Guidance for Industry on Providing Regulatory Information in Electronic Format

TIGes Harmonised Guidance for eCTD Submissions in the EU

Version 2.0

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1. INTRODUCTION

This guidance document is intended to assist pharmaceutical companies with the submission of regulatory information in electronic Common Technical Document format (eCTD) to the National Competent Authorities (hereafter referred to as NCAs) and the European Medicines Agency (hereafter referred to as EMA). The eCTD format is regarded as the principal electronic submission format in EU and is the only electronic format that is accepted by the EMA. However, the Non eCTD electronic Submissions (NeeS) format is also accepted by most NCAs and therefore a guidance document for NeeS has been published on the EMA eSubmission website as well.

The guidance has been created by the TIGes Harmonisation Group, a sub-group of the Telematics Implementation Group for electronic submissions (TIGes), and has been adopted for publication by the TIGes.
It should be stressed that this guidance 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 of using information submitted in electronic format.

This document consists of four parts: Introduction, General Considerations, Module Specific Information and Advice on Specific Application Types together with associated annexes.

1.1 Glossary

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. 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 in the EEA as well as the EMA. 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 (ASMF) and Plasma Master Files (PMF). For variations, ASMF and PMF there are also specific guidance documents (see references in Part 4).

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, Orphan drug designations, PIP submissions 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. In the centralised procedure, this will be equivalent to all dosage forms and strengths covered by an EMA application number (e.g. EMEA/H/C/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/dosage form 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/EMA 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

Changing format from paper or NeeS to eCTD can be done at a *start* of any regulatory activity such as an extension, a renewal or a variation, *ideally when no other regulatory activities are ongoing for that product* in another format. A baseline submission is recommended at the time of changing to eCTD (see section 2.12.) When the eCTD lifecycle is initiated and accepted by the authorities, all further submissions related to that product dossier should from that day be submitted in eCTD format. This may also include submissions concerning other ongoing regulatory activities related to that eCTD application (e.g. responses to questions to ongoing variations), in which case, it will obviously not be possible to use the related sequence attribute correctly since the start of the regulatory activity is not present as an eCTD sequence to refer to and therefore the validation criterion 14 BP1 will not be met. This should be reflected in the cover letter.

If the dossier has already been provided in NeeS format, you should submit the new data in eCTD format starting the lifecycle in accordance with eCTD specifications. The first submission in eCTD format will normally be sequence 0000, even if sequential numbers were used for the NeeS format. As the documents already exist in an electronic format, it would be preferable to first re-send the currently valid documents, especially module 3, as a baseline eCTD dossier in sequence number 0000 and then the first new regulatory activity as 0001. In that case, the submission type *reformat* should be used in the envelope for the 0000 sequence. This is also applicable when changing from paper, but might mean that the current valid documents are provided as scanned documents when this kind of baseline is submitted (further recommendations can be found in Annex 2). For clarity, you should always explicitly state in the cover letter that you want to switch to eCTD format. Please see section 2.12 for further information on the content of baseline applications and the acceptability of scanned document.

In the case, you have for some time submitted applications in eCTD format to some agencies within MRP or DCP when paper or NeeS were still requested by some other NCAs, these remaining agencies would now be pleased to receive all former sequences when switching to eCTD format in connection to a new regulatory activity for that product. The "old" eCTD sequences should be provided together with this new eCTD sequence and it should be clearly stated in the cover letter to the concerned NCAs that the "old" sequences have the same content as formerly submitted paper or NeeS format documents. When submitting earlier sequences to other agencies, no changes to envelopes or metadata is required, it is accepted that the envelopes might not be entirely correct for agencies receiving a sequence previously submitted to another agency. Any historical sequences should not be technically validated by the agencies receiving them for the first time, for details see the CMDh BPG for eCTD in MRP and DCP. However, if there are problems with loading or reading the "old" files, the applicant should assist in solving the technical problems on the sequences to facilitate their use in the "new" NCA, for example due to mistakes in burning or problems with the XML, which can be resolved without affecting future lifecycle.

In any case, a tracking table is essential to understand the sequencing of your eCTD submission (please refer to section 3.2.3).

Where the change from paper or NeeS to eCTD format for a product dossier is planned to be done in connection to a repeat use procedure (i.e. for the complete dossier), the change of format should first be made in the RMS and the "old" CMSs by submitting the current dossier as a so called baseline dossier (see section 2.12), before the start of the repeat use procedure in the new CMSs.

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. Careful consideration is needed when deciding the level of Module 3 granularity (please refer to Annex 3, section 3.1)

2.5.2 File Naming

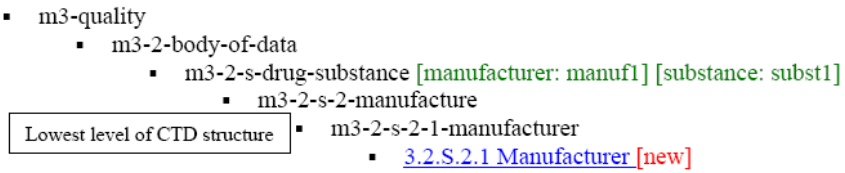
The eCTD file naming conventions described in the ICH M2 eCTD Specification and EU Module 1 Specification are highly recommended, as best practice. If an applicant wishes to submit multiple files in one section, where only one highly recommended name is available, this can be achieved using a suffix to the filename, using the file name-*var*.pdf convention as described in the EU Module 1 Specification (e.g. pharmaceutical-development-*container*.pdf). Also the variable part of the name must not contain "illegal" characters.
File names, including the extension, must not exceed 64 characters. Also folder names must not exceed 64 characters and the total file folder path length must not exceed 180 characters. Counting starts from the first digit of the sequence number in the sequence number folder name.

For further guidance on file naming, please refer to the "File-Folder Structure & Names" work sheet included in the eCTD Validation Criteria version 3.1.

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 EMA post-authorisation guidance for centralised applications.

In the submission structure, leaves may only exists at the lowest level of the CTD structure. Also, the lowest levels (including node-extensions) must contain at least one leaf.



Every leaf must have a value for the 'title' attribute.

2.6 Correspondence

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. Therefore, formal responses to questions should always be submitted in eCTD format, as well as any correspondence that relates directly to the content of the dossier.
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 authority, and not all correspondence is directly relevant to the application dossier. This additional, other correspondence should be exchanged outside the eCTD via the usual electronic means (email, Eudralink etc).

2.7 Paper Requirements

In general, electronic submissions should be accompanied by an original signed application form and cover letter, but there can be exceptions from this in some NCAs. Detailed information on each NCA's specific requirements can be found at the CMDh website and/or websites of the individual NCA.

Please note that the EMA requests the original signed hard copy of the cover letter together with the CD/DVD. The signed scanned application form should only be provided within the eCTD sequence.

Guidance on the minimum requirements to produce a paper submission from an eCTD has also been published see - "Practical Guidance For the Paper Submission of Regulatory Information in Support of a Marketing Authorisation Application When Using an eCTD or a NeeS as the Source Submission."

2.8 Hardware

NCAs and the EMA 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 EMA 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 (see next section on the use of PDF file versions). Files that might be requested by NCAs in MS Word or RTF format should *not* be included in the eCTD structure (refer to 2.9.9.).

The use of XML for application 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.
- PDF file version 1.4 or 1.7 should normally be used, except where there is an agency specific requirement for another version for example for application forms.
- PDF 1.3 or earlier versions are not acceptable for technical reasons. No exceptions will be made. For example, if a literature reference is received in PDF 1.3 or earlier, then the applicant must convert it to PDF 1.4 or 1.7.
- If the use of other versions of PDF is unavoidable then the applicant should explain the reason for it in the cover letter/explanation note as it is not in line with the Best Practice validation.
- Documents generated by the applicant should be created from electronic source documents and not from scanned material. Where access to the source electronic file is unavailable please refer to Annex 2.
- Normally, for the application form and cover letter, there is no requirement to scan wet signatures. The signature could in these cases appear only on the paper copy. However, the EMA and some NCAs do require that wet signatures are scanned – for details refer to national guidance.

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 lifecycle of the product. The review tools being used by most NCAs and the EMA 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 CMDh BPG for eCTD in MRP and DCP.

A similar tracking table is recommended for national applications and also for applications through the Centralised Procedure. (This is to ensure that gaps are avoided in the lifecycle management and to inform the member states about possible ongoing procedures that are handled by the EMA.)

The initial eCTD lifecycle submission should normally have a sequence number of 0000, even if sequential numbers were already used for a NeeS format of the same product. If applicants consider that there are good reasons to use another number they should explain this in the cover letter.

When additional information is submitted in response to questions or when information in a previously submitted sequence is modified in any way, the sequence number of the submission will advance, 0001, 0002, etc. Only in the case of a technically invalid submission, at request from or agreement with the EMA (CP) or an NCA (MRP/DCP/NP), a sequence can be replaced with another using the same number (e.g. the initial sequence "0000" will be replaced by another "0000"). The new sequence should be sent to all concerned authorities. No new documents may be included in these cases, but only technical problems should be fixed. The reason for resending the same sequence must be clearly stated in a paper note included in the package containing the submission (e.g. a hand written note on the paper copy of the original cover letter). If the eCTD needs to be updated due to content/regulatory validation, any revised content should be provided with a new sequence number and the changes clarified in the cover letter.

