

## **Certification of Substances Division**

FK/CB

### **PUBLIC DOCUMENT**

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*English only/Anglais seulement*

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## **Certification of suitability to Monographs of the European Pharmacopoeia**

### **Guidance for electronic and paper submissions for Certificates of Suitability (CEP) applications**

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## 1. Introduction

This document is guidance for electronic and paper submissions for Certificates of Suitability (CEPs) applications. Information and requirements described in this document are intended to facilitate the handling and assessment of submissions for certificates of suitability (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 submissions sent to EDQM in the context of applications for CEPs, and whatever the support selected (electronic or paper).

Currently the EDQM accepts paper dossiers, as well as 3 electronic submission formats: pdf, NeeS and eCTD. Paper submissions are still accepted but it is intended to move to 100% electronic submission in the future, therefore it is strongly recommended to initiate electronic submissions.

Changing the format for a CEP application is possible at the start of a procedure (eg. when applying for a revision or renewal). This means moving from paper to electronic submission, moving from a pdf to a NeeS or eCTD, or from a NeeS to eCTD.

**Once a company has made an e-submission, changing back to paper is no longer possible.** In addition, a mixture of paper and electronic files is not allowed (only the format chosen in the application form will be taken into consideration).

## 3. Electronic submission formats

Three possible submission formats are accepted for electronic submissions: eCTD, NeeS, or a single bookmarked PDF file for Module 3. Submissions in eCTD format are recommended by the EDQM.

This is applicable to all types of applications and communication. 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 the 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 and products for veterinary use only**

A single pdf (see [annex 5](#)) or VNeS submission format (see the guidance available by the following link <http://esubmission.ema.europa.eu/tiges/vetesub.htm>) may be used for such products.

### ***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 eCTD dossier and lifecycle.***

### **Building the envelope:**

According to the current EU Module 1 specification, for a CEP application, the envelope should be filled in as follows:

<b>Element</b>	<b>Attribute</b>	<b>Description/Instructions</b>
eu-envelope		
envelope		
	country	ema
submission		
	type	Active Substance Master File (asmf)
	mode	Blank
number		Blank
tracking number		Blank except if CEP application number known
applicant		Holder/Intended Holder name for the CEP
agency		
	code	EU-EMA
procedure		
	type	Use "centralised"
invented-name		Substance name
inn		Refer to the EU Module 1 specification.
sequence		Refer to the EU Module 1 specification.
related-sequence		Blank
submission-description		Certificate of suitability / EDQM

When submitting the first eCTD submission, an initial sequence 0000 should be provided. For the content of the submission refer to the [section 5](#).

When switching from another submission format to eCTD, any information already assessed and approved previously should be included in a "baseline" sequence 0000 (refer to the [section 6](#)). 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 if needed, 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 6](#)).

### ***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/doc/>

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](#)).

For the content of the submission refer to [section 5](#).

### ***3.3. PDF format***

It is possible to provide an application containing:

- For Module 1, a maximum of 4 PDF files or a single PDF file bookmarked according to the content of Module 1 (see [section 5](#))
- For Module 2, one single PDF file
- For Module 3 a single PDF file containing all the appropriate sections and compliant with the CTD requirements (naming convention etc). The structure given in [annex 5](#) has to be applied and bookmarks should be included using an acceptable [granularity](#) (See [annex 2](#)).

A single file containing all the Modules 1, 2 and 3 is not allowed. For the content of the submission refer to the [section 5](#).

The use of bookmarks is strongly recommended for Module 1, especially when responding to an EDQM deficiency letter (responses to questions and supportive data).

## 4. Submission of paper dossiers

Paper submissions are scanned at receipt at EDQM, therefore the clock-start for the dossier may be delayed accordingly (the delay increases with the volume of the submission). After validation, the paper documents are destroyed and the electronic copies are used by EDQM.

The structure to be followed is the same as for the pdf format (refer to [annex 5](#)), with the Modules 1, 2 and 3 being separated. The CTD structure shall be implemented and the submission should contain a table of content separating information related to each module 1, 2 and 3. An appropriate [granularity](#) should be included in module 3 (refer to [annex 2](#)).

The paper submission should have appropriate quality to allow the scanning process (in particular graphs and chromatograms); otherwise the submission may be rejected.

For the content of the submission refer to the [section 5](#).

### **CEP applications for the TSE risk**

Applicants are invited to separate the documents and adapt the directory structure/document naming as proposed in [annex 1](#).

### **CEP applications for products for veterinary use only**

Applicants are invited to separate the documents and adapt the directory structure/document naming as proposed in [annex 5](#)).

## 5. Content and structure of an application

Annexes [3](#) and [4](#) describe how to structure a CEP application in eCTD or NeeS submission formats.

[Annex 5](#) describes the recommended file/directory structure for the pdf submission format and similarly for the paper submission format.

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,...

- **Revisions:** a completed comparative table outlining the approved and proposed updated text of module 3.

### **In Module 2:**

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

### **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.
- 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 6](#). 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.

## **6. 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.

**Granularity:** subdivision into small parts of a larger entity. For example, the CTD section 3.2.S.3. could be subdivided into 2 subsections (3.2.S.3.1, 3.2.S.3.2), which can each be subdivided into subsections (3.2.S.3.2.1, 3.2.S.3.2.2,..).

