Certification of Substances Department

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Certification of Suitability to the Monographs of the European Pharmacopoeia

Guidance for electronic submissions for Certificates of Suitability (CEP) applications

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1. Introduction

This document provides guidance for electronic submissions for Certificate of Suitability (CEPs) applications submitted to the EDQM. Information and requirements described in this document are intended to facilitate the handling and assessment of submissions for CEPs and to maintain their lifecycle even if the submission is not an eCTD.

2. Scope and general requirements

This guidance should be applied for all electronic submissions sent to EDQM in the context of applications for CEPs.

EDQM does not accept any paper applications. All submissions should be in electronic format.

The following electronic submission formats are accepted: PDF, NeeS, VNeeS and eCTD, but the acceptability of the format depends on the type of submission as described in section 3.

Changing the electronic format for a CEP application is possible at the start of a procedure (e.g. when applying for a revision or renewal). This means moving from PDF to NeeS or eCTD, or from NeeS to eCTD. Coming back to a previous submission format is not allowed (e.g. sending a NeeS submission when previously an eCTD submission was sent.)

3. Electronic submission formats

For new CEP applications, eCTD format is required (except for applications for the TSE risk and for substances for veterinary use only, see below).

For revisions, renewals and notifications, the following possible submission formats are accepted: eCTD or NeeS. Submissions in eCTD format are recommended by the EDQM.

The identification of the submission format type in the CEP application form is important.

Electronic files should be in accordance with specific Guidance for Industry on Providing Regulatory Information in Electronic Format (see the links in the sections below for each submission format).

All files should be in PDF and the folder and file-naming convention of ICH M2 eCTD Specification and EU Module 1 Specification should be applied. Other types of files are not accepted (Word, JPEG, Excel,...), with the exception of the files required for publishing an eCTD submission.

The use of attached files in a pdf file is not allowed nor are pdf files with active javascripts (form fields,…) or containing watermarks.

CEP applications for the TSE risk

The eCTD or NeeS submission format is not appropriate for CEP applications for the TSE risk, consequently, applicants are invited to submit a single PDF for Module 3, and adapt the directory structure/file naming as proposed in annex 1.

CEP applications for substances for veterinary use only

eCTD, NeeS (for revisions/renewals) or VNeeS format may be used for such products (see guidance available by the following link http://esubmission.ema.europa.eu/tiges/vetesub.htm).

3.1. eCTD submission format

The eCTD structure should be in accordance with the current versions of the related documents (specifications, guidance, etc.) available on the following websites:

- http://esubmission.ema.europa.eu
- http://estri.ich.org/eCTD/index.htm

It should be clarified that the eCTD CEP dossier remains, from a technical perspective, a ***standalone*** **dossier and is distinct from any marketing authorisation dossier and lifecycle.**

When submitting the first eCTD submission, an initial sequence 0000 should be provided. When switching from another submission format to eCTD, it is strongly recommended to include any information already assessed and approved previously in a "baseline" sequence 0000 (refer to section 5). If files or sections of the eCTD contain a lot of information, additional bookmarks or "levels of granularity" are recommended for facilitating the review (refer to annex 2). The use of bookmarks is allowed, especially when responding to an EDQM deficiency letter (responses to questions and supportive data).

Before submitting an eCTD to EDQM, it should be technically validated using an appropriate checker/validation tool. If pass/fail errors are detected during EDQM validation at receipt, the submission will be blocked or rejected.
The operation attributes chosen should be appropriate to allow the lifecycle of the submission (refer to section 5).

Building the envelope and module 1:

According to the current EU Module 1 specification (3.0.1 and 3.0.2 in January 2018) the envelope for a CEP application should be filled in as follows:

Element	Attribute	Description/Instructions
eu-envelope		
envelope		
	country	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. Refer to EU Module 1 Specification.
submission		
	type	cep
	mode	Blank
number		Blank
procedure-tracking		
	number	CEP application number or blank if not known (in the

		case of a new CEP application)
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. Refer to EU Module 1 Specification.
applicant		Holder/Intended Holder name for the CEP
agency		
	code	EU-EDQM
procedure		
	type	centralised
invented-name		Substance name
inn		International Non-proprietary Name, used to identify pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property.
sequence		This is the sequence number of the submission – this should start at 0000 for the initial submission, and then increase incrementally with each subsequent submission related to the same product e.g. 0000, 0001, 0002, 0003 etc.
related-sequence		This is the sequence number of previous submission(s) to which this submission relates e.g. the responses to questions to a particular variation. In the case of submission unit types 'initial' and 'reformat' related sequence is identical to the sequence number.
submission-description		This element is used to provide a free text description of the submission.

For existing sequences based on old DTD versions, the DTD version should ideally be changed at the start of a new regulatory activity.

The country code "edqm" should be selected for the application form and other documents in module 1, according to the current EU M1 Specification, available on the following website: http://esubmission.ema.europa.eu/eumodule1/index.htm

3.2. NeeS submission format

The NeeS structure and specification as well as the validation criteria should be in accordance with the guidance and documents available on the following website:

http://esubmission.ema.europa.eu/tiges/cmbdocumentation.html

The CTD file/directory structure and naming shall be implemented with the addition of a Table of Content(s) as appropriate.

