Guidance for Industry on Providing Regulatory Information in Electronic Format

Harmonised Technical Guidance for eCTD Submissions in the EU

Version 4.0

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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 for human medicinal products and is the only electronic format that is accepted by the EMA (except for some specified procedures) and is stepwise becoming mandatory within the Decentralised, Mutual Recognition Procedures and purely National Procedures as well depending on national decisions. However, the Non eCTD electronic Submissions (NeeS) format is still accepted within these procedures and for National Procedures and therefore a guidance document for NeeS is also published on the EMA eSubmission website.

This guidance was initially created by the TIGes Harmonisation Group, a sub-group of the Telematics Implementation Group for electronic submissions (TIGes), and is now being maintained by the Human Harmonisation Maintenance Group (HHMG), a sub-group of the eSubmission Change Management Board (CMB).
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 and EMA using information submitted in electronic format. If needed, there are also Q&A documents published in between versions of this guidance as a response on change requests or new requirements to be addressed (see EMA eSubmission website)

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 or also known as a dossier	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 *regulatory activities*. In the EU an eCTD application may comprise several dosage forms and strengths, all under one invented product name. This is understood to be equivalent to a Global Marketing Authorisation according to Art. 6 para 2 Dir. 2001/83/EC as amended.
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.
Regulatory Activity	A *single sequence or a collection of sequences* covering the start to the end of a specific business process, e.g. an MA application or Type II variation. To allow a more precise handling, the regulatory activity will be classified using a controlled vocabulary (submission type or regulatory activity type) and a free text field for a short narrative description.
Sequence	A single set of information and / or electronic documents submitted at one particular time by the applicant as a part of, or the complete application .Any collection of content assembled in accordance with the eCTD specification (ICH and EU) will be described using metadata as defined by the EU envelope. Sequences may be related to one another within one regulatory activity. The related sequence number should always be stated. In case of activities with only one sequence the same sequence number will be used.
Submission Type	The submission type describes the *regulatory activity* to which the content will be submitted.
Submission Unit Type	The submission unit type element of the envelope metadata set describes the content at a lower level (a "sub-activity") which is submitted in relation to a defined regulatory activity such as the initial submission, the applicant response to validation issues or list of questions or any other additional information.

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 but is not limited to prescription, over the counter medicines, innovative and generic product submissions. The product types include for example small molecules, biotech products, herbals, vaccines, homeopathics or 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 (including PSUR Single Assessment PSUSA), active substance master files (ASMF), Plasma Master Files (PMF) and withdrawals, submission of redacted clinical trial reports as well as any kind of paediatric submissions and referral related or post authorisation measures related submissions. For variations, PSUSAs, ASMF and PMF there are also specific guidance documents (see references in Part 4).

2.1.3 Types of Submission Units
This allows sequences to be grouped together that make up a Regulatory Activity. The submission unit will describe the sub-activity within a Regulatory Activity, such as initial, validation-response, response and closing in case of a new MAA.
The submission unit 'additional-info' should be used for additional information (which could include, for example, missing files), and should only be used when 'validation-response' or 'response' is not suitable. The submission type 'corrigendum' should only be used in exceptional circumstances in the CP to correct information, typically for product information, after the Regulatory Activity has concluded.

2.1.4 Types of Procedures
This guidance covers applications made in any of the applicable Community procedures (National, Mutual Recognition, Decentralised and Centralised). For submissions within MRP and DCP, please refer to the specific CMDh guidance 'Requirements on submissions for New Applications within MRP, DCP or National procedures'

2.1.5 Exceptions
This guidance does not apply to the electronic submission of pre-marketing authorisation (MA) information such as scientific advice, clinical trial applications, orphan drug designations, PIP submissions and related submission correspondence as well as dossier content explicitly excluded from the commonly maintained electronic dossier. These exceptions may be subject to change in the future. (Please refer to the EMA website and to CMDh website on eSubmission for the BPG and Q&As for further exceptions.)

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/000123). 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 Table 16 (A3): Advantages and disadvantages of eCTD application structures.

Please check for specific NCA guidance when preparing national eCTDs. However, note that the selection of separate lifecycles for national (MRP/DCP/NP) products will mean in practice that submissions for EU PSUR Single Assessment must be made for each product separately in accordance with the existing dossier structure (for details see Section 4.5).

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 on-going for that product in another format. A baseline submission is recommended at the time of changing to eCTD (see Section 2.12.) to give the agencies access to all or at least part of the previously submitted documentation within the eCTD lifecycle. 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 BP2 will not be met. This should be reflected in the cover letter.

If the dossier has already been provided in NeeS format, the applicant 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. For clarity, the cover letter should always explicitly state that the submission involves a switch to eCTD 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. Please see Section 2.12 for further information on the content of baseline applications and the acceptability of scanned documents.

If an applicant has been submitting applications in eCTD format to some agencies within MRP or DCP when paper or NeeS were still requested by some other NCAs – in the context of the switch to eCTD format of these remaining paper/NeeS-based agencies, it would be of help if applicants would submit all former eCTD sequences 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 guidance 'Requirements on submissions for New Applications within MRP, DCP or National procedures'. 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 transmission or creating the submission 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 "original" 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 specification. 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, such as using the file name-*var*.pdf convention as described in the EU Module 1 Specification (e.g. pharmaceutical-development-*container*.pdf). 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 current validation criteria

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 should typically be placed at the lowest level of the CTD structure, although there are some exceptions to this guidance, for example, in 32p4-contr-excip, where the files excipients.pdf, excipients-human-animal-var.pdf or novel-excipients-var.pdf can be placed alongside folders containing details of other excipients. The lowest levels of the CTD structure (including node-extensions) must contain at least one leaf, although this should normally be managed automatically by the eCTD building tool.

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. If this correspondence is not directly relevant to the application dossier then it should not be included in the eCTD. This is because the eCTD exchange is currently one way only, from applicant to authority. Other correspondence should be exchanged outside the eCTD via the usual electronic means (email, EudraLink etc.).

2.7   Paper Requirements

Some NCAs may still require paper copies of some documents in addition to the eCTD; refer to the CMDh guidance 'Requirements on submissions for New Applications within MRP, DCP or National procedures' for further details.

2.8   Hardware

NCAs and the EMA will not accept any hardware (laptops, desktops, external hard 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   Identifier for Applications

To help enable archiving the sequence with the correct dossier (eCTD lifecycle), applicants must state a unique identification of the dossier in the form of a UUID. The identifier must be defined with the first sequence of a new dossier (or the first sequence using EU M1 version 3.0 or later), and it must be consistent throughout the eCTD lifecycle. The identifier must be changed if – and only if – the eCTD lifecycle is restarted. Examples of this are addressed in Section 2.12.3.

The UUID is a 32 digit (8+4+4+4+12) hexadecimal string, for example: "123e4567-e89b-12d3-a456-426655440000". When defining a UUID the string should be decided at random. The string should contain no information referring to any other metadata. This is to ensure consistency even if the relevant metadata should change. The chance of two different dossiers having the same UUID is next to none if the UUIDs are truly defined at random.

2.9.2   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 or the EMA in MS Word format should *not* be included in the eCTD structure (refer to Section 2.9.10).

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

2.9.3   Portable Document Format (PDF)

Portable Document Format (PDF) is an ISO standard (ISO 19005-1:2005 Document management – Electronic document file format for long-term preservation – Part 1: Use of PDF 1.4 (PDF/A-1) and ISO 32000-1:2008 Document management – Portable document format – Part 1: PDF 1.7). 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 version 1.4, 1.5, 1.6 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, 1.5, 1.6 or 1.7, either electronically or by scanning. .
- 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.

Additionally, the following requirements should be taken into consideration:
- Different requirements apply in the EU to NCAs and the EMA for signatures on application forms and cover letters. – For details refer to Section 2.10.4. Make sure that scanned cover letters are text searchable.
- The fonts used in the PDF should be embedded in the PDF where possible.
- Rendition to PDF should preferably create documents which are "tagged".
- Use 'Fast Web View' to ensure optimum performance of the review system. Due to technical constraints for eAF documents the fast web view cannot be enabled. Therefore, the BP warning for eAF can be ignored.
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Additional details on PDF, including those relating to the good presentation of tables, can be found in the ICH eCTD Specification, Appendix 7. Refer also to the ICH M2 recommendations.

2.9.4   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, as sometimes a higher sequence is technically related to the previous – not yet submitted – sequence which will result in technical invalidation. A Sequence Tracking Table should always be included in section 1.0 in every submission within MRP/DCP as a separate PDF file named cc-tracking-var.pdf. For details see Section 3.2.3.2.

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 accordingly, e.g. 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 comment in the delivery file (CESP, working documents or separate note in case of CD/DVD submissions). For submissions to the EMA it is mandatory to use the eSubmission Gateway / Web Client and no additional comment is required. 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.

2.9.5   Related Sequence

All submissions should contain a value for "related sequence". If the submission unit type is 'initial' or 'reformat' then the related-sequence attribute must have a value equal to the current sequence.

If the submission unit type is another one than 'initial' or 'reformat' then the entry for related sequence should be populated with the number of the sequence that started the regulatory activity.

Table 1 : Example of a PSUSA

Sequence number	Submission Description	Submission Type	Related Sequence	Submission Unit
0008	PSUR single assessment procedure	psusa	0008	initial
0009	Validation update	psusa	0008	validation-response
0010	Comments on Assessment Report	psusa	0008	response

Table 2 : Example of a Referral for CAPs

Sequence number	Submission Description	Submission Type	Related Sequence	Submission Unit
0008	Responses to LoQ	referral	none	initial
0009	Comments on Assessment Report	referral	0008	validation-response
0010	Responses to LoOI	referral	0008	response

Table 3 : Example of a Referral for NAPs

Sequence number	Submission Description	Submission Type	Related Sequence	Submission Unit
0008	Responses to LoQ	referral	none	initial
0009	Comments on Assessment Report	referral	0008	validation-response
0010	Responses to LoOI	referral	0008	response

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 PAM related sequences (sequence 0005 and sequence 0006) and a single response (sequence 0007) is produced that relates to both PAM related sequences.
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.

Further examples are provided in the EU eCTD M1 Specification document.

