Title	*Study Report 1*
	Element	m4-2-3-4-1-long-term-studies
	File	module-4/study-reports/toxicology/carcinogenicity/long-term-studies/*study-report-1.pdf*
	Comment	
236	Number	4.2.3.4.1.2
	Title	*Study Report 1 Data*
	Element	m4-2-3-4-1-long-term-studies
	File	module-4/study-reports/toxicology/carcinogenicity/long-term-studies/*study-report-1-data.pdf*

	Comment	
237	Number	4.2.3.4.1.3
	Title	*Study Report 2*
	Element	m4-2-3-4-1-long-term-studies
	File	module-4/study-reports/toxicology/carcinogenicity/long-term-studies/*study-report-2.pdf*
	Comment	
238	Number	4.2.3.4.1.4
	Title	*Study Report 2 Data*
	Element	m4-2-3-4-1-long-term-studies
	File	module-4/study-reports/toxicology/carcinogenicity/long-term-studies/*study-report-2-data.pdf*
	Comment	
239	Number	4.2.3.4.1.5
	Title	*Study Report 3*
	Element	m4-2-3-4-1-long-term-studies
	File	module-4/study-reports/toxicology/carcinogenicity/long-term-studies/*study-report-3.pdf*
	Comment	
240	Number	4.2.3.4.1.6
	Title	*Study Report 3 Data*
	Element	m4-2-3-4-1-long-term-studies
	File	module-4/study-reports/toxicology/carcinogenicity/long-term-studies/study-report-3-data.pdf
	Comment	
241	Number	4.2.3.4.2
	Title	Short- or medium-term studies (including range-finding studies that cannot be appropriately included under repeat-dose toxicity or pharmacokinetics)
	Element	m4-2-3-4-2-short-or-medium-term-studies
	Directory	module-4/study-reports/toxicology/carcinogenicity/short-medium-term-studies
	Comment	
242	Number	4.2.3.4.2.1
	Title	*Study Report 1*

	Element	m4-2-3-4-2-short-or-medium-term-studies
	File	module-4/study-reports/toxicology/carcinogenicity/short-medium-term-studies/*study-report-1.pdf*
	Comment	
243	Number	4.2.3.4.2.2
	Title	*Study Report 1 Data*
	Element	m4-2-3-4-2-short-or-medium-term-studies
	File	module-4/study-reports/toxicology/carcinogenicity/short-medium-term-studies/*study-report-1-data.pdf*
	Comment	
244	Number	4.2.3.4.2.3
	Title	*Study Report 2*
	Element	m4-2-3-4-2-short-or-medium-term-studies
	File	module-4/study-reports/toxicology/carcinogenicity/short-medium-term-studies/*study-report-2.pdf*
	Comment	
245	Number	4.2.3.4.2.4
	Title	*Study Report 2 Data*
	Element	m4-2-3-4-2-short-or-medium-term-studies
	File	module-4/study-reports/toxicology/carcinogenicity/short-medium-term-studies/*study-report-2-data.pdf*
	Comment	
246	Number	4.2.3.4.2.5
	Title	*Study Report 3*
	Element	m4-2-3-4-2-short-or-medium-term-studies
	File	module-4/study-reports/toxicology/carcinogenicity/short-medium-term-studies/*study-report-3.pdf*
	Comment	
247	Number	4.2.3.4.2.6
	Title	*Study Report 3 Data*
	Element	m4-2-3-4-2-short-or-medium-term-studies
	File	module-4/study-reports/toxicology/carcinogenicity/short-medium-term-studies/*study-report-3-data.pdf*
	Comment	
248	Number	4.2.3.4.3

	Title	Other studies
	Element	m4-2-3-4-3-other-studies
	Directory	module-4/study-reports/toxicology/carcinogenicity/other-studies
	Comment	
	Number	4.2.3.4.3.1
	Title	*Study Report 1*
249	Element	m4-2-3-4-3-other-studies
	File	module-4/study-reports/toxicology/carcinogenicity/other-studies/*study-report-1.pdf*
	Comment	
	Number	4.2.3.4.3.2
	Title	*Study Report 1 Data*
250	Element	m4-2-3-4-3-other-studies
	File	module-4/study-reports/toxicology/carcinogenicity/other-studies/*study-report-1-data.pdf*
	Comment	
	Number	4.2.3.4.3.3
	Title	*Study Report 2*
251	Element	m4-2-3-4-3-other-studies
	File	module-4/study-reports/toxicology/carcinogenicity/other-studies/*study-report-2.pdf*
	Comment	
	Number	4.2.3.4.3.4
	Title	*Study Report 2 Data*
252	Element	m4-2-3-4-3-other-studies
	File	module-4/study-reports/toxicology/carcinogenicity/other-studies/*study-report-2-data.pdf*
	Comment	
	Number	4.2.3.4.3.5
	Title	*Study Report 3*
253	Element	m4-2-3-4-3-other-studies
	File	module-4/study-reports/toxicology/carcinogenicity/other-studies/*study-report-3.pdf*
	Comment	

254	Number	4.2.3.4.3.6
	Title	*Study Report 3 Data*
	Element	m4-2-3-4-3-other-studies
	File	module-4/study-reports/toxicology/carcinogenicity/other-studies/*study-report-3-data.pdf*
	Comment	
255	Number	4.2.3.5
	Title	Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following subheadings should be modified accordingly.)
	Element	m4-2-3-5-reproductive-and-developmental-toxicity
	Directory	module-4/study-reports/toxicology/repro-development-toxicity
	Comment	
256	Number	4.2.3.5.1
	Title	Fertility and early embryonic development
	Element	m4-2-3-5-1-fertility-and-early-embryonic-development
	Directory	module-4/study-reports/toxicology/repro-development-toxicity/fertility-embryonic-develop
	Comment	
257	Number	4.2.3.5.1.1
	Title	*Study Report 1*
	Element	m4-2-3-5-1-fertility-and-early-embryonic-development
	File	module-4/study-reports/toxicology/repro-development-toxicity/fertility-embryonic-develop/*study-report-1.pdf*
	Comment	
258	Number	4.2.3.5.1.2
	Title	*Study Report 1 Data*
	Element	m4-2-3-5-1-fertility-and-early-embryonic-development
	File	module-4/study-reports/toxicology/repro-development-toxicity/fertility-embryonic-develop/*study-report-1-data.pdf*
	Comment	
259	Number	4.2.3.5.1.3
	Title	*Study Report 2*
	Element	m4-2-3-5-1-fertility-and-early-embryonic-development

	File	module-4/study-reports/toxicology/repro-development-toxicity/fertility-embryonic-develop/*study-report-2.pdf*
	Comment	
260	Number	4.2.3.5.1.4
	Title	*Study Report 2 Data*
	Element	m4-2-3-5-1-fertility-and-early-embryonic-development
	File	module-4/study-reports/toxicology/repro-development-toxicity/fertility-embryonic-develop/*study-report-2-data.pdf*
	Comment	
261	Number	4.2.3.5.1.5
	Title	*Study Report 3*
	Element	m4-2-3-5-1-fertility-and-early-embryonic-development
	File	module-4/study-reports/toxicology/repro-development-toxicity/fertility-embryonic-develop/*study-report-3.pdf*
	Comment	
262	Number	4.2.3.5.1.6
	Title	*Study Report 3 Data*
	Element	m4-2-3-5-1-fertility-and-early-embryonic-development
	File	module-4/study-reports/toxicology/repro-development-toxicity/fertility-embryonic-develop/*study-report-3-data.pdf*
	Comment	
263	Number	4.2.3.5.2
	Title	Embryo-fetal development
	Element	m4-2-3-5-2-embryo-fetal-development
	Directory	module-4/study-reports/toxicology/repro-development-toxicity/embryo-fetal-develop
	Comment	
264	Number	4.2.3.5.2.1
	Title	*Study Report 1*
	Element	m4-2-3-5-2-embryo-fetal-development
	File	module-4/study-reports/toxicology/repro-development-toxicity/embryo-fetal-develop/*study-report-1.pdf*
	Comment	
265	Number	4.2.3.5.2.2
	Title	*Study Report 1 Data*

	Element	m4-2-3-5-2-embryo-fetal-development
	File	module-4/study-reports/toxicology/repro-development-toxicity/embryo-fetal-develop/*study-report-1-data.pdf*
	Comment	
	Number	4.2.3.5.2.3
	Title	*Study Report 2*
266	Element	m4-2-3-5-2-embryo-fetal-development
	File	module-4/study-reports/toxicology/repro-development-toxicity/embryo-fetal-develop/*study-report-2.pdf*
	Comment	
	Number	4.2.3.5.2.4
	Title	*Study Report 2 Data*
267	Element	m4-2-3-5-2-embryo-fetal-development
	File	module-4/study-reports/toxicology/repro-development-toxicity/embryo-fetal-develop/*study-report-2-data.pdf*
	Comment	
	Number	4.2.3.5.2.5
	Title	*Study Report 3*
268	Element	m4-2-3-5-2-embryo-fetal-development
	File	module-4/study-reports/toxicology/repro-development-toxicity/embryo-fetal-develop/*study-report-3.pdf*
	Comment	
	Number	4.2.3.5.2.6
	Title	*Study Report 3 Data*
269	Element	m4-2-3-5-2-embryo-fetal-development
	File	module-4/study-reports/toxicology/repro-development-toxicity/embryo-fetal-develop/*study-report-3-data.pdf*
	Comment	
	Number	4.2.3.5.3
	Title	Prenatal and postnatal development, including maternal function
270	Element	m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function
	Directory	module-4/study-reports/toxicology/repro-development-toxicity/pre-postnatal-develop
	Comment	
271	Number	4.2.3.5.3.1

	Title	*Study Report 1*
	Element	m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function
	File	module-4/study-reports/toxicology/repro-development-toxicity/pre-postnatal-develop/*study-report-1.pdf*
	Comment	
272	Number	4.2.3.5.3.2
	Title	*Study Report 1 Data*
	Element	m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function
	File	module-4/study-reports/toxicology/repro-development-toxicity/pre-postnatal-develop/*study-report-1-data.pdf*
	Comment	
273	Number	4.2.3.5.3.3
	Title	*Study Report 2*
	Element	m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function
	File	module-4/study-reports/toxicology/repro-development-toxicity/pre-postnatal-develop/*study-report-2.pdf*
	Comment	
274	Number	4.2.3.5.3.4
	Title	*Study Report 2 Data*
	Element	m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function
	File	module-4/study-reports/toxicology/repro-development-toxicity/pre-postnatal-develop/*study-report-2-data.pdf*
	Comment	
275	Number	4.2.3.5.3.5
	Title	*Study Report 3*
	Element	m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function
	File	module-4/study-reports/toxicology/repro-development-toxicity/pre-postnatal-develop/*study-report-3.pdf*
	Comment	
276	Number	4.2.3.5.3.6
	Title	*Study Report 3 Data*
	Element	m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function
	File	module-4/study-reports/toxicology/repro-development-toxicity/pre-postnatal-develop/study-report-3-data.pdf
	Comment	

277	Number	4.2.3.5.4
	Title	Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
	Element	m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated
	Directory	module-4/study-reports/toxicology/repro-development-toxicity/juvenile
	Comment	
278	Number	4.2.3.5.4.1
	Title	*Study Report 1*
	Element	m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated
	File	module-4/study-reports/toxicology/repro-development-toxicity/juvenile/*study-report-1.pdf*
	Comment	
279	Number	4.2.3.5.4.2
	Title	*Study Report 1 Data*
	Element	m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated
	File	module-4/study-reports/toxicology/repro-development-toxicity/juvenile/*study-report-1-data.pdf*
	Comment	
280	Number	4.2.3.5.4.3
	Title	*Study Report 2*
	Element	m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated
	File	module-4/study-reports/toxicology/repro-development-toxicity/juvenile/*study-report-2.pdf*
	Comment	
281	Number	4.2.3.5.4.4
	Title	*Study Report 2 Data*
	Element	m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated
	File	module-4/study-reports/toxicology/repro-development-toxicity/juvenile/*study-report-2-data.pdf*
	Comment	
282	Number	4.2.3.5.4.5
	Title	*Study Report 3*
	Element	m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated
	File	module-4/study-reports/toxicology/repro-development-toxicity/juvenile/*study-report-3.pdf*