2.9.4 Related Sequence

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.

For a new Regulatory Activity, the appropriate submission type should be used. Applicants should refer to the submission type descriptions in the EU Module 1 specification. For the sequence that initiates a Regulatory Activity 'supplemental-info' and 'corrigendum' must not be used.

The submission type 'supplemental-info' should be routinely used for all subsequent sequences until the conclusion of the Regulatory Activity. The submission type 'corrigendum' should only be used in exceptional circumstances to correct information, typically for product information in the CP, after the Regulatory Activity has concluded.

Only the submission types 'supplemental-info' and 'corrigendum' should have related sequences.
Tables 1, 2 and 3 provide examples of this convention.

Table 1: Example of an initial MAA in the Centralised Procedure

Sequence number	Submission Description	Submission Type	Related Sequence
0000	Initial MAA	initial-maa	none
0001	Validation update	supplemental-info	0000
0002	Day 121 responses	supplemental-info	0000
0003	Day 181 responses	supplemental-info	0000
0004	Final translations of product information (Decision)	supplemental-info	0000
0005	Correction of errors in Danish product information after Decision	corrigendum	0000

Table 2: Example of an initial MAA in the Decentralised Procedure

Sequence number	Submission Description	Submission Type	Related Sequence
0000	Initial MAA	initial-maa	none
0001	Validation update	supplemental-info	0000
0002	Day 106 responses	supplemental-info	0000
0003	Day 180 responses	supplemental-info	0000
0004	Day 210 Agreed English product information	supplemental-info	0000

Table 3: Example of a Variation

Sequence number	Submission Description	Submission Type	Related Sequence
0008	Variation for new indication of COPD	var-type2	none
0009	Validation update	supplemental-info	0008
0010	Responses to questions	supplemental-info	0008

It is generally expected that there is usually just one Related Sequence, but, there are some occasions where more than one Related Sequence should be provided as for example:

1) When there are two FUMs (sequence 0005 and sequence 0006) and a single response (sequence 0007) is produced that relates to both FUMs.
2) When there are two parallel variations (sequence 0002 and sequence 0003) and there is a sequence (0004) that brings the label up to date by including the changes made in both variations.

On these occasions multiple related sequences are used, but if a subsequent sequence relates to only one of the original regulatory activities, then only the related sequence for that particular regulatory activity should be used

If the related sequences refer to both a single and grouped variation, the metadata should state 'grouped' as being the highest level of regulatory activity.

2.9.5 Leaf Lifecycle Operations

The leaf lifecycle operation attributes, as stated in the eCTD Specifications, are 'new', 'append', 'replace' and 'delete'. However, in the EU, it is recommended that applicants avoid the use of 'append' due to the potential for increased lifecycle complexity.
In general, leaf lifecycle operations cannot take place between leaf elements in different CTD sections. E.g. a leaf to be submitted in Module 4.2.2.5 in Sequence 0012 cannot replace/delete a leaf submitted in Module 4.2.2.2 of Sequence 0010.

This applies across all of the modules of the CTD and is not specific to either the regional or ICH Modules.

One scenario where leaf lifecycle operations between different CTD sections **must not** be used is to "correct errors" in the placement of content in the submission structure. If the applicant company places content in the wrong CTD section and needs to correct this (either upon request from the agency receiving the eCTD or because they wish to correct the mistake) then the way to do this is to create two leaf elements in a subsequent sequence. The first leaf will use a "delete" operation to remove from view the incorrectly placed content. The second leaf will usually use a "new" leaf operation to locate the content in the correct CTD section. The file does not need to be resubmitted, the "new" leaf can use the xlink:href attribute to point to the originally submitted content in the earlier sequence.

The reason for not allowing leaf lifecycle operations across CTD sections is because the CTD section describes the context for the use of a piece of scientific or regulatory content (usually a document or report). The implication for lifecycle operations across CTD sections is that content being used in one context is being changed by content submitted in a different context. This is not possible because the lifecycle for the context of use of a piece of content is independent to the lifecycle of that same piece of content used in a different context. In addition, the CTD section defines the location of the content in multi-sequence views such as the 'current view'. Having content in one section replacing, deleting or being appended to content in another section will make it impossible to build such views in eCTD viewing tools. Therefore, lifecycle operations acting on leaf elements in different CTD sections are not allowed.

You should note that the definition of a "different CTD section" also includes two CTD sections with the same CTD module number but different associated metadata (e.g. a different dosage form definition in Module 3.2.P). Therefore, Module 3.2.P.1 for Wonderpill Tablets is a "different CTD section" to Module 3.2.P.1 for Wonderpill Capsules.

However, exceptions might arise as described below:

1. There are regulatory and business reasons why a CTD section's title might change and, exceptionally, also the CTD section numbering might change. In this scenario, the context of use of the content remains the same. It is just placed in a differently named or numbered section. Leaf lifecycle operations in this scenario are allowed.
For example, prior to April 2006 Module 1.3.4 of the EU dossier was known as "Readability Testing" and this was the section title used in v1.0 and v1.1 of the European Module 1 eCTD specification with an abbreviated form of this title used in the DTD (m1-3-4-readability). After April 2006 Module 1.3.4 was renamed "Consultation with Target Patient Groups" and the element in the DTD was renamed accordingly (m1-3-4-consultation). In this example, leafs submitted under the m1-3-4-consultation element must be able to replace/append/delete leafs originally submitted under the m1-3-4-readability element.

2. To assist with the transition between versions of the EU Module 1 specification where new CTD sections have been added, EU Transition Guidance has been published that allowed content to be placed in the "Additional Data" section of the old version of the specification and then, for subsequent eCTD sequences using the newer DTD, to correctly place the content under the new appropriate heading. In these transition cases leaf lifecycle should be allowed between the two sections.
However, it should be noted this scenario is allowed only under specific circumstances arising from the transition between specific versions of the EU DTD. This exception is only allowed when the transition guidance for a particular change specifies that this is acceptable (as for example when the section for Paediatrics, 1.10, was added to the CTD) and is not an allowance that is automatically applied to all changes between DTD versions.

2.9.6 Bookmarks and Hypertext Links

Navigation through an electronic submission is greatly enhanced by the appropriate use of bookmarks and hypertext links. ICH Q&A number 53 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 lifecycle management.

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

With the current version of the eCTD specification, it is not possible to cross refer from one eCTD application to another.

2.9.7 Node Extensions

Node extensions may be used where additional navigation in the XML backbone is required. The primary place where they may be used is in Module 5 where a node extension for each study may be useful so as to allow multiple files for a single study to be grouped together and separated distinctly from other studies. Also, it could be useful to differentiate reports associated with a different dosing regimen for the same indication. For Module 4 where there are multi-file reports, node extensions can also be useful, or in Module 1, for differentiating different responses in m1-responses – for further details see section 3.2.6. Currently, there is no provision for additional folders in Module 4, so the use of node extensions and an additional folder will result in the fail of the check 15 BP2. If node extensions have been used, the applicant should therefore explain this in the cover letter.

However, the use of node extensions should be limited to those areas where it is critical and consideration should be given regarding the impact of the view for the reviewer since the inconsistent use of node extensions can lead to unanticipated effects in the cumulative view of a submission.

When node-extensions are used the 'title' attribute in the XML backbone must have a value.

2.9.8 Extensible Mark-up Language (XML)

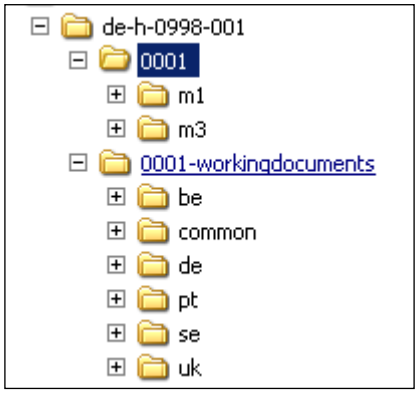
XML is the format for the backbone files for the eCTD. Details on XML can be found in the ICH eCTD Specification Document, Appendix 7. Initiatives on the use of XML structured information are supported by NCAs and the EMA for e-application forms. Please refer to EMA eSubmission website for further details.

2.9.9 Other File Formats

Other file formats such as rich text (RTF) or MS Word formats may be required by some NCAs or the EMA *in addition* to the PDF requirement of the eCTD, especially for the provision of product information documents or the Module 2 documents. Please refer to the CMDh website for further details on NCAs requirements.

The files referred to above should not be added as leaf elements within the eCTD structure. When submitted with an eCTD, they should always be provided in a separate folder called "xxxx-workingdocuments" on the same CD/DVD containing the eCTD, where the number (xxxx) matches the number of the eCTD sequence being submitted.

If working documents for more than one NCA are submitted on the same CD, sub folders with the country code should be used.



For information on translations being provided outside of the eCTD refer to section 3.2.5

If, at any stage in a procedure, an e-mail or Eudralink message is used to send information, this does not change the format requirement. The subject line of the message should always include as a minimum the product name and procedure number for identification purposes.

2.9.10 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 EMA have adopted a common set of technical validation criteria against which all eCTDs can be checked using eCTD review and validation tools.

