

DRAFT FOR TESTING

Guidance for Industry on Providing Regulatory Information in Electronic Format: eCTD electronic Submissions

**This document is published under the auspices of the
EU Telematic Implementation Group - electronic submissions (TIGes)**

Please note that this document is being published on the EMEA eSubmission website so that both agencies and applicants can gain practical experience of building, submitting and receiving eCTDs.

The Topic Group consider that through this process we will gain valuable experience of what works and what additional information is required to ensure that eCTDs become the de facto submission standard across the EU.

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Document Control

Change Record

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1.0	eCTD Topic Group	This document has been prepared by the eCTD Guidance Topic Group of the TIGes. It is largely based on the NeeS guidance document 1.4.

Coming into Operation

Version	Date in operation	Comment
1.0	May 2009	This document is specifically called a "Draft for Testing". The Topic Group fully anticipate comments from NCAs and applicants which will enable future versions to reflect practical experience of users. In this way the document will evolve to become an essential work of reference in this area.

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1. INTRODUCTION

In 2005 the Heads of Medicines Agencies agreed that all Member States would be able to accept eCTD (electronic Common Technical Document) applications, without accompanying paper copies, by the end of 2009. The benefits of moving to e-working are considered to be:

- Reduction in administrative overheads from less paper movement,
- Reduction of physical archiving space,
- Facilitation of the review process.

This Guidance Document is intended to assist pharmaceutical companies with the submission of regulatory information in electronic format to the National Competent Authorities (hereinafter referred to as NCAs) and the European Medicines Agency (hereinafter referred to as EMEA). This document details the requirements for the submission of eCTD electronic submissions. A separate document, covering NeeS (Non-eCTD electronic Submissions), has already been published on the EMEA's eSubmission website and is available via this [link](#).

This document has been created by the eGuidance Topic Group, a sub-group of the Telematics Implementation Group – Electronic Submissions (TIGes), consisting of agency representatives from Belgium, Denmark, EMEA, France, Germany, Hungary, The Netherlands, Portugal, Sweden and the United Kingdom, together with industry representatives from EFPIA and EGA. It has also been endorsed by the TIGes. National Competent Authorities have been strongly recommended to adopt this guidance as the basis for their dealings with applicants.

It should be stressed that this Guidance Document reflects the *current* situation and will be regularly updated in the light of changes in national and/or European legislation together with further experience gained within NCAs and the EMEA of using information submitted in electronic format. It should be emphasised that eCTD applications should now be regarded as the principal submission format in the EU.

This document assumes a certain basic understanding of eCTD applications. A list of background publications can be found in [Annex 1](#). Applicants should pay special attention to the recommendations of the ICH M2 Expert Working Group on the eCTD and the TIGes in the EU. Consolidated specifications can also be found on the Commission Eudralex [website](#). International standards development through ICH, ISO and HL7 will eventually lead to the eCTD becoming part of a wider group of regulated product submissions, covering medical devices, veterinary products and food additives as well as medicinal products.

This Guidance Document consists of four parts: Introduction, General Considerations, Module Specific Information and Advice on Specific Application Types together with associated annexes. In addition please refer to Chapter 7 of the [Notice to Applicants](#), Volume 2A for specific NCA requirements.

A brief glossary of terms (for the purpose of this document only) is indicated below:

Term	Definition
Applicant	A pharmaceutical company or its agent that is submitting information in support of an application .
Applicant's information	Regulatory information submitted by an applicant for, or to maintain, a marketing authorisation that falls within the scope of this guidance document.
eCTD application	A collection of electronic documents compiled by a pharmaceutical company or its agent in compliance with European legislation and guidelines in order to seek a marketing authorisation or any amendments thereof. An eCTD application may comprise a number of sequences . In the EU an eCTD application may comprise several dosage forms and strengths, all under one invented product name. This is understood to be equivalent to a Global Marketing Authorisation according to Art. 6 para 2 Dir. 2001/83/EC as amended. Some review tools describe such a collection as a dossier.
Procedure	A Community registration procedure for the authorisation of medicinal products in the European Community. There are 4 types of procedure that operate within the EC – Centralised, Decentralised, Mutual Recognition and National.
Submission or Sequence	A single set of information and/or electronic documents supplied at one particular time by the applicant as a part of, or the complete, eCTD Application . In the context of eCTD, this is equivalent to a sequence .
Regulatory activity	A collection of sequences covering the start to the end of a specific business process, e.g. an initial MA application or Type II variation. It is a concept used in some review tools to group together several business related sequences.

2. GENERAL CONSIDERATIONS

2.1 Scope

2.1.1 Types of product

This guidance covers the submission of electronic regulatory information for all *human* medicinal products falling within the competence of NCAs and the EMEA. This includes prescription, over the counter medicines, innovative and generic product submissions. The product types include small molecules, biotech products, herbals, vaccines, homeopathics and blood products.

2.1.2 Types of submission

This guidance applies to all submissions related to the authorisation and maintenance of medicinal products, including new marketing authorisations, variations, renewals, PSURs, active substance master files.

2.1.3 Types of procedures

This guidance covers applications made in any of the applicable Community procedures (National, Mutual Recognition, Decentralised and Centralised).

2.1.4 Exceptions

This guidance does not apply to the electronic submission of pre-MA information such as scientific advice, clinical trial applications and related submission correspondence.

2.2 Structure of submissions

This document provides guidance on how to organise application information for electronic submission using the eCTD specifications. Guidance on the detailed information to be included is described in the [Common Technical Document \(CTD\)](#), and relevant ICH and EU Q&A documents.

The structure and organisation of an eCTD submission is defined by the following standards:

- ICH M2 eCTD Specification
- EU Module 1 Specification
- Relevant ICH and EU Q&A docs

[Annex 1](#) contains links to the currently approved version of these documents.

Typically, an eCTD application will cover all dosage forms and strengths of a product with any one invented name. In the centralised procedure, this will be equivalent to all dosage forms and strengths covered by an EMEA application number (e.g. EMEA/H/123). In MRP/DCP, a single eCTD application should preferably be used for the procedure. However if an applicant decides not to apply for all strengths and dosage forms in every member state in the procedure, the possibility of having one eCTD application per strength should be considered. Applicants should carefully consider what an eCTD application should cover before submitting the first sequence, as the choice could have implications for workload for the lifespan of the product. For example, if the applicant decides to have one eCTD per strength or dosage form, it is expected that each of these eCTD applications will be maintained individually, such that submission of a single sequence that covers more than one strength or dosage form will no longer be possible if very good reasons are not presented for a change over. [In these rare cases, please contact the NCA/RMS/EMEA concerned at an early planning stage.](#)

For further details on the pros and cons of the different approaches to dossier structure, see Annex 3, Table 1.

Please check for specific NCA guidance when preparing national eCTDs. .

2.3 Transitional arrangements

The specifications mentioned in section 2.2 above will change over time and are likely to affect both eCTD building tools and the applicant's internal business processes as well as the agencies review tools and processes. Once a new specification has been agreed and endorsed by the appropriate EU body, eCTD building tools will need to be updated. Specific transitional guidance will be provided on each occasion that the ICH and/or EU specifications are updated.

Please note that it should not be necessary to reformat and resubmit previously submitted applications to reflect such changes.

2.4 Moving to eCTD format from paper or NeeS type applications

An eCTD product life cycle can be started with an initial, variation or renewal MA application. However, changing to eCTD format should not be performed in the middle of an on-going regulatory activity (i.e. do not submit responses to questions as an eCTD if the corresponding application to which they relate has not been submitted as an eCTD).

Where a repeat use procedure in eCTD format is planned, the change of format should be made before the start of the process.

Where an eCTD application is being used for the first time for a variation or renewal application, applicants are encouraged to submit a technical baseline for the product as this will greatly aid the review process. Please see [section 2.12](#) for further information on the content of baseline applications.

2.5 General Submission Considerations

2.5.1 Document granularity

Submissions are a collection of documents and each document should be provided as a separate file. The detailed structure of the eCTD should conform to the [ICH Granularity Document](#) and EU M1 specifications.

2.5.2 File Naming

The eCTD file naming conventions described in the ICH M2 eCTD Specification and EU Module 1 Specification are highly recommended. If an applicant wishes to submit multiple files in one section, where only one highly recommended name is available, this can be achieved using a suffix to the filename, using the file name-*var*.pdf convention as described in the EU Module 1 Specification, where the -*var* component has no dashes or illegal characters (e.g. pharmaceutical-development-*container*.pdf).

2.5.3 Placement of Documents

Guidance on the placement of documents within the eCTD structure for particular submission types can be found in the [EU-CTD Notice to Applicants](#) and/or in the [EMEA post-authorisation guidance](#) for centralised applications.

2.6 Correspondence

In addition to the eCTD application information may need to be exchanged to assist the processing or handling of the application. Not all that correspondence should be included in the eCTD. This is because the eCTD exchange is currently one way only, from applicant to Agency, and not all correspondence is directly relevant to the application dossier.

Accordingly, only the minimum amount of correspondence that relates directly to the content of the dossier should be included in eCTD submissions to NCAs and the EMEA. All other correspondence should be exchanged outside the eCTD via the usual electronic means (email, Eudralink etc). Such documentation is likely to be handled in different ways within the authorities and normally not within the eCTD review system.

Where correspondence acknowledges the final change to details submitted in the body of the dossier, the agreement cannot be documented by that correspondence alone. The revised information should be provided in an accompanying replacement document situated in the appropriate place in the body of the dossier, with the relevant information contained in a covering letter. See further detailed information in [section 3.2.3](#)

The eCTD is designed to ensure that users have a current view of the information submitted in the appropriate place in the dossier at all times.

2.7 Paper requirements

An overview of the requirements for paper and electronic copies is specified for each NCA and EMEA in the [Notice to Applicants](#), Volume 2A, Chapter 7.

Guidance on the minimum requirements to produce a paper submission from an eCTD has also been published in the [Notice to Applicants, Volume 2B](#)

2.8 Hardware

NCAs and the EMEA will not accept any hardware (laptops, desktops, zip drives, etc.) from applicants in connection with the submission of information in electronic format. The electronic information should be directly readable and usable on NCAs and EMEA hardware and software.

2.9 General Technical eCTD Information

2.9.1 File formats

In general terms the majority of documents included in electronic submissions should be in PDF format, file version 1.4 (see next section on the use of later PDF file versions).

The use of XML for applications forms in particular is likely to increase as agency systems develop the functionality to handle it in their own business processes. See [Section 3.2.4](#) for further information.

Further detailed guidance on file formats can be found in the ICH eCTD specification document and EU Module 1 specifications.

2.9.2 Portable Document Format (PDF)

Portable Document Format (PDF) is an open, de facto, electronic publishing standard. Although created by Adobe Systems Incorporated there are several alternative suppliers of PDF software. Applicants need to check that their PDF documents meet the following key requirements:

- Files should be legible with Acrobat Reader, version 5.0 or higher.
- Only PDF file version 1.4 should be used, except where there is an agency specific requirement for a later version for application forms.
- Documents should be generated from electronic source documents and not from scanned material, except where access to the source electronic file is unavailable or where a signature is required. See Annex 2 for further guidance on text searchable documents.