If files or sections of the NeeS contain a lot of information, additional levels of granularity are recommended for facilitating the review (refer to annex 2).

4. Content and structure of an application

Annexes 3 and 4 describe how to structure a CEP application in eCTD or NeeS submission formats.

Annex 1 describes the recommended file/directory structure for the pdf submission format, for TSE applications only.

An application should contain 3 modules as described below:

In Module 1:

- Cover letter
- EDQM Application Form including signed declarations (as relevant)
- Information about the Expert, CV as relevant (for a new application)
- Responses: when responding to an EDQM deficiency letter, applicants should include a document/file listing the questions with the corresponding responses and supportive data.
- Additional data: a section/folder which may contain if relevant a toxicological report, a signed copy of a CEP, etc.
- Revisions: a completed comparative table (annex 7 to the application form) outlining the approved and proposed updated text of module 3.

In Module 2 (new CEP applications):

- Quality Overall Summary, prepared preferably using the EDQM template (the "Word" file template should be converted into a pdf file).

In Module 3:

- For a new CEP application: technical documentation structured in accordance with the CTD as defined by ICH guidance documents.
- Splitting the data between an Applicant's and a Restricted part is not encouraged for CEP applications, but if these are submitted, the EMA "Practical guidelines on the use of the eCTD format for ASMFs for Active Substance Master File Holders and Marketing Authorisation Holders" should be used as a basis; the CTD sections should be clearly identified with the part they belong to.
- **The use of annexes/attachments is not allowed in Module 3.**
- For a response to an EDQM deficiency letter, or for a notification/revision/renewal application, the module 3 should be updated as described under section 5. Updated sections should be in line with the granularity chosen in the initial submission.
- Any changes to a previous sequence should be highlighted and shall allow printing.

5. Lifecycle management of applications

For the lifecycle of a CEP application, it is necessary to have at any time a current view of the approved dossier, and to maintain an appropriate granularity. Applicants are requested to implement the following requirements, which will be checked at receipt at EDQM.

5.1 Granularity

Large sections should be subdivided into smaller parts. For example, the CTD sections 3.2.S.2, 3.2.S.3 and 3.2.S.4 should be subdivided into subsections according to annex 2. It is important that the dossier can be easily navigated. The addition of too many subsections to Module 3 can result in the dossier being difficult to navigate and may result in blocking at receipt, thus delaying its treatment.

5.2 Updated sections

Any update of a CEP application (eg. response to EDQM deficiency letters or requests for revision) should include the related updated sections and the level of granularity of the data submitted should be in line with the level chosen in the last procedure (see annex 2). Updated pages only are not accepted (except if the complete CTD section is on one page).

For each update of the dossier and whatever the submission format, the following instructions should be implemented:

- Responses to an EDQM deficiency letter: Module 1 and 3 should be updated. Module 1 should contain the responses to the questions and supportive data; in Module 3 the complete updated sections affected by the Questions & Answer process should be included (with the changes highlighted if applicable).

- Notifications or requests for revision/renewal: Module 1 and 3 should be updated. All sections from Module 3 affected by the proposed change(s) at the relevant granularity level should be updated and the changes highlighted. A comparative table of the approved & proposed data should be given in Module 1.

Specific instructions apply also, depending on the submission format chosen:

- **For an eCTD:** for each update a new sequence 000(X+1) should be provided containing Modules 1, 3 as appropriate, with updated files in the relevant sections, using the same structure and granularity as the original submission. The files should have the appropriate operation attributes: "New", "Replace", "Delete". The use of the "Append" attribute should be avoided since it leads frequently to lifecycle difficulties.

- **For a NeeS**: the Modules 1, 3 should be provided as appropriate, with updated files in the relevant sections, using the same structure and granularity as the original submission, and with a table of content.

- **For a PDF**: in Module 3, the updated sections should be supplied in one single pdf file, and the bookmarks should be in line with the original granularity of the dossier.

Only the necessary updated information should be sent, and no other changes to the content of the dossier should be introduced. Failure to submit a complete

documentation set in the appropriate modules and sections will block the assessment process and may ultimately lead to blocking or rejecting the application at receipt.

5.3 When to submit a baseline Module 3?

An electronic "baseline" Module 3 is a consolidated picture of all the CTD sections corresponding to the regulatory information that has already been submitted and approved. If no baseline has been submitted so far, applicants are strongly encouraged to submit a baseline application to EDQM to facilitate the management of its lifecycle for both the applicants and the EDQM.

It is strongly recommended to submit a baseline Module 3 in the following circumstances:

- Switch from a paper to an e-submission
- Switch from a pdf/NeeS to an eCTD

It is strongly recommended to submit a baseline Module 3 at the time of a renewal, a revision or a notification.