From September 1st 2011, two categories of validation rules apply: "Pass/Fail", and "Best Practice":

- **Pass/Fail Criteria**
  eCTDs that fail to meet one or more of the "Pass/Fail" criteria will not be processed and the applicant will be advised to rectify the problems and resubmit with the same sequence number. In these cases the procedure will only start upon the new receipt date.

- **Best Practice Criteria**
  These are validation criteria that it is considered good practice to ensure are correct in the submitted eCTD. The applicant should make every effort to address these areas before the eCTD is submitted to the agency. For any Best Practice criteria that are not met, the applicant should be prepared to include a justification in

the submission cover letter, the reviewer's guide or in an added note to the submission (to prevent changing the MD5 checksum). eCTDs that fail to meet one or more of these criteria will still be accepted by the agency during technical validation and it is possible that agencies may not even check these criteria during technical validation.

Note: 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.

There could be situations where the sequence passes technical validation but the information provided in the eCTD envelope is incorrect (e.g. refers to different product name, different product number, and/or different sequence number, procedure number or worksharing number identifiers are incorrect), and this would not be acceptable, since there is a potential risk that the sequence is imported into the wrong product folder. In such cases, the applicant may also be required to provide a corrected eCTD sequence, with the same sequence number, even though the original sequence may have been deemed technically valid.

If, for any reason, historical sequences that have already been submitted in other MS in the EU are supplied to a new NCA, the receiving NCA should not technically validate these sequences, as they will have already been accepted when originally submitted. This could be the case where, for example, repeat use, switching from parallel national to comprehensive model, supply of eCTD sequences to an NCA where this same eCTD submission had been formerly submitted to this NCA in NeeS or paper format but in eCTD format to other NCAs. However, if there are problems with loading or reading the newly submitted files, the applicant should assist in solving the technical problems on the sequences to facilitate their use in the “new” NCA.

2.10 Other Technical Information

2.10.1 Security Issues

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

2.10.2 Security Settings

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.

There must be no security setting to open any individual file. This includes passwords, certificate security, adobe policy server settings, etc. There must be no further security settings applied to any individual file (except for files in Modules 3.3, 4.3 and 5.4). For example, in Adobe Acrobat, all "restrictions" should be "allowed" when viewing the Document Preferences > Security settings>.

2.10.3 Protection against Malware

The applicant is responsible for checking the submission for malware such as viruses. Checking should be performed with an up-to-date virus checker. After receipt at NCAs and the EMA, 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 EMA do not have a system for verification and therefore require that certain specific documents (covering letters, Application Forms), where needed, are authenticated by separate signed paper copies.

2.10.5 Transmission Media

Currently CD-R and DVD-R are the generally accepted media standards. However, some NCAs may accept eCTD submissions or working documents over Eudralink/e-mail or via portals. However, this would of course not be possible where signed cover letters and/or application forms are required. See CMDh website for further details. Note that the EMA does not accept Eudralink as formal submission for applications and therefore a CD/DVD should still be dispatched.

2.10.6 Procedure for Sending Electronic Information

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 normally include a cover letter. Please see section 3.2.3 for details on the format of cover letters.

Agencies 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 or eCTD should be directly readable and usable on the agency's hardware (e.g. CD/DVD drive) using its own software. The media should be labeled as specified in section 2.10.6.

Note - it is the policy of EMA to maintain desktop configurations and IT infrastructure in line with common, office standards. Hard media (e.g. CD, DVD) must be used for the submission of all eCTD sequences.

Eudralink/e-Mail (where applicable)

In order to send the eCTD sequence over Eudralink the entire sequence has to be zipped first. Some zip formats are not widely readable and therefore a submission could be rejected if the zipped format cannot be read by the agency. If in doubt, please check the intended format with the agency before sending. Please note there is a size limit of 80 MB per file. It is not possible to split an eCTD sequence. Therefore submission of an initial submission is not recommended over Eudralink as the file size will be usually over 80 MB.
EMA does not accept Eudralink submissions, except where specified for the provision of the annexes.

When using Eudralink, it is important that the expiry date is set to the maximum of 90 days to ensure that it can be opened during the process at the receiving authority. In addition, all information relating to the submission must be contained within the zipped sequence; no formal information should be included in the body of the Eudralink message.

Please note, in order to re-obtain the correct eCTD structure, unpack or extract the zip-file and save the content on your local path system. Otherwise the eCTD structure is not displayed in the correct way. When using Eudralink, some NCAs require an additional copy on hard media, check individual NCA web sites for details.

Portals

Generally only small (<100MB) applications can be handled this way. Applicants should check with individual agencies for details of this process. If submissions are uploaded via a portal no data corruption should occur as a result of the process.

CD/DVD

Zipped files should not be used when sending CDs or DVDs.

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.

Submissions for workshare/grouping variations concerning several eCTD submissions are recommended to be supplied together on a single CD/DVD. The CD/ DVD should contain clearly marked subfolders for each product that takes part in a worksharing or grouping procedure.

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 label (see 2.10.6).

It is, however not recommended to include previously submitted sequences to the same agency on a CD that contains a new eCTD sequence.

Generally, it is recommended to only submit once in one format. If an additional transmission type is used (for example, a sequence is submitted via Eudralink and followed up with another copy of the same sequence on CD), then this should be explained with a note or hard copy letter such that the receiving agency can easily identify that it is a re-submission.

2.10.7 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
  - If there are too many sequences to list on the CD/DVD label itself, a separate list should be provided in the cover letter.
- 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

The above is required to be in accordance with the information provided in the cover letter and the eCTD envelope.

2.11 Number of Media Requested

Please refer to the CMDh website and question number 23 of the Human/Pre-authorisation Q&A for details of the number of copies of media 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 Universal Disk Format (UDF), which has replaced the former ISO standard 9660.

2.12 Technical Baseline Applications

A baseline submission is a compiled submission of the current status of the dossier, i.e. resubmission of currently valid documents that have already been provided to an agency but in another format. The sections provided to make up a baseline can be defined by the applicant, but any omissions should not render the submitted content misleading. A baseline would typically consist of the Module 3 documents that tend to change over time during the lifecycle of the product.

It is highly recommended but not obliged, to use a baseline as a start of an eCTD when changing from paper or NeeS and to reformat as much as possible. Preferably it should be text source documents included, but good quality scanned images would also be acceptable in these cases, preferably with Optical Character Recognition (OCR) to facilitate text searching.

It should be clearly stated in the cover letter of the "baseline eCTD sequence" that the content of the current dossier has not been changed but only the dossier format and consequently, there should be no need for the NCAs to assess baseline submissions and hyperlinks between documents are therefore not needed in baseline submissions.

2.12.1 Baselines Starting as Sequence 0000

The baseline should normally be submitted as sequence 0000, but could in some justified situations also be submitted at a later stage (see section 2.12.2). The baseline should always be a separate submission and should never include new applications. The first new regulatory activity, e.g. the next variation, in eCTD format should then be submitted as sequence 0001, see table below.

Table 4: Example for starting an eCTD with a baseline sequence

Sequence number	Submission Description	Submission Type	Related Sequence
0000	Baseline of Module 3	reformat	None
0001	Variation for new indication of COPD	var-type2	None
0002	Response to Questions	supplemental-info	0001
0003	Variation to shelf life	var-type1b	None
0004	Extension for 8mg tablet	extension	None

2.12.2 Baselines Starting Later in Lifecycle

A baseline can also be submitted later in the lifecycle. If documents have already been provided in previous submissions in the sections now covered by the baseline, these should not be re-submitted. Instead, the remaining incomplete sections should be filled up with earlier dossier content (paper or NeeS), now provided in eCTD format for the first time.

It could be justified to use multiple sequences to submit a baseline**,** e.g. one sequence for the baseline for Modules 4 and 5 followed later by one sequence for the baseline for Module 3. The submission type 'reformat' should be used in each case (the submission type 'supplemental-info' should not be used for the second reformat submission). The related sequence should not be used in any case.
An example is given below.

Table 5: Example for starting an eCTD with regulatory activity sequence

Sequence number	Submission Description	Submission Type	Related Sequence
0000	Variation concerning Modules 4 & 5	var-type2	None
0001	Variation for new indication of COPD	var-type2	None
0002	Response to Questions	supplemental-info	0000
0003	Baseline of Module 3	reformat	None
0004	Extension for 8mg tablet	extension	None

In cases where a product nationally approved in more than one EU country becomes an MRP product through a referral, it is quite likely that the eCTD dossiers submitted nationally are incompatible and thus cannot be used to continue the MRP dossier. The dossier might then have to start anew, from sequence 0000 and be done in line with CMDh guidance. In such cases, a baseline submission might be justified in order to give all the CMSs access to the previously submitted documentation. For details on how to transfer existing eCTD lifecycle from one procedure to another (e.g. at the end of an Article 30), see Section 2.12.3.

For eCTD dossiers created with old tools and/or in accordance with technical criteria which are now outdated, a baseline can be submitted in order to "clean up" the dossier from any technical issues that would cause problems. However, the applicant should first, ensure that there are no other ways of rectifying these technical issues so that a baseline is not created unless it is absolutely necessary.

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 (see 2.12.3). 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 normally only be allowed once during the lifecycle, and must be agreed by the relevant authority.