### ***6.1 Granularity and 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](#) for the levels of granularity). Updated pages only are not accepted (except if the complete CTD section is on one page).

### **The use of annexes is not encouraged.**

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 revisions/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 attribute: "New", "Replace", "Delete", "Append". The use of the "Replace" attribute should be used rather than the "Append" attribute. The use of the "Append" attribute should be avoided since it leads frequently to lifecycle difficulties. The "Append" may only be used when new information should be annexed to a section.
- **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.
- **For a Paper submission:** in Module 3, the updated sections should be supplied, respecting the [granularity](#) (refer to the [annex 2](#)). Even if a unique page is updated in a CTD section, the full updated section should be provided in accordance with the granularity initially chosen.

**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 the rejection of the application at receipt.**

## ***6.2 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. Applicants are encouraged to submit a baseline application to EDQM to facilitate the management of its lifecycle for both the applicant and the EDQM.

*It is mandatory 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

*Unless an eCTD has already been submitted, it is 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 (eg. when responding to a deficiency letter or any other information requested), nor when it is not linked to any submission.

## 7. 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 6](#).

## 8. Routes (or pathways) of submission

**One** of the following routes of submission can be used to send a submission or communication relating to a CEP dossier:

- *Carrier* for paper, CD-ROM, DVD, USB stick:

The submission should be identified (name of the company, name of the substance and dossier number if known). If the identification of the dossier is not clear, this may delay the clock start of the submission. Electronic devices such as CD-ROM may be accompanied by a paper cover letter, provided that the cover letter is also included in the electronic version.

- *EDQM secured Dropbox for electronic submissions up to 300 MB:*

Access codes are needed and can be obtained upon request at [cep@edqm.eu](mailto:cep@edqm.eu). The modules should be zipped together and sent by the contact person appointed for the application using a **unique upload**; otherwise the submission cannot be accepted.

If the size of the dossier does not allow a unique upload, then a CD-ROM, DVD or USB stick should be sent.

To improve the handling of a submission sent by the Dropbox, the CEP reference number (if known) and the relevant type of submission should be indicated. If necessary, a message can be prepared to give additional indications (for example when submitting grouped notifications/revisions).

The EDQM is currently investigating other options for electronic submissions.

## 9. 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 electronic and paper data from the receipt, whatever route of submission is selected from the choices above.

## **Annexes:**

[Annex 1: Directory structure/file naming for TSE risk applications](#)

[Annex 2: Recommended granularity levels](#)


[Annex 3: eCTD structure for a CEP dossier](#)

[Annex 4: NeeS structure for a CEP dossier](#)

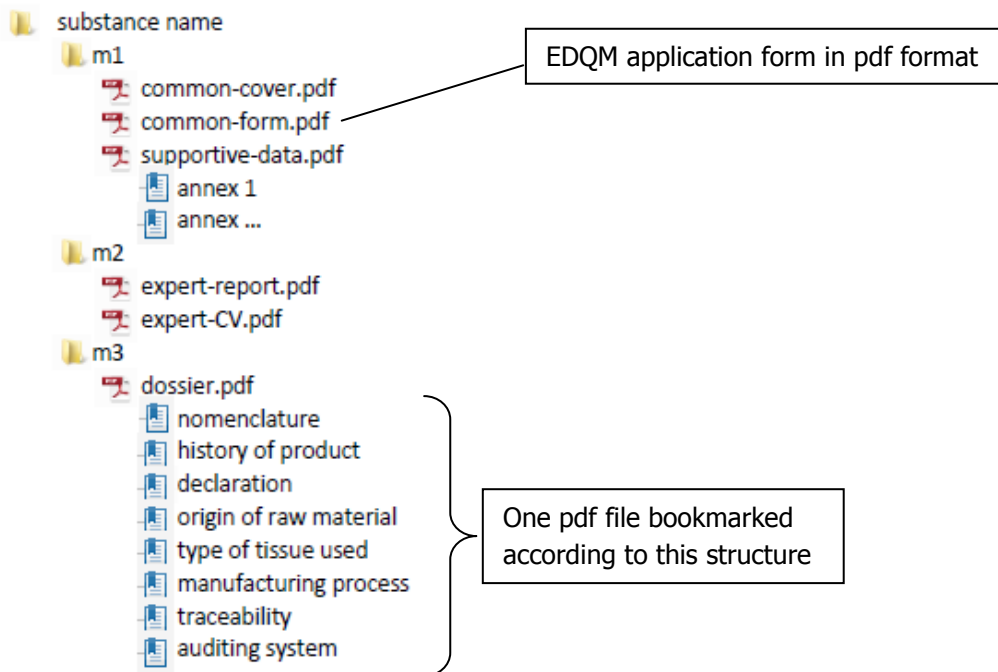
[Annex 5: PDF structure and granularity](#)

[Annex 6: Main issues which may lead to block administratively a submission](#)