On the other hand *a baseline Module 3 will not be accepted* during the course of a procedure (e.g. when responding to a deficiency letter or any other information requested), nor when it is not linked to a regulatory activity (revision/renewal/notification).

6. Validation by the EDQM

At receipt of a submission by EDQM, a validation step is performed. Validation includes verification of the submission format, compliance with the requirements described in this guidance document and in EU validation rules for NeeS and eCTD. The most frequent issues which may lead to block a dossier at receipt and consequently delay the start of assessment are summarised in Annex 5.

7. Routes (or pathways) of submission

Electronic submissions should be submitted through the **"Common European Submission Portal" (CESP).** Users should first register with the CESP (https://cespportal.hma.eu) before sending submissions to the EDQM.

8. Security

The files submitted should not have any password protection, encryption or other security settings; such files will not be accepted at the validation phase at EDQM. The applicant should check any electronic submission for absence of virus before sending it to EDQM.

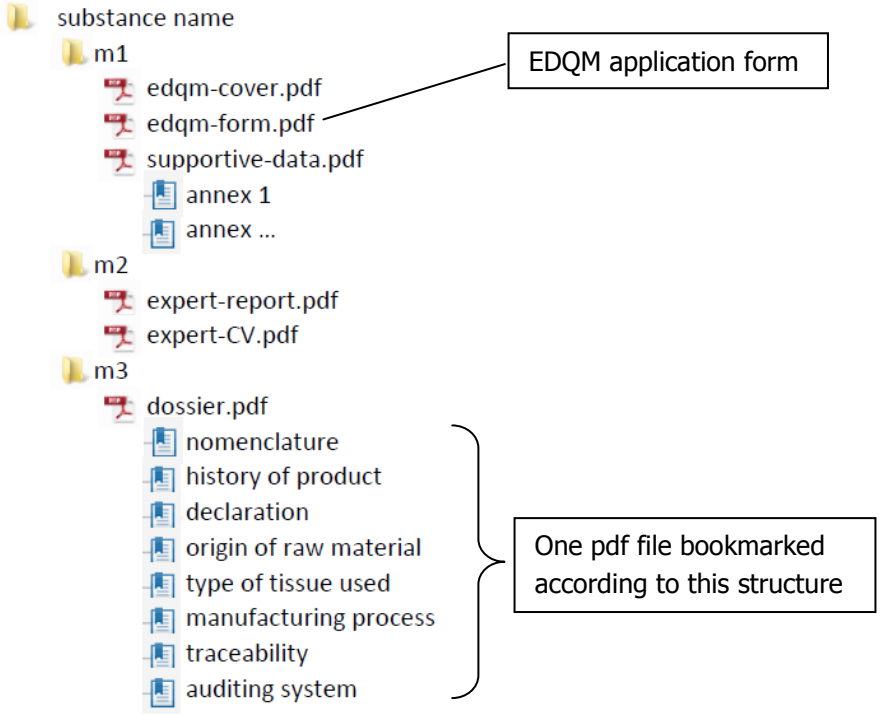
The EDQM guarantees the security and confidentiality of data from receipt.

Annexes:

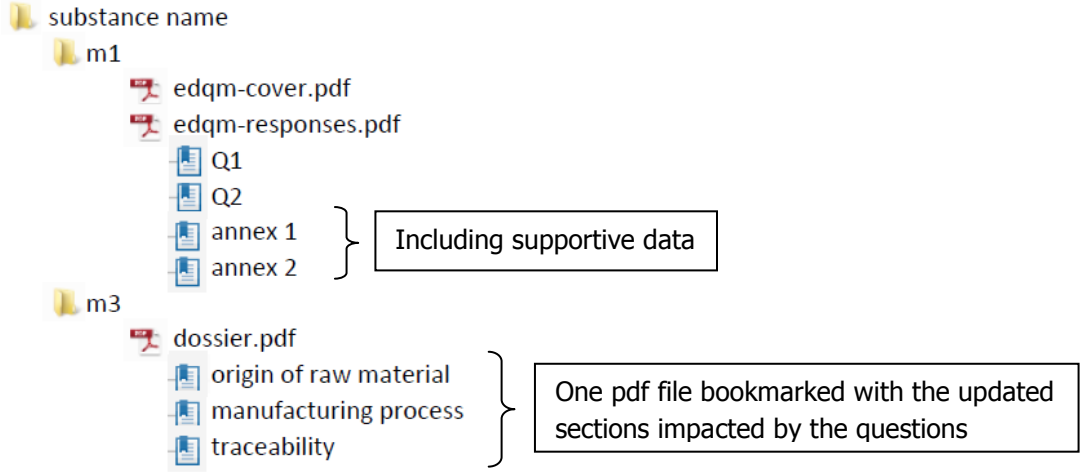
ANNEX 1: Directory structure/file naming for TSE applications