2.9.6   Leaf Lifecycle Operation Attributes

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.

Lifecycle operations where the leaf targeted by the modified file is in a different CTD section are not allowed. This applies across all of the modules of the CTD and is not specific to either the regional or ICH Modules.

Where elements are repeatable, both the element itself and the attributes that define a different position in the table of contents must be identical when modifying a leaf element in a previous sequence. Where node extensions are allowed, the node extension title element should be identical when modifying a leaf element in a previous sequence. However, it is acceptable occasionally if inconsistencies have been introduced in the past. In those cases, it is recommended to use the most recent version of the title attribute.

Table 4 : Repeatable Elements and Attributes that Define Different Sections

Element	Attributes also identifying a section
Module 1	
m1-0-cover	country
m1-2-form	country
m1-3-1-spc-label-pl	country xml:lang type
m1-3-2-mockup	country
m1-3-3-specimen	country
m1-3-4-consultation	country
m1-3-5-approved	country
m1-responses	country
m1-additional-data	country
Module 2	
m2-3-s-drug-substance	substance manufacturer
m2-3-p-drug-product	product-name dosageform manufacturer
m2-7-3-summary-of-clinical-efficacy	indication
Module 3	
m3-2-s-drug-substance	substance manufacturer
m3-2-p-drug-product	product-name dosageform manufacturer
Module 5	
m5-3-5-reports-of-efficacy-and-safety-studies	indication

The only exception to this is the change in agency name at the EMA; leaves with the specific country attribute 'ema' or 'emea' should be considered equivalent and lifecycle must be allowed between them.

Note, in the eCTD XML, sections, leaves and node extensions may have other attributes, such as xml:lang, font-library, version, keywords, ID etc. These attributes, if supplied, do not result in a new logical section in the eCTD table of contents and therefore lifecycle between leaves where these attributes are not identical is allowed; only the attributes in the table above define different eCTD sections.

Examples:

Pass/Fail
- A leaf to be submitted in m4-2-2-5 in Sequence 0012 cannot replace/delete a leaf submitted in m4-2-2-2 of Sequence 0010.
- A leaf in m1-responses cannot modify content in m1-0-cover (different section)
- A leaf in m3-2-s-drug-substance [manufacturer: abcd] [substance: xyz] cannot modify content in m3-2-s-drug-substance [manufacturer: other] [substance: xyz], or any section other than the specific manufacturer 'abcd' and substance 'xyz' section.
- A leaf in m1-0-cover with the specific attribute 'uk' cannot modify a leaf in m1-0-cover with a specific attribute of anything other than 'uk'.
- A leaf in m1-3-pi with the specific attributes <pi-doc xml:lang="en" type="combined" country="ema"> cannot modify a leaf with different attributes, such as <pi-doc xml:lang="fr" type="other" country="ema">.

Best Practice Criteria
- A leaf in a node extension should only be modified by a leaf in the same equivalent node extension in a subsequent sequence. For example, a leaf in a node extension in m5-3-5-1 of sequence 0000 with a <title> attribute 'Study 1234' should not be modified by a leaf in a different node extension with a <title> attribute 'Study 1234 – update' in sequence 0001 – the append/replace/delete leaf ideally needs to be in an identical node extension in 0001 ('Study 1234' in the same location, m5-3-5-1).

If the applicant 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.

However, applicants cannot submit a dossier using the old specification and DTD. Therefore, deleting the content in the old section will involve lifecycle from the changed section (for example, m1-additional-data) deleting content in the equivalent section with the original name (in this example, m1-additional). This may not be possible in all eCTD building tools, and if so, applicants are advised to leave the original content as it is, but to start providing new or replacement content in the revised section.

Note: Lifecycle operations across eCTD applications are not allowed.

2.9.7 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. However, hyperlinks back to previously submitted documents are welcome as well if pointing to the correct location.

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.

2.9.8 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 to group together the multiple leaves that make up the study and its modular appendices. 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 m1-responses. Therefore, the use of an additional folder in combination with a node extension is not allowed. 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.

2.9.9 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 electronic application forms (eAFs). Please refer to EMA eSubmission website for further details.

2.9.10 Other File Formats

Other file formats such as 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 submission zip package or on the same CD/DVD containing the eCTD, where the number (xxxx) matches the number of the eCTD sequence being submitted.

For PMF certification submissions the ePMF should be provided within the working documents folder. The folder should be called "xxxx-workingdocuments" as for all other documents. For more information please refer to the guidance on PMF eCTD Guidance document.

If working documents for more than one NCA are submitted on the same submission, sub folders with the country code should be used.
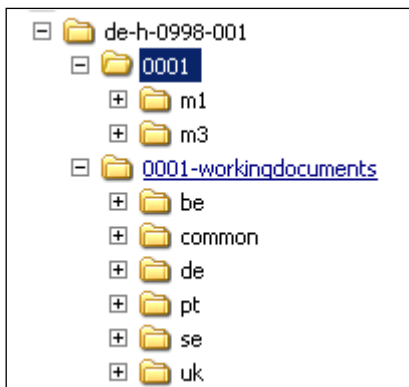
Figure 1 : Sample of folder structure

For information on translations being provided outside 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.

The EMA does not accept submissions sent by email or EudraLink.

2.9.11   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. It is strongly recommended that all sequences are checked and found technically valid according to the published validation criteria.

Two categories of validation rules apply: "Pass/Fail", and "Best Practice":

Pass/Fail Criteria
These are a set of technical validation criteria that can either be passed or failed. eCTDs that fail to meet one or more of these criteria will be returned to the applicant for correction and resubmission of the same sequence number. All Centralised Procedure (CP) eCTD submissions via the eSubmission Gateway / Web Client to the EMA are automatically run through a full technical eCTD validation and an automated 'success' or 'failure' acknowledgement is sent to the applicant/MAH. eCTD submissions for PSURs authorised via MRP/DCP/NP are checked using a 'tolerant' eCTD validation checking only the structure of the eCTD submission. This means that even if your submission has been successfully submitted via the eSubmission Gateway/Web Client, a technical validation issue can be found by an NCA at a later stage but will be coordinated by the EMA in that case.

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. eCTDs that fail to meet one or more of these criteria will still be accepted by the receiving agency/agencies during technical validation and it is possible that agencies may not even check these criteria during technical validation.

Note: These criteria cannot test the correctness of the metadata. Therefore, applicants need to make sure that all metadata are filled in correctly.

Errors found during the content validation including misleading information in the cover letter or an application form to be corrected for e.g. one or a few member states should be resolved through the submission of a new eCTD sequence using the next sequence number. These errors must never be resolved by resubmitting an existing sequence by re-using the same sequence number.

If historical sequences that have already been submitted in another MS in the EU are supplied to a new NCA, the receiving NCA should not technically validate these sequences, as they have already been accepted when originally submitted. This could be the case where, for example, in repeat use, switching from parallel national to comprehensive model, supply of eCTD sequences to an NCA where this same submission had been formerly submitted 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 submission.

2.10.4   Signatures
Electronic signatures are currently accepted in the EU as being legally equivalent to handwritten signatures (Directive 1999/93/EC). Some NCAs and EMA already have this capability, or are developing it.

The NCAs have different requirements for wet signatures or scanned signatures although a signature is not always required - refer to the CMDh guidance 'Requirements on submissions for New Applications within MRP, DCP or National procedures' for more details. In regard to electronic submissions to the EMA see for details on the eSubmission Gateway and on eSignatures.

2.10.5   Procedure for Sending Electronic Information
There are different ways of submitting electronic dossiers to NCAs and the EMA, including portals, CD-R and DVD-R, and EudraLink/e-mail, if accepted by agencies.   See CMDh website for further details on NCA requirements, and the EMA website for details on the centralised procedure. Normally, only **one way** should be used, to avoid sending multiple copies of the same submission to the authority. If an additional transmission is requested by an agency (for example, a sequence is submitted via EudraLink and followed up with another copy of the same sequence through a different channel), 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. The EMA does not accept any transmissions on CDs / DVDs or Eudralink.

If required any necessary paper documentation should be provided at the same time as the electronic submission, see CMDh website for further details. Submissions that are sent to the NCAs in split packages (ie. cover letter without a CD/DVD), or on a separate date in duplicates, might be processed with a delay.

Authorities will not accept any hardware (laptops, desktops, separate hard 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 authority's hardware (e.g. CD/DVD drive) using its own software.

2.10.5.1   Portals
For the submission of applications, it is strongly recommended to use portals instead of CD/DVD wherever possible.

There are two European portals in use for regulatory submissions. The Common European Submission Platform (CESP) can be used to send national or MRP/DCP submissions to majority of NCA(s) - please refer to the CESP website for further details. In addition, CESP can be used for submission of human centralised procedure dossiers to many NCAs for those submission types that are not available via the Common Repository. The EMA eSubmission Gateway/Web Client must be used for submissions to the EMA in the centralised procedure and from 13 June 2016 as announced by the EMA Management Board, for all PSUR submissions. For further details see the eSubmission website and the eSubmission Roadmap.

There are also national portals in some countries, see CMDh website and individual NCA websites for further details.

2.10.5.2   CD / DVD
The current standard to burn CDs / DVDs is Universal Disk Format (UDF), which has replaced the former ISO standard 9660. 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.

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.

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

The EMA does not accept CDs / DVDs for Centralised Procedure submissions or for Referral submissions.

2.10.5.3   EudraLink / e-Mail (where applicable)
EudraLink and e-mail are not recommended submission channels for eCTD submissions and in most cases, eCTD sequences should not be sent by EudraLink or e-mail. Details on the dossier requirements in National Competent Authorities are available on the CMDh website. Also, normally only *one* route for submissions should be used (CESP, EudraLink/e-mail or CD/DVD). Please note that EMA does not accept eCTD sequences via EudraLink.
If EudraLink is used for sending an eCTD sequence, the entire sequence has to be zipped first. Some zip formats are not widely readable and therefore a submission may be rejected if the zipped format cannot be read by the agency. If in doubt, please check the intended format with the concerned NCA before sending. Please also note there is a size limit, refer to the EudraLink User Guide for further details (request). Applicants should not split an eCTD sequence over more than one zip/EudraLink. 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, it is strongly recommended that the expiry date is set to the maximum (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.