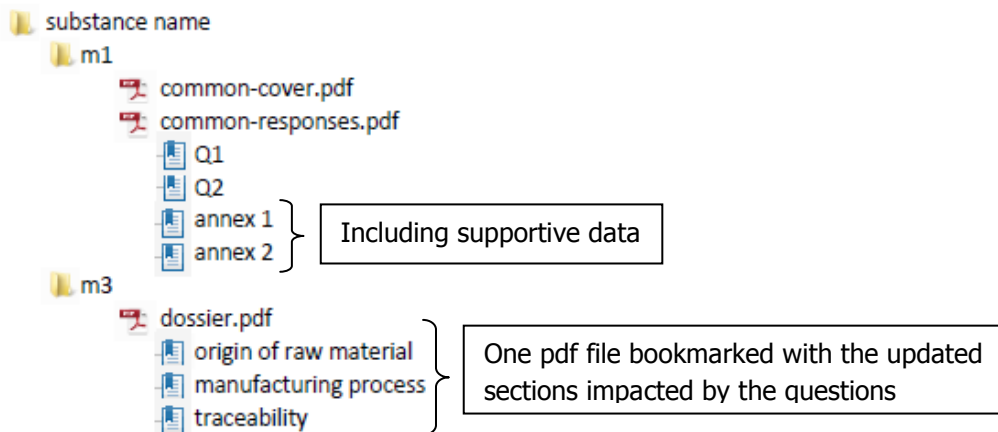
## ANNEX 1: Directory structure/file naming for TSE applications