	Comment	
283	Number	4.2.3.5.4.6
	Title	*Study Report 3 Data*
	Element	m4-2-3-5-4-studies-in-which-the-offspring-juvenile-animals-are-dosed-and-or-further-evaluated
	File	module-4/study-reports/toxicology/repro-development-toxicity/juvenile/*study-report-3-data.pdf*
	Comment	
284	Number	4.2.4
	Title	Local Tolerance
	Element	m4-2-4-local-tolerance
	Directory	module-4/study-reports/local-tolerance
	Comment	
285	Number	4.2.4.1
	Title	*Study Report 1*
	Element	m4-2-4-local-tolerance
	File	module-4/study-reports/local-tolerance/*study-report-1.pdf*
	Comment	
286	Number	4.2.4.2
	Title	*Study Report 1 Data*
	Element	m4-2-4-local-tolerance
	File	module-4/study-reports/local-tolerance/*study-report-1-data.pdf*
	Comment	
287	Number	4.2.4.3
	Title	*Study Report 2*
	Element	m4-2-4-local-tolerance
	File	module-4/study-reports/local-tolerance/*study-report-2.pdf*
	Comment	
288	Number	4.2.4.4
	Title	*Study Report 2 Data*
	Element	m4-2-4-local-tolerance

	File	module-4/study-reports/local-tolerance/*study-report-2-data.pdf*
	Comment	
289	Number	4.2.4.5
	Title	*Study Report 3*
	Element	m4-2-4-local-tolerance
	File	module-4/study-reports/local-tolerance/*study-report-3.pdf*
	Comment	
290	Number	4.2.4.6
	Title	*Study Report 3 Data*
	Element	m4-2-4-local-tolerance
	File	module-4/study-reports/local-tolerance/*study-report-3-data.pdf*
	Comment	
291	Number	4.2.5
	Title	Other Toxicity Studies (if available)
	Element	m4-2-5-other-toxicity-studies
	Directory	module-4/study-reports/other-toxicity-studies
	Comment	
292	Number	4.2.5.1
	Title	Antigenicity
	Element	m4-2-5-1-antigenicity
	Directory	module-4/study-reports/other-toxicity-studies/antigenicity
	Comment	
293	Number	4.2.5.1.1
	Title	*Study Report 1*
	Element	m4-2-5-1-antigenicity
	File	module-4/study-reports/other-toxicity-studies/antigenicity/*study-report-1.pdf*
	Comment	
294	Number	4.2.5.1.2
	Title	*Study Report 1 Data*

	Element	m4-2-5-1-antigenicity
	File	module-4/study-reports/other-toxicity-studies/antigenicity/*study-report-1-data.pdf*
	Comment	
	Number	4.2.5.1.3
	Title	*Study Report 2*
295	Element	m4-2-5-1-antigenicity
	File	module-4/study-reports/other-toxicity-studies/antigenicity/*study-report-2.pdf*
	Comment	
	Number	4.2.5.1.4
	Title	*Study Report 2 Data*
296	Element	m4-2-5-1-antigenicity
	File	module-4/study-reports/other-toxicity-studies/antigenicity/*study-report-2-data.pdf*
	Comment	
	Number	4.2.5.1.5
	Title	*Study Report 3*
297	Element	m4-2-5-1-antigenicity
	File	module-4/study-reports/other-toxicity-studies/antigenicity/*study-report-3.pdf*
	Comment	
	Number	4.2.5.1.6
	Title	*Study Report 3 Data*
298	Element	m4-2-5-1-antigenicity
	File	module-4/study-reports/other-toxicity-studies/antigenicity/*study-report-3-data.pdf*
	Comment	
	Number	4.2.5.2
	Title	Immunotoxicity
299	Element	m4-2-5-2-immunotoxicity
	Directory	module-4/study-reports/other-toxicity-studies/immunotoxicity
	Comment	
300	Number	4.2.5.2.1

	Title	*Study Report 1*
	Element	m4-2-5-2-immunotoxicity
	File	module-4/study-reports/other-toxicity-studies/immunotoxicity/*study-report-1.pdf*
	Comment	
301	Number	4.2.5.2.2
	Title	*Study Report 1 Data*
	Element	m4-2-5-2-immunotoxicity
	File	module-4/study-reports/other-toxicity-studies/immunotoxicity/*study-report-1-data.pdf*
	Comment	
302	Number	4.2.5.2.3
	Title	*Study Report 2*
	Element	m4-2-5-2-immunotoxicity
	File	module-4/study-reports/other-toxicity-studies/immunotoxicity/*study-report-2.pdf*
	Comment	
303	Number	4.2.5.2.4
	Title	*Study Report 2 Data*
	Element	m4-2-5-2-immunotoxicity
	File	module-4/study-reports/other-toxicity-studies/immunotoxicity/*study-report-2-data.pdf*
	Comment	
304	Number	4.2.5.2.5
	Title	*Study Report 3*
	Element	m4-2-5-2-immunotoxicity
	File	module-4/study-reports/other-toxicity-studies/immunotoxicity/*study-report-3.pdf*
	Comment	
305	Number	4.2.5.2.6
	Title	*Study Report 3 Data*
	Element	m4-2-5-2-immunotoxicity
	File	module-4/study-reports/other-toxicity-studies/immunotoxicity/*study-report-3-data.pdf*
	Comment	

306	Number	4.2.5.3
	Title	Mechanistic studies (if not included elsewhere)
	Element	m4-2-5-3-mechanistic-studies
	Directory	module-4/study-reports/other-toxicity-studies/mechanistic-studies
	Comment	
307	Number	4.2.5.3.1
	Title	*Study Report 1*
	Element	m4-2-5-3-mechanistic-studies
	File	module-4/study-reports/other-toxicity-studies/mechanistic-studies/*study-report-1.pdf*
	Comment	
308	Number	4.2.5.3.2
	Title	*Study Report 1 Data*
	Element	m4-2-5-3-mechanistic-studies
	File	module-4/study-reports/other-toxicity-studies/mechanistic-studies/*study-report-1-data.pdf*
	Comment	
309	Number	4.2.5.3.3
	Title	*Study Report 2*
	Element	m4-2-5-3-mechanistic-studies
	File	module-4/study-reports/other-toxicity-studies/mechanistic-studies/*study-report-2.pdf*
	Comment	
310	Number	4.2.5.3.4
	Title	*Study Report 2 Data*
	Element	m4-2-5-3-mechanistic-studies
	File	module-4/study-reports/other-toxicity-studies/mechanistic-studies/*study-report-2-data.pdf*
	Comment	
311	Number	4.2.5.3.5
	Title	*Study Report 3*
	Element	m4-2-5-3-mechanistic-studies
	File	module-4/study-reports/other-toxicity-studies/mechanistic-studies/*study-report-3.pdf*

	Comment	
312	Number	4.2.5.3.6
	Title	*Study Report 3 Data*
	Element	m4-2-5-3-mechanistic-studies
	File	module-4/study-reports/other-toxicity-studies/mechanistic-studies/*study-report-3-data.pdf*
	Comment	
313	Number	4.2.5.4
	Title	Dependence
	Element	m4-2-5-4-dependence
	Directory	module-4/study-reports/other-toxicity-studies/dependence
	Comment	
314	Number	4.2.5.4.1
	Title	*Study Report 1*
	Element	m4-2-5-4-dependence
	File	module-4/study-reports/other-toxicity-studies/dependence/*study-report-1.pdf*
	Comment	
315	Number	4.2.5.4.2
	Title	*Study Report 1 Data*
	Element	m4-2-5-4-dependence
	File	module-4/study-reports/other-toxicity-studies/dependence/*study-report-1-data.pdf*
	Comment	
316	Number	4.2.5.4.3
	Title	*Study Report 2*
	Element	m4-2-5-4-dependence
	File	module-4/study-reports/other-toxicity-studies/dependence/*study-report-2.pdf*
	Comment	
317	Number	4.2.5.4.4
	Title	*Study Report 2 Data*
	Element	m4-2-5-4-dependence

	File	module-4/study-reports/other-toxicity-studies/dependence/*study-report-2-data.pdf*
	Comment	
318	Number	4.2.5.4.5
	Title	*Study Report 3*
	Element	m4-2-5-4-dependence
	File	module-4/study-reports/other-toxicity-studies/dependence/*study-report-3.pdf*
	Comment	
319	Number	4.2.5.4.6
	Title	*Study Report 3 Data*
	Element	m4-2-5-4-dependence
	File	module-4/study-reports/other-toxicity-studies/dependence/*study-report-3-data.pdf*
	Comment	
320	Number	4.2.5.5
	Title	Metabolites
	Element	m4-2-5-5-metabolites
	Directory	module-4/study-reports/other-toxicity-studies/metabolites
	Comment	
321	Number	4.2.5.5.1
	Title	*Study Report 1*
	Element	m4-2-5-5-metabolites
	File	module-4/study-reports/other-toxicity-studies/metabolites/*study-report-1.pdf*
	Comment	
322	Number	4.2.5.5.2
	Title	*Study Report 1 Data*
	Element	m4-2-5-5-metabolites
	File	module-4/study-reports/other-toxicity-studies/metabolites/*study-report-1-data.pdf*
	Comment	
323	Number	4.2.5.5.3
	Title	*Study Report 2*

	Element	m4-2-5-5-metabolites
	File	module-4/study-reports/other-toxicity-studies/metabolites/*study-report-2.pdf*
	Comment	
324	Number	4.2.5.5.4
	Title	*Study Report 2 Data*
	Element	m4-2-5-5-metabolites
	File	module-4/study-reports/other-toxicity-studies/metabolites/*study-report-2-data.pdf*
	Comment	
325	Number	4.2.5.5.5
	Title	*Study Report 3*
	Element	m4-2-5-5-metabolites
	File	module-4/study-reports/other-toxicity-studies/metabolites/*study-report-3.pdf*
	Comment	
326	Number	4.2.5.5.6
	Title	*Study Report 3 Data*
	Element	m4-2-5-5-metabolites
	File	module-4/study-reports/other-toxicity-studies/metabolites/*study-report-3-data.pdf*
	Comment	
327	Number	4.2.5.6
	Title	Impurities
	Element	m4-2-5-6-impurities
	Directory	module-4/study-reports/other-toxicity-studies/impurities
	Comment	
328	Number	4.2.5.6.1
	Title	*Study Report 1*
	Element	m4-2-5-6-impurities
	File	module-4/study-reports/other-toxicity-studies/impurities/*study-report-1.pdf*
	Comment	
329	Number	4.2.5.6.2

	Title	*Study Report 1 Data*
	Element	m4-2-5-6-impurities
	File	module-4/study-reports/other-toxicity-studies/impurities/*study-report-1-data.pdf*
	Comment	
330	Number	4.2.5.6.3
	Title	*Study Report 2*
	Element	m4-2-5-6-impurities
	File	module-4/study-reports/other-toxicity-studies/impurities/*study-report-2.pdf*
	Comment	
331	Number	4.2.5.6.4
	Title	*Study Report 2 Data*
	Element	m4-2-5-6-impurities
	File	module-4/study-reports/other-toxicity-studies/impurities/*study-report-2-data.pdf*
	Comment	
332	Number	4.2.5.6.5
	Title	*Study Report 3*
	Element	m4-2-5-6-impurities
	File	module-4/study-reports/other-toxicity-studies/impurities/*study-report-3.pdf*
	Comment	
333	Number	4.2.5.6.6
	Title	*Study Report 3 Data*
	Element	m4-2-5-6-impurities
	File	module-4/study-reports/other-toxicity-studies/impurities/*study-report-3-data.pdf*
	Comment	
334	Number	4.2.5.7
	Title	Other
	Element	m4-2-5-7-other
	Directory	module-4/study-reports/other-toxicity-studies/other
	Comment	