2.10.6   Labelling/Metadata
The information provided on either the physical media or metadata provided when using a portal must be consistent with the information provided in the cover letter and the eCTD envelope.

When using the CESP portal this metadata should go into the XML delivery file.

For submissions to EMA the relevant information is included in the eSubmission Gateway / Web Client file naming convention or XML delivery file or in the XML delivery file for PSUR submissions.

Each CD or DVD submitted 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 procedure number(s) (if known) (e.g. UK/H/1234/001-005/II/0034)

- ➢ 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

2.11 Number of Media Requested

The details of the number of copies for media required for archiving and reviewing purposes are published on the CMDh website and under question 'How and to whom should I submit my dossier?' of the Human/Pre-authorisation Q&A on the EMA's website. Where an NCA requires the disc to be archived they may have additional requirements.

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 mandatory to use a baseline as a start of an eCTD when changing from paper or NeeS and to provide as much content as possible in the eCTD. The baseline would preferably consist of high quality electronic source documents, 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 previously submitted dossier has not been changed, only the format. There is no need for the NCAs or EMA to assess baseline submissions and hyperlinks between documents are not needed. The submission type *reformat* should be used in the envelope for the baseline sequence.

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 below). 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 5 : Example for starting an eCTD with a baseline sequence

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

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 is possible 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. An example is given below.

Table 6 : Example for starting an eCTD with regulatory activity sequence

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

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 compiled in line with CMDh guidance 'Requirements on submissions for New Applications within MRP, DCP or National procedures'. 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 below.

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 this option is not used unless 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 Section 2.12.3 below). For the switch, the pros and cons of the different approaches to dossier structure, as described in Annex 3, 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.

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, 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. If the lifecycle re-starts a new UUID for the application is required.

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 agreement between the MA holder and the receiving NCA (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. Also in these cases a new UUID for the application is required.

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.

- A new UUID need to be assigned to the application.
- The submission type would be "none"
- The submission unit 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 from the previous lifecycle, 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 historical parallel national model 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. In those cases the UUID must not change.
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. In those cases the assigned UUID of the application maintained will also serve for future lifecycle. Any re-use of existing sequences or changes to sequence numbering should be agreed with the relevant authorities.

Re-baselining where the previously submitted sequences cannot be used in the new lifecycle and must be archived

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 with a new UUID in each sequence built with EU eCTD m1 v3.0 or later. 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.

Scenario 1 – previously submitted sequences archived, new eCTD started
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:
** MA 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

Re-baselining where the previously submitted sequences in at least one MS can be used as exisiting lifecycle

In the case that previous lifecycle can be continued, but submitted in additional member states, then there would be no need to change the identifier or UUID. In an MRP, the tracking table should indicate which member states originally had the sequences, and which member states are now getting them as lifecycle history.

Scenario 2 – previously submitted sequences valid, lifecycle continued
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 without making changes to the scope of the eCTD application, **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.

## 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.

 "Not Applicable" Module 1 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 'ema'. 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. In case of submissions to EDQM the envelope need display the entry 'edqm'.
Identifier	A UUID as specified by ISO/IEC 11578:1996 and ITU-T Rec X.667	ISO/IEC 9834-8:2005. The same UUID will be used for all sequences of an eCTD application.
Submission Type	This value represents the regulatory activity which will be started and the type of material sent to the agency. The entry is chosen from a picklist based on the EUTCT controlled term list on Applicant Submission Type, see EU M1 Specification for further details.
Submission Unit	Submission unit type describes the content at a lower level (a "sub-activity") which is submitted in relation to a defined regulatory activity. The entry is chosen from a pick list, see EU M1 Specification for further details.
Submission Mode	This element should only contain a value in variation, PSUSA 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'.
Submission Number	This number represents the high level procedure number related to the regulatory activity in case of worksharing submissions and for submissions of grouped Type 1A variations and PSUSA if **multiple** products are concerned**.** Samples are provided in the EU M1 Specification. Note: not required in case only one product is concerned.

	If submission mode is set to either 'grouping' or 'worksharing' there should be a Submission Number (Number element in the DTD). This Number element should be identical with the variation procedure number included in a Variation eAF.
Procedure tracking number	Always to be completed. In case of using the submission number, the Procedure Tracking Number (PTN) refers to the product involved in the worksharing, grouped or PSUSA procedure. 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 for a CP submission (after allocation of the specified procedure number by EMA) and DE/H/0126/001/MR for an MRP submission (depending from the national business rules which might allocate procedure tracking numbers at receiving time point only. In those cases the field remains empty until submission). If the PTN is not known in advance, it is recommended to use the product number instead. For a full list of expected number types per agency refer to EU M1 Specification. Note: When a submission is not relevant for all products covered by the dossier or new products are added to the dossier, please clearly state this in the cover letter. This number should be congruent with the variation procedure number included in a Variation eAF or with the procedure number included in a MAA eAF or in a Renewal eAF.
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	Select from picklist in the most recent EU M1 Specification. Assure that Country and Agency name will be consistent.
Procedure type	The entry is chosen from a picklist, see EU 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 Cover letter and on the XML delivery file for CESP submissions, the file naming conventions for eSubmission Gateway/Web Client submissions and the XML delivery file for PSUR submissions via the eSubmission Gateway/Web Client. If the submission is provided on CD/DVD this should match the label of the CD/DVD.
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. Please note, when resubmitting content due to technical validation issues or sequences missing at NCA side, a note (a comment in the delivery file (CESP, working documents or separate note in case of CD/DVD submissions) may be provided to clarify the reason for resubmitting and the original cover letter in the eCTD should not be changed, see Section 2.9.4. For submissions to the EMA it is mandatory to use the eSubmission Gateway / Web Client and no additional comment is required.

For CP there is a cover letter template published on the EMA website under the Post Authorisation Guidance. For MRP / DCP guidance is provided here.

3.2.3.2   Tracking Table

A tracking table should <u>always</u> 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-tracking-var.pdf* and be placed in /XXXX/m1/eu/10-cover/cc. (e.g. ema-tracking-var.pdf for the CP, common-tracking-var.pdf in an MRP/DCP, or be-tracking-var.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".

Some 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 in addition to the electronic application form, 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.

The electronic Application Form (eAF), should be provided in PDF format only (with the extractable data), inside the eCTD. The use of the eAFs is mandatory from 1st July 2015 for the CP applications, and from 1st January 2016 for all other procedures. These forms can be found from the electronic Application Forms webpage.

The file named cc-form.pdf should contain the eAF in all cases (without using any variable part of the file name).
Supportive documents, which are not part of any M2-5 section or Response to Questions, should be placed in the application form section of the eCTD, and not appended to the form itself. Each annex should be provided as a separate attachment in m1/eu/12-form/cc, using the variable part of the file name and the leaf title to clearly describe the content of the document. E.g. file name: fr-form-proofpayment.pdf, Leaf Title: "France, Proof of Payment".

3.2.5   Product information

Product information should be supplied as PDF files within the eCTD. In addition Word files (with or without tracked changes as relevant) should be provided in the separate folder XXXX-workingdocuments within the same submission. Alternatively, certain procedures require word working files to be sent via Eudralink. Details can be found in Section 2.9.9 and from Section 4. Advice on specific application types.

Additional tracked changes version in PDF format are required only in the Centralised Procedure for either product labelling or risk management plan documentation.

In MRP/DCP national translations should be managed outside of the eCTD (see CMDh guidance 'Requirements on submissions for New Applications within MRP, DCP or National procedures').

In MRP/DCP, ensure that common product information is always placed under m1/eu/13-pi/131-spclabelpl/common/en. If these documents are placed under country specific folders, e.g. the country folder of the RMS, the agencies will not be able to use the country filtering options of their eCTD viewer tools as intended.

In the Centralised Procedure, national translations are only required in the eCTD for the commission decision documents in a closing sequence. 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 NtA Presentation and format of the dossier (CTD) Document, using the operation attributes of "new", "replace", or "delete" as appropriate. ("Append" should be avoided, see Section 2.9.6.)

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 the applicant provides 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.

In m1-responses/cc, it is recommended to use the variable component of the filename and the leaf title, to present the information clearly to the assessor. The response files should preferably be named as:

cc-responses-<regulatory activity type identifier>-<timeline identifier>-<content identifier>.pdf, using the -var component of the filename to define the content.

Table 7 : Examples of Filenames and Leaf Titles for Response Documents

Suggested Filename	Suggested Leaf Title
common-responses-maa-d106-clin.pdf	Day 106 Clinical Responses, MAA
common-responses-maa-d120-clin.pdf	Day 120 Clinical Responses, MAA
common-responses-maa-d145-clin.pdf	Day 145 Clinical Responses, MAA
common-responses-maa-d120-clinq4.pdf	Day 120, Clinical Response Question 4, MAA
common-responses-maa-d120-clinq7.pdf	Day 120, Clinical Response Question 7, MAA
common-responses-var03-d45-clin.pdf	Day 45 Clinical Responses, Var03
common-responses-var03-d59-clin.pdf	Day 59 Clinical Responses, Var03
common-responses-maa-d106-qual.pdf	Day 106 Quality Responses, MAA
common-responses-maa-d120-qual.pdf	Day 120 Quality Responses, MAA
common-responses-maa-d145-qual.pdf	Day 145 Quality Responses, MAA
common-responses-var05-d44-qual.pdf	Day 44 Quality Responses, Var 05
common-responses-var05-d59-qual.pdf	Day 59 Quality Responses, Var 05
common-responses-var12-d33-qual.pdf	Day 33 Quality Responses, Var 12

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. An exemption to this is the use of this section for justifications for active substances or justification of eligibility of the product for the Centralised Procedure.

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

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 details refer to the 'File-Folder Structure & Names' tab in the EU Validation criteria spread sheet.

If an existing document is revised, the lifecycle operator 'replace' should be used. However, if changes of content only affect one section of that document then updates should normally be submitted as a separate summary with the document operation attribute "new" as it would help clarifying what to assess within the specific submission.

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. 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* (e.g. 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 2.9.8 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 E3) 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 eCTD 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 eCTD section 5.3.6, Post Marketing Experience.