Additional details on PDF, including those relating to the good presentation of tables, can be found in the [ICH eCTD Specification](#), Appendix 7.

2.9.3 Sequence Numbers

Sequence numbers are used to differentiate between different submissions of the same application over the life cycle of the product. The review tools being used by most NCAs and the EMEA are able to handle sequences submitted out of numerical order, i.e. 0003 submitted after 0004. This can occur when the preparation of a sequence is delayed. However, it is recommended that, sequence numbers should normally follow the order of submission of the sequences. A Sequence Tracking Table should always be included as an annex to the cover letter in every submission within MRP/DCP (see [CMD\(h\) recommendations on the cover letter](#)). Specific recommendations for MR and DC Procedures are given in the CMD(h) [guidance on e-submission](#). A similar tracking table is recommended for national applications.

The initial eCTD life cycle submission should normally have a sequence number of 0000. If applicants consider that there are good reasons to use another number they should explain this in the cover letter.

As additional data is submitted in response to questions, the sequence number of the submission will advance, 0001, 0002, etc. Only in the case of a technically invalid submission can a sequence be replaced with one using the same number, e.g. the initial sequence "0000" will be replaced by another "0000".

When starting an eCTD product life cycle at a point other than with an initial MA application, such as a variation or renewal, the initial eCTD sequence serving as the baseline, should preferably be numbered as "0000".

The relationship of one sequence to another is managed using the related sequence number. This allows sequences to be grouped together that make up an application or a regulatory activity.

2.9.4 Bookmarks and hypertext links

Navigation through an electronic submission is greatly enhanced by the intelligent use of bookmarks and hypertext links. ICH guidance states "It is expected that any document that has a Table of Contents (TOC) will have bookmarks (see the eCTD specification for details). Documents without TOCs should have bookmarks included where it aids in the navigation around the document content. For example, a 4 page document summarising findings could require bookmarks to aid navigation. However, a 300 page file containing a single data listing might not require bookmarks as there is no further internal structure. Please consult regional guidance documents for further details."

In general terms, bookmarks and hyperlinks should be used to aid navigation. The overuse of hyperlinks may confuse rather than help assessors and may cause problems later in life cycle management.

Additional details on creating bookmarks and hypertext links in PDF documents can be found in the [ICH eCTD Specification](#), Appendix 7.

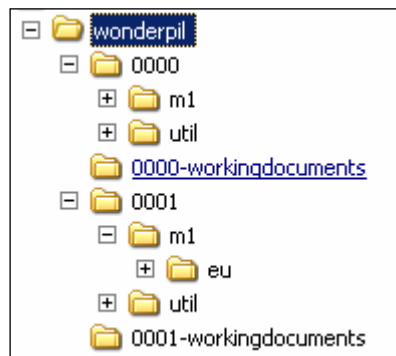
2.9.5 Extensible Mark-up Language (XML)

XML is the format for the backbone files for the eCTD. Details on XML can be found in the [ICH eCTD Specification](#) Document, Appendix 7. Initiatives on the use of XML structured information are supported by NCAs and the EMEA for the Product Information Management (PIM) system and e-application forms. Please refer to EMEA e-submission website for further details.

2.9.6 Other File Formats

Other file formats such as rich text (RTF) or MS Word formats may be required in addition to the PDF requirement of the eCTD, by specific NCAs or the EMEA, especially for the provision of product information documents or the Module 2 documents. Please refer to the [Notice to Applicants](#), Volume 2A, Chapter 7 for further details.

These files should not be added as leaf elements within the eCTD structure. They should be provided in a separate folder called, e.g. "<sequence>-workingdocuments" on the CD/DVD containing the eCTD.



2.9.7 Technical validation of eCTD submissions

The technical validation of an eCTD is a separate activity to the content validation of a submission and takes place irrespective of the type of the submission. NCAs and the EMEA have adopted a [common set of technical criteria](#) against which all eCTDs can be checked using eCTD review and validation tools.

The general process for the validation of eCTD submissions is divided into two parts: technical and content validation. An eCTD must pass technical validation before it undergoes content validation. Technical validation errors of category A will result in the applicant being asked to resubmit the eCTD sequence with the same sequence number, category B errors will normally not require resubmission but may require fixing in a subsequent sequence, category C do not require resubmission but may be fixed in subsequent sequences at the applicant's discretion.

Errors found during the content validation should be resolved through the submission of a new eCTD sequence. These errors must never be resolved by resubmitting an existing sequence.

2.10 Other Technical Information

2.10.1 Security issues

The physical security of the submission during transportation is the responsibility of the applicant. Once received by NCAs and the EMEA, security and submission integrity is the sole responsibility of NCAs and the EMEA.

2.10.2 Password protection

Submission or file level security is not permitted. If one-time security settings or password protection of electronic submissions are used this could constitute grounds for the rejection of the submission.

2.10.3 Virus protection

The applicant is responsible for checking the submission for viruses. Checking should be performed with an up-to-date virus checker and be confirmed in the cover letter. After receipt at NCAs and the

EMEA, a similar internal virus check will be performed. If a virus is detected it will constitute grounds for rejection of the electronic submission.

2.10.4 Electronic signatures

Although electronic signatures are currently accepted in the EU as being legally equivalent to handwritten signatures (Directive 1999/93/EC), the majority of NCAs and EMEA do not have a system for that yet and therefore require that certain specific documents (covering letters, Application Forms) are authenticated by separate signed paper copies. Please refer to each NCA for detailed guidance on this matter or the [Notice to Applicants](#), Volume 2A, Chapter 7.

2.10.5 Transmission Media

Currently CD-ROM, CD-R, DVD-R are considered acceptable media standards. Applicants should provide the electronic information on the smallest number of discs possible, taking into consideration the size of the submission.

If an individual eCTD submission is of such a size as to span several CDs, the provision of a DVD is recommended. However, if CD-R must be used, when large applications are submitted it is inevitable that the application will necessarily span multiple CDs. Where possible, individual modules should not be split over multiple CDs (e.g. if possible, a single CD should contain Module 1, Module 2, if too large to fit on the same CD should then go onto the next CD even if this requires CD 1 not to be filled to capacity and so on). If, in the case of larger modules, where a split over multiple CDs is inevitably necessary, subfolders should be distributed in sequence, and these subfolders should not be split between CDs, even if this requires a CD to be sent not full to capacity.

It is the choice of the applicant if a separate CD/DVD is provided for each new sequence or if several sequences (e.g. concerning several variations) for the same medicinal product (same eCTD) is provided on the same CD/DVD. This should be clearly described in the cover letter and indicated on the disc (see 2.10.6).

2.10.6 Labelling of Media:

Each CD or DVD submitted with an eCTD should include the following label information, clearly presented and printed on the media:

- Format: eCTD
- The applicant's name
- The product (invented) name(s)
- The International Non-proprietary Name (INN) of the active substance(s)
- The full application number(s) (if known)
- The sequence number(s) of the eCTD submissions contained on the CD/DVD
- Number of media units per full set and an indication of the place of the individual CD/DVD within this set (e.g. 1(5), 2(5), etc.
- The submission type(s) of each eCTD submission(s) contained on the CD/DVD (e.g. Initial Application, Variation Type II), as per the eCTD envelope information

2.10.7 Procedure for sending electronic information

Some NCAs are able to accept eCTDs submitted via their portals. Generally only small (<100MB) applications can be handled this way. Applicants should check with individual NCAs for details of this process. If submissions are uploaded via a portal no data corruption should occur as a result of the process.

In all other cases the eCTD submission should be sent to the address referred to in the [Notice to Applicants](#), Volume 2A, Chapter 7.

Electronic media sets should be submitted at the same time as any required paper documentation. The electronic media should be packed adequately to prevent damage and the package should include a cover letter. Please see [section 3.2.3](#) for details on the format of cover letters.

2.11 Archiving and working copies

Please refer to the [Notice to Applicants](#), Volume 2A, Chapter 7 for details of the number of copies of electronic submissions required for archiving and review purposes. Many NCAs destroy discs after data has been uploaded into their systems. Where an NCA requires the disc to be archived they may have additional requirements.. Note: The current standard to burn CDs / DVDs is [UDF](#), which has replaced the former [ISO standard 9660](#).

2.12 Technical baseline applications

These should normally be submitted as sequence 0000. It should be clearly stated in the cover letter of the “baseline eCTD” that the content of the current dossier has not been changed, only its format. Consequently the first variation in eCTD format should then be submitted as sequence 0001. It is not necessary for the baseline eCTD to contain document hyperlinks as it would not normally be assessed.

The technical baseline application can also be used by applicants to switch from one eCTD sequence per strength, to one eCTD sequence covering multiple strengths. For the switch the pros and cons of the different approaches to dossier structure, as described in Annex 3, Table 1, should be taken into consideration. The switch from one approach to another should only be allowed once during the life cycle.

3. MODULE SPECIFIC INFORMATION

3.1 General information

The following subfolders should be used to organise the files for each module in a submission: *m1*, *m2*, *m3*, *m4*, and *m5* following the principles set out for the CTD in [Notice to Applicants, Volume 2B](#). There is also a subfolder *util* to organise eCTD technical files in the submission. If a module is not appropriate for a particular submission it should be omitted. Empty subfolders should not be included.

Each document should be provided as an individual PDF file, except those specifically requested in a different format, e.g. e-Application Form or PIM data.

A single eCTD application can cover multiple drug substances (e.g. in case of fixed combination products), multiple manufacturing sites, multiple medicinal products based on one invented name (different pharmaceutical forms or strengths). Careful planning is required to ensure that the dossier can be expanded as the product range is expanded or reduced by the submission of later sequences. Please see Annex 3 for further details.

Currently it is outside the scope of current eCTD specifications to allow cross references to documents, sections or modules in other eCTD dossiers.

3.2 Module 1 eCTD envelope, administrative information and prescribing information folder

3.2.1 General considerations

In the case of country specific files or folders the country code should appear in the file and folder name as the differentiating marking.

Module 1 “Not Applicable (N/A)” documents should not be included in the eCTD. However, when a justification for the absence of a certain document in module 1 is required, such justification should be provided in its corresponding section in the eCTD structure. In any case, all section titles should always appear in the module 1 eCTD backbone, displayed by the style sheet, even if these sections are not populated.

3.2.2 Creation and Management of Envelope Information

The eCTD envelope should be used to describe the eCTD sequence:

Country	In the centralised procedure, there should only be one envelope with the entry ‘emea’. For MRP/DCP, each country in the procedure needs to have a separate envelope entry. Common must not be used as a country identifier in the envelope.
Application number	The application number should be the centralised procedure/application number (EMA/H/C/...), MRP/DCP procedure number (e.g. SE/H/1234...) or other national application or licence number as required by NCAs. Multiple entries are possible. The full application number including the regulatory activity identifier should be used if known.
Applicant	Entries for ‘applicant’ should be consistent for all eCTDs from any single applicant (legal entity), as they define where eCTDs are stored in internal systems. Consistency of spelling is also relevant over time to allocate the eCTD correctly.
Agency-name	Self explanatory, from picklist in the most recent EU m1 eCTD specification. Assure that Country and Agency name will be consistent.