335	Number	4.2.5.7.1
	Title	*Study Report 1*
	Element	m4-2-5-7-other
	File	module-4/study-reports/other-toxicity-studies/other/*study-report-1.pdf*
	Comment	
336	Number	4.2.5.7.2
	Title	*Study Report 1 Data*
	Element	m4-2-5-7-other
	File	module-4/study-reports/other-toxicity-studies/other/*study-report-1-data.pdf*
	Comment	
337	Number	4.2.5.7.3
	Title	*Study Report 2*
	Element	m4-2-5-7-other
	File	module-4/study-reports/other-toxicity-studies/other/*study-report-2.pdf*
	Comment	
338	Number	4.2.5.7.4
	Title	*Study Report 2 Data*
	Element	m4-2-5-7-other
	File	module-4/study-reports/other-toxicity-studies/other/*study-report-2-data.pdf*
	Comment	
339	Number	4.2.5.7.5
	Title	*Study Report 3*
	Element	m4-2-5-7-other
	File	module-4/study-reports/other-toxicity-studies/other/*study-report-3.pdf*
	Comment	
340	Number	4.2.5.7.6
	Title	*Study Report 3 Data*
	Element	m4-2-5-7-other
	File	module-4/study-reports/other-toxicity-studies/other/*study-report-3-data.pdf*

	Comment	
341	Number	4.3
	Title	Literature References
	Element	m4-3-literature-references
	Directory	module-4/references
	Comment	
342	Number	4.3.1
	Title	*Reference 1*
	Element	m4-3-literature-references
	File	module-4/references/*reference-1.pdf*
	Comment	Applicants can use an alternative approach whereby a single PDF file includes all references with bookmarks to each individual reference. However, this option means that the whole file should be replaced if any update is made to its components.
343	Number	4.3.2
	Title	*Reference 2*
	Element	m4-3-literature-references
	File	module-4/references/*reference-2.pdf*
	Comment	
344	Number	4.3.3
	Title	*Reference 3*
	Element	m4-3-literature-references
	File	module-4/references/*reference-3.pdf*
	Comment	

345	Number	5
	Title	Clinical Study Reports
	Element	m5-clinical-study-reports
	Directory	module-5
	Comment	
346	Number	5.2
	Title	Tabular Listing of all Clinical Studies
	Element	m5-2-tabular-listing-of-all-clinical-studies
	File	module-5/tabular-listing.pdf
	Comment	
347	Number	5.3
	Title	Clinical Study Reports
	Element	m5-3-clinical-study-reports
	Directory	module-5/clinical-study-reports
	Comment	
348	Number	5.3.1
	Title	Reports of Biopharmaceutic Studies
	Element	m5-3-1-reports-of-biopharmaceutic-studies
	Directory	module-5/clinical-study-reports/biopharmaceutic-studies
	Comment	
349	Number	5.3.1.1
	Title	Bioavailability (BA) Study Reports
	Element	m5-3-1-1-bioavailability-study-reports
	Directory	module-5/clinical-study-reports/biopharmaceutic-studies/bioavailability
	Comment	
350	Number	5.3.1.1.1
	Title	*Study Report 1*
	Element	m5-3-1-1-bioavailability-study-reports

	File	module-5/clinical-study-reports/biopharmaceutic-studies/bioavailability/*study-report-1.pdf*
	Comment	The applicant can choose to submit this logical document as a single file or multiple files. If multiple files are used they should be organised and named in accordance with the naming of sections of a clinical study report as defined in the ICH E3 guideline. It is possible to have the additional graphic file(s) inserted directly into the PDF file, thus making management of the file easier. Alternatively, the applicant can choose to manage these independently. This comment is applicable to all study reports in Module 5.
351	Number	5.3.1.1.2
	Title	*Study Report 2*
	Element	m5-3-1-1-bioavailability-study-reports
	File	module-5/clinical-study-reports/biopharmaceutic-studies/bioavailability/*study-report-2.pdf*
	Comment	
352	Number	5.3.1.1.3
	Title	*Study Report 3*
	Element	m5-3-1-1-bioavailability-study-reports
	File	module-5/clinical-study-reports/biopharmaceutic-studies/bioavailability/*study-report-3.pdf*
	Comment	
353	Number	5.3.1.2
	Title	Comparative BA and Bioequivalence (BE) Study Reports
	Element	m5-3-1-2-comparative-ba-and-bioequivalence-study-reports
	Directory	module-5/clinical-study-reports/biopharmaceutic-studies/comparative-ba-be
	Comment	
354	Number	5.3.1.2.1
	Title	*Study Report 1*
	Element	m5-3-1-2-comparative-ba-and-bioequivalence-study-reports
	File	module-5/clinical-study-reports/biopharmaceutic-studies/comparative-ba-be/*study-report-1.pdf*
	Comment	
355	Number	5.3.1.2.2
	Title	*Study Report 2*

	Element	m5-3-1-2-comparative-ba-and-bioequivalence-study-reports
	File	module-5/clinical-study-reports/biopharmaceutic-studies/comparative-ba-be/*study-report-2.pdf*
	Comment	
	Number	5.3.1.2.3
	Title	*Study Report 3*
356	Element	m5-3-1-2-comparative-ba-and-bioequivalence-study-reports
	File	module-5/clinical-study-reports/biopharmaceutic-studies/comparative-ba-be/*study-report-3.pdf*
	Comment	
	Number	5.3.1.3
	Title	In vitro – In vivo Correlation Study Reports
357	Element	m5-3-1-3-in-vitro-in-vivo-correlation-study-reports
	Directory	module-5/clinical-study-reports/biopharmaceutic-studies/in-vitro-in-vivo
	Comment	
	Number	5.3.1.3.1
	Title	*Study Report 1*
358	Element	m5-3-1-3-in-vitro-in-vivo-correlation-study-reports
	File	module-5/clinical-study-reports/biopharmaceutic-studies/in-vitro-in-vivo/*study-report-1.pdf*
	Comment	
	Number	5.3.1.3.2
	Title	*Study Report 2*
359	Element	m5-3-1-3-in-vitro-in-vivo-correlation-study-reports
	File	module-5/clinical-study-reports/biopharmaceutic-studies/in-vitro-in-vivo/*study-report-2.pdf*
	Comment	
	Number	5.3.1.3.3
	Title	*Study Report 3*
360	Element	m5-3-1-3-in-vitro-in-vivo-correlation-study-reports
	File	module-5/clinical-study-reports/biopharmaceutic-studies/in-vitro-in-vivo/*study-report-3.pdf*
	Comment	
361	Number	5.3.1.4

	Title	Reports of Bioanalytical and Analytical Methods for Human Studies
	Element	m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies
	Directory	module-5/clinical-study-reports/biopharmaceutic-studies/bioanalyt-analyt-methods
	Comment	
	Number	5.3.1.4.1
	Title	*Study Report 1*
362	Element	m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies
	File	module-5/clinical-study-reports/biopharmaceutic-studies/bioanalyt-analyt-methods/*study-report-1.pdf*
	Comment	
	Number	5.3.1.4.2
	Title	*Study Report 2*
363	Element	m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies
	File	module-5/clinical-study-reports/biopharmaceutic-studies/bioanalyt-analyt-methods/*study-report-2.pdf*
	Comment	
	Number	5.3.1.4.3
	Title	*Study Report 3*
364	Element	m5-3-1-4-reports-of-bioanalytical-and-analytical-methods-for-human-studies
	File	module-5/clinical-study-reports/biopharmaceutic-studies/bioanalyt-analyt-methods/*study-report-3.pdf*
	Comment	
	Number	5.3.2
	Title	Reports of Studies Pertinent to Pharamacokinetics using Human Biomaterials
365	Element	m5-3-2-reports-of-studies-pertinent-to-pharmacokinetics-using-human-biomaterials
	Directory	module-5/clinical-study-reports/pk-human-biomaterials
	Comment	
	Number	5.3.2.1
	Title	Plasma Protein Binding Study Reports
366	Element	m5-3-2-1-plasma-protein-binding-study-reports
	Directory	module-5/clinical-study-reports/pk-human-biomaterials/plasma-protein-binding
	Comment	

367	Number	5.3.2.1.1
	Title	*Study Report 1*
	Element	m5-3-2-1-plasma-protein-binding-study-reports
	File	module-5/clinical-study-reports/pk-human-biomaterials/plasma-protein-binding/*study-report-1.pdf*
	Comment	
368	Number	5.3.2.1.2
	Title	*Study Report 2*
	Element	m5-3-2-1-plasma-protein-binding-study-reports
	File	module-5/clinical-study-reports/pk-human-biomaterials/plasma-protein-binding/*study-report-2.pdf*
	Comment	
369	Number	5.3.2.1.3
	Title	*Study Report 3*
	Element	m5-3-2-1-plasma-protein-binding-study-reports
	File	module-5/clinical-study-reports/pk-human-biomaterials/plasma-protein-binding/*study-report-3.pdf*
	Comment	
370	Number	5.3.2.2
	Title	Reports of Hepatic Metabolism and Drug Interaction Studies
	Element	m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies
	Directory	module-5/clinical-study-reports/pk-human-biomaterials/hepatic-metab-interactions
	Comment	
371	Number	5.3.2.2.1
	Title	*Study Report 1*
	Element	m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies
	File	module-5/clinical-study-reports/pk-human-biomaterials/hepatic-metab-interactions/*study-report-1.pdf*
	Comment	
372	Number	5.3.2.2.2
	Title	*Study Report 2*
	Element	m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies
	File	module-5/clinical-study-reports/pk-human-biomaterials/hepatic-metab-interactions/*study-report-2.pdf*

	Comment	
373	Number	5.3.2.2.3
	Title	*Study Report 3*
	Element	m5-3-2-2-reports-of-hepatic-metabolism-and-drug-interaction-studies
	File	module-5/clinical-study-reports/pk-human-biomaterials/hepatic-metab-interactions/*study-report-3.pdf*
	Comment	
374	Number	5.3.2.3
	Title	Reports of Studies Using Other Human Biomaterials
	Element	m5-3-2-3-reports-of-studies-using-other-human-biomaterials
	Directory	module-5/clinical-study-reports/pk-human-biomaterials/other-human-biomaterials
	Comment	
375	Number	5.3.2.3.1
	Title	*Study Report 1*
	Element	m5-3-2-3-reports-of-studies-using-other-human-biomaterials
	File	module-5/clinical-study-reports/pk-human-biomaterials/other-human-biomaterials/*study-report-1.pdf*
	Comment	
376	Number	5.3.2.3.2
	Title	*Study Report 2*
	Element	m5-3-2-3-reports-of-studies-using-other-human-biomaterials
	File	module-5/clinical-study-reports/pk-human-biomaterials/other-human-biomaterials/*study-report-2.pdf*
	Comment	
377	Number	5.3.2.3.3
	Title	*Study Report 3*
	Element	m5-3-2-3-reports-of-studies-using-other-human-biomaterials
	File	module-5/clinical-study-reports/pk-human-biomaterials/other-human-biomaterials/*study-report-3.pdf*
	Comment	
378	Number	5.3.3
	Title	Reports of Human Pharmacokinetic (PK) Studies
	Element	m5-3-3-reports-of-human-pharmacokinetics-pk-studies

	Directory	module-5/clinical-study-reports/pk-studies
	Comment	
	Number	5.3.3.1
	Title	Healthy Subject PK and Initial Tolerability Study Reports
379	Element	m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports
	Directory	module-5/clinical-study-reports/pk-studies/healthy-subject-pk
	Comment	
	Number	5.3.3.1.1
	Title	*Study Report 1*
380	Element	m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports
	File	module-5/clinical-study-reports/pk-studies/healthy-subject-pk/*study-report-1.pdf*
	Comment	
	Number	5.3.3.1.2
	Title	*Study Report 2*
381	Element	m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports
	File	module-5/clinical-study-reports/pk-studies/healthy-subject-pk/*study-report-2.pdf*
	Comment	
	Number	5.3.3.1.3
	Title	*Study Report 3*
382	Element	m5-3-3-1-healthy-subject-pk-and-initial-tolerability-study-reports
	File	module-5/clinical-study-reports/pk-studies/healthy-subject-pk/*study-report-3.pdf*
	Comment	
	Number	5.3.3.2
	Title	Patient PK and Initial Tolerability Study Reports
383	Element	m5-3-3-2-patient-pk-and-initial-tolerability-study-reports
	Directory	module-5/clinical-study-reports/pk-studies/patient-pk
	Comment	
384	Number	5.3.3.2.1
	Title	*Study Report 1*