= bookmark

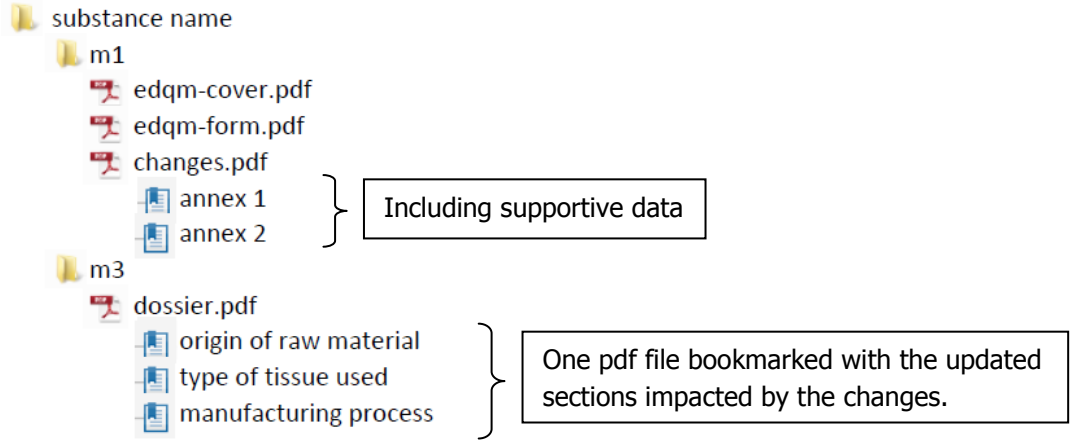
NEW APPLICATION



RESPONSE TO DEFICIENCY LETTER



REVISION/NOTIFICATION/RENEWAL

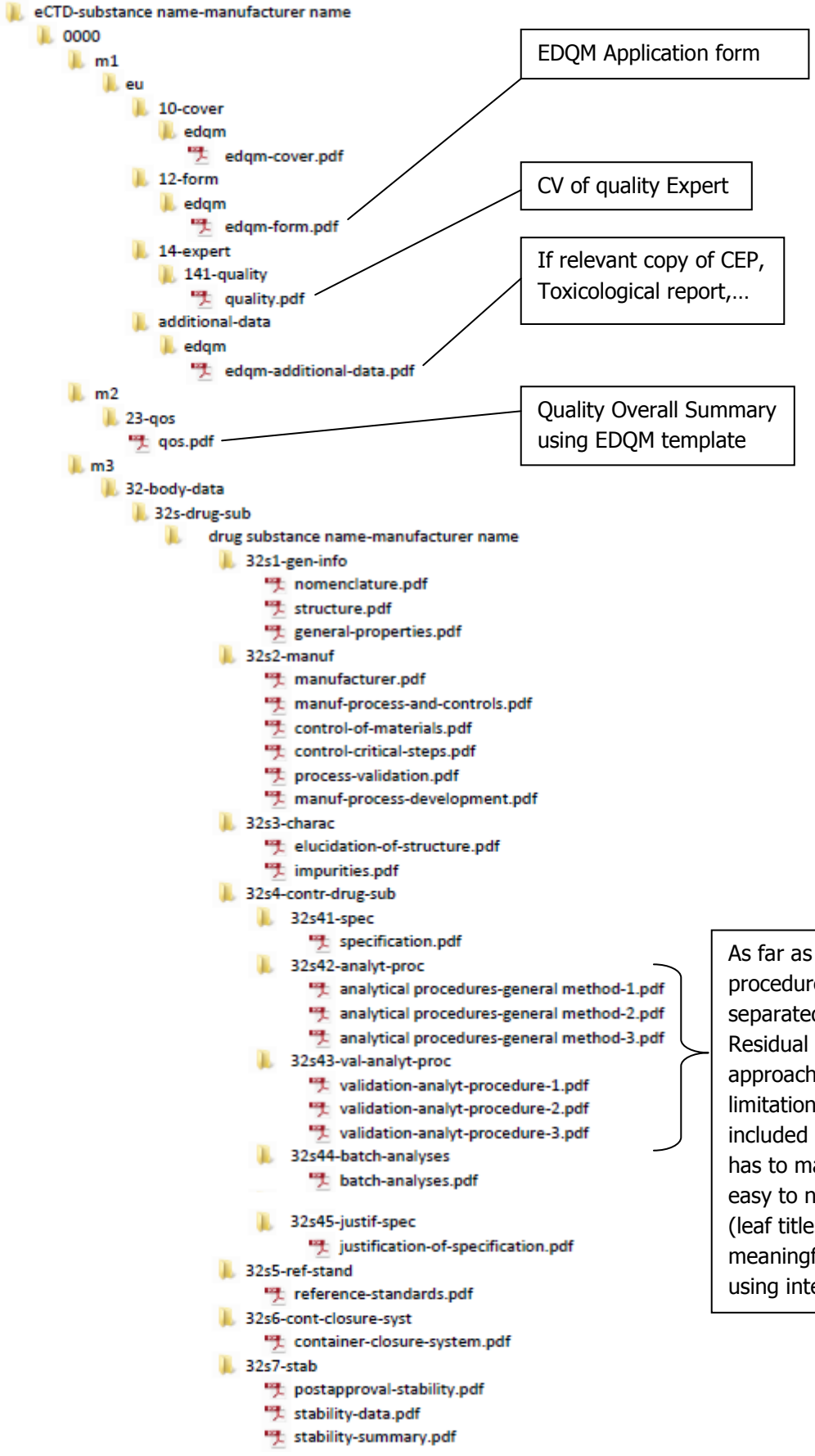


ANNEX 2: Recommended granularity levels

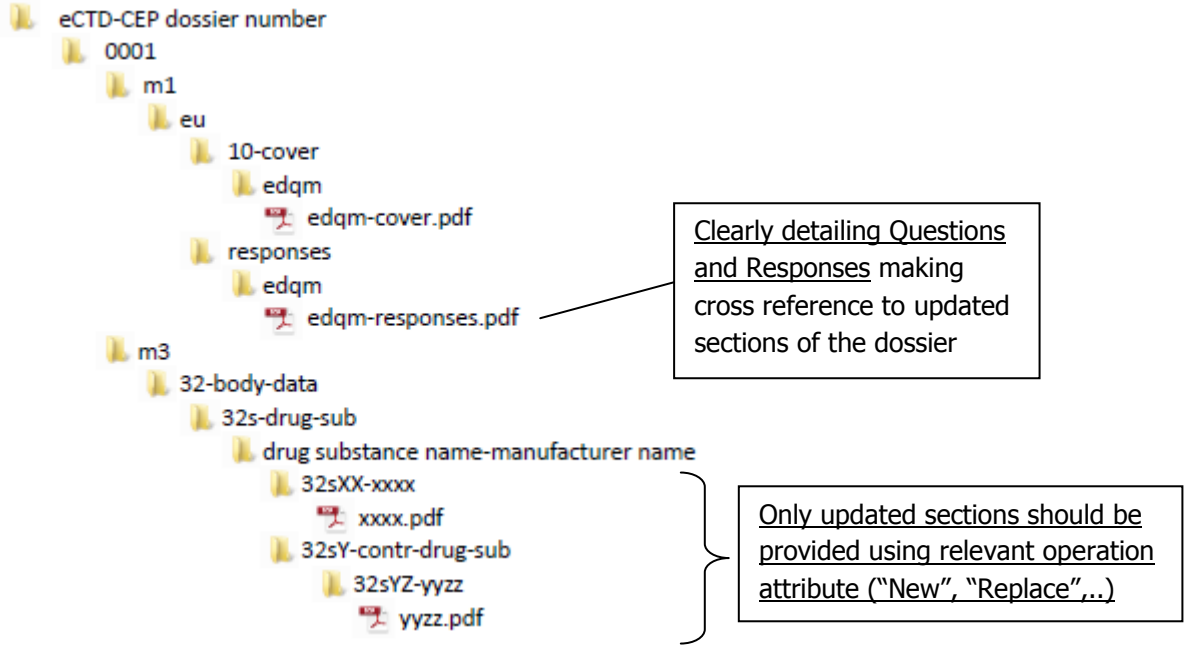
Granularity required				Acceptability A = accepted R = Recommended NA = Not accepted
Level 1	**Level 2**		**Level 3**	
3.2.S.1	General Information			A
	3.2.S.1.1	Nomenclature		R
			3.2.S.1.1.X	NA
	3.2.S.1.2	Structure		R
			3.2.S.1.2.X	NA
	3.2.S.1.3	General Properties		R
			3.2.S.1.3.X	NA
3.2.S.2	Manufacture			NA
	3.2.S.2.1	Manufacturer(s)		R
			3.2.S.2.1.X	A
	3.2.S.2.2	Description of Manufacturing Process and Process Controls		R
			3.2.S.2.2.X	A
	3.2.S.2.3	Control of Materials		A
			3.2.S.2.3.X	R
	3.2.S.2.4	Controls of Critical Steps and Intermediates		R
			3.2.S.2.4.X	A
	3.2.S.2.5	Process Validation and/or Evaluation		R