ATC	If unknown at the time of submission, the entry can say 'to be confirmed'.
Submission type	From picklist, see m1 specification for further details.
Procedure type	From picklist, see m1 specification for further details.
Invented-name	The trade name/invented name for the medicinal product covered by the application. If the eCTD covers multiple strengths or dosage forms, this entry does not need to describe the complete name, a simple entry, for example, 'Wonderdrug' will suffice.
INN	The International non-Proprietary name for the drug substance.
Sequence	The sequence number here must match the sequence number in the folder structure.
Related-sequence	For a description and example of how to use the 'related sequence' entry, see the EU m1 specification, p14.
Submission-description	This element is used to describe this particular eCTD sequence

3.2.3 Cover letter

The cover letter should, at least for MRP and DCP applications, include as a minimum, the information specified in the [CMDh Guidance document](#). There is also a [template](#) that can be used. Please see the [Notice to Applicants](#), Volume 2A Chapter 7, for details on the provision of signed paper copies of the cover letter and application form. The omission of submitted data from certain sections can also be explained here.

The cover letter should also mention if the product information is being provided as PIM data..

The cover letter should be submitted with the document operation attribute "new" which is in line with EU M1 specifications. As eCTD viewing tools will display all "new" leaf elements in a current or cumulative view, it is recommended that you place additional descriptive text in the leaf title to help you identify specific cover letters. This will help identify each cover letter leaf and the submission it is in, rather than having the cover letters named the same in each sequence. Some examples for the leaf titles could be:

Cover Letter for Sequence 0000
 Cover Letter for Germany for Sequence 0000
 Cover Letter for France for Type II Variation 028 (0023)

3.2.4 XML application forms

Some NCAs request that applicants create an application form on their portals which assist in their internal case creation process. Specific NCA advice should be obtained on where to locate them in the eCTD structure.

The majority of NCAs and EMEA require the application form to be provided as a PDF file together with separate signed paper copies. Please refer to Chapter 7 of the [Notice to Applicants](#) volume 2A for further details.

3.2.5 Product information

Product information should normally be supplied as PDF files but some NCAs require an RTF or Word file in addition to facilitate assessment. Details can be found in section 2.9.6. If the Product Information Management (PIM) system is being used files are required in XML format. Please refer to the [Notice to Applicants](#), Volume 2A, Chapter 7 for details.

3.2.6 Use of response documents section

The submission of electronic information in response to a list of questions from NCAs and EMEA should follow the same basic principles as the first submission. The written response should be submitted following the EU recommended response folder and file structure. Please note that all data

related documents are aligned with the CTD structure, refer to EU CTD question 4.c. using the operation attributes of “new”, “replace”, “append” or “delete” as appropriate.

To help in the management of responses over the lifecycle of the eCTD, the responses relating to a particular regulatory activity should be grouped under a node-extension in the eu-regional.xml file. The title of the node-extension should identify the regulatory activity (e.g. Responses to Questions for the Initial Application, Responses to Questions for Type II Variation 028, etc.). It is recommended that you provide a full copy of the list of questions received from the agencies as the first leaf in this section.

It is recommended that the responses be split up into separate files for each major section of the submission (e.g. Quality, Non-clinical and Clinical). You should use the leaf title to identify the particular set of responses (e.g. Response to Major Objections - Quality). If responses to more than one question are submitted in a single file then you should use bookmarks within the PDF file to clearly identify each response. It is possible to submit the response to each question in a separate file but if you choose to do so then you must use node-extensions and leaf titles to group and identify the responses under the top level node-extension.

All of the files for the response documents should be placed in the folder m1/eu/responses/CC, where CC is the appropriate country identifier code for use in MRP/DCP.

3.2.7 Use of the additional data section

The 'Additional Data' section should only be used for nationally required information in National, MR and Decentralised Procedures.

In addition this section can be used for all procedures when an old version of a DTD is being used during an agreed transition period, to support inclusion of a newly defined section of Notice to Applicants (refer to transition guidance issued with specification).

3.3 Module 2 overviews and summaries folder

3.3.1 General considerations

Each document should be provided as an individual PDF.

3.3.2 Structure of Module 2 Documents

Documents in module 2 should normally be submitted with the document operation attribute “new” as it would help clarifying what to assess with each submission. As eCTD viewing tools will display all “new” leaf elements in a current or cumulative view, it is recommended that you place additional descriptive text in the leaf title to help identifying the documents related to each submission.

New information in module 2 could also be integrated into the former document and then replace the former one with the operation attribute “replace”

The summaries should be used to justify the absence of data in module 3-5 instead of submitting placeholder files stating “No data submitted” or N/A.

3.4 Module 3 quality folder

3.4.1 Module 32S drug substance

If the product contains multiple drug substances, then documentation for each substance should be provided in its own *m32s* section. If a drug substance is manufactured at multiple sites or by multiple different manufacturing companies, documentation can be provided in multiple *m32s* sections.

However, it may be possible to write documentation that covers multiple manufacturers in one CTD section – the way the information is provided is left up to the applicant. For further details, please see [Annex 3](#).

3.4.2 Module 32p drug product

Each dosage form covered by an eCTD application should be described in its own *m32p* section. If an application describes multiple strengths of any one dosage form, then documentation that covers all strengths can be provided in a single *m32p* section, or alternatively each strength can be covered by its own strength-specific documents in multiple strength-specific CTD sections. For further details, see [Annex 3](#).

3.5 Module 4 Nonclinical study reports folder

3.5.1 Guidance on the handling of granular study reports

Submissions created in eCTD format for the use within the FDA may provide more granular study reports using study tagging files. There is no need to re-organise the reports for submission to the EMEA or NCAs. See 3.6.2.below for further information.

3.6 Module 5 clinical study reports folder

3.6.1 Management and handling of multiple indications

In cases where the application includes multiple therapeutic indications, the reports should be organized in a separate Section *m535* for each indication. In such cases, if a clinical efficacy study is relevant to only one of the indications included in the application, it should be included in the appropriate section in *m5* (eg *m5\53-clin-stud-rep\535-rep-effic-safety-stud\anxiety\5351-stud-rep-contr*). If a clinical efficacy study is relevant to multiple indications, the study report should be included in the most appropriate subsection of *m535* and referenced as necessary in the equivalent section under the different indication. In Module 2, a separate “Summary of Clinical Efficacy” module should be submitted for each indication, although closely related indications can be within a single document.

Regardless of which way is chosen, it is important to give clear guidance to the assessor when the supportive data/study report documents are applicable to more than one indication.

3.6.2 Management and handling of granular clinical study reports

ICH Q&A 22 recommends use of E3 granularity for clinical study reports. In Europe, node extensions should be used to group together individual files. STFs from submissions in the US are not required but a submission will not be rejected if they are included. If a US NDA is repurposed for submission in the EU, the study content (the study report and any relevant appendices) should be placed under a node extension. The STF xml file itself and any content not usually provided in Europe (eg datasets) should be removed. In order to keep the cumulative and current dossier views of the eCTD consistent, applicants are advised to use node extensions for all clinical study reports, regardless of the granularity of the content (i.e. even reports that consist of only one document should also be presented in node extensions). For further details see [EU eCTD Q&A 10](#).

3.6.3 Provision of CRFs and data when requested

If case report forms and individual patient data listings are submitted in *m537* (as appendices 16.3 and 16.4 in the ICH clinical study report guideline E 3) they should be placed in the same order as the clinical study reports appearing in *m535* and should be indexed by study. Please note that bookmarks will not be required as there will be no further internal structure.

3.6.4 Provision of synopses of individual studies

It is acceptable either to include copies of the synopses for each study in Section 2.7.6 or to provide hyperlinks to synopses located in Module 5 without providing copies in section 2.7.6. In either case a

Listing of Clinical Studies should be provided and this should include hyperlinks to the first page of each synopsis.

4. ADVICE ON SPECIFIC APPLICATION TYPES

4.1 Initial MA Applications

The recommended start for an eCTD life cycle is the initial MA application. It should normally be provided as sequence 0000. Any other number should be justified in the cover letter. All documents included should have the operation attribute "New" and be placed in the relevant sections in line with the different eCTD specifications.

The submission type should be initial-maa. The procedure type depends on the application that is made. Please find below an overview of the different application types:

Procedure	Procedure type
Centralised Procedure (CP)	centralised
Decentralised Procedure (DCP)	decentralised
Mutual Recognition Procedure (MRP)	mutual-recognition
National	national
Repeat Use Procedure (RUP)	mutual-recognition

For responses to questions documents, see [section 3.2.6](#).

The following milestones of the procedures are proposed as appropriate sequences to be submitted during the assessment of an initial new application. Although the example relates to the centralised procedure similar principles can be applied to other procedures.

Day Number	eCTD milestone sequence	Notes
-14	Initial submission	
-1	Response to business validation issues	if required
121	Response to List of Questions (LoQ)	
181	Response to List of Outstanding Issues (LoOI)	
210	Final English	Application as agreed at opinion
215	Provision of translations	
245	Provision of final agreed translations following linguistic review	It is not also required to send interim working versions of the product information before this point as eCTD
270	Decision	I.e. final amended documentation if any changes occur during the Standing Committee phase

4.2 Variation Applications

All types of variations should be submitted within the eCTD as new sequences. The cover letter and application form should be included in the eCTD but the majority of NCAs also require these items to be submitted in signed paper format. Please refer to the [Notice to Applicants](#), Volume 2A, Chapter 7 for details. In the eCTD, the documents should be included as electronic sourced document and not as a scanned copy of the signed documents.

Documents related to the variation should be included in relevant sections or be deleted by use of the appropriate document operation attribute.

The submission type for the sequence has to be for:

Variation type	Submission type
Type IA variation	var-type1a
Type IB variation	var-type1b
Type II variation	var-type2

The procedure type should be for variation of the procedure:

Procedure	Procedure type
Centralised Procedure (CP)	centralised
Mutual Recognition Procedure (MRP)	mutual-recognition
National	national

However, in relation to the first variation in eCTD format, the applicant is strongly encouraged to also submit a so called “baseline eCTD”, i.e. to submit the current dossier in an eCTD format, at least Module 1, the cover letter and product information as a minimum, and Module 3. This “baseline eCTD” would then be submitted as sequence 0000 and the first variation in eCTD format submitted as sequence 0001.

It should be clearly stated in the cover letter of the “baseline eCTD” that the content of the current dossier has not been changed but only the dossier format.

Parallel variations should be submitted as individual sequences. Problems can occur in cases where a variation is not approved whilst a subsequent variation is approved. In such case a new sequence could be submitted containing the old section by replacing or deleting the submitted sections reaffirming the registered status of the modules.

