

Certification of Substances Division

HB/CB

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Certification of Suitability to Monographs of the European Pharmacopoeia

Guidance for submission of electronic applications for Certificates of Suitability (CEPs): Revised procedures

1. Introduction

In order to run the Certification procedure efficiently and in line with ICH guidance, the Certification Division has revised the requirements for electronic submissions for CEP applications.

2. Scope

All applications and communication related to CEP applications can be submitted electronically:

- New applications for CEPs
- Notifications
- Requests for revision or renewal
- Answers to EDQM deficiency letters
- Any other communication related to CEP applications.

It is possible to move from a paper submission to an electronic submission at any time of the life-cycle of a CEP application or a granted CEP. This choice can be selected in the relevant application form. However once an electronic dossier is sent, any future data related to the application should also be in electronic format: no mixture of paper and electronic data is allowed.

3. Format of the submissions

Three possible formats are accepted for electronic submissions: eCTD, NeeS, or a single bookmarked PDF file for Module 3. This is applicable to all types of applications and communication as listed above.

While any of the 3 electronic formats is applicable to CEP dossiers for the chemical purity, the eCTD format is not intended for CEP dossiers for the TSE risk. In this case, applicants may still use the NeeS or pdf format, adapting the directory structure/file naming as relevant.

- eCTD format:

Submission of an eCTD is recommended. The eCTD structure should be in accordance with the current ICH M2 EWG eCTD specification which can be found at:

- ICH eCTD specification: <http://estri.ich.org/eCTD/index.htm>
- EU M1 eCTD specification: <http://esubmission.ema.europa.eu/eumodule1/index.htm>

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

According to the current EU Module 1 specification, an eCTD dossier requires a submission type, and description of the agency, the application and procedure. For a CEP application, the envelope may be filled in as follows:

Element	Attribute	Description/Instructions
eu-envelope		
envelope		
	country	emea
submission		
	type	Active Substance Master File (asmf)
	mode	Not to be used with CEP
number		Blank
tracking number		Blank except if CEP application number known
applicant		Holder/Intended Holder name for the CEP
agency		
	code	EU-EMEA
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		Not be used with the ASMF/CEP application
submission-description		Certificate of suitability / EDQM

Before submitting an eCTD sequence to EDQM, it should be technically validated using an appropriate checker tool.

- NeeS format:

The NeeS structure and specification should be in accordance with the following guidance:

http://esubmission.emea.europa.eu/doc/eGuidance_Document_1.4.pdf

The validation criteria for NeeS may be found at:

<http://esubmission.emea.europa.eu/doc/EU%20NeeS%20validation%20Criteria%20v1.0.pdf>

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

- PDF format:

It is acceptable to provide a single PDF file for Module 3 containing all the appropriate sections, provided the CTD requirements are met, the structure given in Annex 3 is implemented and full bookmarking of each section is made. Separate files have to be submitted for the Modules 1 and 2.

4. Content and structure of an application

In Module 1:

- Cover letter
- EDQM Application Form including signed declarations (as relevant)
- Quality (information about the Expert, CV as relevant). There is no need to provide a signed document.
- Responses: when responding to an EDQM deficiency letter, applicants should include in this section a document which lists the questions with the corresponding narrative text of the responses to each question.
- Additional Data: this folder may contain if relevant a toxicological report, a signed copy of a CEP, or any other information.

In Module 2:

- Quality Overall Summary, in PDF format, prepared using the template available on the EDQM website (not required for revision/renewal).

In Module 3:

- For a new CEP application: technical documentation in accordance with the CTD format 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.
Asmf eCTD Guidance may be found at: <http://esubmission.ema.europa.eu/doc/index.html>
- For further submissions: Module 3 should be updated as described under "5. Lifecycle management of applications" below.

Annexes 1, 2, 3 describe the recommended file/directory structure, depending on the format of the e-submission applied.

It should be stressed that when the first e-submission is a request for revision/renewal, it is highly recommended to provide a full module 3. At the time when the applicant decides to switch to e-submissions, this is a unique opportunity to have a clear picture of the regulatory information that has already been submitted and approved, along with the changes triggering the request for revision. It will also facilitate the management of the lifecycle of the application for both the applicant and the EDQM.