			3.2.S.2.5.X	A
	3.2.S.2.6	Manufacturing Process Development		R
			3.2.S.2.6.X	A
3.2.S.3	Characterisation			NA
	3.2.S.3.1	Elucidation of Structure and other Characteristics		R
			3.2.S.3.1.X	A
	3.2.S.3.2	Impurities		R
			3.2.S.3.2.X	A
3.2.S.4	Control of Drug Substance			NA
	3.2.S.4.1	Specification of Drug Substance		R
			3.2.S.4.1.X	A
	3.2.S.4.2	Analytical Procedures		R
			3.2.S.4.2.X	A
	3.2.S.4.3	Validation of Analytical Procedures		A
			3.2.S.4.3.X	R
	3.2.S.4.4	Batch Analyses		R
			3.2.S.4.4.X	A
	3.2.S.4.5	Justification of Specification		R
			3.2.S.4.5.X	A
3.2.S.5	Reference Standards or Materials			R
	3.2.S.5.X			A
3.2.S.6	Container Closure System			R
	3.2.S.6.X			A
3.2.S.7	Stability			NA
	3.2.S.7.1	Stability Summary and Conclusions		R
			3.2.S.7.1.X	NA
	3.2.S.7.2	Post-approval Stability Protocol and Stability Commitment		R
			3.2.S.7.2.X	NA
	3.2.S.7.3	Stability Data		R
			3.2.S.7.3.X	NA