4. ADVICE ON SPECIFIC APPLICATION TYPES

4.1 New 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 'maa'.

See Section 2.9.5 for an example on the use of the submission units.

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 a new application.

Table 8 : 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)	If applicable
181	Response to List of Outstanding Issues (LoOI)	If applicable
Any time between D181-220	Redaction Proposal Document Package	For details see Section 4.12
Commission Decision + 15 days or prior to the next regulatory activity whichever is first.	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 • Final mock-ups reviewed during the procedure.	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.
20 calendar days post consultation notification	Final Redacted Document Package	For details see Section 4.12

Table 9 : Centralised Procedure - 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 10 : New MAA – Decentralised Procedure

Day Number/ Milestone	eCTD milestone sequence	Notes
- 10	New 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 further details on MRP and DCP, please refer to the specific CMDh guidance 'Requirements on submissions for New Applications within MRP, DCP or National 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). 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.

See Section 2.9.5 for an example on the use of the submission units.

For details on how to handle parallel variations, please refer to Annex 4 of this guidance.

Although Type IA variations usually should not be revised if they are invalid from regulatory point of view, it is necessary to correct technical invalid submissions in the same way as required for any other eCTD sequence.

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 11 : Type II Variations – Centralised Procedure

Day Number / Milestone	eCTD milestone sequence	Notes
Submission deadline	Initial submission	Please observe the published submission timetables, 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 + 30	For Type II variations which are **not** followed by an immediate Commission Decision: 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	For Type II variations which are **not** followed by an immediate Commission Decision
Commission Decision + 15 days or prior to the next regulatory activity whichever is first.	For Type II variations following worksharing or with immediate Commission Decision: 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 • Final mock-ups reviewed during the procedure.	For Type II variations following worksharing or with immediate Commission Decision

Table 12 : Type IA & IB Variations – Centralised Procedure

Day Number	*eCTD milestone sequence*	*Notes*
Submission	Start of the procedure <description>	e.g. "Start of the procedure, phone number changes"
RSI Submission deadlines	Response to Request for Supplementary Information (RSI)	If applicable

Table 13 : Type IB Variations with linguistic review - Centralised Procedure

Day Number	*eCTD milestone sequence*	*Notes*
Submission deadline	Start of the procedure <description> English PI (pdf) – inside the eCTD English PI + translations (word) (Outside eCTD but within the same submission package in the workingdocuments folder)	e.g. "Start of the procedure, phone number changes"

Start + 5	Provision of translations (Eudralink)	
Start + 25	Provision of final agreed translations following linguistic review (Eudralink)	
RSI Submission deadlines	Response to Request for Supplementary Information (RSI)	If applicable
Notification + 15	Closing sequence – including final translations (pdf) inside the eCTD	

For MRP and DCP, please refer to the CMDh guidance 'Requirements on submissions for New Applications within MRP, DCP or National procedures'.

4.3 Extension Submissions

Several dosage forms can be managed within a single eCTD application, and this helps to 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".

See Section 2.9.5 on examples on the use of the submission units.

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 14 : Renewals

5 year Renewal – Centralised Procedure

Day Number	*eCTD milestone sequence*	**Notes**
Submission deadline	Initial submission	As per published submission calendar
91	Response to Request for Supplementary Information (RSI)	If applicable
Commission Decision + 15	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	

Annual Renewal of conditional marketing authorisation – Centralised Procedure

Day Number	*eCTD milestone sequence*	**Notes**
Submission deadline	Initial submission	As per published submission calendar

Table 15 : Centralised Procedure – Outside eCTD via EudraLink

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

For renewals in MRP and DCP, the general principles in the CMDh guidance 'Requirements on submissions for New Applications within MRP, DCP or National procedures' can be applied.

4.5   PSURs

As per the Article 107b paragraph 1 and Article 28(2) Regulation 726/2004) all Periodic Safety Update Reports (PSUR) shall be submitted electronically.

The PSUR is a part of the product lifecycle and for products with eCTD lifecycle the PSUR must be submitted in eCTD. The PSUR should be provided as the next relevant sequence in the products lifecycle. This applies to all products, also for those for which the PSUR is part of an EU Worksharing procedure or the EU PSUR Single Assessment (PSUSA) procedure.

Centrally Authorised Products (CAPs) for which the PSURs are submitted as part of the PSUR single assessment should be submitted in eCTD format into their existing eCTD lifecycle.

Nationally Authorised Products (incl. MRP/DCP/NP) that are submitted to the EMA as part of the PSUR single assessment need to be submitted in eCTD or NeeS format as appropriate.

A separate eCTD sequence must be submitted for each respective product/presentation with its own lifecycle.

If a single PSUR has been prepared covering multiple products for which the lifecycle is in eCTD format, a separate submission (of that same PSUR document) must be made for each respective product. Separate standalone eCTD sequences grouping multiple products should not be created.

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 literature will be included in *m533* or *m54* as appropriate. The naming of the leaf element in *m536* shall indicate the number of the PSUR or the period covered. In case of proposed changes to the product information texts, new (if there is no previous lifecycle in the product information section) or replace versions need to be submitted in *m131* in a closing sequence. The closing sequence usually contains all the agreed translations in all languages.

When multiple products from the same MAH are submitted, all products must be listed in the cover letter. It should also be clarified in the cover letter that the content of each sequence/submission is identical. For PSUR Worksharing procedures, the same principles apply. However, exemptions to this principle might be necessary in the future, and if so please refer to any specific guidance from EMA and NCAs.

More information on the use of the cover letters for the PSUR submissions can be found from the EMA [Post-Authorisation Guidance](#).

The submission type should be "psur" for 'pure, single PSURs', i.e. those products for which the active substance is not included in the EURD list.

For PSURs included in the EU PSUR Single Assesment (PSUSA), the submission type is "psusa"

See [Section 2.9.5](#) for an example on the use of submission unit.

Please refer to the [PSUR Repository website](#).

Note: MAHs should not submit full study reports as part of a PSUR. Final study reports should always be submitted as a C.1.13 variation. In the case of interim PASS study results, these can be summarised in the PSUR under the section "*Findings from non-interventional studies*" or alternatively if the reporting to EMA does not coincide with the PSUR submission, the full interim report should be submitted as a separate, stand-alone submission (post-authorisation measure (PAM)) relevant to CAPs only.
Additionally, submission of RMP updates cannot be accepted with PSURs subject to a PSUSA of:
- a mixture of CAPs pertaining to different GMAs;
- a mixture of centrally and nationally authorised medicinal products;
- a mixture of NAPs.

The submission of an imposed, non-interventional Post Authorisation Study protocol or study report should not be combined with a PSUR or PSUSA sequence. Please, use the submission type 'pass107n' in case of the protocol and 'pass107q' in case of the study report.

4.6   Referrals

4.6.1   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".

4.6.2   Referral procedures for Centrally Authorised Products (CAPs):
eCTD format is mandatory for all submissions for CAPs involved in the referral procedure. Submissions should be sent via EMA eSubmission Gateway or eSubmission Web Client only. All eCTD format submissions for CAPs sent to EMA via eSubmission Gateway/Web Client are available via the Common Repository and will be considered delivered to all National Competent Authorities' (NCAs) representatives, alternates and scientific

experts. No additional copies of the submissions should be sent directly to the NCAs on CD/DVD or via CESP as this might lead to validation issues and cause delays.

CAP referral submissions should always be submitted as the next sequence in the product lifecycle for each CAP. Standalone eCTD submissions for the active substance are not allowed for CAPs included in referral procedures.

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 (unless requested by the authorities), but a new sequence with only the information/documentation that concerns the referral.

The type of submission of the new sequence should be "referral".
See Section 2.9.5, tables 1 to 6 on examples on the use of the submission units.

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 (please refer to CTD structure in 4.6.3). 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.

4.6.3   Referral procedures for Nationally Authorised Products (NAPs):

All submissions for NAPs involved in the referral procedure should be sent to EMA via eSubmission Gateway or eSubmission Web Client. EMA strongly recommends sending all NAP submissions in eCTD or NeeS format. Submissions for NAPs, sent in any format, **are not** available via the Common Repository and should be sent separately to each NCA via Portal or on DVD/CD-ROM as applicable (please refer to Dossier requirements for referral procedures).

More information on the referral submissions can be found on the eSubmission Gateway webpage. For more information and updates please refer to eSubmission website.

There is no need to send any separate paper cover letters for these submissions, as the cover letter will be in the relevant part of eCTD/CTD module 1 in PDF format.

4.7   Active Substance Master Files

For MAAs in eCTD format, applicants should incorporate the applicant's part (AP) documents of the ASMF into the eCTD structure as per the relevant guidelines. This is applicable even if the ASMF itself is not handled in eCTD format. It is recommended to use a suffix of '-ap' on the filename of these documents.

For further information, please refer to the specific eASMF page on the eSubmission website.

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).

4.8   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, keep the documents manageable and to assure the correct alignment of the complete VAMF 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.

4.9 Plasma Master Files (PMFs) and medicinal products containing PMFs

4.9.1 Plasma Master Files
The Plasma Master File documentation for certification is submitted to the EMA as a stand-alone eCTD dossier of a medicinal product. This documentation contains all the information related to the starting material for the manufacture of the medicinal product but submitted separately from MAA dossier (EC Regulation Commission Decision 2003/83/EC, part III of Annex I) when follows the PMF certification evaluation procedure.

ePMF should be provided within the 'workingdocuments' folder for PMF certification submissions.

For practical on PMF eCTD guidance, the reader is referred to the see the PMF eCTD Guidance document found via this link. More information on PMF submission can be found here.

4.9.2 Medicinal products containing PMFs
All concerned medicinal products that include one or more plasma supplier in their dossier (i.e. one or more PMF(s)) are required to have their dossier updated and implement this update submitting the relevant variations to the MA (for eCTD guidance, see point 4.2 of this guideline).

4.10 Applicant Initiated Withdrawals of the MA or certain strengths, dosage forms
Applicants may decide to withdraw their marketing authorisation during any stage of the product lifecycle and this section explains the general principles that should be followed in terms of managing the eCTD lifecycle.