 = bookmark

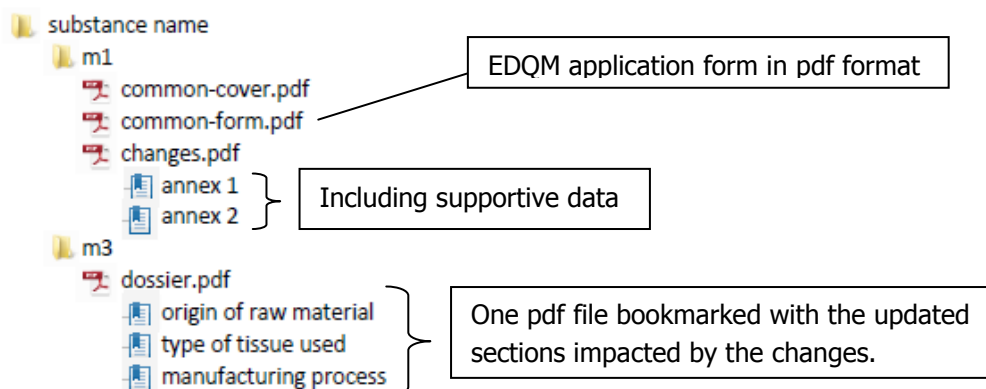
### NEW APPLICATION



### RESPONSE TO DEFICIENCY LETTER



### REVISION/NOTIFICATION/RENEWAL

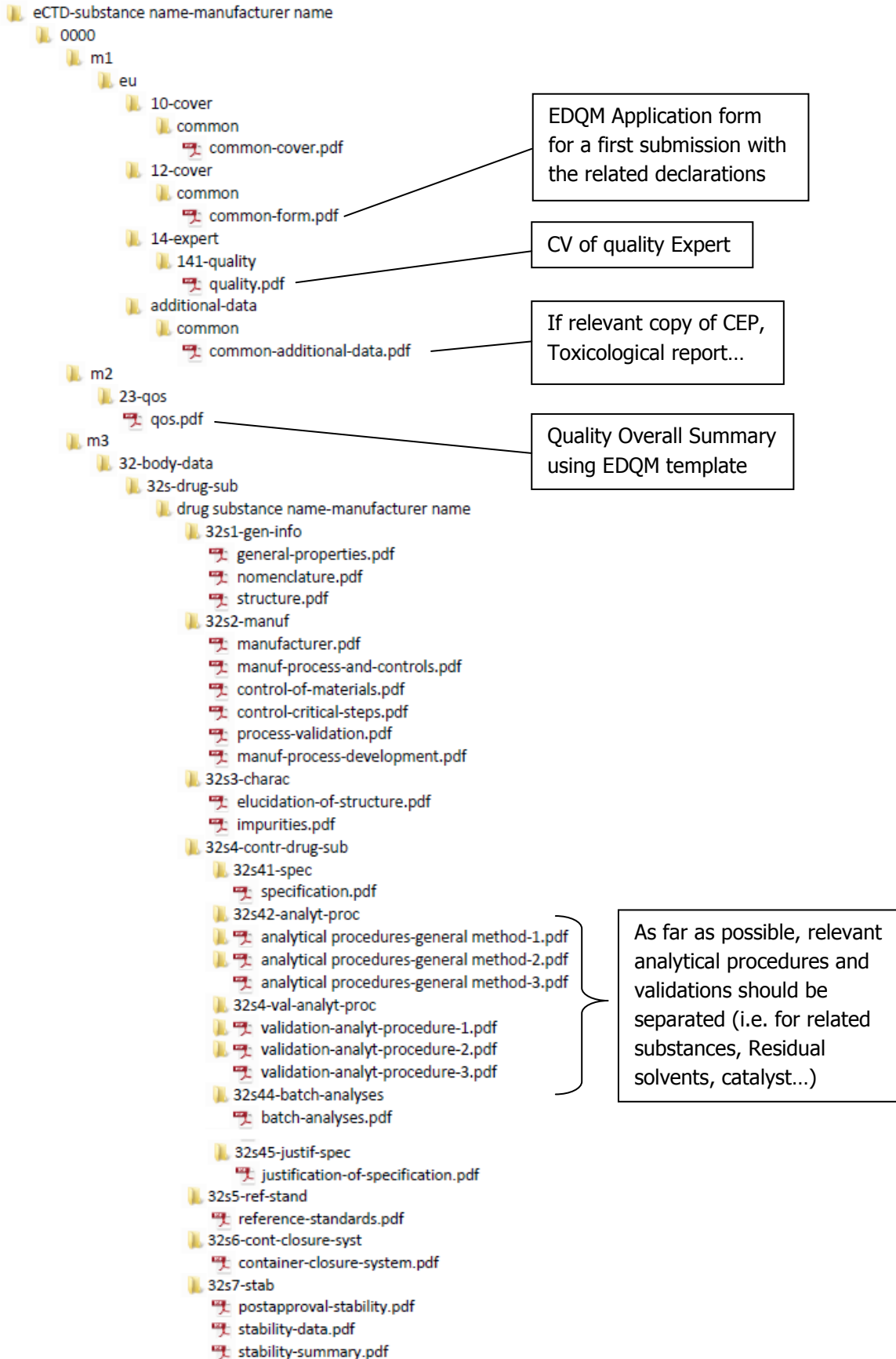


## ANNEX 2: Recommended granularity levels

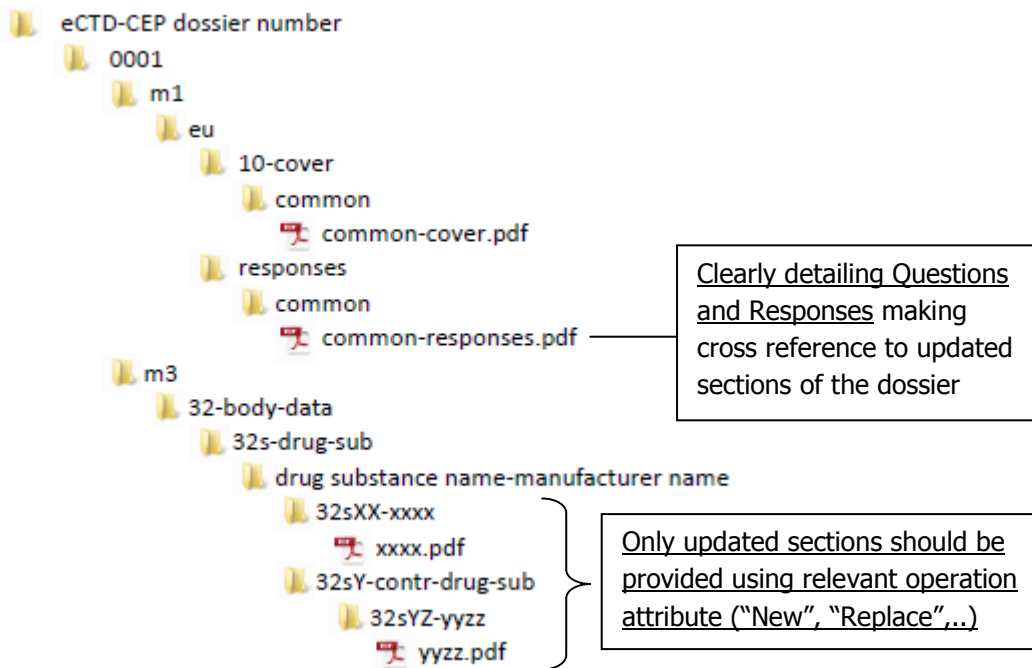
<b>Granularity required</b>			<b>Acceptability</b> A = accepted R = Recommended NA = Not accepted
<b>Level 1</b>	<b>Level 2</b>	<b>Level 3</b>	
3.2.S.1	General Information		A
	3.2.S.1.1	Nomenclature	R
		3.2.S.1.1.X	NA
	3.2.S.1.2	Structure	R
		3.2.S.1.2.X	NA
	3.2.S.1.3	General Properties	R
		3.2.S.1.3.X	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**