ANNEX 3: eCTD structure for a CEP dossier

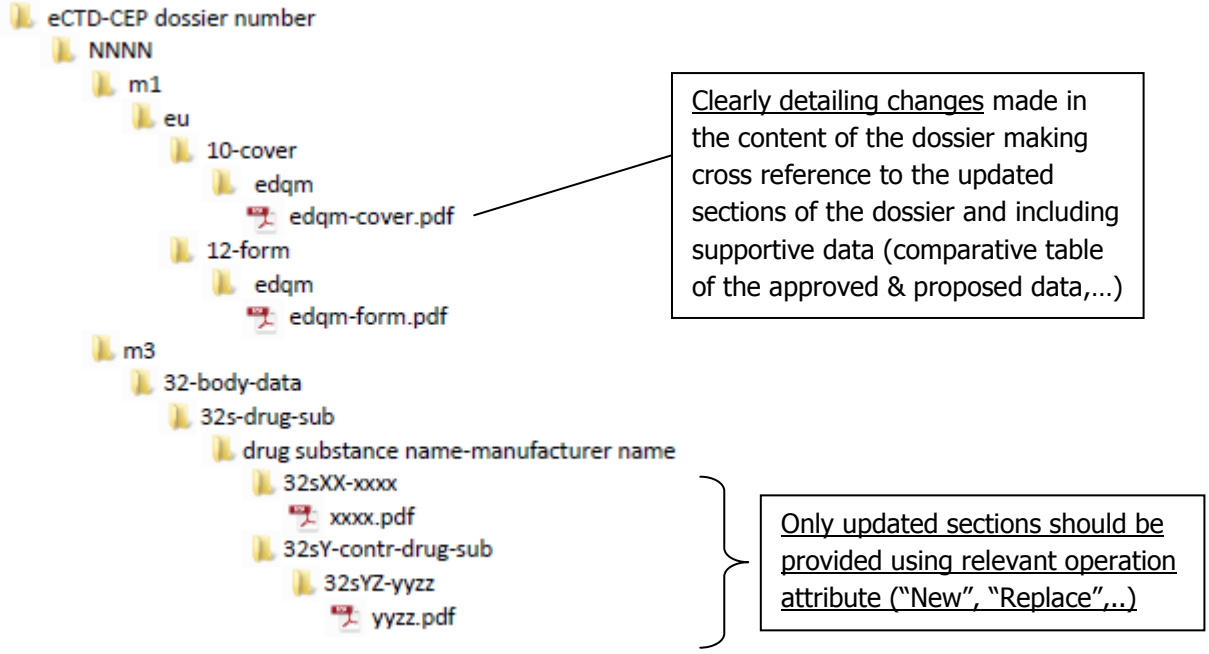
NEW APPLICATION (OR BASELINE) → SEQUENCE 0000