If the application for withdrawal does not include all strengths and/or dosage forms covered by the same eCTD, the application should be submitted as a new sequence, with the operation attribute "delete" for documents that are no longer relevant. Furthermore, if relevant, it should also include updated documents with the operation attribute "replace" for documents that covered several other strengths and/or dosage forms and that now need to be revised to exclude the withdrawn strengths and/or dosage forms from the document.

Withdrawal of the whole product (all dosage forms and strengths) 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.

The submission type 'withdrawal' or the relevant variation category for the change, depending on the regulatory procedure being followed should be used.

4.11 Applicant Withdrawal or Agency Rejections of Post-Authorisation Regulatory Activities
If a regulatory activity is withdrawn, fully or partially or rejected fully or partially, then the documentation has to be updated accordingly with a consolidation sequence. Documents that are no longer relevant should be deleted, and documents where the content needs to be adjusted to reflect the withdrawal or rejection replaced. A consolidation sequence should be submitted to restore the current view of the dossier to what it was before the rejected activity was submitted.. This would also apply where documentation needs to be adjusted as a result of a commitment or a partially rejected variation. The submission type should be 'consolidating'.
Note, it is not possible to delete a sequence from the life cycle to accommodate the withdrawal or rejection.

Scenario on consolidation sequence
Applicant X has submitted sequences:
0027   Variation 011
0028   Day xx response
Letter of rejection of variation 011
**0029   consolidating sequence to restore the previous status of dossier
0030   Variation 012
0031 = Next submission

The variation 011 has been rejected and those parts affected by the proposed variation need to be restored to present the previous status in the current view of the eCTD.

Examples for this scenario:
** After full or partial rejection of sequence 0027, (variation 011), a following sequence 0031 may change the same technical content. If the change previously applied for in variation 011 has not been fully restored, the new variation may not be displayed correctly, for example, the next submission cannot refer to content which was proposed in variation 011 but subsequently removed. Therefore, the consolidating sequence, 0029, must remove any new and now rejected content from the rejected variation, and also reinstate any documents that were deleted or replaced in sequence 0027/0028, such that sequence 0030 can itself replace or delete the content as required. i.e. Sequence 0029 must restore the current view, (in terms of what is current, not deleted or replaced), to what it was before sequences 0027 and 0028 were submitted.

4.12   Publication of Clinical Data for Medicinal Products

Clinical reports will be published, under Policy 0070 (The European Medicines Agency policy on the publication of clinical data for medicinal products for human use) following conclusion of the regulatory decision-making in the frame of centralised marketing authorisation procedures.

Key components of the process from the point of submission by an applicant/MAH to the point of publication are following:

"Redaction Proposal Document" package (eCTD sequence to be included in the eCTD lifecycle with the attribute « new »)

"Final Redacted Document" package (eCTD sequence to be included in the eCTD lifecycle with the attribute « new »)

For further details please refer to the Guidance for the publication of clinical data:

4.13   Duplicate Applications and Informed Consent Applications

One eCTD per so called duplicate application has to be submitted and maintained separately in the post-authorisation lifecycle phase (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.

Duplicates are independent marketing authorisations and therefore the eCTD lifecycle will need its own UUID. The term is used for practical reasons and understood as a MA application which is a 'copy' of another application. Duplicates can be submitted under the same legal basis as the initial application (e.g. Art. 8(3) of Dir 2001/83/EC). The legal basis of the dossier will trigger the dossier requirements. There is no definition of a "duplicate" in the pharmaceutical legislation. However, for practical purposes, a duplicate application is defined for MRP/DCP 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 on multiple applications see the document 'Handling of Duplicate Marketing Authorisation Applications'.

However, the life cycle for those dossiers needs to be handled as independent stand-alone dossiers with their own life cycles and is following eCTD life cycle maintenance rules.

Applications under the legal base of Art. 10c – Informed consent will follow the same rules.

Annex 1: eCTD Reference Documents

A number of relevant documents can be found on the Documentation tab on the eSubmission website at the EMA. It is recommended that owing to the speed that information changes the following websites should be consulted regularly in addition:

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

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

http://www.hma.eu/277.html

EU Module1 Specification

Most important documents to be considered are the following (as of March 2016):

- http://estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf

- http://estri.ich.org/eCTD/eCTDQAV1_27.zip

- http://esubmission.ema.europa.eu/eumodule1/index.htm

EMA Pre submission guidance 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

EMA Post-authorisation Q&As

- http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000166.jsp&mid=WC0b01ac0580023399

ICH M4

- http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R3_Organisation/M4_R3__organisation.pdf

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

EMA Gateway:

- http://esubmission.ema.europa.eu/esubmission.html

Common European Submission Platform (CESP)

- http://cespportal.hma.eu

Electronic Application Form (eAF)

- http://esubmission.ema.europa.eu/eaf/index.html

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.

It is recognized 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 user's identity and do not require handwritten signatures on Cover Letters and/or 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 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 Attribute Information in the eCTD XML

In addition to CTD-Q documents, eCTD applications provide quality information in XML attributes in the following locations:

- Module 1: Envelope – *INN, Invented Name* (Trade Name)
- Leaf: eCTD *Title* (Submission Description)
- Module 3:
    - 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].

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

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.

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
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).

A3-2.2.1   Centralised Procedures
For the Centralised Procedure, a single eCTD application should always cover all strengths and dosage forms within the procedure. A duplicate must always be submitted and maintained as a separate individual eCTD application.

A3-2.2.2   MR and DC Procedures
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 16– Advantages and disadvantages of eCTD application structures.

Table 16 (A3): 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

One Combined eCTD For Multiple Strengths And Dosage Forms

	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

A3-2.2.3   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. **Note**: 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 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]

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[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 2 (A3) : 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
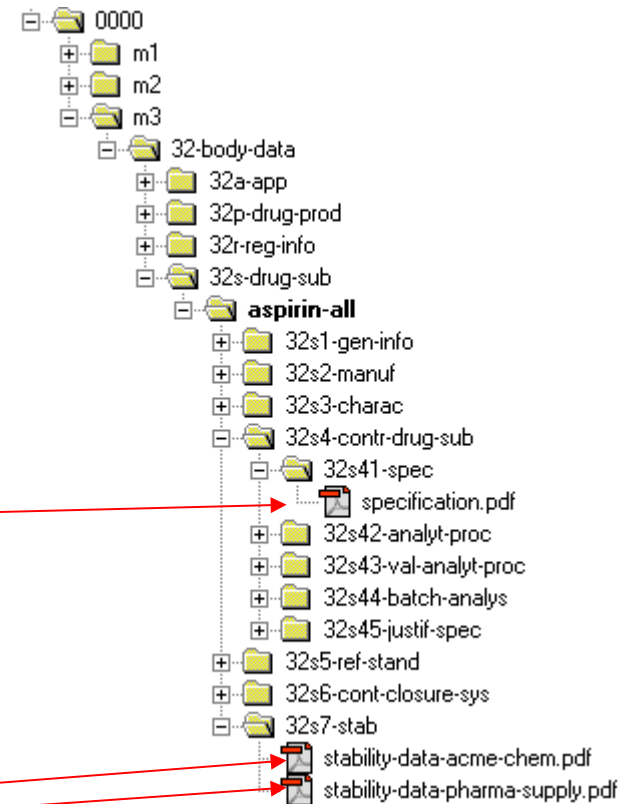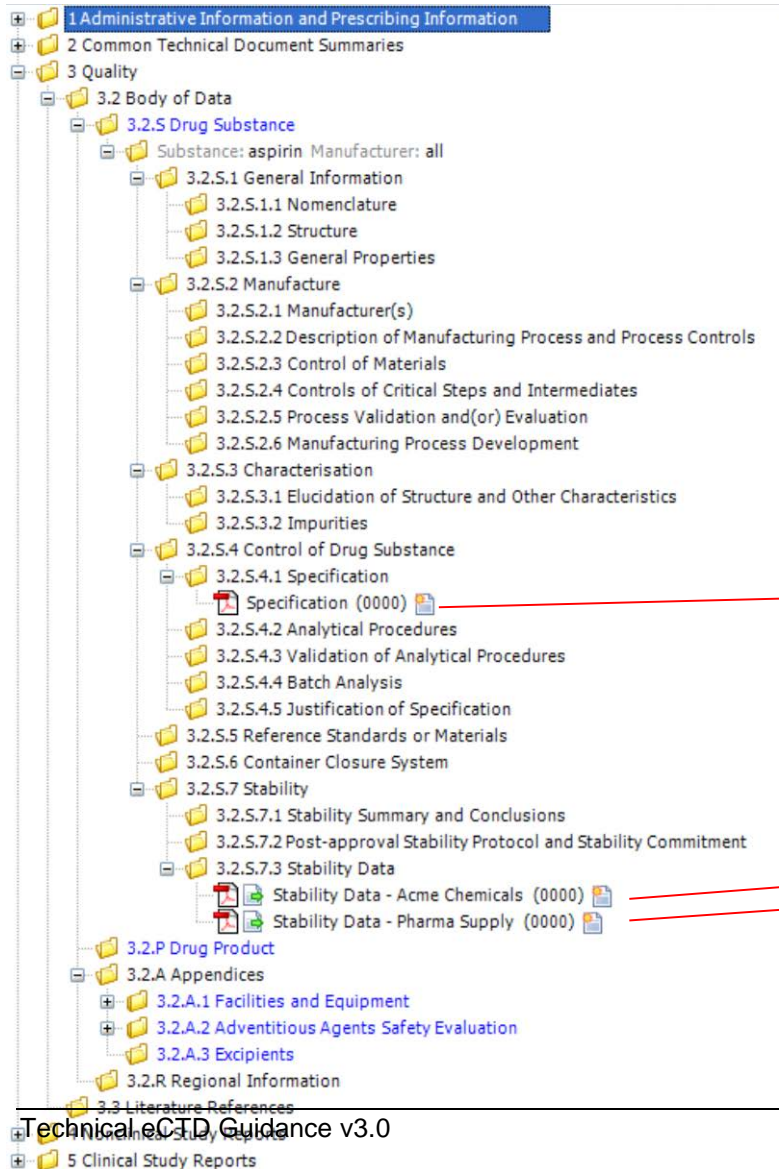
Arrows indicate destination of xlink:hrefs