If a baseline is submitted later during the lifecycle, it has to be noted that baseline submissions reset the lifecycle management of any previously submitted eCTD sequences and should therefore be created only

when really needed. This should normally be discussed in advance with the relevant authority. Below (2.12.3) are some examples of situations when this kind of baseline submission might be justified.

2.12.3 Re-Baselining a Broken eCTD Lifecycle

One of the principles of eCTD is that with the use of the operation attributes, it is possible to manage the lifecycle of a product and generate a view of the "current dossier".

However, in certain cases, the lifecycle at the side of the applicant may be broken.

This situation can occur in cases such as:

- An MA is transferred to another MAH who is unable to import any existing eCTD sequences into its building tool
- An applicant switches to a new publishing tool and is unable to import their submitted sequences
- An applicant is working with a lifecycle where previously submitted sequences are actually invalid, and were not tested at the time by the receiving agency

The problem with all of these situations is that the applicant cannot continue with the existing lifecycle of the product. Any subsequent submission (sequence) for the product where previously submitted content is changed and needs to be referred to (using the operation attributes replace, append, or delete) cannot be built in the tool, or, if built, would be invalid. This is because it is impossible to create the link back to the original submitted documentation, because it no longer resides in the eCTD building tool.

In these first three examples, the preferred situation would be that the previous submitted sequences are imported in the new tool and the lifecycle of the product will continue. However, this might not be possible, due to technical issues in uploading previous sequences into a different tool, or particularly when the previous sequences were invalid.

In addition, in exceptional cases, there may be a benefit to both the applicant and to the agency if the current lifecycle is archived in some way and re-started. For example:

- An applicant has chosen in the past to submit more eCTD applications than needed under current guidelines, for example, one for each strength of a product
- An applicant has used the parallel national model in MRP/DCP and needs to switch to the comprehensive model
- At the end of an Article 30 procedure, the applicant is switching from national eCTD in one or more MS to a comprehensive eCTD for the new MRP

In order to ensure that in future the lifecycle of the product is correctly maintained, it is proposed that in these exceptional circumstances, and with prior written agreement of the receiving agency (national procedures) the RMS (MRP/DCP), or EMA (centralised procedures), applicants are able to resubmit the current registered dossier as a baseline consisting of all valid documents as seen in "current view", leaving the existing sequences in place, but essentially resubmitting the content in a new eCTD application.

In the cover letter the applicant provides details of why the lifecycle is broken, and that a new eCTD sequence is being submitted in order to restart the lifecycle.

- The submission type would be "reformat".
- The operation attributes of the leaves would be all "new".
- The sequence number of the submission would normally be restarted at 0000 and not continued, since continuation of existing numbering could lead to complex lifecycle issues.

However, if there is a valid eCTD lifecycle available that can be re-used, this should be considered by the applicant – for example, if moving from the parallel national to the comprehensive model in an MRP/DCP, if one of the national countries has a number of valid sequences, these could be provided to the remaining countries and used as a basis for the comprehensive eCTD.
Also, when compiling several eCTDs built per strength or form of a product into only one combined eCTD for that product, normally one of the strengths lifecycle could be kept and be completed with the missing

documents from the current view of the other strengths to give the complete current dossier. Any re-use of existing sequences or changes to sequence numbering should be agreed with the relevant authorities.

For the agency, the former submitted sequences have to be handled as "history", and the new set of sequences would need another identifier to be set by the authority to differentiate them from this previous lifecycle. The lifecycle will begin from scratch again from the time of the baseline submission.

In an MRP, there is no need to mention the previous (archived) sequences in the tracking table, so the new tracking table should only refer to the re-established lifecycle.

Scenario1
Applicant X has submitted sequences:
0000 Initial application
0001 Validation update
0002 Day xx response
0003 Day yy response
0004 Variation 001
****** Problem occurs in continuing lifecycle, **see examples below**
0005 → 0000 - Next submission

0005 is not submitted. Instead, 0000 – 0004 are archived, and a new eCTD is started at 0000.

Examples for this scenario:
****** MAH is transferred, previous sequences 0000-0004 cannot be imported into a tool by the new holder.
** Applicant changes their eCTD Building tool, previous sequences will not import into the new tool
** Previous sequences 0000-0004 were technically invalid according to the specification at the time, but were accepted by the agency because eCTD checking was not yet established
** Sequences 0000-0004 were "not mutual" (parallel national) – not all countries in the procedure may have received all of them with the same sequence number

Scenario 2
Applicant X has submitted sequences:
0000 Initial application
0001 Validation update
0002 Day xx response
0003 Day yy response
0004 Variation 001
** Problem occurs in continuing lifecycle, **examples below**
0005 = Next submission

The original sequences are maintained, but a "new" eCTD lifecycle is started at 0005, where more countries receive the lifecycle.

Examples for this scenario:
** Sequences 0000-0004 were "not mutual" (parallel national) – all countries in the procedure have received all of the sequences as individual national sequences with the same sequence number
** Earlier sequences 0000-0004 referred to only one strength or dosage form, but the new lifecycle will cover more multiple strengths/forms. Note there is no need to alter the metadata from the previously submitted sequences, the additional strengths / dosage forms can be added in subsequent sequences.
** Earlier sequences 0000-0004 were used in national procedure prior to an Article 30 procedure, but can be re-purposed for the new MRP

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.

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 applications.

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, and this should have 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.
Submission Type	This value represents the type of material sent to the agency. For a picklist, see m1 specification for further details.
Submission Mode	This element should only contain a value in variation or line extension regulatory activities and must be included in every sequence of that activity. The value can be set to ‘single’, ‘grouping’ or ‘worksharing’.
Number	In case of worksharing submissions and for submissions of grouped Type 1A variations that affect multiple marketing authorisations a high-level submission number must be provided. In case the number is not known yet, the value ‘to be advised’ can be used.
Tracking number	Any value used by an agency or applicant to track the submission, in any procedure, in relation to a particular product, e.g. EMEA/H/C/000123/II/14 for a CP submission and DE/H/0126/001/MR for an MRP submission. For more examples refer to m1 specification.
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.

	In case of 'worksharing' procedures, only the name of the applicant designated for the worksharing submission should be used.
Agency Code	Self explanatory, from picklist in the most recent EU m1 eCTD specification. Assure that Country and Agency name will be consistent.
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, on the label of the CD and on the Cover letter.
Related-sequence	For a description and example of how to use the 'related sequence' entry, see section 2.9.4 and the EU m1 specification.
Submission-description	This element is used to describe this particular eCTD sequence

3.2.3 Module 1.0 Containing Cover Letter and Tracking Table

3.2.3.1 Cover Letter

The cover letter should always be submitted with the document operation attribute "new". As eCTD viewing tools will display all "new" leaf elements in a current or cumulative view, it is recommended that additional descriptive text is included in the leaf title to help 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 (0042)

Please see also the CMDh website for requirements of signed paper copies of the cover letter and application form to each NCA.

For CP there is a template for submitting information that is published on the EMA website under the Post Authorisation Guidance.

3.2.3.2 Tracking Table

A tracking table should always be included as an annex to the cover letter for MRP and DCP. This is also highly recommended for CP and NP. The file should be named CC-cover-tracking.pdf or CC-cover-tracking.xml and be placed in /XXXX/m1/eu/10-cover/CC. (e.g. emea-cover-tracking.pdf for the CP, common-cover-tracking.pdf in an MRP/DCP, or be-cover-tracking.pdf in a NP.)

3.2.4 Application Forms

The application form should always be submitted with the document operation attribute "new" (as for the cover letter, see above)., unless an error has been made in the form and an updated application form is being provided, in which case the operation attribute should be "replace",

Documents which do not fit into the M2-5 sections or Response to Questions (e.g.justifications for changes, additional administrative information) should be placed as single documents after the application form.

Most NCAs do require the application form to be submitted as a signed paper original together with the eCTD submission. Some NCAs, on the other hand, request that applicants create a web-based application form on their portals, which assist in their internal case creation process. Please refer to the CMDh website or the individual NCA's web sites for further details on specific requirements.

3.2.5 Product information

Product information should be supplied as PDF files but some NCAs require an RTF or Word file in addition to facilitate assessment. Those additional files should be provided in the separate folder XXXX-workingdocuments on the same CD / DVD. Details can be found in section 2.9.9.

It is not required to provide the tracked changes version in PDF format, if it is submitted as Word document in the working documents folder.

National translations in MRP/DCP and the CP, should be managed outside of the eCTD (see CMDh BPG for eCTD in MRP/DCP). This is also applicable for Type IA or IB variations, when translations of the product information are required with the first submission. In such cases, the translations should be provided in a separate working documents folder, in MS Word format only.

Note, in the CP, an eCTD sequence is however required for commission decision documents. Please refer to section 4.1.

3.2.6 Use of Response Documents Section

The submission of electronic information in response to a list of questions from NCAs and EMA 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 Implementation, using the operation attributes of “new”, “replace”, “append” (not recommended) 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). Leaf titles should be used 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 bookmarks should be used within the PDF file to clearly identify each response. It is possible to submit the response to each question in a separate file but in that case node-extensions must be used and leaf titles to group and identify the responses under the top level node-extension.