The following milestones of the procedures are proposed as appropriate sequences to be submitted during the assessment of variations. Although the example relates to the centralised procedure it could be applied to other procedures:

Type IA & IB Variations

Day Number	eCTD milestone sequence	Notes
1	Start of the procedure <description>	e.g. “Start of the procedure phone number changes”

Type II Variations

Day Number	eCTD milestone sequence	Notes
1	Start of the procedure <description>	e.g. “Start of the procedure indication enlargement”
91	Response to RSI	If applicable
91	Final English	
+5	Provision of translations	
+30	Provision of final agreed translations following linguistic review	It is also not required to send interim working versions of the product information before this point as eCTD

4.3 Extension Submissions

Several dosage forms can be managed within a single eCTD application, and this helps avoid submission of data multiple times (e.g. active substance changes). Submissions for an extension can either be submitted within an existing eCTD application, as a new sequence (continuous sequence numbering), or as a new eCTD application (sequence 0000), depending on the procedure. In MRP/DCP, an extension will be submitted within the same procedure, but with a different product number, and as such, the recommendation is to submit the line extension as a new sequence within the original eCTD application, submitting a new module 1, an updated module 2 and new or updated 32P section. If *m32p* is combined for all previous existing strength/dosage form(s), an updated section should be provided, replacing existing documents where necessary. If a separate *m32p* is being provided for the additional strength/dosage form to describe the extension, then all documents should have the operation attribute of 'new'.

For Extension applications, only new data should be submitted as a new sequence in the already submitted eCTD. The submission type has to be "extension". If single eCTDs are used for each strength or form of a product, full data concerning the extension applied for has to be included in the submitted eCTD and therefore clear information should be given to the assessor on what is new compared to earlier submitted data for the product to avoid unnecessary assessment.

In the centralised procedure, extensions are typically managed under the same procedure number as the original dosage form, and again the recommendation is to submit the extension as a new sequence within the original eCTD application, using a new *m32p* to describe the different dosage form.

For national applications, the applicant should discuss with the relevant NCA.

4.4 Renewal Submissions

Please note that a renewal application can be used as the first eCTD in a product lifecycle in a similar manner to variations. The recommendation given in the section above applies likewise.

The submission type has to be "renewal". The procedure type depends on the procedure:

Procedure	Procedure type
Centralised Procedure (CP)	centralised
Mutual Recognition Procedure (MRP)	mutual-recognition
National	national

The following milestones of the procedures are proposed as appropriate sequences to be submitted during the assessment of renewals:

Day Number	eCTD milestone sequence	Notes
1	Start of the procedure <description>	e.g. "Start of the procedure annual reassessment"
61	Final English	
+5	Provision of translations	
+30	Provision of final agreed translations following linguistic review	It is not also required to send interim working versions of the product information before this point as eCTD

4.5 PSURs

The submission of a Periodic Safety Update Report (PSUR) should consist of a cover letter, eventually (depending upon national requirements) an application form and the report itself as a new document in *m536* as well as perhaps some amendments on *m25*. The structure for a PSUR should follow the respective [guidance documents](#). The naming of the leaf element shall indicate the number of the PSUR or the period covered.

The submission type has to be “psur”. The procedure type depends on the procedure:

Procedure	Procedure type
Centralised Procedure (CP)	centralised
Mutual Recognition Procedure (MRP)	mutual-recognition
National	national

4.6 MR and DCP Applications

Please refer to the following specific [CMDh guidance document](#) on the use of eCTDs in MRP and DCP procedures. In general, it is expected that the application covers the full dossier without cross-referencing to other applications using the same dossier.

4.7 Referrals

4.7.1 CMD referral:

The response that the applicant has to prepare to the list of questions prepared by the CMD(h) will be sent as an eCTD sequence to all CMD(h) members, according to the timelines as defined. The applicant will create this new sequence in which the documentation is stored according to the recommended CTD format.

The type of submission of the new sequence should be “referral”. The procedure type depends on the procedure:

Procedure	Procedure type
Centralised Procedure (CP)	centralised
Mutual Recognition Procedure (MRP)	mutual-recognition
National	national

4.7.2 CHMP referral:

In case of a CHMP referral and the applicant wants to submit documentation/information, a new eCTD sequence will be created and submitted. The applicant doesn't submit the entire history of all sequences, but a new sequence with only the information/documentation that concerns the referral. This sequence will be sent out to all involved parties (as defined in CMD(h) Standard Operation Procedure).

Only in case the authority/EMEA request the documentation of previous submitted sequences, the applicant will send a copy of the relevant sequence(s).

The type of submission of the new sequence should be “referral”. The procedure type depends on the procedure:

Procedure	Procedure type
Centralised Procedure (CP)	centralised
Mutual Recognition Procedure (MRP)	mutual-recognition
National	national

In case of a newly created/submitted sequence, the cover letter contains background information for the reason of the referral. Any other document, which concerns the referral, has to be included according to the CTD structure. Any additional documentation that doesn't have a place in the dossier, for example overview of the registrations/applications involved in the referral, should be placed in *m10-cover*.

4.8 Active Substance Master Files

The ASMF consists of two parts, applicant's ("open") and restricted ("closed") part, and both should be submitted by the ASMF holder. The ASMF can be submitted as an eCTD regardless if an application for Marketing Authorisation for a medicinal product referring to the ASMF is submitted in eCTD format or not. It should follow the structure of Module 3.2.S of the CTD. All "not applicable" place holders of the eCTD should be left empty in accordance with the eCTD specifications. The ASMF will be a stand-alone eCTD with possibilities for LCM.

The applicant's "open" part of the ASMF should be included in section m3/32S of the eCTD for the medicinal product application. If there are more than one ASMF used for the active substance(s), each ASMF "open" part should be provided in its own m32S section, clearly distinguished by appropriate file names.

A copy of the "Letter of Access" addressed to the regulatory authority shall be included in Annex 6.10 of the application form and be placed in m12/cc (i.e. in the respective folder for each concerned NCA).

Even if an application for Marketing Authorisation for a medicinal product is submitted in eCTD format and there is a reference to an ASMF, the ASMF submitted by the ASMF holder does not have to be provided in eCTD format. Documents from the "open" part ASMF may be included in the eCTD for the medicinal product.

The submission type has to be "asmf". The procedure type normally depends on the procedure. However as one ASMF application can be used for different types of procedure (national, CP, MRP, DCP and RUP), the procedure type "national"/"centralised": should be used.

4.9 Vaccine Antigen Master Files

The VAMF consists of the scientific data according to Part III of Annex I of [Commission Directive 2001/83/EC](#) as amended. To support the life cycle on the one hand side, to keep the documents manageable and to assure the correct alignment of the complete VAMF on the other hand side it is required that the manufacturer submits the VAMF (including versioning), preferably in an electronic format following the principles of eCTD, The complete VAMF can be processed with its own submission / case / procedure number separately.

The application of a medicinal product will contain the same data package including the certificate of compliance with Community legislation, together with the evaluation report attached.

4.10 Plasma Master Files

The PMF consists of the scientific data according to Part III of Annex I of [Commission Directive 2001/83/EC](#) as amended. To support the life cycle on the one hand side, to keep the documents manageable and to assure the correct alignment of the complete PMF on the other hand side it is required that the manufacturer submits the PMF (including versioning), preferably in [eCTD] format, The complete PMF can be processed with its own submission / case / procedure number separately.

Guidance for Industry on Providing Regulatory Information in Electronic Format: eCTD Applications
Version: 1.0 May 2009

The application of a medicinal product will contain the same data package including the certificate of compliance with Community legislation, together with the evaluation report attached.

4.11 Applicant Initiated Action

Applicants may decide to withdraw their application during any stage of the product life cycle and this section explains the general principles that should be followed.

Withdrawal of the whole product covered by an eCTD should preferably be submitted as a new sequence only including a cover letter. The operation attribute “delete” is not required to be used for the documents.

However, if the application for withdrawal only concerns for example one strength or dosage form out of several covered by the same eCTD, the application should be submitted as a new sequence, but normally include the operation attribute “delete” for documents only relevant for this strength. Furthermore, if relevant it should also include updated documents with the operation attribute “replace” for documents that covered several other strengths and that now need to be revised to exclude from the document the strength or dosage form to be withdrawn.

The submission type has to be “withdrawal”. The procedure type is depending on the procedure:

Procedure	Procedure type
Centralised Procedure (CP)	centralised
Mutual Recognition Procedure (MRP)	mutual-recognition
National	national

4.12 Duplicate Applications

As a duplicate is an independently authorised medicinal product, there is no definition of a “duplicate” in the pharmaceutical legislation. However, for practical purpose, a duplicate application is defined by reference to the first application or marketing authorisation as follows based on [CMD\(h\) recommendations on multiple / duplicate applications](#):

- same dossier (copy of modules 1, 2, 3, 4 and 5);
- same legal basis according to Directive 2001/83/EC, as amended;
- different tradename;
- same or different applicant/marketing authorisation holder.

Since this is the case only at the time of submission and can later on lead to different, independent dossiers, one eCTD per duplicate application has to be submitted (with the possibility of including several strengths, pharmaceutical forms etc. if relevant). It should however be clearly written in the cover letter that it is exactly the same content (with the only exemption of different tradename and maybe different MAH), so that redundant review work is avoided.

Annex 1 eCTD Reference Documents

A number of relevant documents can be found on the Documentation tab on the [e-Submission website](#) at the EMEA. It is recommended that owing to the speed that information changes the following websites should be consulted regularly:

<http://estri.ich.org> or <http://estri.ich.org/eCTD/index.htm>

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm

<http://esubmission.emea.europa.eu/>

<http://www.hma.eu/27.html>

Most important documents to be considered are the following (as of October 1st, 2008):

- http://estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf
- http://estri.ich.org/eCTD/eCTDQAV1_16.xls
- <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm>

EMEA Q&As

- <http://www.emea.europa.eu/htms/human/genguidance/genreg.htm>

ICH M4

- <http://www.ich.org/LOB/media/MEDIA554.pdf>

ICH M4 Q&As:

- <http://www.ich.org/LOB/media/MEDIA1189.pdf>

EU CTD Q&As:

- http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/b/ctd_qa_05_2006.pdf

Annex 2 Guidance on Text Searchable Documents

1. General

Applicants are requested to ensure that all submissions contain the maximum amount of text searchable content. Documents with searchable text will aid the assessor, or any other user, in searching for specific terms and also in copying and pasting information into another document, such as an assessment report.

We recognize that not all documents need to be text searchable. This short document provides some guidance about what must be text searchable and the ways to ensure that files are created appropriately.

1.1 Creating Text Searchable Files

PDF files with searchable text can be created by all PDF tools from a source file in a text format (e.g. MS Word, SAS, MS Powerpoint, Rich Text Files, etc.). When created in this way, the file will usually be the smallest in size (measured in kilobytes or megabytes) that they can be.

If the only version of a document available is in paper, then scanning to PDF and using an Optical Character Recognition (OCR) routine is the only way to create searchable text. PDF files created in this way tend to be much larger in size, for the same number of pages (from 10 to 100 times as large), and the quality of the text that is created will almost certainly not be a 100% match to the original text. It is noted that tools for checking and correcting this text tend to be somewhat cumbersome. For these reasons, applicants are recommended to use scanning/OCR only as a last resort.