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

XML   **Files and Folders (directory)**
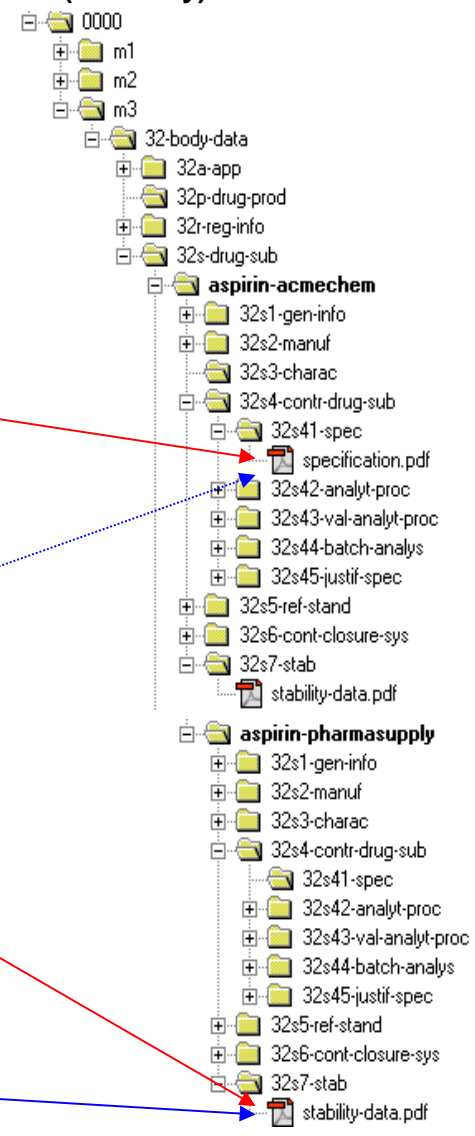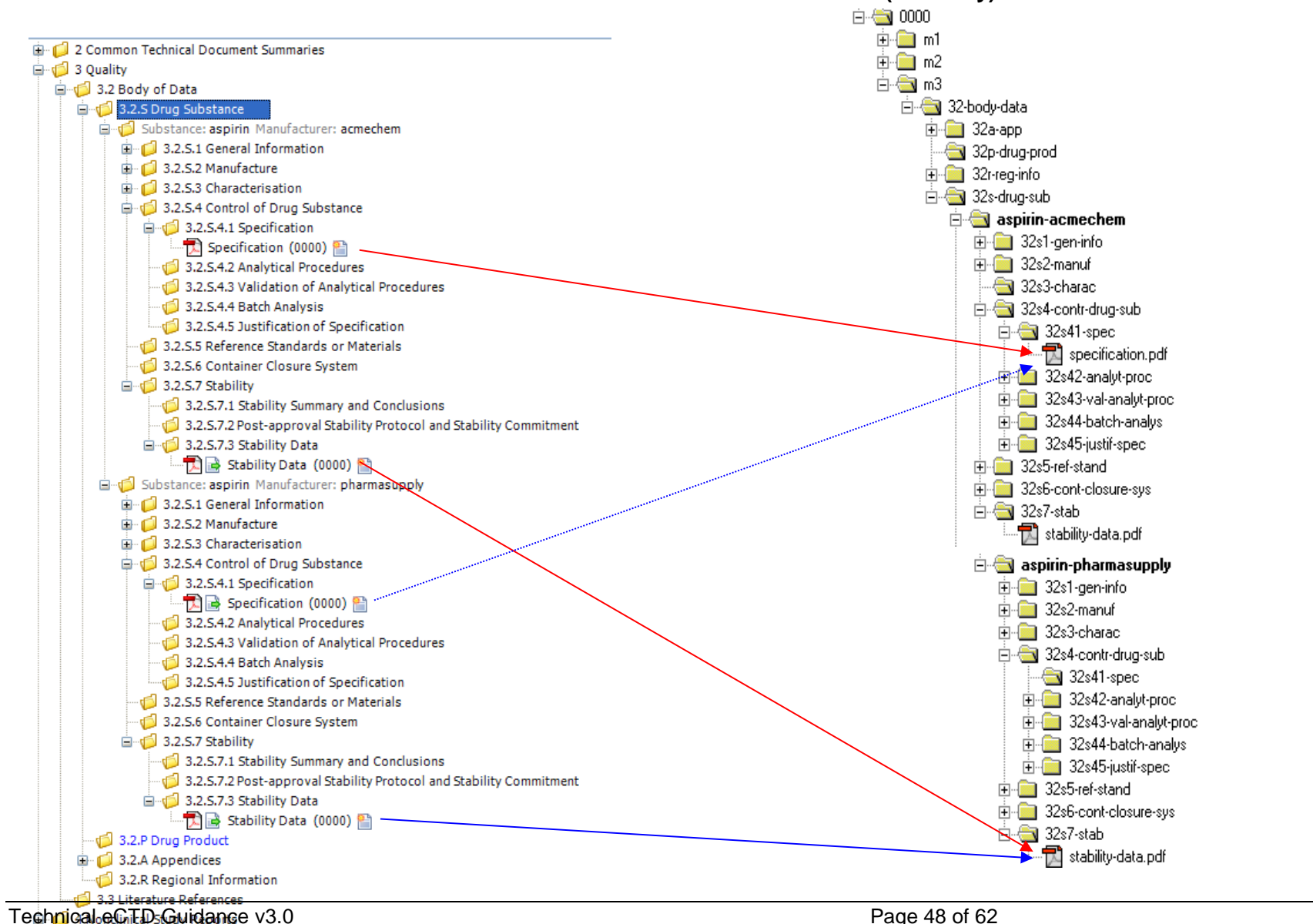
A3-3.3 Drug Product (32p) – Product/Dosage Form/Manufacturer
The use of these attributes is optional. Refer to IICH eCTD Q&As #68, 69 and 70 for guidance.

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 take into consideration that trade names can occasionally 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 4.

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

Figure 4 (A3) : Approach 1 – One 32p for all Strengths, any strength specific documents identified by the XML title, not by adding an additional XML section
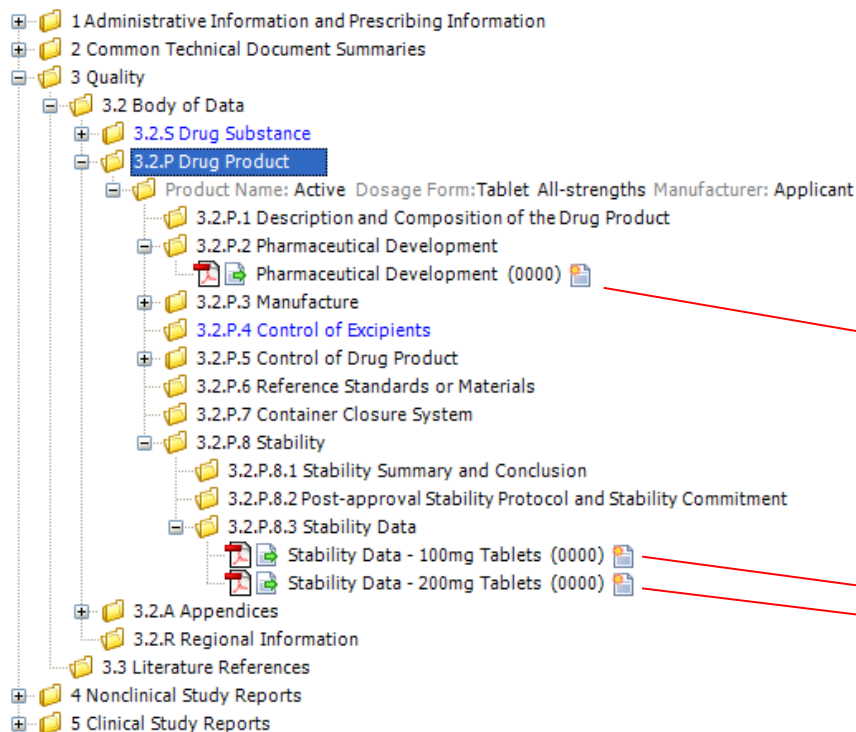
XML   **Files and Folders (directory)**
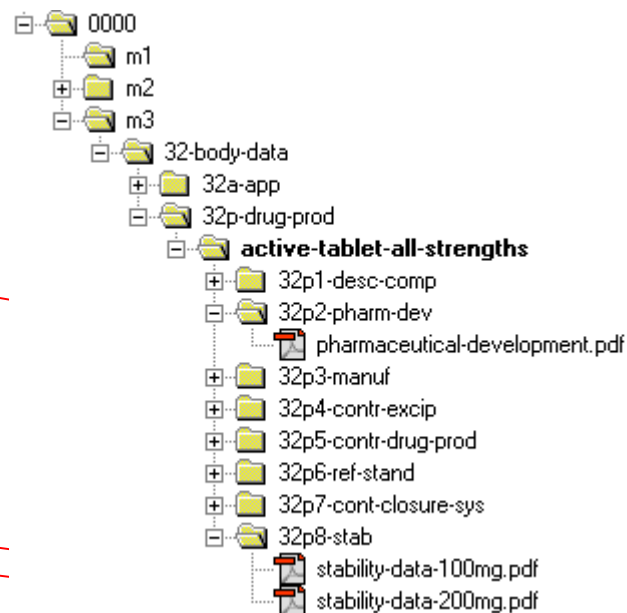
Note: The use of the term 'all-strengths' will mean that if the applicant subsequently submits a line extension for an additional strength (e.g. 1000mg) where the documentation is significantly different, and approach 2 is preferred for the new strength, then the attribute 'all-strengths' will not include 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 5.