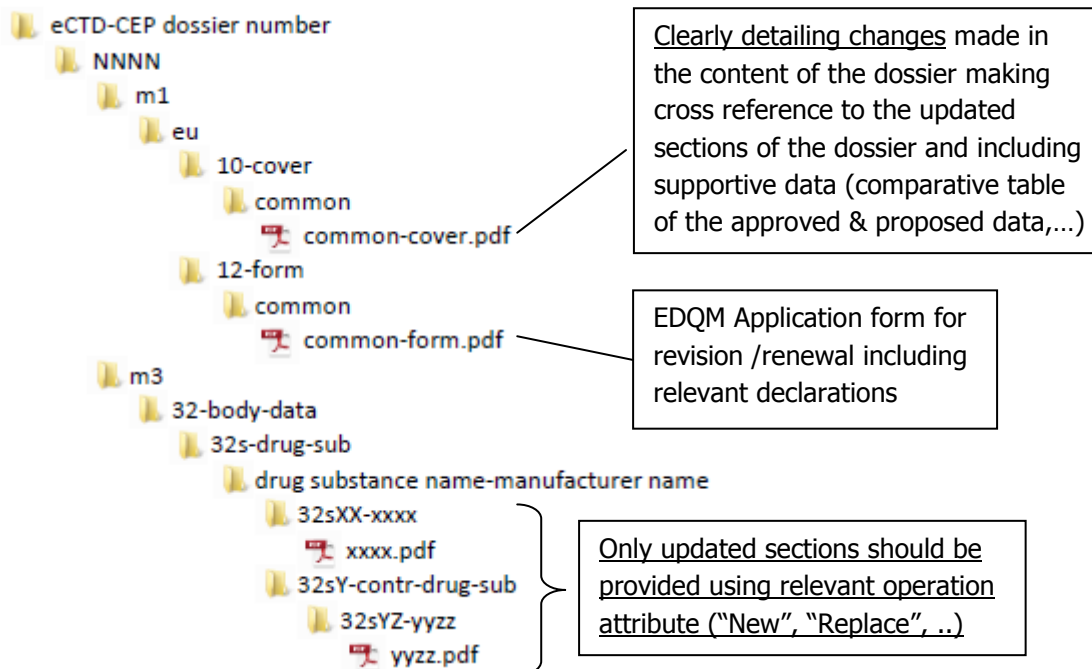
**NEW APPLICATION (OR BASELINE) → SEQUENCE 0000**