Applicants are reminded that the text produced by the OCR routine should be “hidden” behind the image of the original page so that the user can refer to the picture of the page and the text on it as final verification of the data. As a result, the applicant should ensure that, as a minimum, the text on the scanned image is legible to the user. Poor quality images should not be provided and you should note that these can only inevitably lead to poor quality OCR text.

2. Documents that must always be text searchable

(i.e. the PDF should be produced wherever possible from a text source, such as MS Word, but if sourced from a scanned original then they **must be** OCR'd.)

- Key administrative documents in Module 1 including, the cover letter, application form, product information documents
 - Applicants are reminded that some NCAs regard logging in through a portal as sufficient to establish a users identity and do not require handwritten signatures on Cover Letters and Application Forms submitted this way.
 - This also covers similar documents provided in non-MAA submissions.
- Any document in Module 2 of the MAA (QOS, Preclinical Overview and Summaries, Clinical Overview and Summaries).
 - This also covers similar documents provided in non-MAA submissions.
- The main body of text and main tables in any preclinical or clinical report required to support the main claim of the application.
 - This also covers similar documents provided in non-MAA submissions.
- The main body of text in any reports, methods, analytical procedures, etc. supplied in Module 3 of the MAA
 - This also covers similar documents provided in non-MAA submissions.
- The main body of text of Periodic Safety Update Reports (PSURs)
- The main body of text of Risk Management Plans
- The main body of text of Environmental Risk Assessment

- Any English translation of a document originally written in a foreign language (see also below)

3. Documents that do not need to be text searchable

(i.e. the PDF should be produced wherever possible from a text source, such as MS Word, but if sourced from a scanned original then there is no need for OCR.)

- Any original GMP certificate
- Any original certificate of analysis
- Any manufacturer's licences
- Any certificate's of suitability
- Any Manufacturing Authorisation
- Any document written in a foreign language where a translation is provided in English (however, the translation should be text searchable, see above)
- Any literature references sourced from journals, periodicals and books (except when these are used in a bibliographic application to support the main claims of the application).
- The blank CRF in a Clinical Study Report
- Patient data listings (when supplied)
- CRFs (when supplied)
- Any page with a signature that does not contain other information key to the understanding of the submission
- Applicants should consider providing signatures on separate pages from key text in reports, overviews, etc.

4. Further Information

If applicants are uncertain whether or not a particular document should be text searchable, they should contact their NCA for guidance.

Annex 3 Guidance and Best Practice on the Structure of Module 3 - CTD-Quality Considerations for eCTD Submissions in Europe

1. Introduction

The ICH eCTD Specification allows the applicant to manage eCTDs at different levels in Module 3. The normal choice should be one single eCTD application that covers multiple drug substances, multiple manufacturers, multiple drug products (components), multiple dosage forms, presentations, invented names and strengths. If the applicant for some reason needs to have one eCTD per strength or dosage form, this should be explained and guidance should be given in the cover letter about which documentation differs to prevent duplicate of work during assessment.

This Annex is based on the use of the ICH eCTD specification v3.2. Refer to the Glossary for an explanation of terms.

1.1 Electronic information in the eCTD

In addition to CTD-Q documents, eCTD applications provide quality information in various locations:

- Module 1 XML attributes: Envelope – INN, Invented Name (Trade Name)
- Leaf XML attribute: eCTD Title
- Module 3 XML Attributes
 - m3-2-s-drug-substance: *substance*
 - m3-2-s-drug-substance: *manufacturer*
 - m3-2-p-drug-product: *product-name*
 - m3-2-p-drug-product: *dosage form*
 - m3-2-p-drug-product: *manufacturer*
 - m3-2-p-4-control-of-excipients: *excipient*

More than 1 entry for each of the XML Attributes above generally results in the replication of the relevant portion of both the XML and the folder architecture, (e.g., 3.2.S Drug Substance, 3.2.P Drug Product, 3.2.P.4 Control of Excipients) ¹.

2. General Principles

2.1 Document Granularity

eCTD applications can handle different authoring strategies for CTD-Q information. For any given CTD-Q topic (e.g., P.1 Description and Composition of the Drug Product), either a single document can be provided that covers multiple strengths and manufacturers, or multiple documents can be provided, e.g. per strength and/or per manufacturer. Regardless of the XML attributes, when there are significant differences in content it is best practice to provide multiple documents, to realise the lifecycle benefit that eCTD offers. If there are multiple files in the same element, the title of each leaf should be used to distinguish the scope of each document's content.

2.2 Identifying to an agency what the application covers

The regulatory procedure drives what options are available for how many eCTD applications to provide per product range. Generally speaking, multiple eCTD applications can be provided for different strengths and dosage forms. However, a single eCTD is preferred, see [Section 1. Introduction](#). A key factor in making this decision is that in Europe the applicant cannot cross-refer from one eCTD to another (e.g., for drug substance).

¹ See '[Manufacturer of Drug Product](#)' as an exception.

For the Centralised Procedure, a single eCTD application should cover all strengths and dosage forms within the procedure, as illustrated in [Figure 1](#).

In MRP/DCP, a single eCTD is needed per procedure that covers all countries regardless of the invented names. However, different dosage forms or strengths can be managed in separate eCTDs at the applicant's discretion, even if one combined eCTD is preferred. Applicants should carefully consider what an eCTD application will cover before submitting the first sequence. Refer to Section 2.2 Structure of Submissions, and [Table 1 – Advantages and disadvantages of eCTD application structures](#).

Figure 1 – Illustration of what an eCTD covers for a product with the invented name 'Wonderdrug', Centralised Procedure

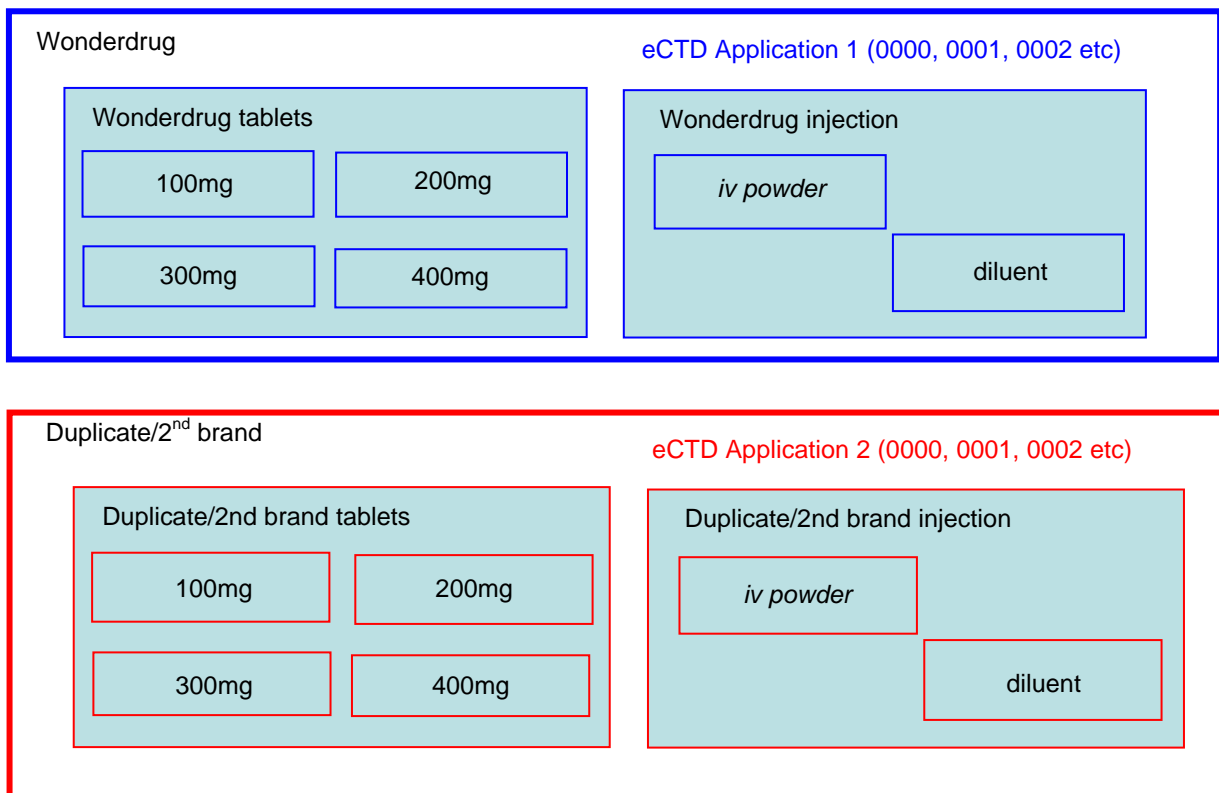


Table 1 – Advantages and disadvantages of eCTD application structures

One Combined eCTD For Multiple Strengths And Dosage Forms	
Advantages	Disadvantages
Clinical and non-clinical documentation is provided only once	Any change to any strength/dosage form will add another sequence to the application, and therefore the application in general will eventually contain a larger number of sequences. Some of these would cover all products covered by the eCTD application, others may affect only one strength or dosage form. Applicants need to use the submission description to describe what each sequence covers.
Any changes to drug substance, or safety related changes that affect the product, will require only one sequence	Adding a new strength (line extension) could involve replacing all 'common' documents with documents covering existing strengths plus the new strength, and also adding new additional strength-specific documents
Common documents can be included only once (e.g., Pharmaceutical Development for multiple tablet strengths)	Life cycle management becomes more complex in the following situations: <ul style="list-style-type: none"> • In MRP, an applicant applies for only certain strengths, in certain countries (e.g. strength 1 and 3 in CMS X and strength 2 and 4 in CMS Y, etc) • An applicant wants to transfer a certain marketing authorisation (certain strength) within one eCTD application to another MAH. • An applicant wishes to withdraw one strength • Variations may be only applicable for one specific strength, and result in the creation of strength specific documents. These would have to be added to the lifecycle and managed alongside the existing documentation, which, if originally 'common', would then only cover the existing (non-affected) strengths
All lifecycle is in one place	Could get complex (e.g., multiple SmPCs)
Documents that are common are presented only once and therefore read only once by the assessor	

One eCTD Application Per Strength Or Dosage Form	
Advantages	Disadvantages
A new strength (line extension) could be handled in a new eCTD and would not affect existing lifecycle	All clinical and non-clinical reports are provided for each strength or dosage form (cannot cross reference across different eCTDs in the EU)
Life cycle management can be maintained per strength so fewer issues when applying for only certain strengths in certain countries within MRP/DCP, or MA-transfer or withdrawals, line extensions, variations, etc.	Any changes to the drug substance or changes that affect all strengths/dosage forms of the product (eg safety related changes to the labelling) would mean building and submitting multiple eCTD sequences, one within each eCTD application.
	Lifecycle is maintained separately, and would need to be managed across multiple potentially identical eCTD applications
If all strengths/dosage forms are not	Common documents must be included in each eCTD

marketed in every country in an MRP Procedure, then a unique application per strength will avoid the possibility that one CMS will not accept the dossier because it contains data on a product which is not being marketed in that country.	application, (cannot cross reference from one eCTD to another in the EU)
	Difficult for the assessor to know what to read/what is unique. This needs therefore to be thoroughly described in each submission, which will typically consist of multiple identical sequences in different eCTD application lifecycles.
	This alternative goes against a founding principle for the management of electronic data insofar as it means : - loss of storage place : the same information will be archived several times at different places, sent several times for long-term filing, and saved several times in the everyday back-up of servers. - multiple data entry : data concerning the common part of the multiple dossiers (i.e. the major part of the dossiers) will have to be entered several times in the document management systems, reviewing systems and workflows, both in NCAs and in Pharmaceutical companies
	At NCAs, uncertainty on whether a MA for a dosage form is granted on the basis of assessment of data pertaining to the dossier of another dosage form

2.2.1 EU Envelope

The Module 1 EU envelope provides the trade name (invented name) of the drug product. The **application number element**, which is repeatable, lists all of the product licences or application numbers covered by the eCTD. Applicants should ensure that entries for invented name, INN, Applicant and Application Number in the EU envelope are complete and consistent. NB The application number and INN may not be known at the time of the first submission and may have to be substituted in later sequences.