5. Lifecycle management of applications

For each update of the dossier (i.e. following a request for additional information issued by the EDQM or for the submission of a request for revision), the following instructions should be implemented:

- For revisions: the cover letter should describe the request for revision, include supportive data, comparative tables, etc, as required by the EDQM guidelines for revisions/renewals.
- Responses: any answer to an EDQM deficiency letter should include in Module 3 all updated files for the sections affected by the Questions & Answer process. This may also

apply to Module 1 (e.g. update of administrative data), as well as Module 2 in cases where extensive data would require inclusion of the relevant summaries and/or overview sections.

The following specific instructions apply also, depending on the format chosen:

- For an eCTD: a new sequence 000(X+1) should be provided containing Modules 1, 2, 3 as appropriate, with updated files in the relevant sections, using the same structure as originally. The files should have the appropriate operation attribute: “New”, “Append”, “Replace”, “Delete”.
- For a NeeS: a folder should be provided containing Modules 1, 2, 3 as appropriate, with updated files in the relevant sections, using the same structure as originally, and with a general Table of Content(s).
- In case a single PDF file has originally been submitted: the updated sections should be supplied as a single bookmarked pdf file, highlighting the modifications.

6. Requirements on electronic files

Electronic files should be in accordance with Guidance for Industry on Providing Regulatory Information in Electronic Format which may be found at:

For eCTD:

<http://esubmission.ema.europa.eu/doc/eCTD%20Guidance%20Document%201.0%20FINAL%20FOR%20PUBLICATION.pdf>

For NeeS:

http://esubmission.ema.europa.eu/doc/eGuidance_Document_1.4

For PDF format:

The principles given in http://esubmission.ema.europa.eu/doc/eGuidance_Document_1.4 should be implemented for the format of the file.

7. Way of submission

The applicant can submit electronic files through the 3 ways described below:

- CD-ROM or DVD properly identified, which should show the name of the company, the name of the substance and the dossier number if known;
- Internet secured Dropbox: for submissions up to 100 MB only. Access codes are needed and can be obtained upon request at cep@edqm.eu. The files should be zipped together.
- E-mail addressed at cep@edqm.eu for letters only.

8. Security

The applicant should check the submission for absence of virus before sending it to EDQM. As for paper applications, EDQM guarantees the security and confidentiality of electronic data from the receipt, whatever route of submission is selected from the choices above.

9. Implementation

The requirements described in this document will allow EDQM to use electronic submissions efficiently. Once a company has made an e-submission, reversion to paper submission is no longer possible.

Annexes:

Annex 1: recommended structure for a CEP application in eCTD format

Annex 2: recommended structure for a CEP application in NeeS format

Annex 3: recommended structure for a CEP application in single PDF file format.

ANNEX 1:
eCTD recommended structure, granularity and format

- **For the first submission (New Application)**
sequence 0000

- **Additional information (responses to EDQM questions) sequence 0001**

Clearly detailing Question and Responses and making cross reference to updated sections of the dossier

Only updated sections should be provided using relevant operation attribute (“New”, “Append”, “Replace” and “Delete”)

- **For revisions/renewal submissions sequence XXXX**

Clearly detailing changes made in the content of the dossier and making cross reference to updated sections