RESPONSE TO DEFICIENCY LETTER → SEQUENCE 0001

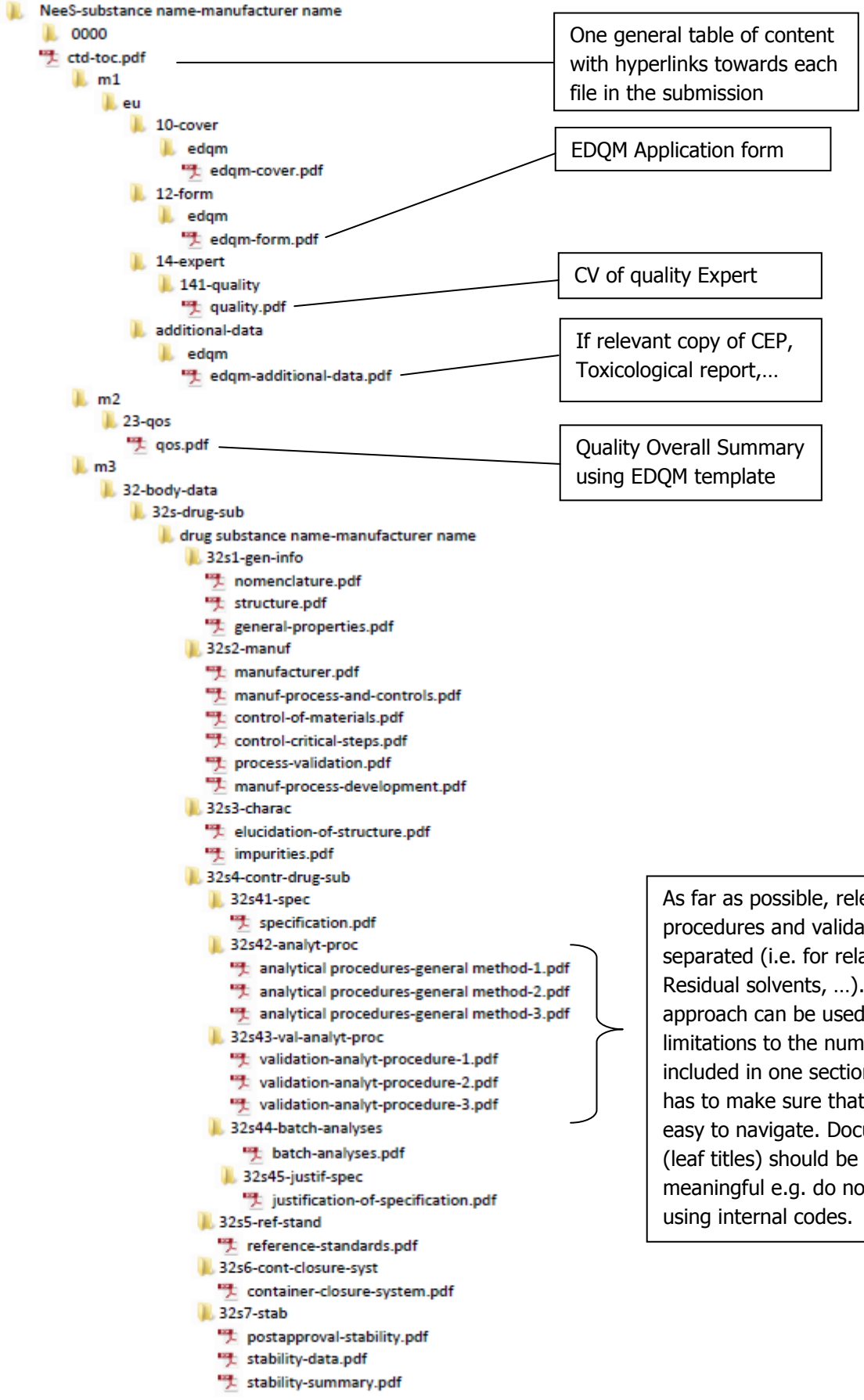


REVISION/NOTIFICATION/RENEWAL → SEQUENCE NNNN



ANNEX 4: NeeS structure for a CEP dossier

NEW APPLICATION (OR BASELINE) → SEQUENCE 0000



One general table of content with hyperlinks towards each file in the submission

EDQM Application form

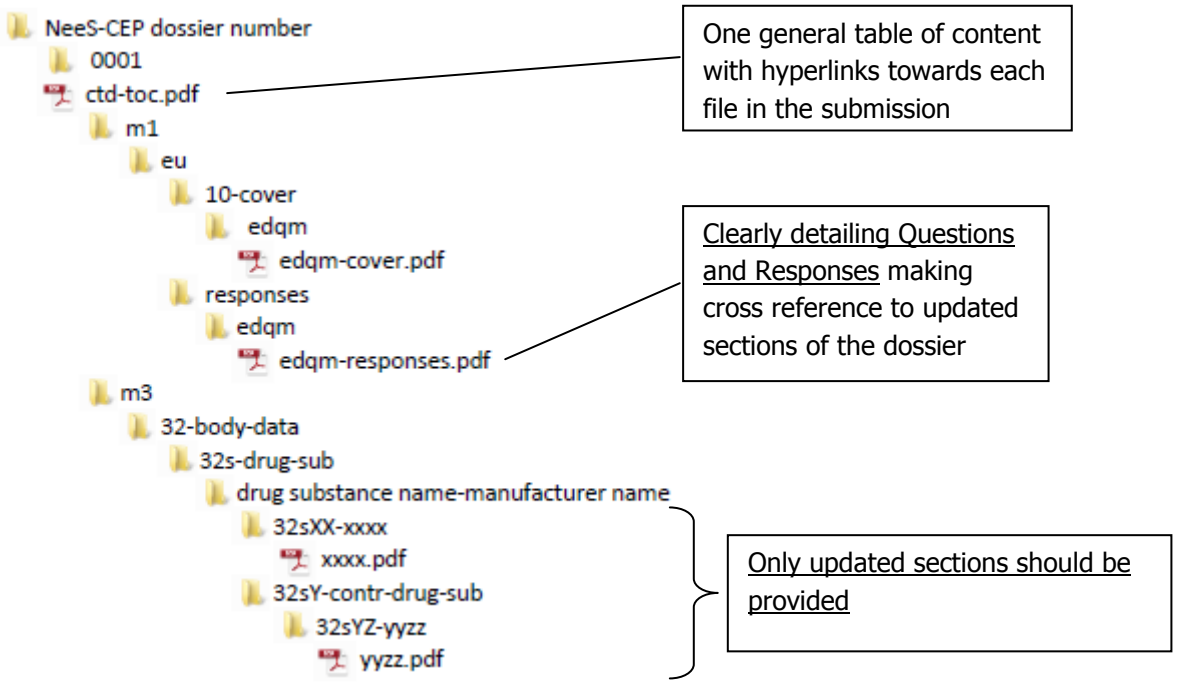
CV of quality Expert

If relevant copy of CEP, Toxicological report,…

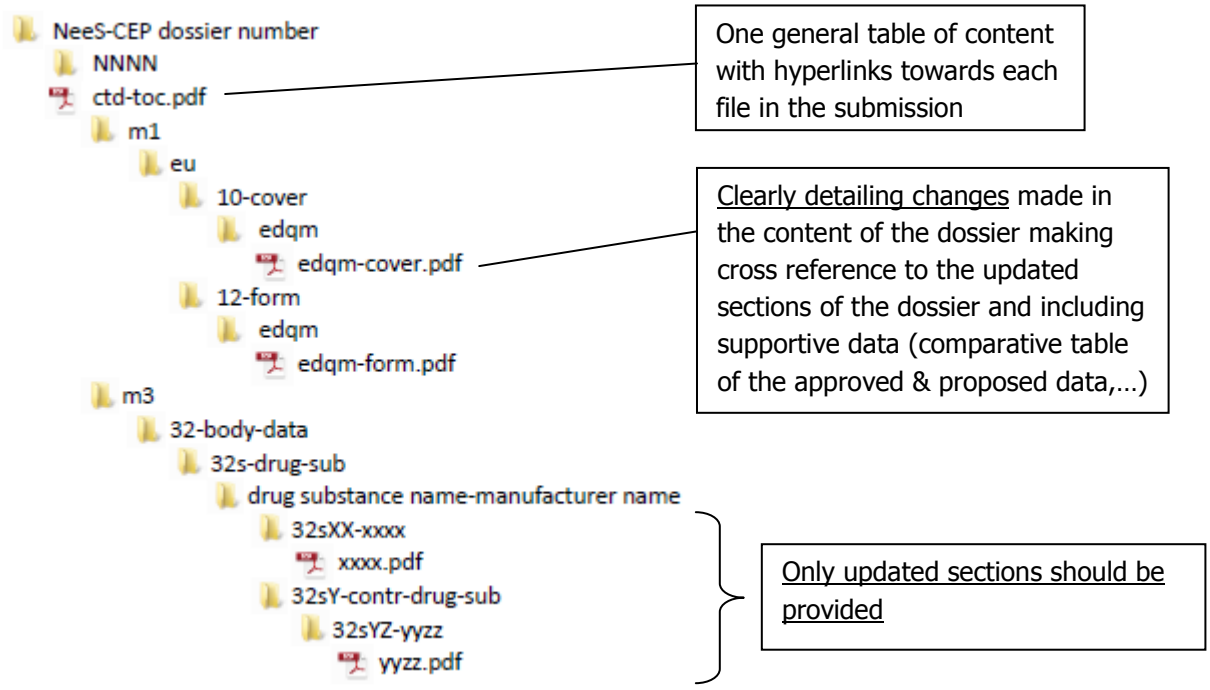
Quality Overall Summary using EDQM template

As far as possible, relevant analytical procedures and validations should be separated (i.e. for related substances, Residual solvents, …). A multiple file approach can be used. There are limitations to the number of files included in one section. The applicant has to make sure that the dossier is easy to navigate. Document titles (leaf titles) should be short and meaningful e.g. do not name titles using internal codes.

RESPONSE TO DEFICIENCY LETTER → SEQUENCE 0001



REVISION/NOTIFICATION/RENEWAL → SEQUENCE NNNN



ANNEX 5: Main issues which may lead to blocking a submission for its format and causing delays

Problem	**Reason for blocking**	**Solution**
Documentation sent via e-mail	The documentation is rejected. It is not a secure way for providing confidential data	Use the "Common European Submission Platform" (CESP).
Level of granularity not appropriate	Dossier cannot be easily navigated	Provide granularity according to annex 2 and refer to annex 3/4/5 depending on your submission format.
Annexes/attachments in module 3	Dossier cannot be easily navigated	Attachments/annexes need to be incorporated into the relevant CTD sections of module 3.
Coming back to previous submission format	Lifecycle of the dossier disrupted	Changing the format is accepted at the start of a procedure from a PDF to a NeeS or eCTD, or from a NeeS to eCTD. A baseline is highly recommended when switching from a paper to an e-submission or switching from a PDF/NeeS to an eCTD.
Documents in Word, Excel, JPEG file format	Not a secure file format for documentation	All files should be in PDF (with the exception of the files required for publishing an eCTD submission). The folder and the file-naming convention of ICH M2 eCTD Specification and EU Module 1 Specification should be applied.
eCTD wrong sequence provided	eCTD lifecycle disrupted	Provide the correct sequence number.
eCTD operation wrong attribute (for example "New" instead of "Replace"	eCTD lifecycle disrupted	Use operation attribute "Replace" for replacing an existing leaf element with a new leaf element.