Figure 5 (A3) : 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)**
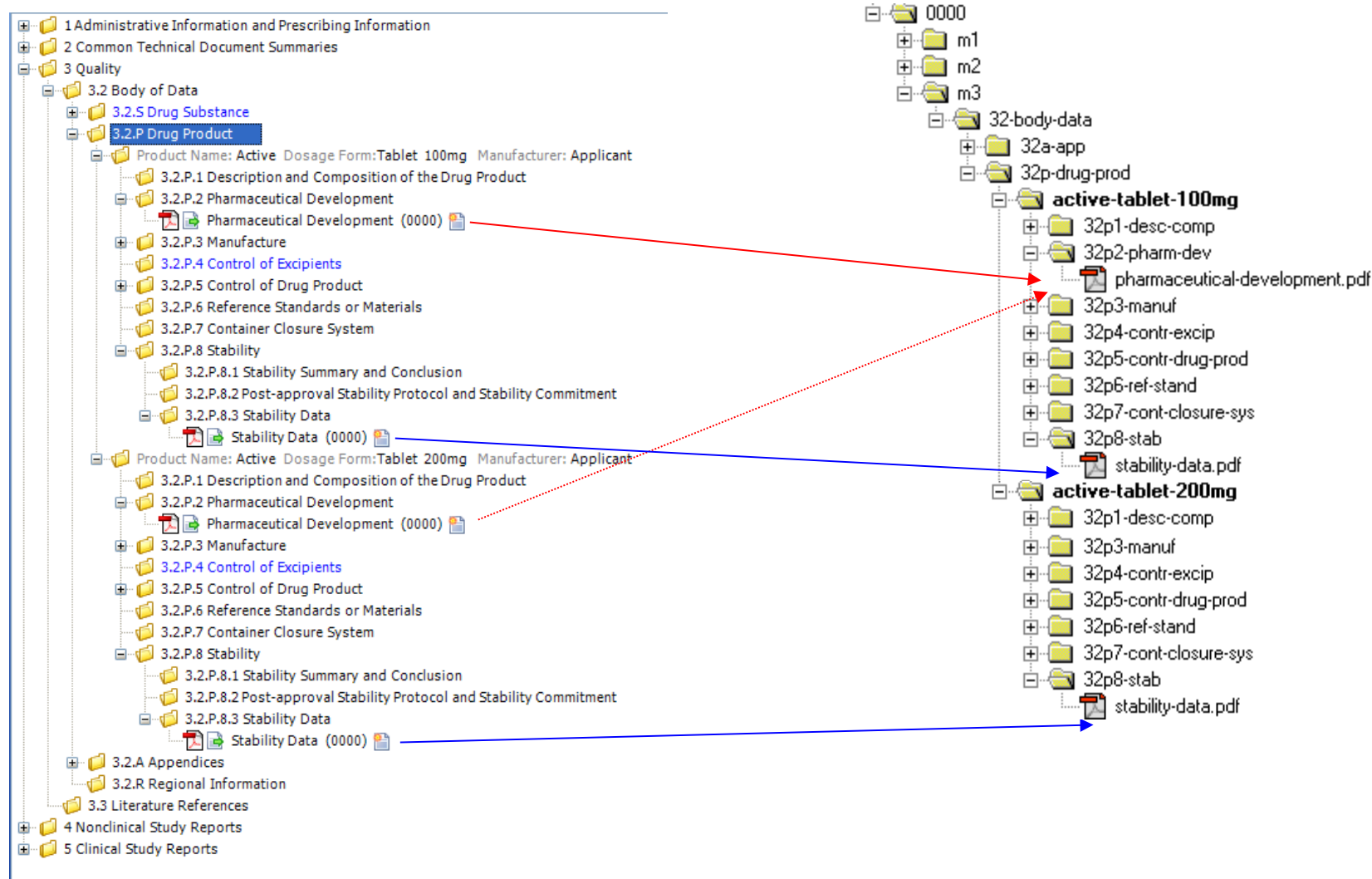
A3-3.4   Excipients

The use of these attributes is optional. It is recognised that the current versions of the EU validation criteria for NeeS and eCTD do not allow for files to be placed directly into 3.2.P.4. This will be changed the next time the criteria are updated. In the meantime, applicants should note that the criterion governing file names for eCTD, 15.BP3, is a Best Practice criterion only, and, as such, applicants are able to use the structures recommended by ICH in Q&A 73. However, for NeeS, the equivalent criterion (2.11) is a Pass/Fail criterion, and, until the validation criteria are updated, applicants submitting NeeS will have to adhere to the current EU file naming rules, which do not allow a single file in 3.2.P.4.

Detailed guidance is provided in the ICH eCTD IWG Question and Answer and Specification Change Request Document, Q&A #73.

A3-3.4.1 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.

Annex 4 – Management of Parallel Variations in the eCTD

A4-1   Background

Parallel variations are variations on-going within a single product lifecycle at the same point in time that are modifying the same content. Tracking these variations and modification of the content representing the current-approved baseline represents a particular business challenge within eCTD.

This annex presents the recommended approach for managing parallel variations in accordance with the ICH and EU eCTD Specifications.

A4-2   Business Challenge

Parallel variations occur when more than one variation is submitted modifying the same approved content, the first of which has not been approved before the next is submitted. Upon approval of one of the variations, the approved content has changed. The remaining pending variations contain proposed content that may be based upon the originally approved content or on the newly approved content. The applicant must track each separate approval, and update the content for each pending variation.

The specific challenges associated with this sequence of events are as follows:
   (i)   Tracking the approved content
   (ii)   Tracking separate on-going variations
   (iii)   Tracking individual or combined approvals for each variation

A4-3   Best Practice

Two options are described in this Q&A. Option 1 is the classic approach to eCTD lifecycle management, where a single document is replaced by a different, updated version, at the initial submission. Option 2 involves leaving the 'approved' content in the eCTD, but introducing 'proposed' documents into the lifecycle, until the outcome of the assessment is clear, and only then replacing the original 'approved' content. This Q&A can provide no guidance on when to use the technique described in option 2, and when to assume that a variation is not happening in parallel, and therefore to use option 1, submitting the proposed content as a leaf with the 'replace' operation attribute. Applicants need to consider whether or not it would be appropriate to use the one or the other option outlined in this guidance on a case by case basis.

A4-4   Description of Figures

Sequence numbers, with related sequence in	

eCTD Leaf Title Attribute and Operation Attribute in brackets

	MAA
0000 (related sequence – none)	Leaf Title (**Operation Attribute**)
0001(related sequence – none)	Leaf Title (**Operation Attribute**)
eCTD Viewer Current View	
0000	Document 1 (**New**) (0000)

The red cross indicates the target of the modified file

How the sequences would appear in an eCTD Viewer in 'current view'
Note – other views may be available,

Figure 6 (A4): Description of elements

A4-4.1   Use of one Lifecycle (Option 1)
This option describes the classic eCTD lifecycle management approach, where existing content is replaced with revised content. When there is only one change and variations do not occur in parallel, and the change is approved, the advantage of this approach is that applicants do not have to follow up with another 'consolidation' sequence after approval, because they have already replaced the content and the current view of the eCTD will be correct.

Figure 7 (A4) : Use of one document lifecycle

	MAA & Variations
0000 **(MAA)** (related sequence – none)	Document 1 (**New**)
0001 (Variation 1) (related sequence – none)	Document 1 Proposal 1 (**replace**)
0002 (Variation 2) (related sequence – none)	Document 1 Proposal 2 (**replace**)
	eCTD Viewer Current View
0000	Document 1 (**New**) (0000)
0000 - 0001	Document 1 Proposal 1 (**replace**) (0001)
0000 - 0002	Document 1 Proposal 2 (**replace**) (0002)

A4-4.1.1 Drawbacks of Option 1
Approval Status and Clarity on the Basis for Further Changes
If option 1 is used, and the most recently submitted document is replaced, regardless of its regulatory status, then it becomes unclear what has been approved, and therefore what the

changes in the incoming new submission are based upon. In this example, it is unclear whether Proposal 2 is based on the content from Proposal 1 or the content from the original Document 1 in sequence 0000. Therefore, when using this approach, if a second variation is submitted before the first is finalised, applicants should specify which document the changes in the second variation are based on.

Impact of Regulatory Outcome
If the operation attribute 'replace' is used in each variation as described in Figure 1, then depending on the progress of the review/approval/rejection of each variation, the eCTD lifecycle may not correctly represent the current or most appropriate lifecycle. For example, if variation 2 were to be approved first, the documentation of variation 1 where changes were based on the content in sequence 0001 may no longer be displayed appropriately. If variation 1 is rejected, and variation 2 was based on changes versus the content in variation 1, the content of variation 2 might be difficult to evaluate.

If either variation 1 or 2 (or both) is rejected, a new sequence has to be submitted reflecting only the approved content.

One advantage of this approach is that if both variations are approved, no additional sequence has to be submitted.

A4-4.2   Creation of separate Approved and Proposed Document Lifecycles (Option 2)

This option can be used in any situation where parallel variations are expected, but this is specifically recommended when submitting labelling changes in the Centralised Procedure, and the terminology used here is therefore specific to the SmPC in Centralised applications. When an applicant expects parallel variations to be submitted, the proposed document for the variation is not submitted as a replacement of the original (approved) content. Instead of using operation attribute "replace", a new document lifecycle is created for each proposed document by submitting it with a title identifying its proposed status and a very brief description of the change being proposed, and an operation attribute of "new". Proposed content submitted in this way can only be submitted as a "new" document, or replace other proposed content in the same location. The approved content in this CTD section has a separate lifecycle, and has a title indicating it is the approved document. This means that eCTD viewing tools will allow viewing of both the approved and proposed content alongside each other in the eCTD "current" view. Specifically, for the m1.3.1 section of the dossier in the Centralised Procedure 'approved' documents are labelled with either 'Final Opinion' or 'Commission Decision' in the leaf title, depending on the stage of the review that resulted in the final agreed labelling. Variations are then submitted as 'new' documents, not replacing this approved content, with appropriately descriptive leaf titles, for example, "Type II Variation Section 4.4 Update June 2012 - Proposed".

A4-4.2.1 Addition of further proposed Document Lifecycles (parallel variations)

If, during the review of the first variation, there is a subsequent variation that also proposes changes to the same content, this is also submitted with an operation attribute of "new", and a title indicating that the document being provided is another proposal. The document submitted in the second proposal should reflect changes made versus the current approved document (in this example, the current decision); the document does not contain the changes from Variation 1. The leaf title should differentiate it from the former proposed document from the previous variation. Assigning descriptive title attributes will allow the proposed document in each variation to be identified by viewing tools displaying the "current" view.

Figure 7 illustrates how the "current" view is able to display each of two parallel variations, when the title attribute is specific to the variation and the operation attribute "new" is used as described.