	Element	m5-3-3-2-patient-pk-and-initial-tolerability-study-reports
	File	module-5/clinical-study-reports/pk-studies/patient-pk/*study-report-1.pdf*
	Comment	
	Number	5.3.3.2.2
	Title	*Study Report 2*
385	Element	m5-3-3-2-patient-pk-and-initial-tolerability-study-reports
	File	module-5/clinical-study-reports/pk-studies/patient-pk/*study-report-2.pdf*
	Comment	
	Number	5.3.3.2.3
	Title	*Study Report 3*
386	Element	m5-3-3-2-patient-pk-and-initial-tolerability-study-reports
	File	module-5/clinical-study-reports/pk-studies/patient-pk/*study-report-3.pdf*
	Comment	
	Number	5.3.3.3
	Title	Intrinsic Factor PK Study Reports
387	Element	m5-3-3-3-intrinsic-factor-pk-study-reports
	Directory	module-5/clinical-study-reports/pk-studies/intrinsic-factor-pk
	Comment	
	Number	5.3.3.3.1
	Title	*Study Report 1*
388	Element	m5-3-3-3-intrinsic-factor-pk-study-reports
	File	module-5/clinical-study-reports/pk-studies/intrinsic-factor-pk/*study-report-1.pdf*
	Comment	
	Number	5.3.3.3.2
	Title	*Study Report 2*
389	Element	m5-3-3-3-intrinsic-factor-pk-study-reports
	File	module-5/clinical-study-reports/pk-studies/intrinsic-factor-pk/*study-report-2.pdf*
	Comment	
390	Number	5.3.3.3.3

	Title	*Study Report 3*
	Element	m5-3-3-3-intrinsic-factor-pk-study-reports
	File	module-5/clinical-study-reports/pk-studies/intrinsic-factor-pk/*study-report-3.pdf*
	Comment	
391	Number	5.3.3.4
	Title	Extrinsic Factor PK Study Reports
	Element	m5-3-3-4-extrinsic-factor-pk-study-reports
	Directory	module-5/clinical-study-reports/pk-studies/extrinsic-factor-pk
	Comment	
392	Number	5.3.3.4.1
	Title	*Study Report 1*
	Element	m5-3-3-4-extrinsic-factor-pk-study-reports
	File	module-5/clinical-study-reports/pk-studies/extrinsic-factor-pk/*study-report-1.pdf*
	Comment	
393	Number	5.3.3.4.2
	Title	*Study Report 2*
	Element	m5-3-3-4-extrinsic-factor-pk-study-reports
	File	module-5/clinical-study-reports/pk-studies/extrinsic-factor-pk/*study-report-2.pdf*
	Comment	
394	Number	5.3.3.4.3
	Title	*Study Report 3*
	Element	m5-3-3-4-extrinsic-factor-pk-study-reports
	File	module-5/clinical-study-reports/pk-studies/extrinsic-factor-pk/*study-report-3.pdf*
	Comment	
395	Number	5.3.3.5
	Title	Population PK Study Reports
	Element	m5-3-3-5-population-pk-study-reports
	Directory	module-5/clinical-study-reports/pk-studies/population-pk
	Comment	

396	Number	5.3.3.5.1
	Title	*Study Report 1*
	Element	m5-3-3-5-population-pk-study-reports
	File	module-5/clinical-study-reports/pk-studies/population-pk/*study-report-1.pdf*
	Comment	
397	Number	5.3.3.5.2
	Title	*Study Report 2*
	Element	m5-3-3-5-population-pk-study-reports
	File	module-5/clinical-study-reports/pk-studies/population-pk/*study-report-2.pdf*
	Comment	
398	Number	5.3.3.5.3
	Title	*Study Report 3*
	Element	m5-3-3-5-population-pk-study-reports
	File	module-5/clinical-study-reports/pk-studies/population-pk/*study-report-3.pdf*
	Comment	
399	Number	5.3.4
	Title	Reports of Human Pharmacodynamic (PD) Studies
	Element	m5-3-4-reports-of-human-pharmacodynamics-pd-studies
	Directory	module-5/clinical-study-reports/human-pd-studies
	Comment	
400	Number	5.3.4.1
	Title	Healthy Subject PD and PK/PD Study Reports
	Element	m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports
	Directory	module-5/clinical-study-reports/human-pd-studies/healthy-subject-pd
	Comment	
401	Number	5.3.4.1.1
	Title	*Study Report 1*
	Element	m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports
	File	module-5/clinical-study-reports/human-pd-studies/healthy-subject-pd/*study-report-1.pdf*

	Comment	
402	Number	5.3.4.1.2
	Title	*Study Report 2*
	Element	m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports
	File	module-5/clinical-study-reports/human-pd-studies/healthy-subject-pd/*study-report-2.pdf*
	Comment	
403	Number	5.3.4.1.3
	Title	*Study Report 3*
	Element	m5-3-4-1-healthy-subject-pd-and-pk-pd-study-reports
	File	module-5/clinical-study-reports/human-pd-studies/healthy-subject-pd/*study-report-3.pdf*
	Comment	
404	Number	5.3.4.2
	Title	Patient PD and PK/PD Study Reports
	Element	m5-3-4-2-patient-pd-and-pk-pd-study-reports
	Directory	module-5/clinical-study-reports/human-pd-studies/patient-pd
	Comment	
405	Number	5.3.4.2.1
	Title	*Study Report 1*
	Element	m5-3-4-2-patient-pd-and-pk-pd-study-reports
	File	module-5/clinical-study-reports/human-pd-studies/patient-pd/*study-report-1.pdf*
	Comment	
406	Number	5.3.4.2.2
	Title	*Study Report 2*
	Element	m5-3-4-2-patient-pd-and-pk-pd-study-reports
	File	module-5/clinical-study-reports/human-pd-studies/patient-pd/*study-report-2.pdf*
	Comment	
407	Number	5.3.4.2.3
	Title	*Study Report 3*
	Element	m5-3-4-2-patient-pd-and-pk-pd-study-reports

	File	module-5/clinical-study-reports/human-pd-studies/patient-pd/*study-report-3.pdf*
	Comment	
408	Number	5.3.5
	Title	Reports of Efficacy and Safety Studies
	Element	m5-3-5-reports-of-efficacy-and-safety-studies
	Directory	module-5/clinical-study-reports/efficacy-safety
	Comment	
409	Number	5.3.5
	Title	Reports of Efficacy and Safety Studies - *Indication Name*
	Element	m5-3-5-reports-of-efficacy-and-safety-studies
	Directory	module-5/clinical-study-reports/efficacy-safety/*indication-1*
	Comment	The folder name should always include the indication being claimed (abbreviated if appropriate) eg. 'asthma'. Where there is more than one indication (eg asthma & migraine) then the first indication has a folder 'asthma' and the second 'migraine'.
410	Number	5.3.5.1
	Title	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
	Element	m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication
	Directory	module-5/clinical-study-reports/efficacy-safety/*indication-1*/controlled-studies
	Comment	
411	Number	5.3.5.1.1
	Title	*Study Report 1*
	Element	m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication
	File	module-5/clinical-study-reports/efficacy-safety/*indication-1*/controlled-studies/*study-report-1.pdf*
	Comment	
412	Number	5.3.5.1.2
	Title	*Study Report 2*
	Element	m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication
	File	module-5/clinical-study-reports/efficacy-safety/*indication-1*/controlled-studies/*study-report-2.pdf*
	Comment	

413	Number	5.3.5.1.3
	Title	*Study Report 3*
	Element	m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication
	File	module-5/clinical-study-reports/efficacy-safety/*indication-1*/controlled-studies/*study-report-3.pdf*
	Comment	
414	Number	5.3.5.2
	Title	Study Reports of Uncontrolled Clinical Studies
	Element	m5-3-5-2-study-reports-of-uncontrolled-clinical-studies
	Directory	module-5/clinical-study-reports/efficacy-safety/*indication-1*/uncontrolled-studies
	Comment	
415	Number	5.3.5.2.1
	Title	*Study Report 1*
	Element	m5-3-5-2-study-reports-of-uncontrolled-clinical-studies
	File	module-5/clinical-study-reports/efficacy-safety/*indication-1*/uncontrolled-studies/*study-report-1.pdf*
	Comment	
416	Number	5.3.5.2.2
	Title	*Study Report 2*
	Element	m5-3-5-2-study-reports-of-uncontrolled-clinical-studies
	File	module-5/clinical-study-reports/efficacy-safety/*indication-1*/uncontrolled-studies/*study-report-2.pdf*
	Comment	
417	Number	5.3.5.2.3
	Title	*Study Report 3*
	Element	m5-3-5-2-study-reports-of-uncontrolled-clinical-studies
	File	module-5/clinical-study-reports/efficacy-safety/*indication-1*/uncontrolled-studies/*study-report-3.pdf*
	Comment	
418	Number	5.3.5.3
	Title	Reports of Analyses of Data from More than One Study
	Element	m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study
	Directory	module-5/clinical-study-reports/efficacy-safety/*indication-1*/multistudy-analyses

	Comment	
419	Number	5.3.5.3.1
	Title	*Study Report 1*
	Element	m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study
	File	module-5/clinical-study-reports/efficacy-safety/*indication-1*/multistudy-analyses/*study-report-1.pdf*
	Comment	
420	Number	5.3.5.3.2
	Title	*Study Report 2*
	Element	m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study
	File	module-5/clinical-study-reports/efficacy-safety/*indication-1*/multistudy-analyses/*study-report-2.pdf*
	Comment	
421	Number	5.3.5.3.3
	Title	*Study Report 3*
	Element	m5-3-5-3-reports-of-analyses-of-data-from-more-than-one-study
	File	module-5/clinical-study-reports/efficacy-safety/*indication-1*/multistudy-analyses/*study-report-3.pdf*
	Comment	
422	Number	5.3.5.4
	Title	Other Study Reports
	Element	m5-3-5-4-other-study-reports
	Directory	module-5/clinical-study-reports/efficacy-safety/*indication-1*/other-studies
	Comment	
423	Number	5.3.5.4.1
	Title	*Study Report 1*
	Element	m5-3-5-4-other-study-reports
	File	module-5/clinical-study-reports/efficacy-safety/*indication-1*/other-studies/*study-report-1.pdf*
	Comment	
424	Number	5.3.5.4.2
	Title	*Study Report 2*
	Element	m5-3-5-4-other-study-reports

	File	module-5/clinical-study-reports/efficacy-safety/*indication-1*/other-studies/*study-report-2.pdf*
	Comment	
425	Number	5.3.5.4.3
	Title	*Study Report 3*
	Element	m5-3-5-4-other-study-reports
	File	module-5/clinical-study-reports/efficacy-safety/*indication-1*/other-studies/*study-report-3.pdf*
	Comment	
426	Number	5.3.6
	Title	Reports of Postmarketing Experience
	Element	m5-3-6-reports-of-postmarketing-experience
	Directory	module-5/clinical-study-reports/postmarketing-experience
	Comment	
427	Number	5.3.7
	Title	Case Report Forms and Individual Patient Listings
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	Directory	module-5/clinical-study-reports/crfs-patient-listings
	Comment	
428	Number	5.3.7.1
	Title	*Study 1*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	Directory	module-5/clinical-study-reports/crfs-patient-listings/*study-1*
	Comment	
429	Number	5.3.7.1.1
	Title	*Document/Dataset 1*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	File	module-5/clinical-study-reports/crfs-patient-listings/*study-1*/*filename-1.txt*
	Comment	The filename and extension should include the description of the file and appropriate file extension according to Appendix 2. Reference should be made to regional guidance for the acceptability of submission of datasets
430	Number	5.3.7.1.2