In MRP/DCP, all of the files for the response documents should be placed in the folder m1/eu/responses/common, regardless which member state raised the question.

3.2.7 Use of the Additional Data Section

The section 'Additional Data’ should only be used for nationally required information in National, Mutual Recognition 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 updates).

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 place holder files stating “No data submitted” or N/A.

In module 2.3 Quality Overall Summary either one file (qos-var.pdf) or separate files per QOS section can be submitted named as: introduction-var.pdf, drug-substance-var.pdf, drug-product-var.pdf, appendices-var.pdf and regional-information-var.pdf.

For submissions covering multiple indications, refer to section 3.6.1.

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 EMA or NCAs. See section 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 provide clear written 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. Ideally, the STF xml file itself and any content not usually provided in Europe (e.g. datasets) should be removed. In order to maintain a consistent looking eCTD lifecycle and table of contents (via index.xml), 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). See also section 2.9.7 Node-extensions.

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.

3.6.5 Company Core Data Sheet

If companies submit their Company Core Data Sheet, this is recommended to be provided in section 5.3.6, Post Marketing Experience.

4. ADVICE ON SPECIFIC APPLICATION TYPES

4.1 Initial MA Applications

The recommended start for an eCTD lifecycle is the initial MA application. It should normally be provided as sequence 0000. To start with another 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.

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.

Table 6: Initial MAA – Centralised Procedure

Day Number/ Milestone	***eCTD milestone sequence***	***Notes***
Submission deadline	Initial submission	As per published submission calendars
-5 or as requested before date of start	Response to business validation issues	If required
121	Response to List of Questions (LoQ)	
181	Response to List of Outstanding Issues (LoOI)	If applicable
Commission Decision + 5	Decision / Closing sequence – including final translations Updates to the dossier which have not yet been submitted in eCTD but which have been agreed by the CHMP at the time of the opinion; e.g • Final RMP • Minor updates to Module 2 or 3 • Final Product Information (Annex I, II, IIIA, IIIB and Annex A) in all languages	I.e. final amended documentation if any changes occur during the Standing Committee phase (SCP) Except from changes during the SCP, the documentation submitted within this eCTD sequence should be identical to the documents submitted to the EMA at the time of the CHMP opinion via Eudralink.

Table 7: Outside eCTD via Eudralink

211 (opinion + 1)	Final English PI	
Opinion + 5	Provision of translations	
Opinion + 25	Provision of final agreed translations following linguistic review	

Table 8: Initial MAA – Decentralised Procedure

Day Number/ Milestone	***eCTD milestone sequence***	***Notes***
- 10	Initial MAA	
Procedure start	Validation update	If required
106	Day 106 Responses to questions	
210	Final agreed EN product information	Or at any day when the procedure can be closed after agreement is reached.

For details, please refer to the specific CMDh guidance document on the use of eCTD in MRP and DCP procedures

4.2 Variation Applications

All types of variations should be submitted within the eCTD as new sequences.

Documents related to the variation should be included in relevant sections or be deleted or replaced by use of the appropriate document operation attribute. Where documents cannot be assigned to specific CTD defined locations, then they should be attached to the 1.2 Application Form.

The submission type should reflect the type of variation. (See Q&A for Variations in eCTD)

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 the principal could be applied to other procedures (except for final translations).

Table 9: Type II Variations

Day Number / Milestone	***eCTD milestone sequence***	***Notes***
Submission deadline	Initial submission	As per published submission calendars, e.g. “Start of the procedure, new indication”
-5 or as requested before date of start	Response to business validation issues	If required
RSI Submission deadlines	Response to Request for Supplementary Information (RSI)	If applicable
Opinion + 75	Decision / Closing sequence – including final translations if applicable Updates to the dossier which have not yet been submitted in eCTD but which have been agreed by the CHMP at the time of the opinion; e.g • Final RMP • Minor updates to Module 2 or 3 • Final Product Information (Annex I, II, IIIA IIIB and Annex A) in all languages	

Table 10: Type IA & IB Variations

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

Table 11: Outside eCTD via Eudralink

Opinion + 1	Final English PI	
Opinion + 5	Provision of translations	
Opinion + 25	Provision of final agreed translations following linguistic review	

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), if a separate lifecycle management is preferred (not applicable in the Centralised Procedure, see below)..

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 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 strengths/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 should 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 should be “renewal”.

The following milestones of the procedures are proposed as appropriate sequences to be submitted during the assessment of renewals: Although the example relates to the centralised procedure the principal could be applied to other procedures (except for final translations).

Table 12: Renewal

Day Number	***eCTD milestone sequence***	**Notes**
Submission deadline	Initial submission	As per published submission calendar
100	Response to Request for Supplementary Information (RSI)	If applicable
Opinion +67	Decision / Closing sequence – including final translations if applicable Updates to the dossier which have not yet been submitted in eCTD but which have been agreed by the CHMP at the time of the opinion; e.g. • Final RMP • Minor updates to Module 2 or 3 • Final Product Information (Annex I, II, IIIA, IIIB and Annex A) in all languages	

Table 13: Outside eCTD via Eudralink

Opinion + 1	Final English PI	
Opinion + 5	Provision of translations	
Opinion + 25	Provision of final agreed translations following linguistic review	

4.5 PSURs

In order to be able to follow-up the lifecycle of a medicinal product it is essential that also Periodic Safety Update Reports (PSUR) become part of the dossier in eCTD format. This also applies when the PSUR is part of a Work Sharing procedure and should therefore be submitted as a separate eCTD sequence in the respective eCTD submission of the concerned products.
The submission of a PSUR should consist of a cover letter and the report itself as a new document in *m536* as well as a new or replace document in *m25* as necessary. Any new study report or literature will be included in *m533* or *m54* as appropriate. In case of proposed changes of the product information texts new or replace versions need to be submitted in *m131*. 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 should be “psur”.

4.6 MRP and DCP Applications

Besides details covered by this guidance, please refer to the following specific CMDh guidance document on the use of eCTDs in MRP and DCP procedures.

4.7 Referrals

4.7.1 Referrals handled through CMDh:

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 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”.

4.7.2 Referrals handled through the centralised procedure:

If the applicant submits new documentation/information, a new eCTD sequence should be created and submitted. The applicant should not submit the entire history of all sequences, but a new sequence with only the information/documentation that concerns the referral. This sequence should be sent to all involved parties.

The applicant should only send a copy of the relevant previously submitted sequence(s) if requested by the authorities

The type of submission of the new sequence should be “referral”.

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 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. Also, the other way around is acceptable, i.e. that 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.

The ASMF will be a stand-alone eCTD with possibilities for lifecycle management.

Please, refer to the specific guidance document for ASMF in eCTD format. This guidance covers how to handle both ASMF eCTD submissions and applications in eCTD format that refers to an ASMF.
An example ASMF in eCTD format can also be downloaded from the EMA website.

It is important for all CP that the eCTD envelope of the ASMF includes the Product Number of the application that the ASMF is related to. This could be obtained from the applicant in all cases prior to submission.

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

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 lifecycle 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 lifecycle 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), in eCTD format. The complete PMF 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.
Please, refer to the specific guidance document for PMF in eCTD format.
.
Do note, that the variations to be submitted in the 2nd step procedure should be submitted for the respective medicinal products concerned and if the applications are in eCTD format, the submissions should be provided as eCTD sequences for each concerned product, building on the respective eCTD lifecycles.

4.11 Applicant Initiated Withdrawals

Applicants may decide to withdraw their application during any stage of the product lifecycle 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 should be “withdrawal”. However, the submission type ‘withdrawal’ should only be used for the notification by the applicant to the regulator of the withdrawal of a marketing authorisation. It should not be used for the withdrawal of a variation, or parts of a grouped variation, during the assessment. In this circumstance the submission type to use is ‘supplemental-info’, refer to Q&A on Variations in eCTD format.

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 trade name;
- same or different applicant/marketing authorisation holder.

For CP specific requirements see the document ‘Handling of Duplicate Marketing Authorisation Applications.

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 EMA. It is recommended that owing to the speed that information changes the following websites should be consulted regularly:

http://www.ich.org/products/electronic-standards.html

http://ec.europa.eu/health/documents/eudralex/index_en.htm

http://esubmission.EMA.europa.eu/

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

Most important documents to be considered are the following (as of August, 2011):

- http://estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf
- http://www.estri.org/eCTD/eCTDQAV1_20.xls
- http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

EMA Q&As

- http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000157.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002251f

ICH M4

- http://www.ich.org/products/ctd.html

ICH M4 Q&As:

- http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R3_Organisation/M4_QAs.pdf

EU CTD Q&As:

- http://ec.europa.eu/health/files/eudralex/vol-2/b/ctd-qa-updatev3_2008-02_en.pdf

Annex 2: Guidance on Text Searchable Documents

A2-1 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.

A2-1.1 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.

A2-2 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.
- Any document in Module 2 (QOS, Preclinical Overview and Summaries, Clinical Overview and Summaries).
- The main body of text and main tables in any preclinical or clinical report required to support the main claim of the application.
- The main body of text in any reports, methods, analytical procedures, etc. supplied in Module 3 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)

A2-3 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.