3. Module 3 XML Attributes in the eCTD

3.1 Choosing Module 3 XML attributes

The XML attributes reflect the document granularity used in Module 3. The actual words for the attributes need not be an exact match of the words used in the content of Module 3 documents. Many eCTD building tool vendors have based their tools on the ICH style sheet, and this means that the original Module 3 XML attributes cannot be changed with later submissions within the same application without losing the lifecycle benefit that eCTD offers. (i.e. if a Module 3 XML attribute is altered mid lifecycle, it will no longer be possible to replace, append to or delete content provided with the previous attribute value.)

More than 1 entry for any attribute generally results in the replication of the relevant portion of both the XML and the folder architecture, (e.g., 3.2.S Drug Substance, 3.2.P Drug Product, 3.2.P.4 Control of Excipients).

3.2 Drug Substance (32s) Attributes – Substance-1, Manufacturer-1

3.2.1 Drug substance

The entry for the drug substance name attribute can be an abbreviation of the INN, or the company's code for the drug substance.

If there is more than 1 drug substance in the product, there is a separate set of 3.2.S.1 to 3.2.S.7 folders and corresponding XML for each drug substance. This also applies for the open (applicant's) parts of Active Substance Master Files (ASMFs).

If a drug substance is covered by a Certificate of Suitability (CEP), the certificate is to be provided in 3.2.Regional Information (and in Module 1.2 for annex 5.10). Only relevant sections of its 3.2.S.1 to 3.2.S.7 folders are used, if needed (e.g., for information not covered by the CEP). See EU CTD Q&As Question 12 (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/b/ctd-qa-updatev3_2008-02.pdf).

3.2.2 Manufacturer of drug substance

In conjunction with the drug substance attribute, each additional manufacturer entry results in additional 3.2.S.1 to 3.2.S.7 XML elements and folders, where there is content provided.

Various approaches are possible depending on the number of manufacturing companies/manufacturing sites and the quantity of documentation that is manufacturer-specific. The general principle is that the resulting XML is a reflection of the document granularity (rather than the eCTD specification driving the attributes).

3.2.2.1 Approach 1 – Single XML section covering all Manufacturers of the Drug Substance

Where drug substance documentation is identical or very similar for all manufacturers (and hence there are a minimal number of manufacturer-dependent documents), then a non-specific manufacturer attribute can be used (such as the parent name of a group of companies, or 'applicant' or 'all'). For CTD topics that are manufacturer-specific, having separate documents enables the applicant to manage lifecycles as-needed. In such cases, the title and file name of each leaf is to be customised to differentiate the files, e.g., leaf title of "Batch Analysis – [manufacturer 1]" where the entry is either the [current company name] or [current manufacturing town] and file name of *batch-analyses-manufacturer1.pdf*. Using leaf titles and filenames to distinguish manufacturers does not involve adding any extra XML attributes for drug substance manufacturer. As an illustration, see [Figure 2](#), where the specification is manufacturer-independent but stability data documentation has been separated by manufacturer.

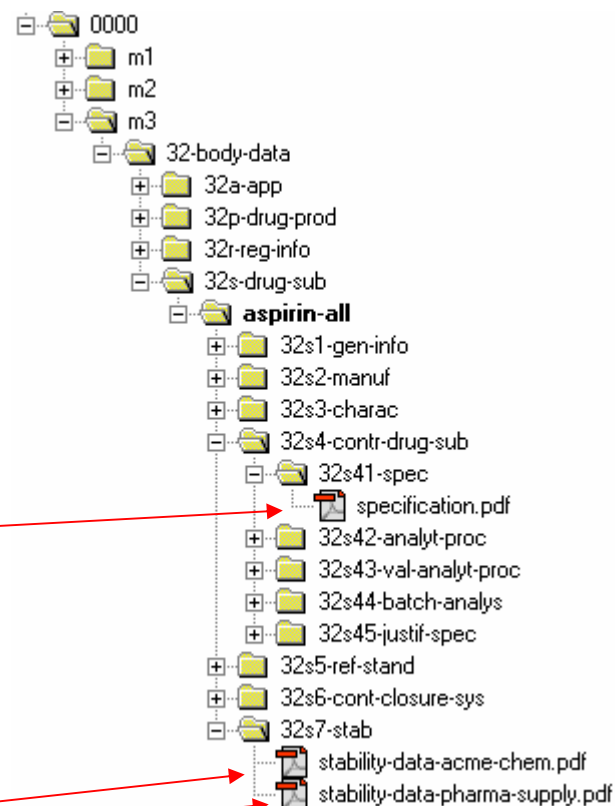
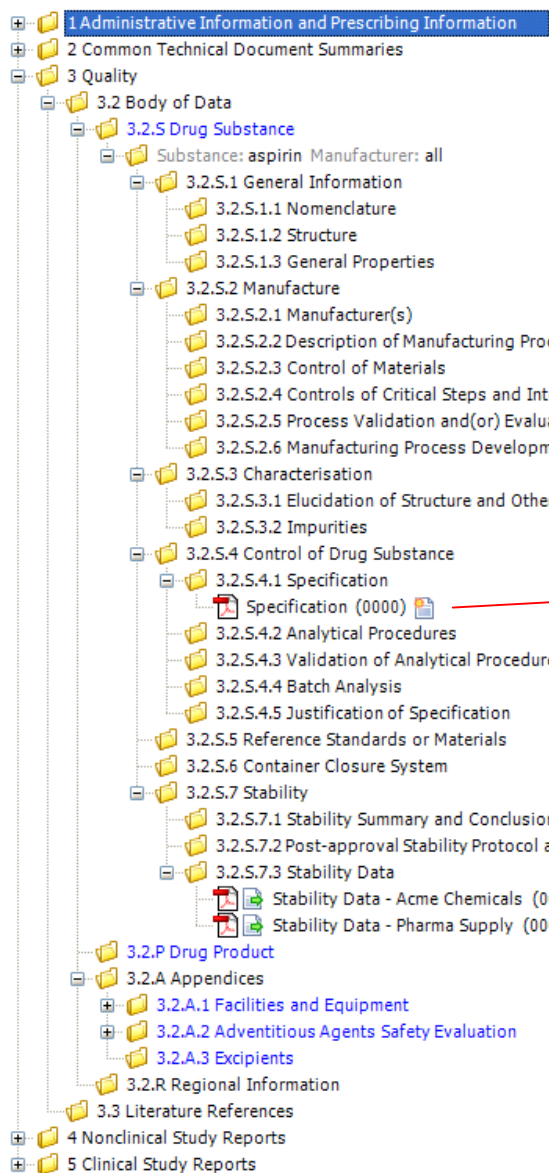
This approach does not prevent a future scenario when a new manufacturer may have its own XML attribute (due to a significant volume of manufacturer-specific documentation). Note that a known limitation of ICH eCTD specification v3.2 is that the original, non-specific XML attribute cannot then be modified in the application.²

² When any XML attributes are no longer accurate nor in accordance with this guidance, it is acceptable to retain original entries. It is not desirable to correct the XML attributes (i.e., applicants need not apply an operation attribute of DELETE to previously-submitted files and re-submit the latest versions with new XML attributes).

Figure 2 - Single Drug Substance, 2 Manufacturers with similar documentation, the few site/manufacturer-specific documents identified by the XML title (not by adding an additional XML section):

XML

Files and folders (directory)



Arrows indicate destination of xlink:hrefs

3.2.2.2 Approach 2 – New XML sections for each Manufacturer of the Drug Substance

When there are many manufacturer-specific documents, it is helpful to have additional XML attributes and equivalent folders for each manufacturer, see [Figure 3](#). Since these files are located in separate elements, the leaf titles and filenames do not need to be customised per manufacturer. In this illustration, since the 'specification' document is manufacturer-independent, it appears only once in the folder structure. Additional XML attribute entries are not expected for each intermediate manufacturing site or packaging site, but can be used.

As an alternative to Approach 1 and Approach 2 (but not illustrated here), an additional entry of 'common' may be used for manufacturer-independent documents (e.g., those in 3.2.S.1 General Information), such that both the XML and the folder structure contain a 'common' entry. If this approach is used, files do not need to be linked from 'common' folders to the named manufacturer folder(s), i.e., these files appear once in the XML and once in the folder directory.