	Title	*Document/Dataset 2*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	File	module-5/clinical-study-reports/crfs-patient-listings/*study-1/filename-2.txt*
	Comment	
431	Number	5.3.7.1.3
	Title	*Document/Dataset 3*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	File	module-5/clinical-study-reports/crfs-patient-listings/*study-1/filename-3.txt*
	Comment	
432	Number	5.3.7.2
	Title	*Study 2*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	Directory	module-5/clinical-study-reports/crfs-patient-listings/*study-2*
	Comment	define element
433	Number	5.3.7.2.1
	Title	*Document/Dataset 1*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	File	module-5/clinical-study-reports/crfs-patient-listings/*study-2/filename-1.txt*
	Comment	
434	Number	5.3.7.2.2
	Title	*Document/Dataset 2*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	File	module-5/clinical-study-reports/crfs-patient-listings/*study-2/filename-2.txt*
	Comment	
435	Number	5.3.7.2.3
	Title	*Document/Dataset 3*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	File	module-5/clinical-study-reports/crfs-patient-listings/*study-2/filename-3.txt*
	Comment	

436	Number	5.3.7.3
	Title	*Study 3*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	Directory	module-5/clinical-study-reports/crfs-patient-listings/*study-3*
	Comment	define element
437	Number	5.3.7.3.1
	Title	*Document/Dataset 1*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	File	module-5/clinical-study-reports/crfs-patient-listings/*study-3/filename-1.txt*
	Comment	
438	Number	5.3.7.3.2
	Title	*Document/Dataset 2*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	File	module-5/clinical-study-reports/crfs-patient-listings/*study-3/filename-2.txt*
	Comment	
439	Number	5.3.7.3.3
	Title	*Document/Dataset 3*
	Element	m5-3-7-case-report-forms-and-individual-patient-listings
	File	module-5/clinical-study-reports/crfs-patient-listings/*study-3/filename-3.txt*
	Comment	
440	Number	5.4
	Title	Literature References
	Element	m5-4-literature-references
	Directory	module-5/references
	Comment	
441	Number	5.4.1
	Title	*Reference 1*
	Element	m5-4-literature-references
	File	module-5/references/*reference-1.pdf*

	Comment	An applicant can use an alternative approach whereby a single PDF file includes all references with bookmarks to each individual reference. However, this option would mean that the whole file should be replaced if any update is made to its components.
442	Number	5.4.2
	Title	*Reference 2*
	Element	m5-4-literature-references
	File	module-5/references/*reference-2.pdf*
	Comment	
443	Number	5.4.3
	Title	*Reference 3*
	Element	m5-4-literature-references
	File	module-5/references/*reference-3.pdf*
	Comment	

444	Number	
	Title	
	Element	
	Directory	util
	Comment	utilities
445	Number	
	Title	
	Element	
	Directory	util/dtd
	Comment	DTDs
446	Number	
	Title	
	Element	
	File	util/dtd/ich-ectd-1-0.dtd
	Comment	DTD for the instance – the version used to create the eCTD submission must be included
447	Number	
	Title	
	Element	
	File	util/dtd/eu-regional-1-0.dtd
	Comment	DTD for the EU specific documentation
448	Number	
	Title	
	Element	
	File	util/dtd/jp-regional-1-0.dtd
	Comment	DTD for the Japan specific documentation
449	Number	
	Title	
	Element	

	File	util/dtd/us-regional-1-0.dtd
	Comment	DTD for the US specific documentation
450	Number	
	Title	
	Element	
	File	util/dtd/xx-regional-1-0.dtd
	Comment	DTD for the xx specific documentation, where xx is a two character country code from ISO-3166-1
451	Number	
	Title	
	Element	
	Directory	util/style
	Comment	Directory for style sheets – default (ICH) and applicant specific stylesheets
452	Number	
	Title	
	Element	
	File	util/style/ectd-1-0.xsl
	Comment	The specific version of the eCTD stylesheet used by the applicant as a reference during the creation of the submission should be included

Appendix 5 Region Specific Information Including Transmission and Receipt

Introduction

This section describes region specific information for content that is not explicitly included in the Common Technical Document and logistical details appropriate for the transmission and receipt of submissions using the electronic Common Technical Document.

Region specific information: Module 1

This module contains administrative information that is unique for each region. There will be local requirements for both the content and electronic component of module 1. The eCTD backbone was developed to allow the transfer of this regional information to be included in a regulatory dossier.

Regional guidance will provide the specific instructions on how to provide the administrative forms and detailed prescribing information. Please refer to this information and appendix 6 when preparing module 1. Module 1 includes all administrative documents (e.g., forms and certifications) and labeling, including the documents described in regional guidance.

Not all regionally specific documents are included in module 1. Technical reports required for a specific region should be placed in modules 2 to 5. These reports should be included in the module most appropriate for the content of the information provided.

Each region provides specific guidance on the format and content of the regional requirements of each module. The Table 5-1 provides contact information for each region.

Table 5-1

Region	Internet Address	Electronic Mail Contact
European Union	http://www.emea.eu.int	esubmission@emea.eu.int
Food And Drug Administration, USA	http://www.fda.gov/cber http://www.fda.gov/cder	Esubprep@cber.fda.gov esub@cder.fda.gov
Ministry of Health, Labour and Welfare, Japan	http://www.mhlw.go.jp http://www.nihs.go.jp	e-submission@nihs.go.jp
Health Canada	http://www.hc-sc.gc.ca/hpb-dgps/therapeut	Bob_kapitany@hc-sc.gc.ca

Submission Addresses

Submissions should be sent directly to the appropriate regulatory authority. Information needed to send physical media to each regulatory authority is found at the reference location in Table 5-2.

Table 5-2

Regulatory Authority	Reference location
EMEA, European Union Or national agencies	http://www.eudra.org/ http://heads.medagencies.org
Ministry of Health, Labour and Welfare, Japan	http://www.mhlw.go.jp http://www.nihs.go.jp
Food and Drug Administration, United States of America	http://www.fda.gov/
Health Canada, Health Protection Branch, Canada	http://www.hc-sc.gc.ca/hpb-dgps/therapeut

Media

Regulatory authorities are prepared to accept electronic submissions provided on the media listed in Table 5-3. To optimize processing efficiency, we recommend choosing media with a capacity most appropriate to the size of the submission. Whenever possible, applicants should choose media capable of holding the submission on the fewest number of units. For example for a submission that has a size of 50 Megabytes, use 1 CD-ROM instead of 50 floppy disks.

Table 5-3

Recommendations for Media		Regulatory Authority
Example Size of Submission	**Media and format**	
Less than 1.4 MB	3.5 inch DOS Formatted Floppy Disks	EU
Less than 10 MB	3.5 inch DOS Formatted Floppy Disks	USA
Less than 650 MB	CD-ROM ISO 9660 – Joliet	EU, Japan
Less than 7 GB	CD-ROM ISO 9660 - Joliet	Japan, USA, Canada
Greater than 7 GB	Digital Tape – Compaq DLT 20/40 and 10/20 GB format using NT server 4.0 with NT backup or BackupExec	USA
More than 650 MB	DVD	EU, Canada

Cover letter

Applicants should provide a cover letter as a PDF file (cover.pdf). A paper cover letter should also be included with non-electronic portions of the submission (such as forms with signatures or seals, and certifications). The cover letter should include:

- A description of the submission including appropriate regulatory information.
- A listing of the sections of the submission filed as paper, electronic, or both paper and electronic.
- A description of the electronic submission including type and number of electronic media, approximate size of the submission, and, if appropriate, format used for DLT tapes.
- A statement that the submission is virus free with a description of the software used to check the files for viruses.
- The printed contents of the index-md5.txt file as an appendix.
- The regulatory and information technology points of contact for the submission.

Preparing the media

CD-ROMs should be packaged carefully to ensure that they arrive in a usable condition. Particularly vulnerable are diskettes and CD-ROM jewel cases shipped in envelopes without bubble-type protective material or stiff backing. The use of a jiffy-type bag by itself to ship media will not provide adequate protection for shipping electronic media.

Transport

Secure data exchange over the Internet is the recommended means for transporting submissions. However, until the regulatory authorities can develop secure electronic gateways, submissions should continue to be physically transported by courier or registered mail.

Security

An MD5 checksum should be included for each physical file in the eCTD. The checksum allows the recipient to verify integrity of the physical files in the submission. The XML eCTD DTD provides the location of the files and a tag name contains the checksums.

A checksum of the XML eCTD instance should be included. Applicants should name this checksum file index-md5.txt and include it as a file in the same directory as the XML eCTD instance. Applicants should print the contents of the index-md5.txt file and include the paper copy with the paper cover letter for the submission.

An applicant can provide the eCTD as an encrypted file in accordance with the ICH M2 Recommendation 4.1, if the regulatory body has implemented it. This solution allows the eCTD to be encrypted and transferred over the Internet (if Internet receipt is implemented regionally) or to be encrypted on one of the approved physical media standards. The purpose of encryption is to protect the privacy of the confidential information and to insure it is only available to the authorized receiver. Encryption is always appropriate when the eCTD is sent via the Internet.

Encryption is not considered necessary if the information is sent using a physical media, although encryption is an option. The applicant should assume all liability for the media until it is delivered to the regulatory authority.

Applicants should not include any file level security settings or password protection for individual files in the eCTD. Applicants should allow printing, changes to the document, selecting text and graphics, and adding or changing notes and form fields. Internal security and access control processes in the regulatory authority should maintain the integrity of the submitted files.

Receipt

Upon arrival at the regulatory authority, the submission is archived according to local regulations. A read-only copy of the submission is then made available to the review community in the regulatory authority. This is typically done by placing the copy on a network server.

Acknowledgment

Each regulatory authority should acknowledge the receipt of the eCTD submission according to the policy and procedure of the individual regulatory authority. Applicants should use the address in Table 5-1 to find guidance regarding acknowledgments

Appendix 6 The eCTD XML Submission

Background

There are many factors that have influenced the design of the eCTD. Some that have had a more significant impact on the design are:

- The submissions should accommodate full regulatory dossiers, supplements, amendments and variations.
- The submissions should be able to accommodate regional requirements that are represented in regional guidance documents, regulations, and statutes.
- The technology should be extensible so that as technology changes, the new electronic solutions can be accommodated.

The eCTD is designed around the concept of a backbone. The backbone is similar to a container that holds the files that are part of the submission. The backbone is based on an XML Document Type Definition (DTD). There is a close relationship between the logical documents defined in the CTD and entities in the backbone. The backbone will provide the navigation links to the various files and information that make up the submission.

The file that is produced based on the XML eCTD DTD is the eCTD XML instance or XML backbone. The XML backbone allows more than one entry or link to point to the same physical file. This should be done with caution since it can be more difficult for the regulatory authority to manage the life cycle of that file if there is more than one pointer to the file.

File Names and Directory Structure

Recipients of the eCTD should be able to directly navigate through the submission at the folder and file level, i.e. without benefit of a customized end user application. The structure of the eCTD and instructions for how to create folder names facilitate this type of navigation.

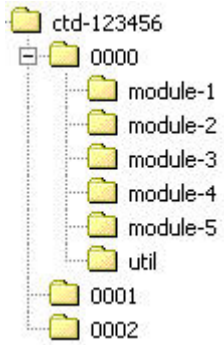
In order to preserve the navigational linkages that can be present in the documents contained in the eCTD, the directory structure should be preserved by the agencies. The navigational links should be relative links within a module.

Specific folder and file names have been defined in appendix 4. The top-level for the directory structure will vary by region. The identification of the top-level folder uniquely identifies the submission in a region. The submission identification should be used as the folder name in the top-level directory. For example, if the submission number were CTD 123456, the root directory would be named “ctd-123456”. The original submission and subsequent amendments and variations should use the same top-level folder name. Submissions should be differentiated by a subfolder named according to the sequence number of the submission in that region. Table 6-1 and Figure 6-1 illustrate this naming convention.

Table 6-1

Submission number	Sequence number	Type of submission
ctd-123456	0000	Original Submission
ctd-123456	0001	First amendment, supplement or variation
ctd-123456	0002	Second amendment, supplement or variation
…		
ctd-123456	nnnn	Nth amendment, supplement or variation

Figure 6-1



You should submit the xml backbone as a single file named *index.xml* which should be placed in the submission sequence number folder for that submission. In the example shown in Figure 6-1, there should be an *index.xml* file in folder "0000", folder "0001" and folder "0002". The MD5 checksum file, *index-md5.txt*, should be in each folder with the corresponding *index.xml* file. The DTD for *index.xml* should be in the "util" folder for each submission.