A2-4. Further Information

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

Annex 3: Guidance and Best Practice on the Structure of Module 3

CTD-Quality Considerations for eCTD Submissions in Europe

A3-1. 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 needs to have one eCTD application 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.

A3-1.1 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 (Submission Description)
- 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*
    - m3-2-a-1-facilities-and-equipment: *substance*
    - m3-2-a-1-facilities-and-equipment: *product-name*
    - m3-2-a-1-facilities-and-equipment: *dosage form*
    - m3-2-a-1-facilities-and-equipment: *manufacturer*
    - m3-2-a-2-adventitious-agent-safety-evaluation: *substance*
    - m3-2-a-2-adventitious-agent-safety-evaluation: *product-name*
    - m3-2-a-2-adventitious-agent-safety-evaluation: *dosage form*
    - m3-2-a-2-adventitious-agent-safety-evaluation: *manufacturer*
    - m3-2-a-3-excipients: *excipient*

More than 1 entry for each of the Module 3 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].

A3-2 General Principles

A general principle is that the XML index is a reflection of the document granularity, i.e. best practice is to assign the metadata to agree with the granularity of the CMC dossier rather than designing the granularity around the metadata.

[1] See section A3-3.3.3 'Manufacturer of Drug Product' as an exception, as in some eCTD building tools only xml is replicated, not the folder structure.

A3-2.1 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. When deciding on the strategy for the single- or multiple-document approach applicants should also take into consideration the ability of the assessor to review the content. 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, and the –var part of the filename used to differentiate each PDF document.

A3-2.2 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 A3-1, Introduction of this annex). 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).

For the Centralised Procedure, a single eCTD application should always cover all strengths and dosage forms within the procedure, as illustrated in Figure A3-1.

In MRP/DCP, a single eCTD is needed per procedure that covers all involved MSs, regardless differences in the invented name. 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 A3-1 – Advantages and disadvantages of eCTD application structures.

Figure A3-1 – Illustration of what an eCTD covers for a product with the invented name 'Wonderdrug', Centralised Procedure

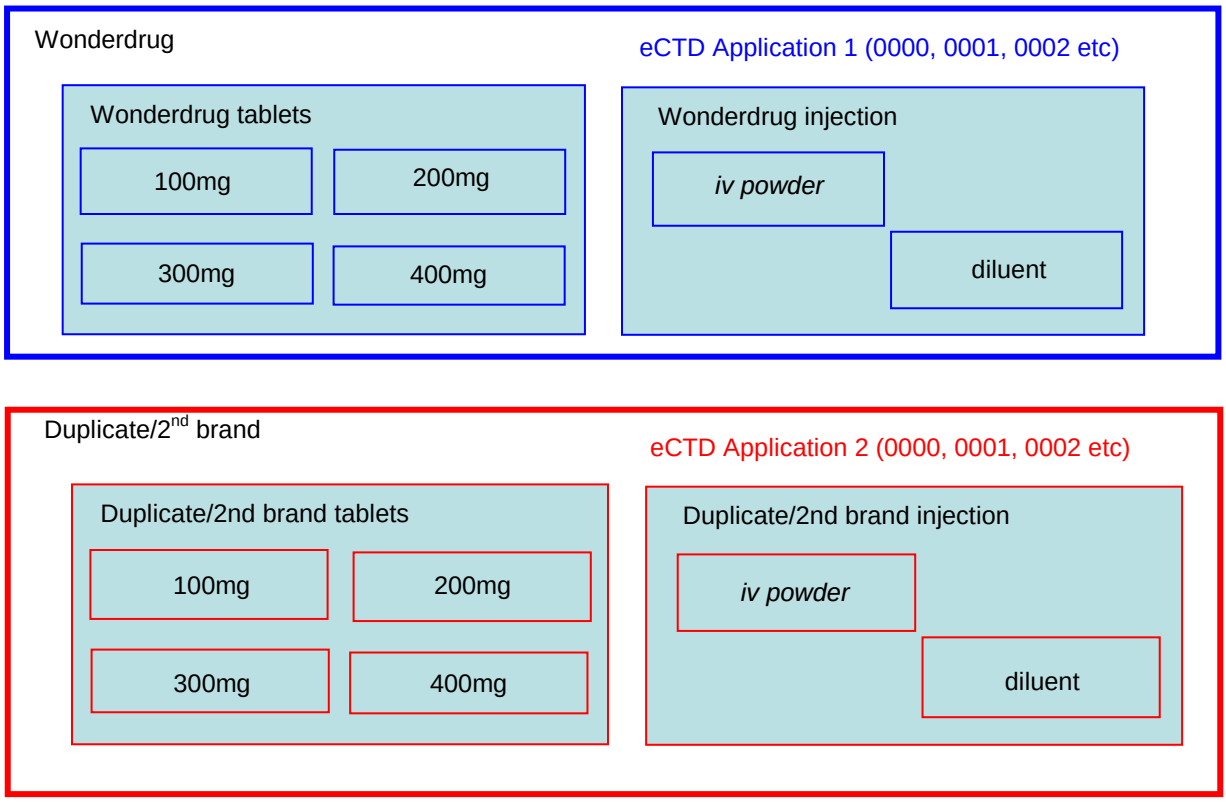


Table A3-1 – Advantages and disadvantages of eCTD application structures.

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 sequences would cover all products covered by the eCTD application, other sequences 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)	Lifecycle management becomes more complex in the following situations: • 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)
Lifecycle 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 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.	Common documents must be included in each eCTD 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 time 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

A3-2.2.1 EU Envelope

The Module 1 EU envelope provides the trade name (invented name) of the drug product. The **tracking number element,** which is repeatable, may list all of the product licences or application numbers covered by the eCTD. Applicants should ensure that the values 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.

A3-3 Module 3 XML Attributes in the eCTD

A3-3.1 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. For example, if an applicant builds an eCTD with ABC Chemical as the manufacturer of substance 1, and subsequently changes supplier to XYZ Chemical, they would normally provide a new eCTD sequence with XYZ Chemical as an additional module 3 XML attribute. It will not be possible to have content in the XYZ Chemical section that replaces or appends to content in the ABC Chemical section. This is because in the eCTD it is not possible to apply lifecycle across different sections. However, it will be possible to delete some or all of the content within the ABC Chemical section if required.

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.A.1 Facilities and Equipment, 3.2.A.2 Adventitious Agents Safety Evaluation, 3.2.A.3 Excipients).

A3-3.2 Drug Substance (32s) Attributes – Substance-1, Manufacturer-1

The use of these attributes is mandatory. Refer to ICH eCTD Q&As #65 and 66 for guidance.

A3-3.2.1 Drug Substance

The entry for the drug substance name attribute can be an abbreviation of the INN, or if not available, then the company's code for the drug substance.

If there is more than 1 drug substance in the application, there is a separate set of 3.2.S.1 to 3.2.S.7 folders and corresponding XML elements 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.

A3-3.2.2 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.

A3-3.2.2.1 Approach 1 – Single XML Section covering all Manufacturers of the Drug Substance

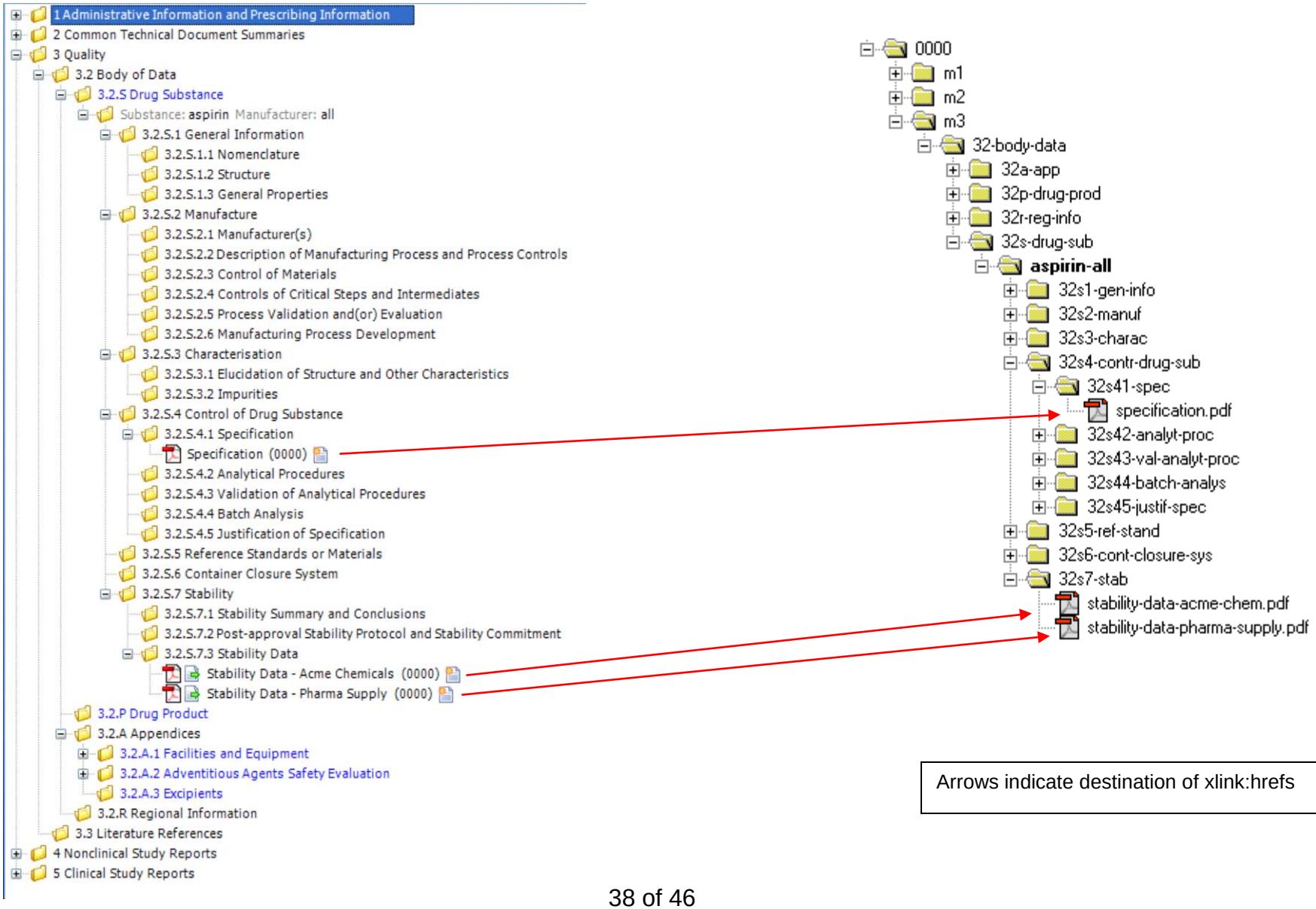
Where drug substance documentation is identical or very similar for all manufacturers (and hence there are a minimal number of manufacturer-dependent documents), then a non-specific manufacturer attribute can be used (such as the parent name of a group of companies (but be aware this can also change), 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 for [manufacturer 1] 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 A3-2, 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 is 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 A3-2 Single Drug Substance, 2 Manufacturers with similar documentation, the few site/manufacturer-specific documents are identified by the XML title (not by adding an additional XML section):