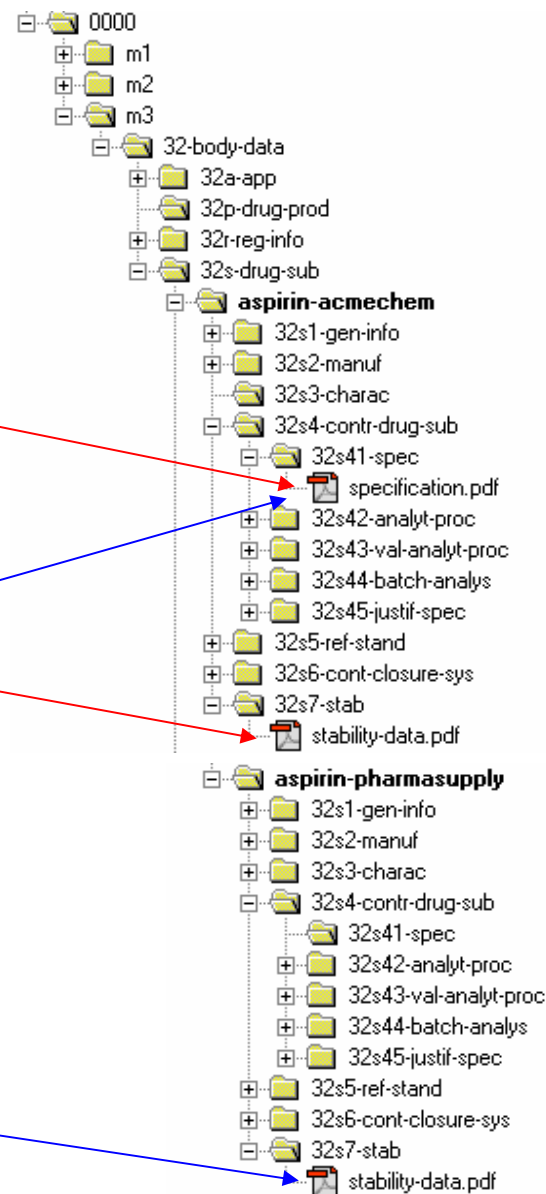
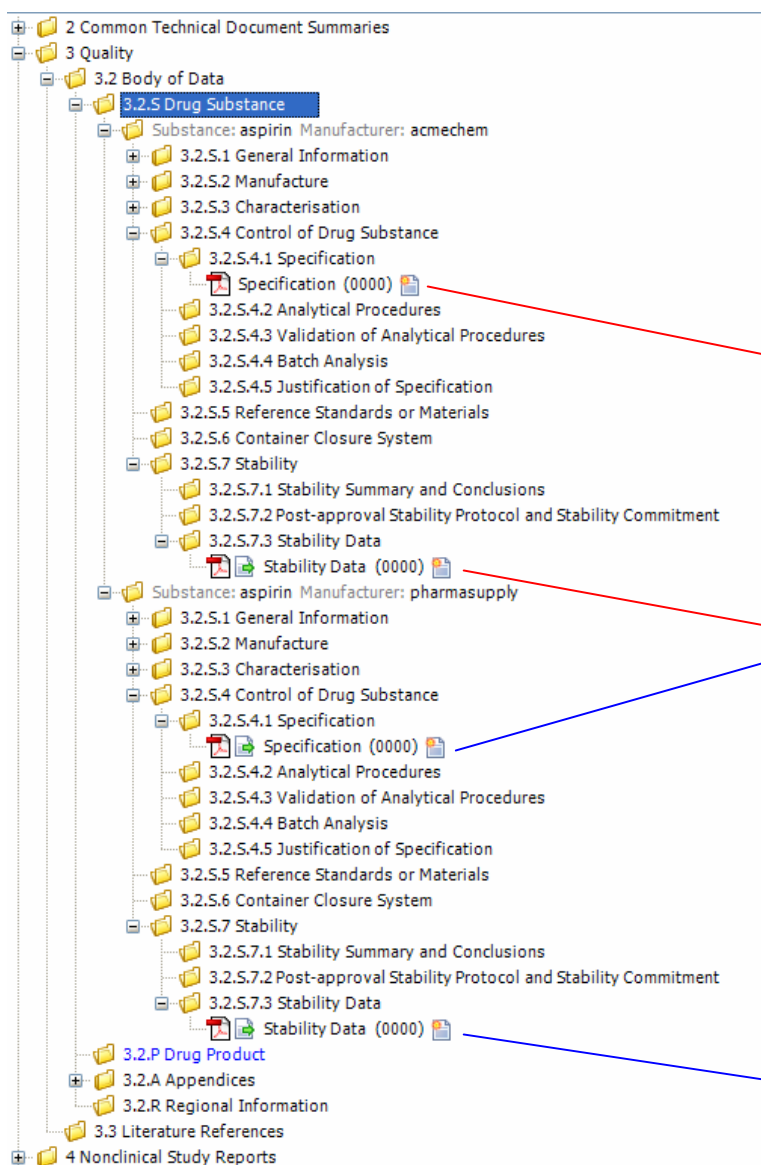
For example, a drug substance section could contain three 32s:

32s-aspirin-manufacturer-1 (containing information specific to the manufacturer e.g. 3.2.S.2)
32s-aspirin-manufacturer-2 (containing information specific to the manufacturer e.g. 3.2.S.2)
32s-aspirin-common (containing manufacturer-independent information)

Figure 3 Single Drug Substance, 2 Manufacturers with significant volume of different documentation (one section for Acme Chemicals, another for Pharnasupply).

XML

Files and Folders (directory)



3.3 Drug Product (32p) – Product/Dosage Form/Manufacturer

3.3.1 Drug product name

Since the M1 EU envelope contains the invented name, it is not necessary to use this name in the product name XML attribute that is used in Module 3. Avoiding the trade name in Module 3 could prove beneficial for original MAAs, since the proposed name is not always accepted and/or is not always applicable to all EU member states.

The entry can be a general term such as 'active', or 'product' that then produces a full set of 3.2.P.1 to 3.2.P.8 XML elements and folders. Alternatively, the internal company code of the drug product name may be used. If applicable, another full set of XML elements and folders can be used as needed, e.g., for 'diluent'.

3.3.2 Dosage form

In conjunction with the above product name, each additional dosage form entry results in an additional full set of 3.2.P.1 to 3.2.P.8 XML elements and folders. When deciding on the degree of detail (e.g., 'tablet' vs. 'film-coated tablet', 'frozen' vs. "refrigerated" formulation for vaccines), consider the potential for future line extensions and the proportion of drug product documents that could be re-used. If that proportion is small, then consider an initial specific dosage form entry.

3.3.3 Strength

Not all 3.2.P documents are, nor need to be, strength-dependent. For example, for a common granulation for six strengths, many documents would have nearly identical content; little benefit would be derived from having strength-specific documentation.

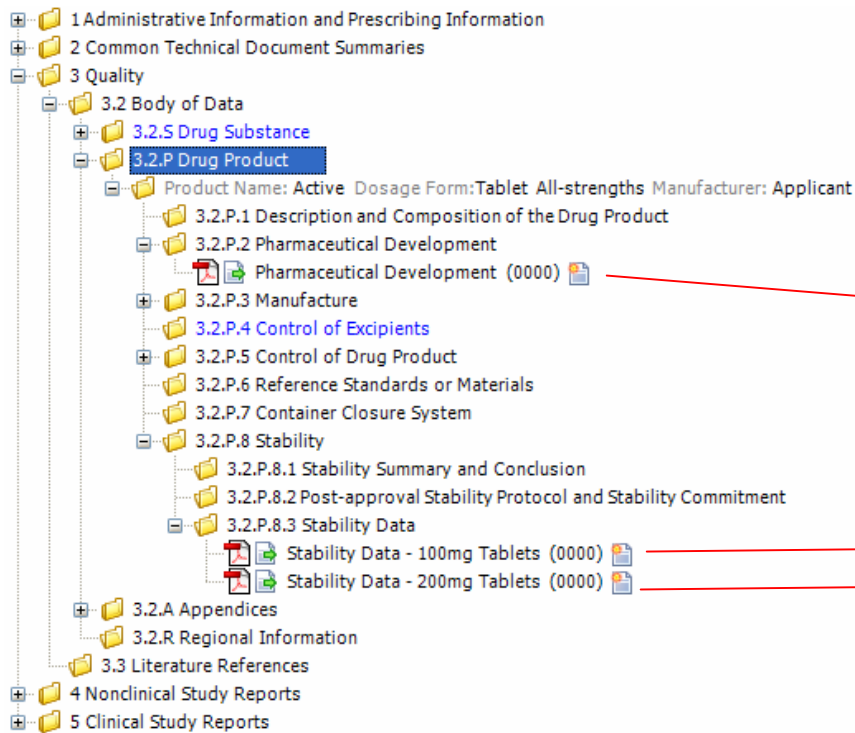
3.3.3.1 Approach 1 – Single General XML Section Covering All Strengths

If there is a limited number of documents in the submission that are strength-specific, there can be a single 3.2.P, with a non-specific XML attribute such as 'tablet'. Where there are multiple files under the same element, the XML title and file name of each leaf is used to differentiate any documents where the content is strength-specific, e.g. 'Stability Data – 100 mg' and 'Stability Data – 200 mg' and 'stability-data-100mg.pdf' and 'stability-data-200mg.pdf', respectively. In this case, the term 'all strengths' can be used to concatenate with the dosage form entry for the XML attribute for the single 3.2.P. This approach does not prevent a future scenario where a new strength has its own XML attribute. However, a known limitation of the ICH eCTD specification v3.2 is that the original, non-specific XML attribute (eg 'all strengths') cannot then be modified - see note below under [Figure 4](#) below.

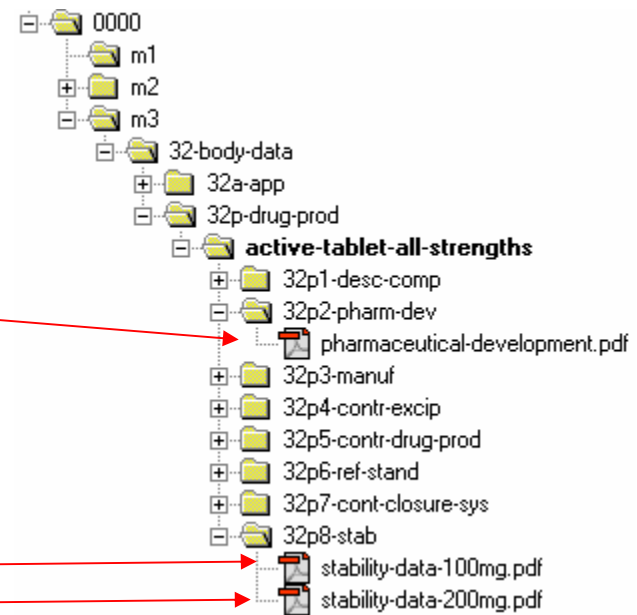
[Figure 4](#) illustrates this approach, where the Pharmaceutical Development document is strength-independent but Stability Data documentation has been split by strength.

Figure 4 - Approach 1 - One 32p for all Strengths, any strength specific documents identified by the XML title, not by adding an additional XML section

XML



Files and Folders (directory)



Note: The use of the term 'all-strengths' will mean that if the applicant subsequently submits a line extension for an additional strength (e.g. 1000mg) where the documentation is significantly different, and approach 2 is preferred for the new strength, then the attribute 'all-strengths' will not include the documentation for the 1000mg tablet.