The regional administrative xml backbone file, if supplied, should be in the region specific module-1 folder for each submission. The DTD for the regional xml backbone file should be in the util folder for each submission.

Table 6-2 presents the file locations for the example in Figure 6-1.

Table 6-2

Submission Folder	Files
ctd-123456/0000	index.xml index-md5.txt
ctd-123456/0000/module-1/us	us-regional.xml
ctd-123456/0000/util	ich-ectd-1-0.dtd us-regional-1-0.dtd

Submission Folder	Files
ctd-123456/0001	index.xml index-md5.txt
ctd-123456/0001/module-1/us	us-regional.xml
ctd-12345/0001/util	ich-ectd-1-0.dtd us-regional-1-0.dtd
ctd-123456/0002	index.xml index-md5.txt
ctd-123456/0002/module-1/us	us-regional.xml
ctd-123456/0002/util	ich-ectd-1-0.dtd us-regional-1-0.dtd

Lifecycle Management

It is important for the recipients of eCTD to be able to establish the location of the submission in the lifecycle of a product.

The eCTD is capable of containing initial submissions, supplements, amendments and variations. There are no uniform definitions for these terms in the three regions, but amendments and supplements are terms used in the United States. Variations apply in Europe. The variations, supplements and amendments are used to provide additional information to an original regulatory dossier. For example, if a new manufacturer for the drug substance were being proposed, this would result in submission of an amendment or supplement to the FDA and a variation to Europe. When regulatory authorities request additional information, the information is also provided as a variation, supplement or amendment to the original submission. Therefore, the regulatory agencies should have a way to manage the lifecycle for the submission. This function should be provided by each regulatory authority in the form of guidance that can include regional DTDs and specifications. Each regional DTD should be referenced in the eCTD DTD by the submitter.

The eCTD DTD provides some facilities for lifecycle management at the file level. When revisions are sent to a regulatory authority, the new file should be submitted as a leaf element associated with the same tag name as the file being amended or deleted. The "modified-file" attribute of the leaf element should contain the name and relative directory path of the file being amended, replaced or deleted. This will allow the regulatory authority to accurately locate the original file and update the original file's status.

Operation Attribute

The operation attribute is a key to managing each individual file in a submission. The applicant uses the operation attribute to tell the regulatory authority how the applicant intends the files in the submission to be used. The operation attribute describes the relation between files in subsequent submissions during the life cycle of a medicinal product. In the very first submission all the files will be new. In the second, third, fourth, etc. submission, all the newly submitted files can have different operation

attributes due to having or not having a relation with previously submitted files. Table 6-2 describes the meaning of each allowed value of the operation attribute.

Table 6-3 Understanding the Operation Attribute

Operation attribute value Meaning		What the reviewer might see when using the Agency review software	
		This file	Previous file
New	The file has no relationship with files submitted previously.	Current	
Append	The file itself is new, but due to the relation this file has with a previously submitted file, the attribute is "append". The append status is linked to a previously submitted file on which this operation has to be executed. The previously submitted file is indicated by the "modified file" attribute of the leaf element.	Current	Current - Appended
Replace	The file itself is new, but due to the relation this file has with a previously submitted file, the attribute is "replace". The "replace" status is linked to a previously submitted file on which this operation is executed. The previously submitted file is indicated by the "modified file" attribute of the leaf element.	Current	Replaced
Delete	There is no new file submitted in this case. Instead, the leaf has the operation of "delete" and the "modified-file" attribute identifies the file in a previous submission that is to be considered no longer relevant to the review.		No longer relevant to the review

The following cases show examples of the use of each of the operation attribute values. These examples are not a complete list of all possible situations. Consult the appropriate regulatory authority if you have specific questions about the use of the operation attribute.

Case 1 – The first submission of a dossier.

Table 6-4

Submission sequence #	File name	Operation	Modified file	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\structure.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 structure.pdf, which is now current and replaces the file structure.pdf in submission 0000.

Table 6-5

Submission sequence #	File name	Operation	Modified file	Sample logical display in a review tool
0000	0000\..\structure.pdf	New		structure.pdf (current)
0001	0001\..\structure.pdf	Replace	0000\..\structure.pdf	*structure.pdf (replaced)* structure.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, which is submitted at a later time, is the submission of the file structure.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.

Table 6-6

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

				structure.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:

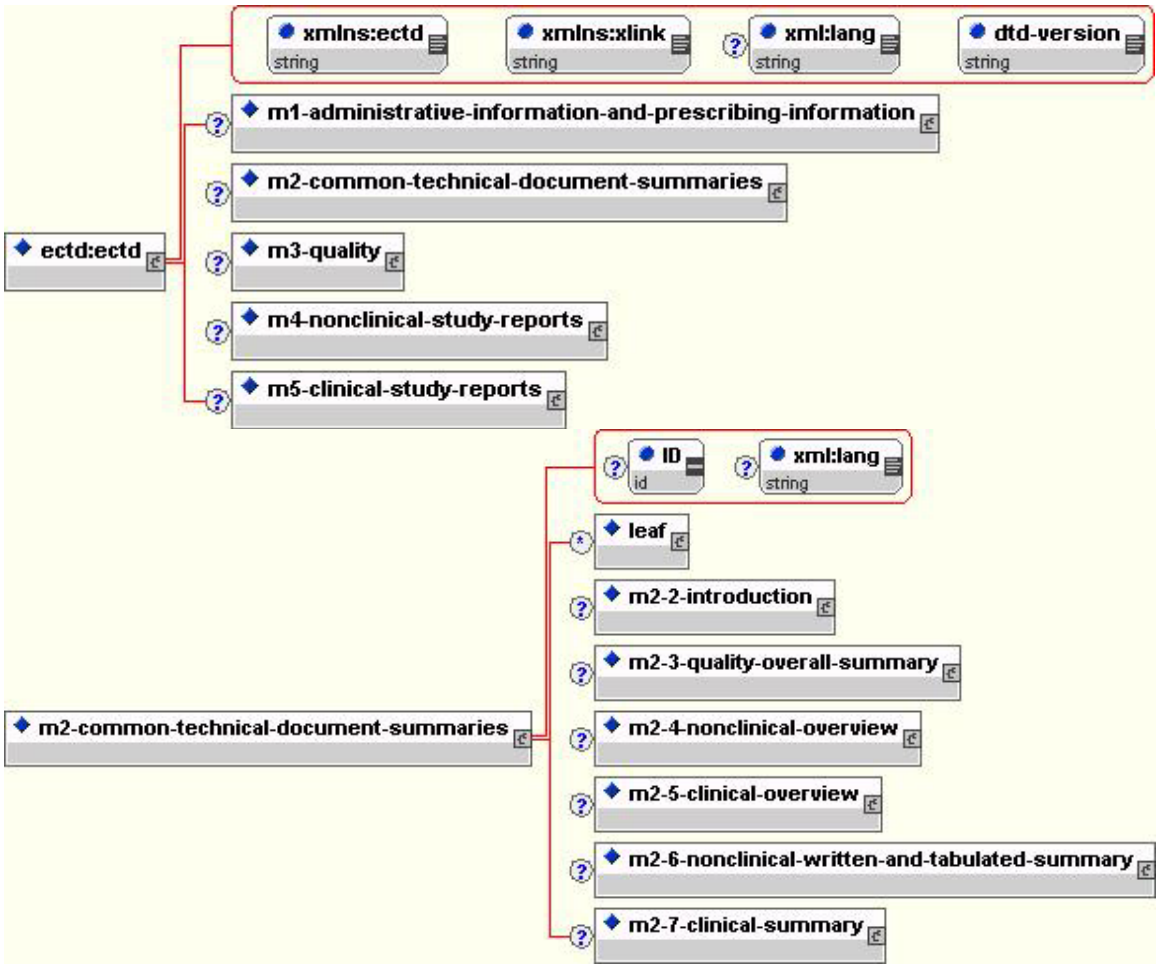
- Submission 0000 is the first submission of the file structure.pdf and this file is the current version of this file.
- Submission 0001, which is submitted at a later time, requests that the file structure.pdf in submission 0000 be deleted and no longer considered relevant to the review of the dossier.

Table 6-7

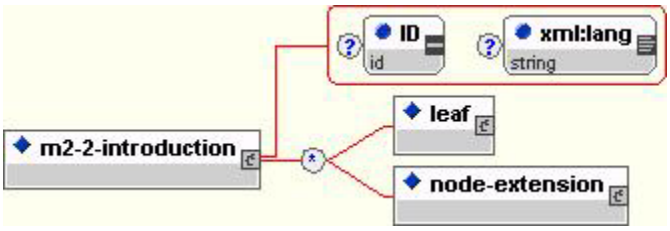
Submission sequence #	File name	Operation	Modified file	Sample logical display in a review tool
0000	0000\..\structure.pdf	New		structure.pdf (current)
0001		Delete	0000\..\structure.pdf	**structure.pdf (no longer relevant to the review)**

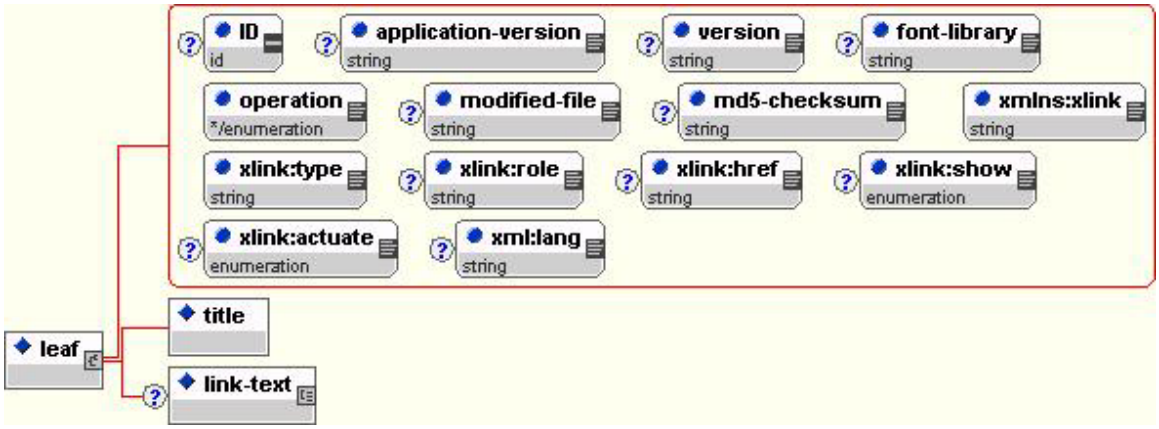
DTD Content Model

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. This example shows how the section of the CTD containing summaries is structured.



Once the appropriate tag has been selected, use the <leaf> element and attributes to specify a file in the submission. See "Instructions for preparing the eCTD" in this appendix for details.




ID
id
application-version
string
version
string
font-library
string
operation
*/enumeration
modified-file
string
md5-checksum
string
xmlns:xlink
string
xlink:type
string
xlink:role
string
xlink:href
string
xlink:show
enumeration
xlink:actuate
enumeration
xml:lang
string
leaf
title
link-text

eCTD Element/Attribute Instructions

The eCTD consists of 5 primary sub 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 first 5 sub modules is further decomposed into sub-elements, each with a distinct <tag> 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. You should select a tag element that best corresponds to the CTD table of contents location for a document or file being submitted. For example, select the tag <m2-4-nonclinical-overview> to submit the nonclinical overview document.
2. You should create a child <leaf> element underneath the <m2-4-nonclinical-overview> tag.
3. You should provide the relative location and file name of the actual file containing the nonclinical overview in the "xlink:href" attribute for the <leaf> element.
4. You should provide a descriptive title for the file that contains the nonclinical overview in the <title> element of the <leaf>.
5. You should provide information for the appropriate attributes of the <leaf> element as described in Table 6-3.

The following table describes each of these elements and attributes in further detail.