### RESPONSE TO DEFICIENCY LETTER → SEQUENCE 0001

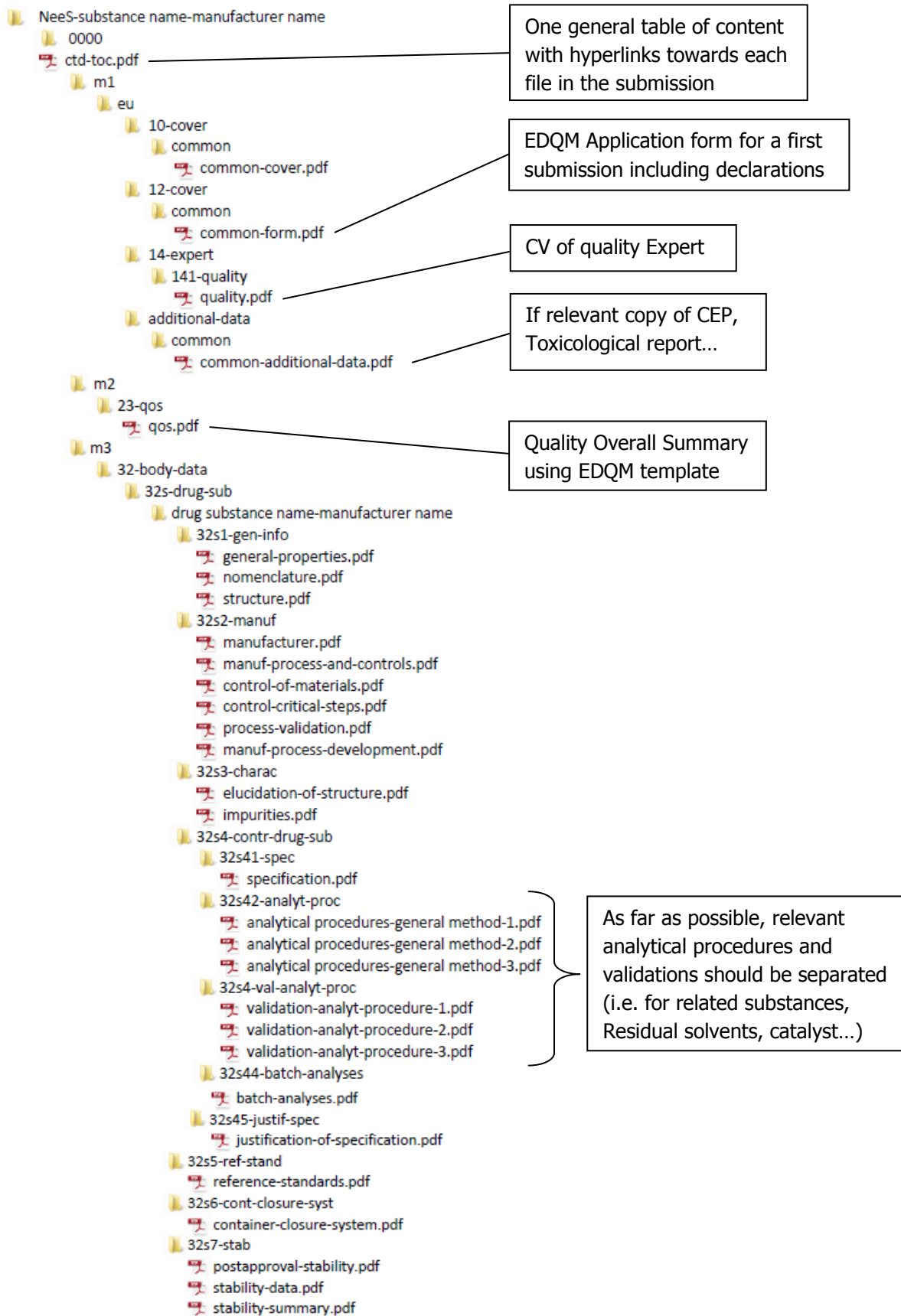


### REVISION/NOTIFICATION/RENEWAL → SEQUENCE NNNN



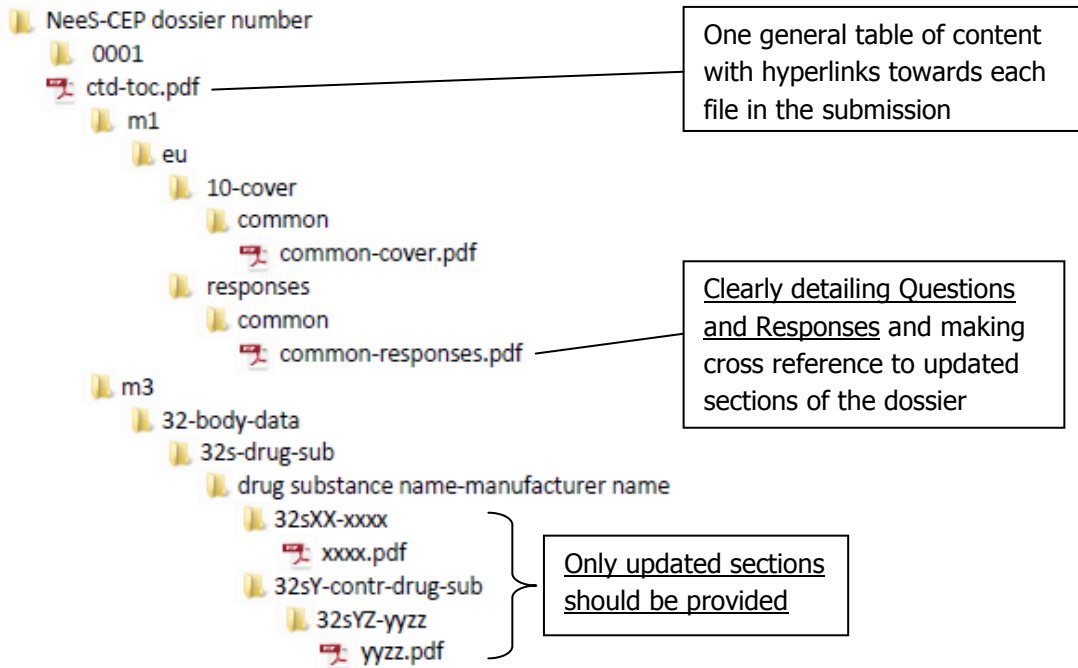
## ANNEX 4: NeeS structure for a CEP dossier