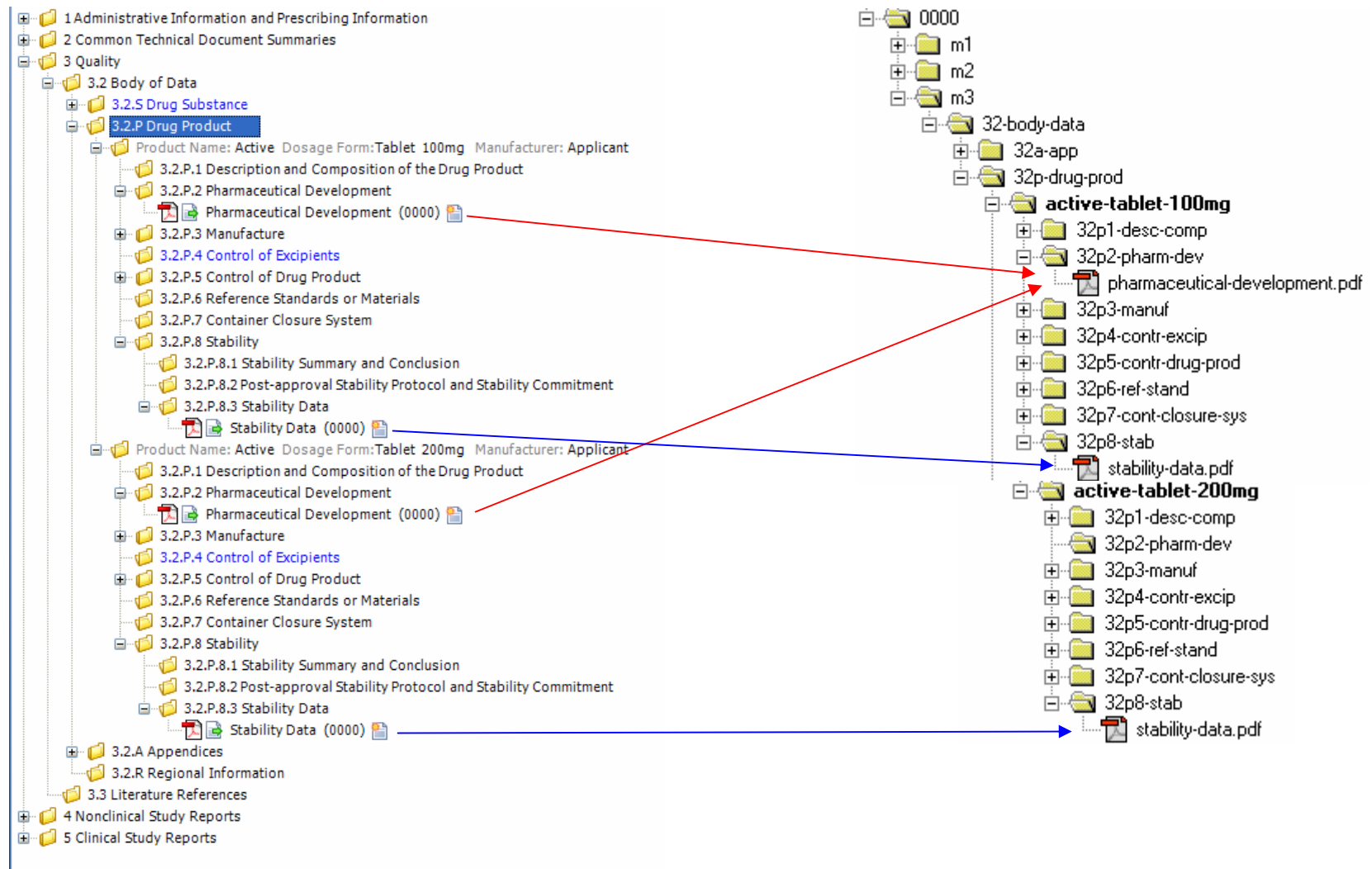
3.3.3.2 Approach 2 – Separate XML section covering one Strength or Dosage Form

If a strength or dosage form is manufactured in a significantly different way from other strength(s)/dosage forms and has a large volume of its own 3.2.P documentation, then a separate 3.2.P branch with appropriate subsections applicable to that manufacturer can be justified. In this case, the dosage form XML attribute and folder includes the strength (e.g., Tablet 5 mg and tablet-5mg, respectively). Documentation that pertains to all strengths should only be included once. Previously-submitted documents or documents that are applicable to more than one strength can be referred to in new XML leaves under each strength specific XML branch, without re-providing the content files themselves, see [Figure 5](#).

Figure 5 – Approach 2- Separate XML and documents for Strengths – significant content differences, but Pharmaceutical Development only provided once in the folder structure and referred to from the XML twice

XML

Files and Folders (directory)



3.3.3.3 Approach 3 – Different XML sections covering each Strength

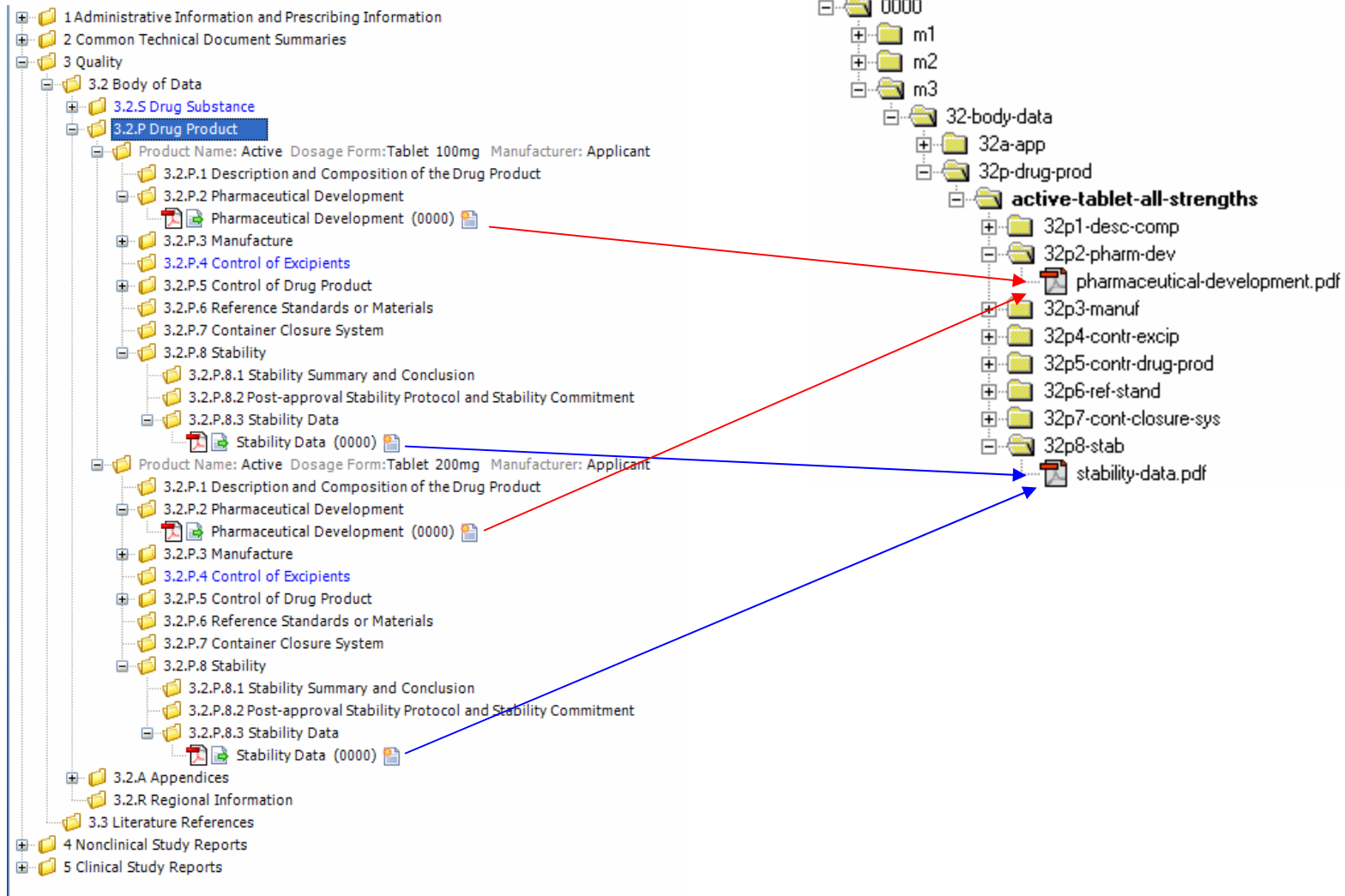
Some applicants may find it beneficial to have different XML sections for each strength. Even though many of the leaves in these XML sections may point to the same document, there is no need to provide a document more than once. See [Figure 6](#) where the Pharmaceutical Development and Stability Data documents are provided one time in the folders, but referenced multiple times from the XML.

However, it should be noted that many eCTD building tools do not include functionality to allow an applicant to use multiple XML leaves to repeatedly reference to a single document in the folder directory, and therefore this approach is not therefore recommended unless the user has significant eCTD experience.

Figure 6 - Approach 3 - Multiple XML leaves per Strength, one document per Strength – this uses the XML to differentiate between strengths, without requiring the applicant to write multiple similar documents – all xlink:href entries point to shared documents in ‘all-strengths’ folder

XML

Files and Folders (directory)



3.3.4 Manufacturer of drug product

In conjunction with the above product name and dosage form, each manufacturer entry results in a set of 3.2.P.1 to 3.2.P.8 and 3.2.A.1 and 3.2.A.2 XML elements. However, in many eCTD building tools, entries for drug product manufacturer do not result in additional directory folders. Hence it is practical to use high-level descriptors such as 'common', 'applicant', or 'not required'. If specific manufacturer entries are provided, then the guidance is similar to that for the ['Manufacturer of Drug Substance'](#). If the building tool did not generate a set of directory folders per manufacturer of drug product, then corresponding filenames should be customised per manufacturer. Alternatively, experienced applicants may wish to manually produce a second set of 3.2.P.1 to 3.2.P.8 folders, which will involve either adding 'manufacturer' to the name of the directory folder, (e.g. tablet-5mg-site1), and editing all xlink:hrefs in the corresponding XML, or editing xlink:hrefs before publishing the eCTD. Applicants should consult their eCTD tool vendor for further details.

3.4 Excipients

Each excipient entry generally produces a full set of 3.2.P.4.1 to 3.2.P.4.6 XML elements and folders. This XML attribute need not be used at all (it is not required per ICH M4Q). The description below reflects current industry practice.

3.4.1 Compendial excipients

There is generally little to register for pharmacopoeial excipients. In this case, an XML attribute entry of 'compendial' is acceptable. A single file that addresses CTD topics 3.2.P.4.1 to 3.2.P.4.4 for all excipients can be provided e.g., in 3.2.P.4.1 with a title for the leaf that accurately describes its content. Alternatively, an entry of 'compendial – [named excipient]' is acceptable, e.g., 'compendial - purified water'. In this case a single file addresses CTD topics 3.2.P.4.1 to 3.2.P.4.4 for each pharmacopoeial excipient. In most cases, these documents will simply consist of statements referring to the relevant pharmacopoeia.

In either case, if additional tests are performed on the pharmacopoeial excipient, these can be located alongside the above file in the relevant folder (e.g., 3.2.P.4.2, 3.2.P.4.3) and with an appropriate title.

3.4.2 Non-compendial excipients

For non-pharmacopoeial excipients, the excipient XML attribute entry can be a general term, e.g., 'coating agent', 'flavouring agent', 'sweetening agent'. In this case, the title and filename of the leaf provides details and differentiates files, e.g., title 'Validation of Assay – Opadry Yellow'. Alternatively, a more specific attribute entry such as 'non-compendial opadry yellow' can be used.