Table 6-8

Element	Attribute	Description/Instructions	Example
Any table of contents tag such as <m2-4-nonclinical-overview>		A table of contents tag represents a grouping of one or more files related to a specific section of the Common Technical Document. One or more child <leaf> elements can be declared for a parent table of contents tag. It is possible to extend a table of contents tag by providing a <node-extension> element. This can be done at the lowest level of the	

Element	Attribute	Description/Instructions	Example
		defined table of contents tags but should be done only when absolutely necessary. See the section "Instructions for extending eCTD tag elements" in this appendix.	
	ID	A unique identifier for this location in the XML instance.	
	xml:lang	The primary language used by the files in this entire section of the submission. Use ISO-639 standard language abbreviations	en
<leaf>		A leaf corresponds to a file. One or more child leaf elements can be submitted for a parent table of contents tag.	
	application-version	The version of the software application that was used to create this file.	Acrobat 5
	Font-library	The commercial name of the font or font library needed to properly view the submitted file.	
	ID	Unique identifier for this location in the XML instance.	
	checksum	The checksum value for the file being submitted.	e854d3002c02a61fe5cbe926fd97b001
	checksum-type	The checksum algorithm used.	MD5
	modified-file	The name of the file to be modified as indicated in the "operation" attribute. This file name should include the relative path to the file. If no file is being modified, then you should not supply the "modified-file" attribute.	/0000/module-2/clinical-summary/references.pdf
	operation	Indicates the operation to be performed on the "modified-file". 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

Element	Attribute	Description/Instructions	Example
	Version	The file submitter's internal version number or version identification for the report.	V23.5
	xlink:actuate	Not Currently Used	
	xlink:href	Provide the pointer to the actual file. Use the relative path to the file and the file name.	module-2/clinical-summary/references.pdf
	xlink:role	Not Currently Used	
	xlink:show	Not Currently Used.	
	xlink:type	Fixed value of "simple".	simple
<title>		This element is associated with a "leaf" and provides a description of the file being submitted.	study report 1234
	ID	Unique identifier for this location in the XML instance	ID050520

Instructions for a Simple New Submission

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-1-0.dtd">
<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>
                        <m2-5-4-overview-of-efficacy xml:lang = "en">
                                <leaf operation = "new" xlink:type = "simple" checksum =
                                    "e854d3002c02a61fe5cbe926fd97b001"
                                    xlink:href = "module-2/clinical-summary/efficacy-overview.pdf"
                                    application-version = "Acrobat 5">
                                        <title>Overview of efficacy</title>
                                </leaf>
                        </m2-5-4-overview-of-efficacy>
                </m2-5-clinical-overview>
        </m2-common-technical-document-summaries>
</ectd:ectd>
```

This submission includes the file "efficacy-overview.pdf" in the relative directory "module-2/clinical-summary" (i.e. the one starting below the Dossier number and submission sequence directories). The file is "new" and has a descriptive name of "Overview of efficacy"

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.

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

Instructions for an Amendment, Supplement or Variation

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

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

```
<?xml version = "1.0" encoding = "UTF-8"?>
<!DOCTYPE ectd:ectd SYSTEM "util/dtd/ich-ectd-1-0.dtd">
<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>
                        <m2-5-4-overview-of-efficacy xml:lang = "en">
                                <leaf operation = "replace"
                                   xlink:type = "simple" checksum =
                                   "e854d3002c02a61fe5cbe926fd973401"
                                    xlink:href = "module2/clinical-summary/efficacy-overview v2.pdf"
                                    application-version = "Acrobat 5"
                                    modified-file = "0000/module2/clinical-summary/efficacy-overview.pdf">
                                        <title>Overview of efficacy</title>
                                </leaf>
                        </m2-5-4-overview-of-efficacy>
                </m2-5-clinical-overview>
        </m2-common-technical-document-summaries>
</ectd:ectd>
```

Instructions for Multiple Indications[7]

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. 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 tags beneath the <m2-7-3-summary-of-clinical-efficacy> and <m5-3-5-reports-of-efficacy-and-safety-studies> tags. This is an example of the a section of the instance showing the submission of information about two indications:

```
<?xml version = "1.0" encoding = "UTF-8"?>
<!DOCTYPE ectd:ectd SYSTEM "util/dtd/ich-ectd-1-0.dtd">
<ectd:ectd xmlns:ectd = "http://www.ich.org/ectd" xmlns:xlink = "http://www.w3c.org/1999/xlink">
```

[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.

```
        <m2-common-technical-document-summaries>
                <m2-7-clinical-summary>
                        <m2-7-3-summary-of-clinical-efficacy indication = "pain">
                                <leaf operation = "new" xlink:type = "simple" xlink:href =
                                    "module-2/summary-clin-efficacy/pain-eff-sum.pdf">
                                        <title>pain efficacy summary</title>
                                </leaf>
                        </m2-7-3-summary-of-clinical-efficacy>
                        <m2-7-3-summary-of-clinical-efficacy indication = "nausea">
                                <leaf operation = "new" xlink:type = "simple" xlink:href =
                                    "module-2/summary-clin-efficacy/nausea-eff-sum.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">
                            <leaf operation = "new" xlink:type = "simple" xlink:href =
                                "module-5/clinical-study-reports/efficacy-safety-pain/pain-sr1.pdf">
                                        <title>pain study report 1</title>
                            </leaf>
                        </m5-3-5-reports-of-efficacy-and-safety-studies>
                        <m5-3-5-reports-of-efficacy-and-safety-studies indication = "nausea">
                            <leaf operation = "new" xlink:type = "simple" xlink:href =
                                "module-5/clinical-study-reports/efficacy-safety-nausea/nausea-sr15.pdf">
                                        <title>nausea study report 15</title>
                            </leaf>
                        </m5-3-5-reports-of-efficacy-and-safety-studies>
                </m5-3-clinical-study-reports>
        </m5-clinical-study-reports>
</ectd:ectd>
```

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. The following table shows the use of these attributes.

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

This is an example of the a section of the instance showing the submission of information about two drug substances, one of which is supplied by two manufacturers:

```
<m3-2-body-of-data>
        <m3-2-s-drug-substance substance = "acetaminophen" manufacturer = "my supplier">
                <leaf operation = "new" xlink:type = "simple" xlink:href =
                    "module-3/body-of-data/drug-substance/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 operation = "new" xlink:type = "simple" xlink:href =
                   "module-3/body-of-data/drug-substance/acetaminophen-bulk-company-2/acetaminophen2.pdf">
                        <title>acetaminophen / company 2 data</title>
                </leaf>
        </m3-2-s-drug-substance>
        <m3-2-s-drug-substance substance = "codeine" manufacturer = "drug company 2">
                <leaf operation = "new" xlink:type = "simple" xlink:href =
                   "module-3/body-of-data/drug-substance/codeine-drug-company-2/codeine-quality-data.pdf">
                        <title>codeine 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. The following table shows the use of these attributes.

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	Name of the dosage form of the drug product	Capsules

This is an example of a section of the instance showing the submission of information about two drug products:

```
<m3-2-body-of-data>
        <m3-2-p-drug-product product-name = "wonder drug" dosageform = "capsules">
                <leaf operation = "new" xlink:type = "simple" xlink:href =
                  "module-3/body-of-data/drug-product/wonder-drug/specifications1.pdf">
                        <title>wonder drug capsule product information</title>
                </leaf>
        </m3-2-p-drug-product>
        <m3-2-p-drug-product product-name = "wonder drug" dosageform = "tablets">
                <leaf operation = "new" xlink:type = "simple" xlink:href =
                  "module-3/body-of-data/drug-product/wonder-drug/specifications2.pdf">
                        <title>wonder drug tablet product data</title>
                </leaf>
        </m3-2-p-drug-product>
</m3-2-body-of-data>
```

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 tag. Using node extensions is discouraged and should only be done when there is no other feasible means to submit information. 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 follow the following principles when using <node-extension>:

1. 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.

2. Do not extend the element more than one level. For example, you should not extend <node-extension> <title>special-fda-summary</title> </node-extension> with another <node-extension>.

The following is an example of a section of the eCTD instance in which an 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-fda-summary</title>
                                <leaf operation = "new" xlink:type = "simple" xlink:href =
                              "module-2/quality-overall-summary/regional/fda/fda-extra-quality-sum.pdf">
                                        <title> FDA 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.

Instructions for Submitting Sections as Paper

During the transition to fully electronic submissions of the CTD, some sections can be submitted as paper only. 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.

```
<m2-5-clinical-overview>
                        <m2-5-4-overview-of-efficacy xml:lang = "en">
                                <leaf operation = "new" xlink:type = "simple" checksum =
                                    "e854d3002c02a61fe5cbe926fd97b001"
                                    xlink:href = "module-2/clinical-summary/efficacy-overview.pdf"
                                    application-version = "Acrobat 5">
                                        <title>Paper Submission </title>
                                </leaf>
```

</m2-5-4-overview-of-efficacy>
</m2-5-clinical-overview>

Appendix 7 Specification for Submission Formats

Introduction

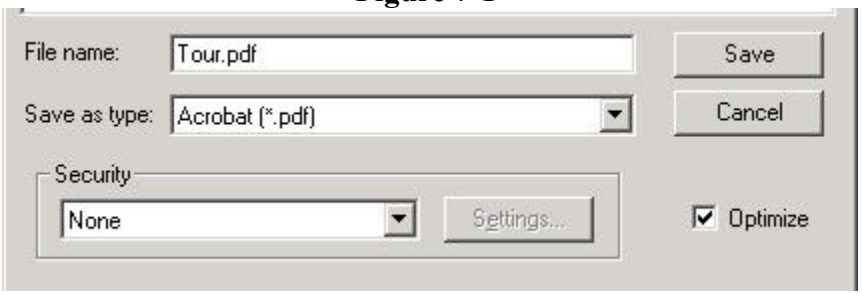
This appendix describes the way in which files should be constructed for inclusion in the eCTD. The file formats included in this section are those formats that are commonly used in electronic submissions. Other formats can be used according to guidance published in each region.

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 50 Megabytes. The files should be saved "optimized" as shown in figure 7-1.

Figure 7-1



Version

Agencies should be able to read all PDF files with version 4.0 or higher of the Acrobat Reader. Agencies should not need any additional software to read and navigate the PDF files. However, review can be facilitated through use of Adobe Acrobat since significantly more functionality is available in this product than with Acrobat Reader.

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, it can affect 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.

One problem associated with embedding fonts is that embedding 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

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 reading 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 point size for tables, a balance should be made between providing sufficient information on a single page that may facilitate data comparisons for the reviewer while still achieving a point size that remains legible. The corollary of this is that in making point size larger, more tables might be necessary, which can complicate data comparisons for a reviewer since data might now be included in separate tables. Generally, point sizes 9-10 are considered acceptable in tables but smaller point sizes should be avoided.

Use of Color fonts

The use of a black font color is recommended. Blue font can be used for hypertext links. If a font color other than black is used, 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 or Letter paper. A sufficient margin (at least 2.5cm) on the left side of each page should be provided in order 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 are allowable (at least 2.0cm at the top and 0.8cm left and right) so as to allow more information, displayed legibly, on the page (see Section 3, Fonts). It is acceptable that header and footer information appears within these margins but not so close to the page edge that it may risk being lost upon printing.

Source of Electronic Document

PDF documents produced by scanning paper documents are usually inferior to those produced from an electronic source document. Scanned documents are more difficult to read and do not allow reviewers to search or copy and paste text for editing. They 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://info.internet.isi.edu/in-notes/rfc/files/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 300 dpi. Hand-written notes should be done in black ink for clarity.

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 are techniques used to improve navigation through PDF documents. Hypertext links can be designated by rectangles using thin lines or by blue text.

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. These bookmarks are essential for the efficient navigation through documents. In general, including a bookmark to the main table of contents for a submission or module is helpful. The bookmark hierarchy should be made 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 body of the document to supporting 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.

Page Numbering

If a submission includes more than one document, no additional volume or page numbering is necessary. Only page numbers for individual documents are needed. 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 initial page of the document should be numbered page 1, with no use of Roman numerals or unnumbered pages in the document. If this is not done, Acrobat Reader would include such numbering within its page count and thus put the Acrobat numbering out of synchrony with the internal document page numbers.

Two exceptions to this rule can occur, details of which can be found in the guidance for the modules of the CTD.