### NEW APPLICATION (OR BASELINE)

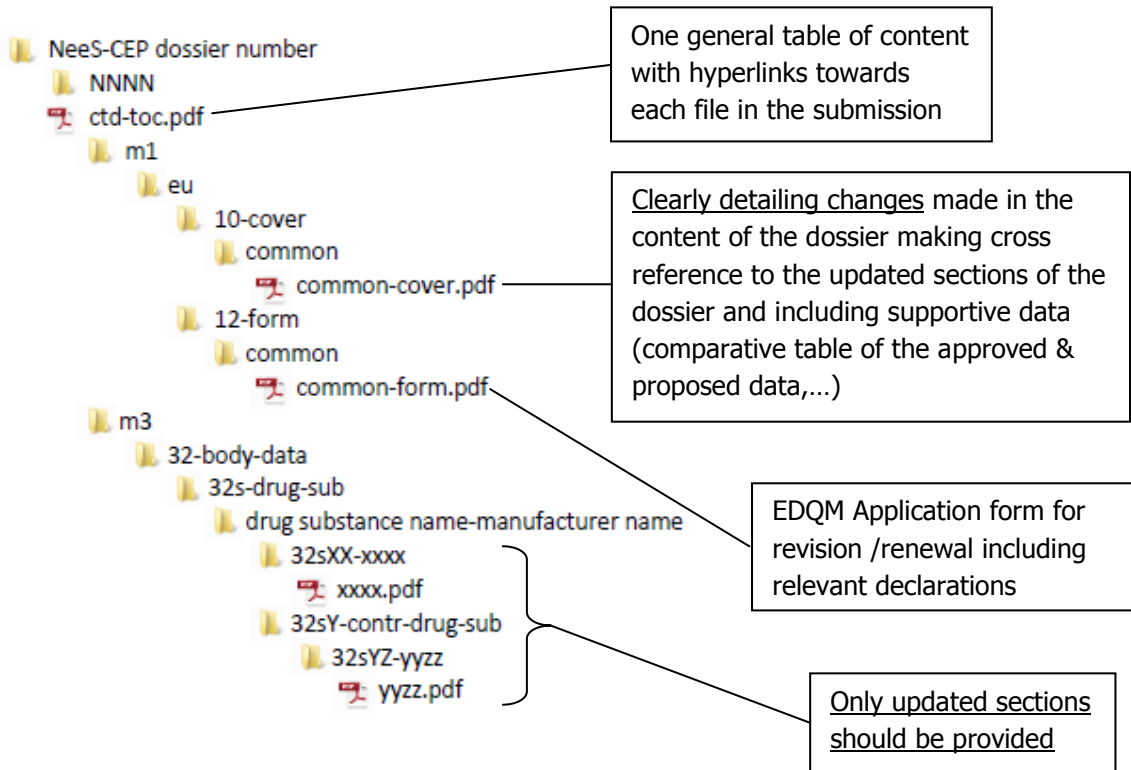




## RESPONSE TO DEFICIENCY LETTER

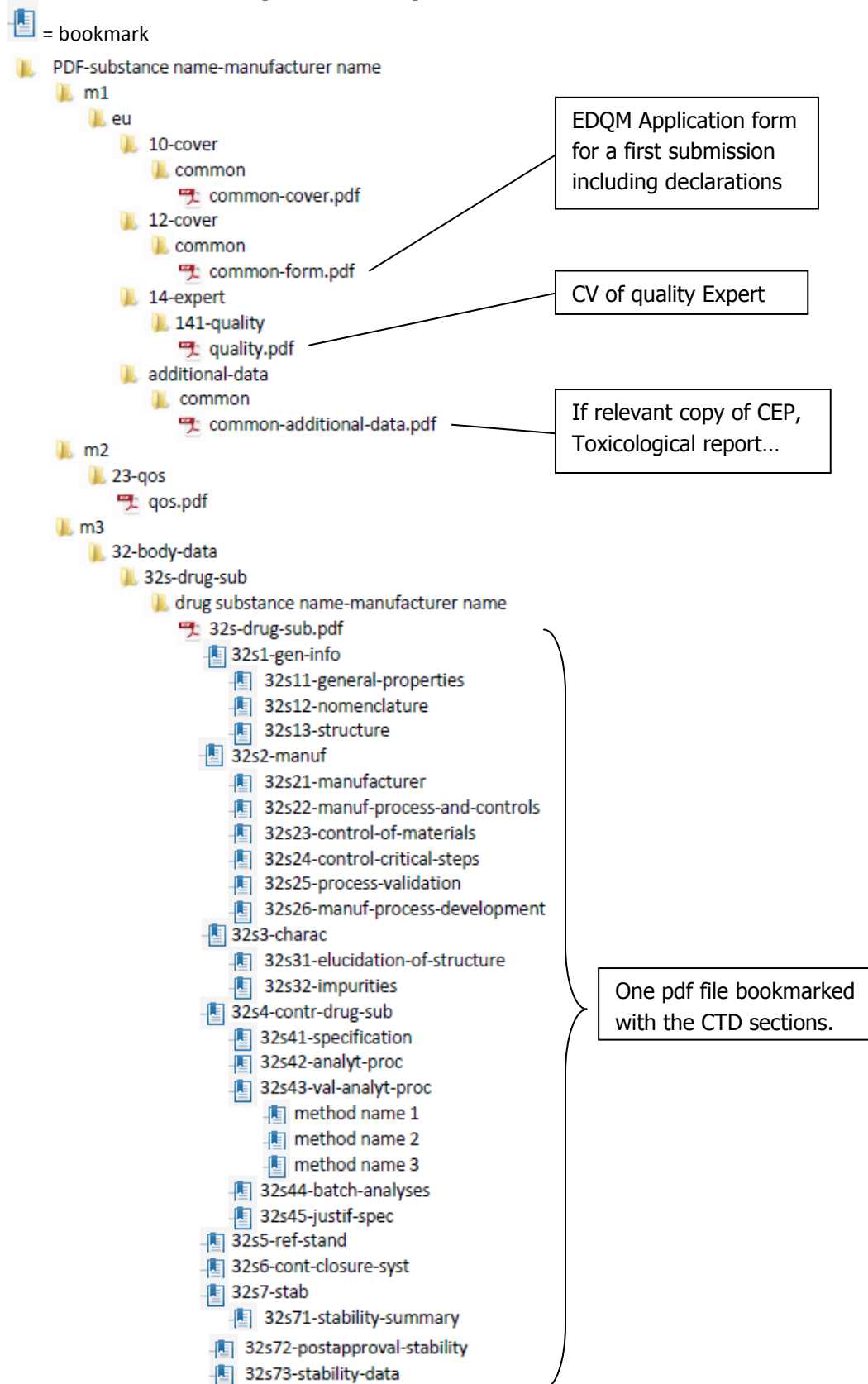


## REVISIONS/NOTIFICATIONS/RENEWAL

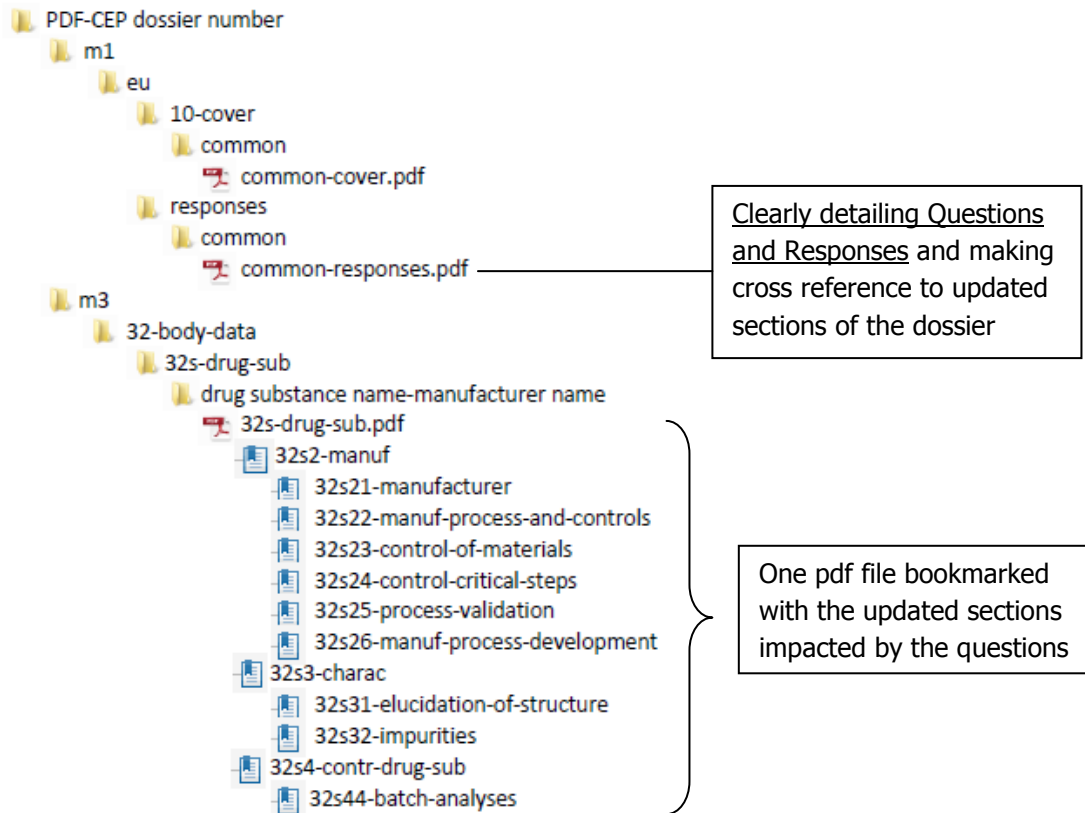


## ANNEX 5: PDF structure and granularity

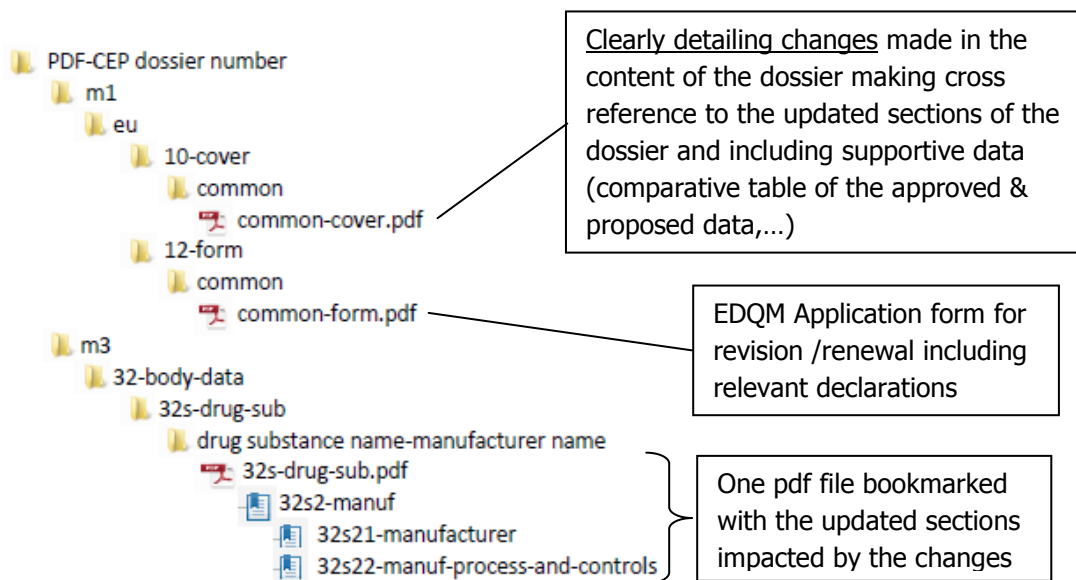
### NEW APPLICATION (OR BASELINE)



## RESPONSE TO DEFICIENCY LETTER



## REVISIONS/NOTIFICATIONS/RENEWAL



## ***ANNEX 6: Main issues which may lead to block a submission for its format***

- *eCTD:*
  - Lifecycle issues (use of an inappropriate attribute etc.)
  - A non-validated eCTD (did not pass the checker)
  - Multiple sequences (history of the CEP application) provided when submitting an eCTD for the first time
- *NeeS:*
  - Structure not in line with requirements and EU validation criteria for NeeS
  - Absence of table of content with hyperlinks
- *PDF:*
  - Structure not in line with requirements
  - Absence of appropriate bookmarking
  - Protected PDF file
- *Paper applications:*
  - Poor quality of the documents which prevents the scanning process
  - A mix between modules 1, 2 and 3 (see [Annex 5](#) for the expected documentation structure)
- *For all submission formats:*
  - Coming back to a previous submission format (e.g from eCTD to NeeS or PDF)
  - Format of the submission not appropriately identified in the application form
  - Level of [granularity](#) not respected when updating the submission
  - Updated sections missing or incomplete