XML **Files and folders (directory**



A3-3.2.2.2 Approach 2 – New XML Sections for Each Manufacturer of the Drug Substance

When there are many manufacturer-specific documents, (e.g., if the route of synthesis or manufacturing process is different per manufacturer), it may be helpful to have additional XML attributes and equivalent folders for each manufacturer, see Figure A3-3. 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 elements:

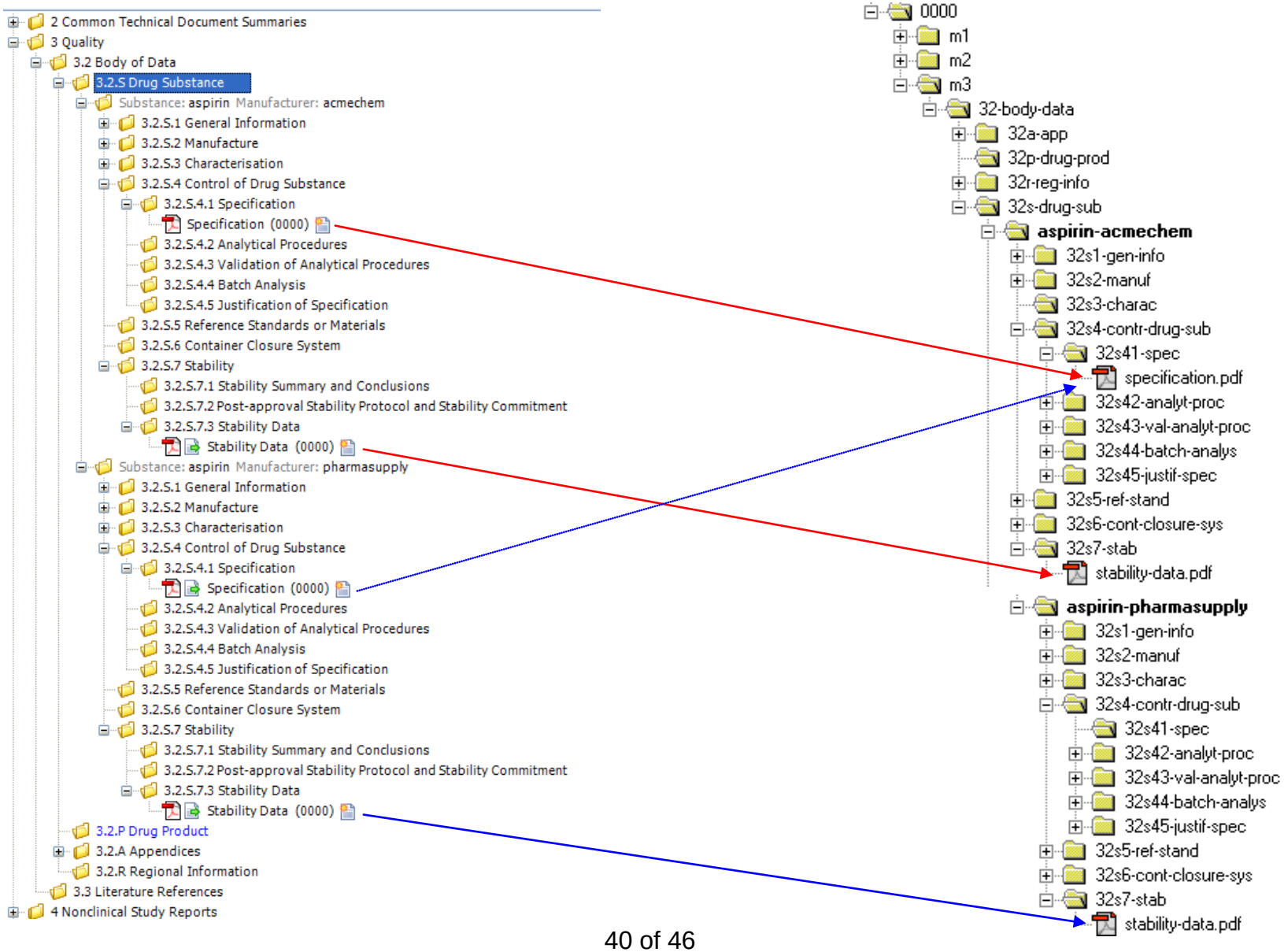
32s-aspirin-manufacturer-1 (containing information specific to the manufacturer e.g. 3.2.S.2)
32s-aspirin-manufacturer-2 (containing information specific to the manufacturer e.g. 3.2.S.2)
32s-aspirin-common (containing manufacturer-independent information)

However, this approach can be difficult to review from an assessors perspective, and can lead to problems later in lifecycle, for example if a third manufacturer is added, and content in the 'common' section now only applies to manufacturer 1 and manufacturer 2, and is no longer really 'common'. Therefore, this third approach is not recommended.

Figure A3-3 Single Drug Substance, 2 Manufacturers with significant volume of different documentation (one section for Acme Chemicals, another for Pharmasupply).

XML

Files and Folders (directory)



A3-3.3 Drug Product (32p) – Product/Dosage Form/Manufacturer

The use of these attributes is optional. Refer to ICH eCTD Q&As #68, 69 and 70 for guidance.

A3-3.3.1 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. Applicants should be aware that trade names can change over time. If the trade name is not well established, applicants should consider alternatives such as 'active', or 'product'. Alternatively, the internal company code of the drug product name may be used. If applicable, additional attributes can be used as needed (e.g. 'diluent' or 'placebo').
This attribute then results in a full set of 3.2.P.1 to 3.2.P.8 XML elements and folders.

A3-3.3.2 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, e.g. 'film-coated tablet' rather than 'tablet'.

Strength(s) need not be mentioned in the attribute. 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. However if there is a chance that some strength(s) may not be approved or may be later handled in another eCTD application, then some CTD topics might benefit in having separate leaves per strength (e.g.3.2.P.5.1 Specification).

A3-3.3.3 Manufacturer

If used and 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, 3.2.A.1 or 3.2.A.2 XML elements.. However, in some eCTD building tools, entries for drug product manufacturer do not result in additional directory folders. Industry practice is either to not use this attribute or to provide a single high-level descriptor. A general term such as 'all' or 'applicant' is acceptable.

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.