- Firstly, where a document is split because of its size (e.g. >50MB), under which circumstances the second or subsequent file should be numbered consecutively to that of the first or preceding file.
- Secondly, where several small documents with their own internal page numbering have been brought together into a single file, under which circumstances it is not

considered necessary to provide additional page numbering, but the start of each sub-document should be book marked.

Document Information Fields

Document information fields should not be used for the common portions of the eCTD, but they may be appropriate for some of the regional documents. 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

Full text indices can be used to help find specific documents and/or search for text within documents. When a document or group of documents is indexed, all words and numbers in the file and all information stored in the Document Information fields are stored in special index files that are functionally accessible using the search tools available in Acrobat. Portions of a document that are imaged are not indexed. Even if the document only contains images, the text in the Document Information fields of the file will be indexed.

These full text indices should not be confused with a table of contents. Adobe Acrobat Catalog is one example of a tool that can be used to index PDF documents. Indices should not require extensions or additions to off-the-shelf Acrobat programs.

Further recommendations for full text indices will be provided in regional guidance.

Use of Acrobat Plug-Ins

It is considered acceptable to use plug-ins to assist in the creation of a submission. However, the review of the submission should not require the use of any plug ins, in addition to those provided with Adobe Acrobat because Agencies should not be required to archive 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 mark up 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.

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 " ". 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. Style sheets 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 declaration (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 style sheet type and address, and the DTD name and address.

Additional information about the XML standard can be found at the W3C web site at http://www.w3c.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 appplication, 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.w3c.org/graphics/svg

Appendix 8 XML eCTD DTD

```
<!-- eCTD Version 0.96 renamed to version 1.0
    Jan 10 - Feb 6, 2002
    Added keywords attribute to leaf element
      This attribute is expected to be a comma-separated list of keywords
    Removed 3+ level of detail in m2-4-nonclinical-overview
    Removed 4+ level of detail in
      m2-6-nonclinical-written-and-tabulated-summary
    Removed 3+ level of detail in m2-7-clinical-summary
    Removed 3+ level of detail in m2-5-clinical-overview
    Changed name of leaf attribute md5-checksum to checksum
    Added attribute checksum-type to leaf element
    Added attribute manufacturer to
      m2-3-p-drug-product and m3-2-p-drug-product
    Removed 4+ level of detail in m2-3-quality-overall-summary
    Removed 6+ level of detail in m3-2-p-2-pharmaceutical-development
-->

<!-- eCTD Version 0.95  -->
<!-- Oct 20, 2001 -->
<!-- Changes according to testing feedback -->
<!-- See separate sheet -->

<!-- eCTD Version 0.92  -->
<!-- Changed incorrect m2-7-4-5-3 attribute -->
<!-- Added namespace info to leaf and xref elements -->

<!-- eCTD Version 0.91  -->
<!-- June 4, 2001 -->
<!-- changed m2-7-3 to be 0 or more instead of 0 or 1 -->

<!-- eCTD Version 0.9  -->
<!-- ICH Tokyo Meeting: May 24, 2001 -->

<!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 "0.96" >

<!-- ========================================================== -->
```

```
<!-- Leaf content -->
<!-- ============================================================= -->

<!ELEMENT leaf  (title, link-text?) >
<!ATTLIST leaf
          ID  ID    #IMPLIED
          application-version  CDATA    #IMPLIED
          version  CDATA    #IMPLIED
          font-library  CDATA    #IMPLIED
          operation (new | append | replace | delete) #REQUIRED
                              modified-file CDATA #IMPLIED
          checksum  CDATA    #IMPLIED
          checksum-type CDATA #IMPLIED
                              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    #IMPLIED
                              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-summary?,
                                                                    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-summary (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-summary %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-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-references?,
                        m2-7-6-synopses-of-individual-studies?) >
<!ATTLIST m2-7-clinical-summary %att; >

<!ELEMENT m2-7-1-summary-of-biopharmaceutic-and-associated-analytical-methods
                                    ((leaf | node-extension)*) >
<!ATTLIST m2-7-1-summary-of-biopharmaceutic-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
#IMPLIED  >

<!ELEMENT m2-7-4-summary-of-clinical-safety  ((leaf | node-extension)*) >
<!ATTLIST m2-7-4-summary-of-clinical-safety %att;  >
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<!ELEMENT m2-7-5-references ((leaf | node-extension)*) >
<!ATTLIST m2-7-5-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;  >
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<!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)*) >
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<!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
                                                        >

<!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*,
                                                m3-2-p-2-1-components-of-the-drug-product?,
                                                m3-2-p-2-2-drug-product?,
                                                m3-2-p-2-3-manufacturing-process-development?,
                                                m3-2-p-2-4-container-closure-system?,
                                                m3-2-p-2-5-microbiological-attributes?,
                                                m3-2-p-2-6-compatibility?) >
<!ATTLIST m3-2-p-2-pharmaceutical-development %att; >

<!ELEMENT m3-2-p-2-1-components-of-the-drug-product ((leaf | node-extension)*) >
<!ATTLIST m3-2-p-2-1-components-of-the-drug-product %att; >

<!ELEMENT m3-2-p-2-2-drug-product ((leaf | node-extension)*) >
<!ATTLIST m3-2-p-2-2-drug-product %att; >
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<!ELEMENT m3-2-p-2-3-manufacturing-process-development  ((leaf | node-extension)*) >
<!ATTLIST m3-2-p-2-3-manufacturing-process-development %att;  >

<!ELEMENT m3-2-p-2-4-container-closure-system  ((leaf | node-extension)*) >
<!ATTLIST m3-2-p-2-4-container-closure-system %att;  >

<!ELEMENT m3-2-p-2-5-microbiological-attributes  ((leaf | node-extension)*) >
<!ATTLIST m3-2-p-2-5-microbiological-attributes %att;  >

<!ELEMENT m3-2-p-2-6-compatibility  ((leaf | node-extension)*) >
<!ATTLIST m3-2-p-2-6-compatibility %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;  >
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<!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
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                                                                    ((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-novel-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; >

<!ELEMENT m3-2-a-2-adventitious-agents-safety-evaluation ((leaf | node-extension)*) >
<!ATTLIST m3-2-a-2-adventitious-agents-safety-evaluation %att; >

<!ELEMENT m3-2-a-3-novel-excipients  ((leaf | node-extension)*) >
<!ATTLIST m3-2-a-3-novel-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?,
                                                    m4-2-4-local-tolerance?,
                                                    m4-2-5-other-toxicity-studies?) >
<!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; >
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<!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?) >
<!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;  >
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<!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;  >

<!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;  >

<!ELEMENT m4-2-3-5-1-fertility-and-early-embryonic-development  ((leaf | node-extension)*) >
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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;  >

<!ELEMENT m4-2-3-5-3-prenatal-and-postnatal-development-including-maternal-function
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<!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;  >

<!ELEMENT m4-2-4-local-tolerance  ((leaf | node-extension)*) >
<!ATTLIST m4-2-4-local-tolerance %att;  >

<!ELEMENT m4-2-5-other-toxicity-studies  (leaf*,
                                     m4-2-5-1-antigenicity?,
                                     m4-2-5-2-immunotoxicity?,
                                     m4-2-5-3-mechanistic-studies?,
                                     m4-2-5-4-dependence?,
                                     m4-2-5-5-metabolites?,
                                     m4-2-5-6-impurities?,
                                     m4-2-5-7-other?) >
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<!ATTLIST m4-2-5-other-toxicity-studies %att;  >

<!ELEMENT m4-2-5-1-antigenicity  ((leaf | node-extension)*) >
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<!ELEMENT m4-2-5-2-immunotoxicity  ((leaf | node-extension)*) >
<!ATTLIST m4-2-5-2-immunotoxicity %att;  >

<!ELEMENT m4-2-5-3-mechanistic-studies  ((leaf | node-extension)*) >
<!ATTLIST m4-2-5-3-mechanistic-studies %att;  >

<!ELEMENT m4-2-5-4-dependence  ((leaf | node-extension)*) >
<!ATTLIST m4-2-5-4-dependence %att;  >

<!ELEMENT m4-2-5-5-metabolites  ((leaf | node-extension)*) >
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<!ELEMENT m4-2-5-6-impurities  ((leaf | node-extension)*) >
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<!ELEMENT m4-2-5-7-other  ((leaf | node-extension)*) >
<!ATTLIST m4-2-5-7-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?) >
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<!ELEMENT m5-2-tabular-listing-of-all-clinical-studies ((leaf | node-extension)*)>
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<!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;  >
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<!ELEMENT m5-3-1-2-comparative-ba-and-bioequivalence-study-reports
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<!ATTLIST m5-3-1-2-comparative-ba-and-bioequivalence-study-reports %att;  >

<!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
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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;  >

<!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
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<!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
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<!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)*) >
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<!ELEMENT m5-3-3-2-patient-pk-and-initial-tolerability-study-reports
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<!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;  >
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<!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 #IMPLIED  >

<!ELEMENT m5-3-5-1-study-reports-of-controlled-clinical-studies-pertinent-to-the-claimed-indication
((leaf | node-extension)*) >
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%att;  >

<!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 %att;  >

<!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 %att;  >

<!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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Appendix 9 Glossary

The intended content of this section is the definition of terms used in the set of documentation associated with the eCTD.

Architecture
A general term for the design and construction of computer systems, including technical infrastructure, information (data), and applications.

ASCII
American Standard Code for Information Interchange. A specification for representing text as computer-readable information.

Browser
A program which allows the user to read hypertext, to view contents of web pages, and to navigate from one page to another, e.g., Netscape Navigator, Mosaic, Microsoft Internet Explorer.

Common Technical Document (CTD)
A harmonized format for a regulatory dossier that is considered acceptable in Japan, Europe, United States and Canada.

Decryption
To reverse encryption.

Directory (see also Folder)
The operating system method of organizing and providing access to individual files. Also called a Folder.

DTD
Document Type Definition. A hierarchical organization or representation of the information contents of a document utilized by SGML or XML.

eCTD
The electronic format of the ICH Common Technical Document

Encryption
The process of reversibly confusing text or data using a secret formula.

EWG
Expert Working Group.

Folder (see also Directory)

The operating system method of organizing and providing access to individual files. Also called a Directory.

HTML
Hypertext Markup Language. Commonly used to format Web pages.

Hypertext
A system that enables links to be established between specific words or figures in a document to other text, tables or image allowing quick access to the linked items (such as on the World Wide Web).

ICH
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Infrastructure
The basic support services for computing; the hardware, operating system, and network on which applications and data are stored and on which the database management systems run.

Internet
The world-wide network of computers for accessing, sending, sharing, and transferring information between sites at different locations. It is uncontrolled and unadministered, and when you connect to the Internet, you actually become a part of it.

ISO
International Standards Organization - founded in 1946, it is the principal international standards-setting organization.

Leaf
The eCTD DTD XML element that describes the content to be provided. The leaf consists of a file and the meta-data associated with that file. Such files are placed in a directory structure that is similar to branches of a tree.

Logical Document
One or more CTD table of contents sections that together contain the minimum amount of information to be exchanged. Ideally, this is a single physical file.

M2
Multidisciplinary Group 2 (ESTRI) of ICH.

Network
A communication system which connects different computers and enables them to share peripherals such as printers, disk drives and databases. Users (clients) can access applications and databases connected by the network.

Node Extension

The extension of the definition of an element beneath a defined table of contents tag.

PDF
Portable Document Format - a proprietary (Adobe Systems) *de-facto* standard for the electronic transfer of documents.

SGML
Standardized Generalized Markup Language. An ISO standard for describing structured information in a platform independent manner.

Software or Software Application
Computer programs or applications. There are two principle types: system software, e.g., computer operating system or a utility program (sometimes called a driver) for printing and application software, e.g., an accounts package or CAD program.

Standard
A technical specification that addresses a business requirement, has been implemented in viable commercial products, and, to the extent practical, complies with recognized standards organizations such as ISO.

Web page
Any page on the World Wide Web. The page usually offers the reader the ability to jump to other topics of interest.

World Wide Web (WWW)
Segment of the Internet offering point and click (hypertext) access to information, as text, image or sound, on an enormous number of topics from around the world.

XML
Extensible Markup Language. An ISO standard for describing structured information in a platform-independent manner.