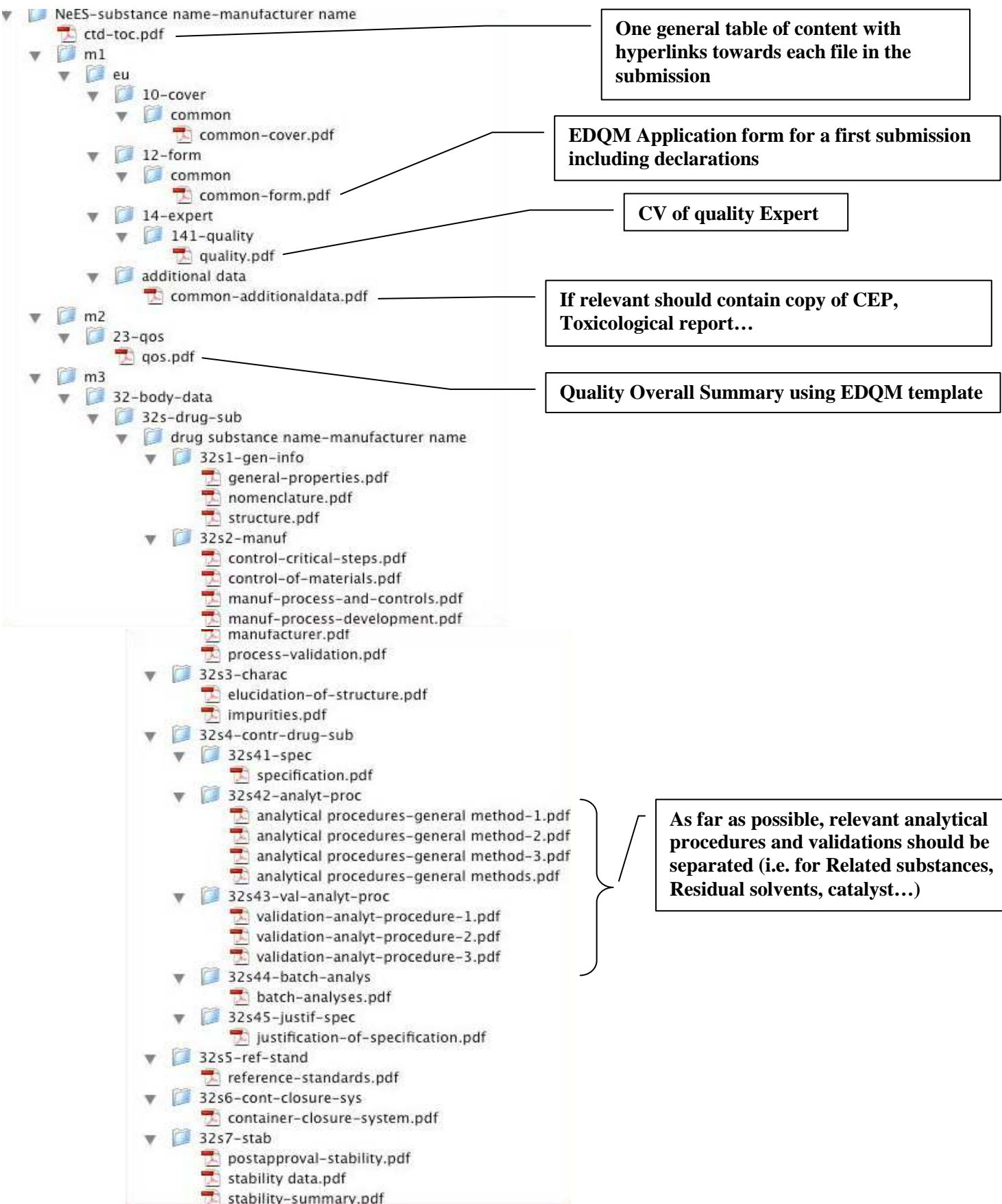
EDQM Application form for revision /renewal including relevant declarations

Only updated sections should be provided with relevant operation attribute

ANNEX 2

NeES recommended structure, granularity and format

- For the first submission (New Application)