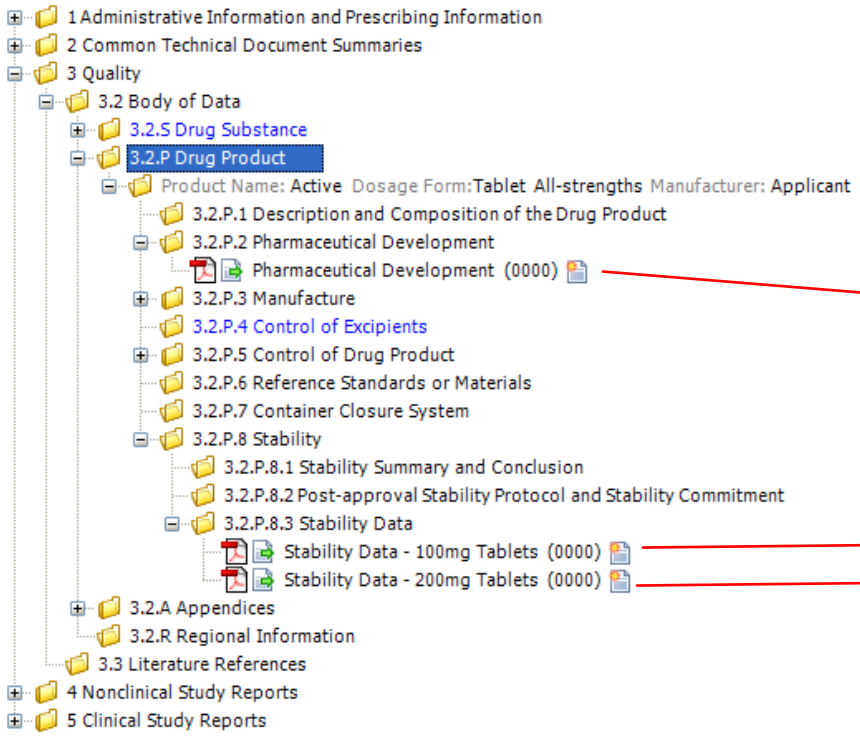
A3-3.3.3.1 Approach 1 – Single General XML Section Covering All Strengths

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. A known limitation of the ICH eCTD specification v3.2 is that the original, non-specific XML attribute cannot then be modified - see note under Figure A3-4.

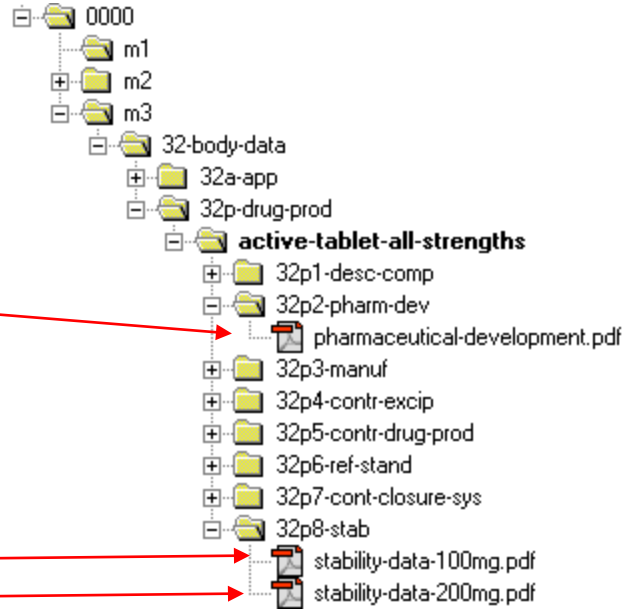
Figure A3-4 illustrates this approach, where the Pharmaceutical Development document is strength-independent but Stability Data documentation has been split by strength.

Figure A3-4 - 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. An alternative would be to not use the term ‘all-strengths’ at all and just use ‘Tablet’ for the dosage form attribute. This implies all strengths and reduces the overall path length.

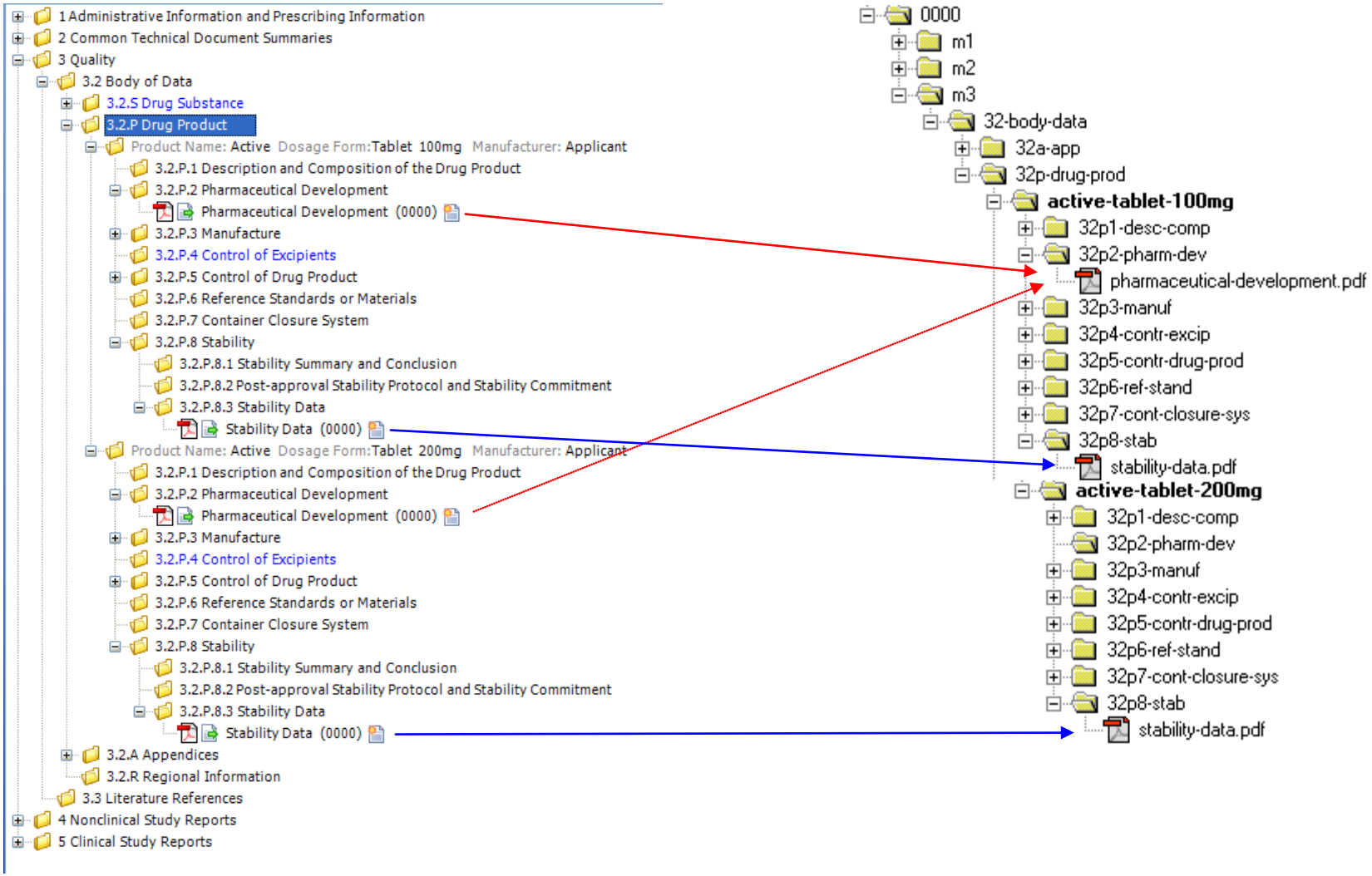
A3-3.3.3.2 Approach 2 – Separate XML Section Covering One Strength or Dosage Form

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 name 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 A3-5.

Figure A3-5 – Approach 2- Separate XML elements 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)



A3-3.4 Excipients

The use of these attributes is optional.

Each excipient entry generally produces a full set of 3.2.P.4.1 to 3.2.P.4.6 XML elements and folders. The description below reflects current industry practice.

A3-3.4.1 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. Avoid multiple files where content is just reference(s) to compendial monograph(s). Instead, a single document containing a list of all compendial excipients can be provided in one of the allowed sections (specifications, analytical procedures etc). The name of the document can be defined by the applicant.

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.

A3-3.4.2 Non-Compendial Excipients

For non-pharmacopoeial excipients, the applicant decides how to use the excipient XML attribute. The entry can be a general term, e.g., 'non-compendial', or can describe functionality such as '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. However, applicants should be aware of the inability to amend attribute entries after the first sequence is submitted (in line with the current ICH eCTD specification). Note, the use of the term 'non-compendial' in the XML attribute will help group together the non-compendial excipients in the table of contents (index.xml), and is therefore recommended.

A3-3.4.3 Excipients of Human or Animal Origin and Novel Excipients

Content under sections 3.2.P.4.5 & 3.2.P.4.6 should be provided under an additional attribute such as 'animal-human-novel', refer to ICH eCTD Q&A no. 4. Note, the files provided under this section should not be in a subfolder to the 32p4-contr-excip folder in the directory structure. Refer to the 'File and Folder Structure Names' worksheet in the eCTD validation rules.

Document Control

Change Record

Version	Author(s)	Comments
1.0	TIGes eCTD guidance 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.
1.1	GW, AN, KG, KM	First draft for revision, made the document in line with agreed text in the NeeS guidance and with the New validation criteria, TIGes Harmonisation group 110309
1.2-1.93	TIGes Harmonisation Group/ AN, KG, MC, KM, BT, KP	Further revisions by TIGes Harmonisation group TC meetings in April-July 2011
1.94	KG	Further revision after TIGes comments and minor update in accordance with EU M1 eCTD specification draft v.1.4.1.
2.0	KG, AN	Following review of TIGes comments and final updates at subgroup TC meeting in August. Final document for TIGes adoption and publication.

Reviewers

Version	Name	Organisation
1.0	TIGes	TIGes eCTD Topic Group
1.1-1.92	Members of the subgroup	TIGes Harmonisation group
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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.
2.0	1 September	Published at the EMA eSubmission website for use