Figure 8 (A4) : Use of separate document lifecycles with different title attributes

	Original MAA	**Final Opinion or Decision Only**	**Variation 1**	**Variation 2**
0000 (rel sequence – none)	Proposed SmPC (**New**)			
0001 (rel sequence – 0000)	RTQ 120 changes to SmPC (**Replace**)			
0002 (rel sequence – 0000)	RTQ 180 changes to SmPC (**Replace**)			
0003 (rel sequence – 0000)		SmPC (English) Decision Jan 2012 (**Replace**)		
0004 (rel sequence – none)			Type II Variation Section 4.4 Update June 2012 - Proposed (**New**)	
0005 (rel sequence – none)				Type II Variation Section 4.6 Update July 2012 - Proposed (**New**)
	eCTD Viewer Current View			
0000	Proposed SmPC (**New**) (0000)			
0000 - 0001	RTQ 120 changes to SmPC (**Replace**) (0001)			
0000 - 0002	RTQ 180 changes to SmPC (**Replace**) (0002)			
0000 - 0003	SmPC (English) Decision Jan 2012 (**Replace**) (0003)			
0000 - 0004	SmPC (English) Decision Jan 2012 (**Replace**) (0003) Type II Variation Section 4.4 Update June 2012 – Proposed (**New**) (0004)			
0000-0005	SmPC (English) Decision Jan 2012 (**Replace**) (0003) Type II Variation Section 4.4 Update June 2012 – Proposed (**New**) (0004) Type II Variation Section 4.6 Update July 2012 - Proposed (**New**) (0005)			

A4-4.2.2 Upon Approval of a Single Variation – Deletion and Replacement

Upon approval of any variation, the proposed content is deleted, and the original (approved) content is replaced with a document containing the revised content. Current view will then show the newly approved content, but also any outstanding proposals, as shown in Figure 8and Figure 9. This additional sequence should be considered part of the same regulatory activity as the proposal that has been approved.

Figure 9 (A4) : Replacement of approved content by newly approved content, and deletion of proposed content

In this example, commission decision received in December 2012 incorporates the changes from the Type II variation submitted in sequence 0004 only. The changes from the Type II variation in sequence 0005 are still under review. In sequence 0006, the 'proposed' label from the first variation is deleted and the new commission decision is provided, replacing the original commission decision from sequence 0003. The content of the second variation is also amended in sequence 0006, to reflect the newly approved content in section 4.4, alongside the still unapproved change in section 4.6, and left in the lifecycle as an outstanding proposal.

	MAA	Final Opinion or Decision Only	Variation 1	Variation 2
0003 (rel sequence – 0000)		SmPC (English) Decision Jan 2012 (**Replace**)		
0004 (rel sequence – none)			Type II Variation Section 4.4 Update June 2012 - Proposed (**New**)	
0005 (related sequence – none)				Type II Variation Section 4.6 Update July 2012 - Proposed (**New**)
0006 (rel sequence – 0004, 0005)		SmPC (English) Decision Dec 2012 (**Replace**)	Type II Variation Section 4.4 Update June 2012 - Proposed (**Delete**)	Type II Variation Section 4.6 + inclusion of approved Type II Variation Section 4.4 Update Dec 2012 – Proposed (**Replace**)
	eCTD Viewer Current View			
0000 - 0005	SmPC (English) Decision Jan 2012 (**Replace**) (0003) Type II Variation Section 4.4 Update June 2012 - Proposed (**New**) (0004) Type II Variation Section 4.6 Update July 2012 - Proposed (**New**) (0005)			
0000 - 0006	SmPC (English) Decision Dec 2012 (**Replace**) (0006) Type II Variation Section 4.6 Update Dec 2012 - Proposed (**Replace**) (0006)			

Figure 10 (A4) : Progression on the 2nd Parallel Proposal

In this example, as the procedure progresses, the proposed change to section 4.6 needs to be further amended as a result of the regulatory review (e.g. updated wording as suggested by the assessor), and this amendment is done with a replacement document in sequence 0007. Once a decision is reached, another sequence, 0008, is submitted, including the new decision replacing the one submitted in sequence 0006, and a deletion of the section 4.6 proposal, as amended by sequence 0007.

	MAA	Final Opinion or Decision Only	Variation 1	Variation 2
0003 (rel sequence – 0000)		SmPC (English) Decision Jan 2012 (**Replace**)		
0004 (relsequence – none)			Type II Variation Section 4.4 Update June 2012 - Proposed (**New**)	
0005 (rel sequence – none)				Type II Variation Section 4.6 Update July 2012 - Proposed (**New**)
0006 (rel sequence – 0004, 0005)		SmPC (English) Decision Dec 2012 (**Replace**)	Type II Variation Section 4.4 Update June 2012 - Proposed (**Delete**)	Type II Variation Section 4.6 + inclusion of approved Type II Variation Section 4.4 Update Dec 2012 – Proposed (**Replace**)
0007 (rel sequence – 0005)				Type II Variation Section 4.6 + inclusion of approved Type II Variation Section 4.4 Update January 2013 – Proposed (**Replace**)
0008 (rel sequence – 0005)		SmPC (English) Decision Mar 2013 (**Replace**)		Type II Variation Section 4.6 + inclusion of approved Type II Variation Section 4.4 Update January 2013 – Proposed (**Delete**)
	eCTD Viewer Current View			
0000 - 0006	SmPC (English) Decision Dec 2012 (**Replace**) (0006) Type II Variation Section 4.6 Update Dec 2012 - Proposed (**Replace**) (0006)			
0000 - 0007	SmPC (English) Decision Dec 2012 (**Replace**) (0006) Type II Variation Section 4.6 Update Jan 2013 - Proposed (**Replace**) (0007)			
0000-0008	SmPC (English) Decision Mar 2013 (**Replace**) (0008)			

A4-4.2.3 Approval of Multiple Variations at the Same Time

There will be occasions where multiple changes are approved at the same time, or within a very short time period. In these instances, it would not be appropriate to submit separate 'approved'

content for each variation; instead, a consolidated document representing all the approved changes should be submitted. This would replace the existing 'approved' content. The eCTD sequence containing the new approved content would also contain leaves deleting the relevant 'proposed' documents, as illustrated in Figure 5.

Figure 11 (A4) : Replacement of approved content by newly approved content, and deletion of multiple proposed documents

In this example, commission decision received in December 2012 incorporates the changes from the Type II variation submitted in sequence 0004, and also the changes from the Type II variation in sequence 0005. In sequence 0006, both 'proposed' documents from the variations are deleted and the new commission decision is provided, replacing the original commission decision from sequence 0003. This leaves only the latest commission decision from sequence 0006 in the current view.

	MAA	Final Opinion or Decision Only	Variation 1	Variation 2
0003 (related sequence – 0000)		SmPC (English) Decision Jan 2012 (**Replace**)		
0004 (related sequence – none)			Type II Variation Section 4.4 Update June 2012 - Proposed (**New**)	
0005 (related sequence – none)				Type II Variation Section 4.6 Update July 2012 - Proposed (**New**)
0006 (related sequence – 0004 & 0005)		SmPC (English) Decision Dec 2012 (**Replace**)	Type II Variation Section 4.4 Update June 2012 - Proposed (**Delete**)	Type II Variation Section 4.6 Update July 2012 - Proposed (**Delete**)
	eCTD Viewer Current View			
0000 - 0005	SmPC (English) Decision Jan 2012 (Replace) (0003) Type II Variation Section 4.4 Update June 2012 - Proposed (**New**) Type II Variation Section 4.6 Update July 2012 - Proposed (**New**)			
0000 - 0006	SmPC (English) Decision Dec 2012 (**Replace**)			

A4-4.2.4 Rejections or Withdrawals

If any proposed changes are rejected or withdrawn by the applicant, then the applicant can provide a sequence deleting the "proposed" content document, but not providing any replacement for the original approved document.

A4-4.2.5 Typical Applications

An applicant is most likely to need to submit parallel variations on dossier content that changes more often, such as the SmPC or the Risk Management Plan (RMP[i]). However, this guidance is not limited to use in these parts of the dossier. Applicants should also note that many variations affecting the SmPC and RMP will not occur in parallel with another variation, and at times, when a variation is initially expected to be completed in isolation, a second parallel variation may become necessary at a later stage.

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.
2.x	KG, AN	Draft for Second revision, made the document in line with agreed text on Q&A, EU M1 Spec v2.0, and in the NeeS guidance and with the updated validation criteria, TIGes Harmonisation group 12/2012-07/2013
2.7	AN, KM	Following review comments edits have been included.
3.1	AN, KM, KG, KP	Preparing the revision to accommodate regulatory changes, improvements and clarifications, editions due to inconsistencies caused by revisions of the EU M1 spec. v3.0, eCTD validation criteria 6.0, eAF usage and further modifications
3.2	KM	Consolidating all changes and formatting modifications
3.3	HHMG	Reviewing modified sections and tiding up comments
3.4	KM	Preparation for publication

Reviewers

Version	Name	Organisation
1.0	TIGes	TIGes eCTD Topic Group
1.1-1.92	Members of the subgroup	TIGes Harmonisation group
1.93	Members of TIGes	TIGes
1.94	Members of the subgroup	TIGes Harmonisation group
2.0	Members of subgroup And the TIGes	TIGes
2.6	Members of the TIGes	TIGes
3.1	Members of HHMG	Human Harmonisation Maintenance Group
3.2	Members of EMA	EMA
3.3	HHMG / eSub CMB	Human Harmonisation Maintenance Group / eSubmission Change Management Board

Distribution

Version	Distributed to	Way of distribution
1.0	General public	Published on the EMA eSubmission website
1.1-1.92	Members of the Subgroup	E-mail April-July 2011
1.93	Members of the Subgroup and Members of TIGes	E-mail July 2011
1.94	Members of the Subgroup	E-mail August 2011
2.0	Members of the Subgroup and Members of TIGes	E-mail August 2011
3.0	Members of TIGes	E-mail August 2013 /
3.1	eSubmission CMB	E-mail December 2015
3.4	eSubmission CMB	E-mail March 2016

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 2011	Published at the EMA eSubmission website for use
3.0	2 September 2013	Published at the EMA eSubmission website for use
4.0	01. July 2016	Published at the EMA eSubmission website for use