- **Additional information (responses to EDQM questions)**

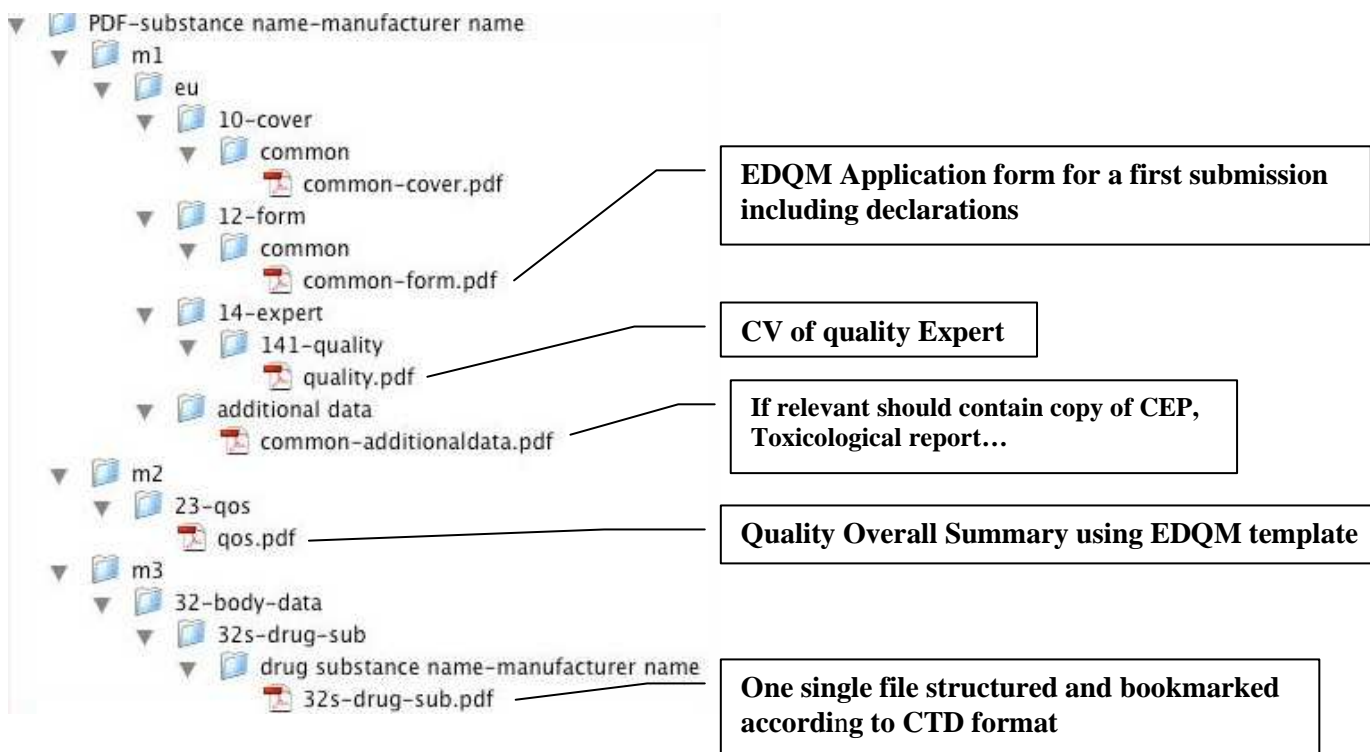
The screenshot shows a file directory structure for 'Additional information (responses to EDQM questions)'. The root folder is 'NeES-CEP number', which contains 'ctd-toc.pdf'. Below it is 'm1', which contains 'eu'. Under 'eu' are '10-cover' and 'responses'. '10-cover' contains a 'common' folder with 'common-cover.pdf'. 'responses' contains a 'common' folder with 'common-responses.pdf'. Below 'm1' is 'm3', which contains '32-body-data'. Under '32-body-data' is '32s-drug-sub', which contains a folder 'drug substance name- manufacturer name'. This folder contains two sub-folders: '32sX-XXX' with 'XXX.pdf' and '32sY-YYY' with 'YYY.pdf'. Three callout boxes provide instructions: one points to 'ctd-toc.pdf' with the text 'One general table of content with hyperlinks towards each file in the submission'; another points to 'common-responses.pdf' with the text 'Clearly detailing Question and Responses and making cross reference to updated sections of the dossier'; and a third points to the '32sX-XXX' and '32sY-YYY' folders with the text 'Only updated sections should be provided'.

- **For revisions/renewal submissions**

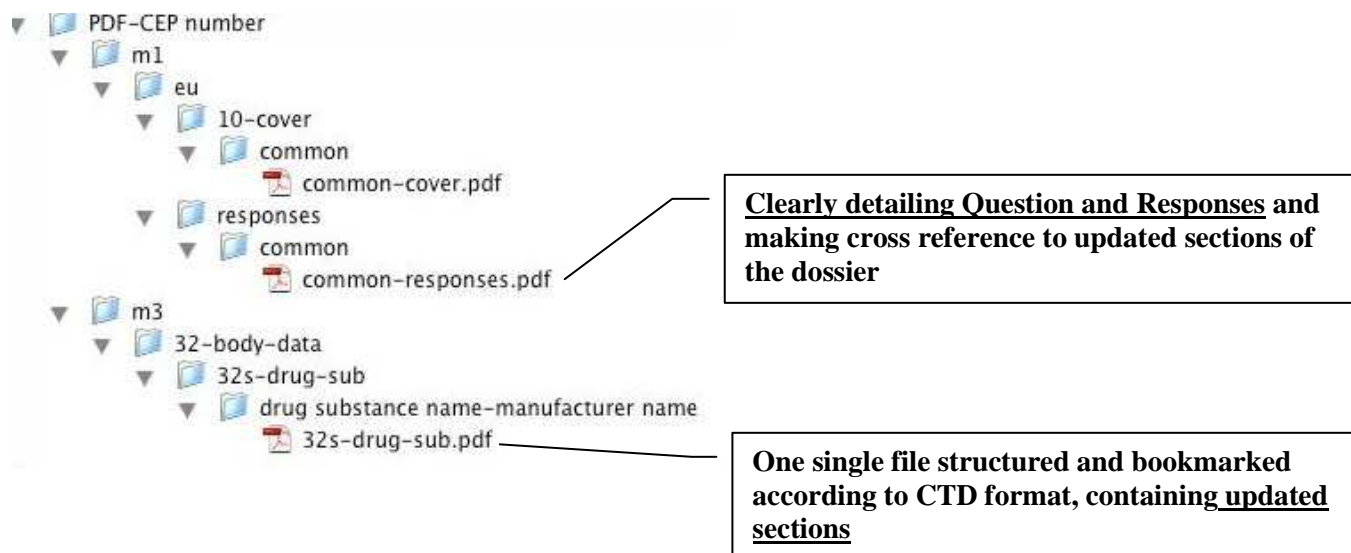
The screenshot shows a file directory structure for 'For revisions/renewal submissions'. The root folder is 'NeES-CEP number', which contains 'ctd-toc.pdf'. Below it is 'm1', which contains 'eu'. Under 'eu' are '10-cover' and '12-form'. '10-cover' contains a 'common' folder with 'common-cover.pdf'. '12-form' contains a 'common' folder with 'common-form.pdf'. Below 'm1' is 'm3', which contains '32-body-data'. Under '32-body-data' is '32s-drug-sub', which contains a folder 'drug substance name- manufacturer name'. This folder contains two sub-folders: '32sX-XXX' with 'XXX.pdf' and '32sY-YYY' with 'YYY.pdf'. Three callout boxes provide instructions: one points to 'ctd-toc.pdf' with the text 'General table of content with hyperlinks towards each updated CTD section'; another points to 'common-cover.pdf' with the text 'Clearly detailing changes made in the content of the dossier and making cross reference to updated sections'; and a third points to 'common-form.pdf' with the text 'EDQM Application form for revision /renewal including relevant declarations'. A fourth callout box points to the '32sX-XXX' and '32sY-YYY' folders with the text 'Only updated sections should be provided'.

ANNEX 3
Single PDF structure, granularity and format

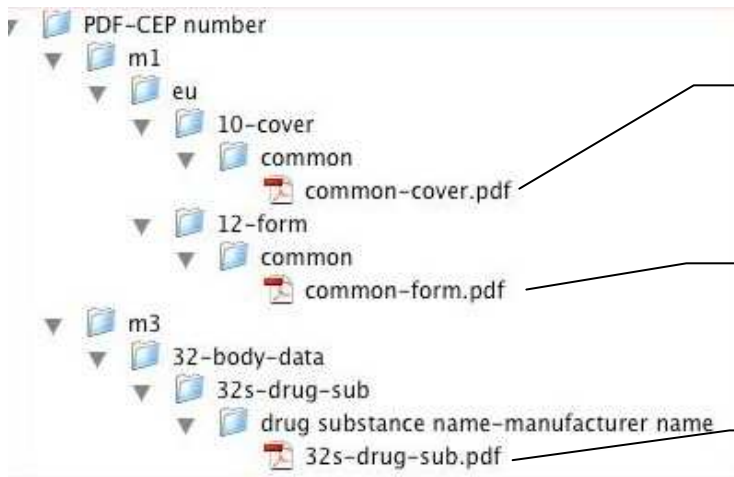
• **For the first submission (New Application)**



• **Additional information (responses to EDQM questions)**



- **For revisions/renewal submissions**



Clearly detailing changes made in the content of the dossier and making cross reference to updated sections

EDQM Application form for revision /renewal including relevant declarations

One single file structured and bookmarked according to CTD format, containing updated sections