**Certification of Substances Division**

HB/CB

**PUBLIC DOCUMENT**
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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

Address: 7 allée Kastner CS 30026 - F 67081 Strasbourg
Telephone: 33 (0) 3 88 41 30 30 - E-mail:cep@edqm.eu - Fax: 33 (0) 3 88 41 27 71
Internet : http://www.edqm.eu

## 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**

```
eCTD-substance name-manufacturer name
  0000
    index-md5.txt
    index.xml
    m1
      eu
        10-cover
          common
            common-cover.pdf
        12-form
          common
            common-form.pdf
        14-expert
          141-quality
            quality.pdf
        additional data
          common-additionaldata.pdf
        eu-regional.xml
    m2
      23-qos
        qos.pdf
    m3
      32-body-data
        32s-drug-sub
          drug substance name-manufacturer name
            32s1-gen-info
              general-properties.pdf
              nomenclature.pdf
              structure.pdf
            32s2-manuf
              control-critical-steps.pdf
              control-of-materials.pdf
              manuf-process-and-controls.pdf
              manuf-process-development.pdf
              manufacturer.pdf
              process-validation.pdf
            32s3-charac
              elucidation-of-structure.pdf
              impurities.pdf
            32s4-contr-drug-sub
              32s41-spec
                specification.pdf
              32s42-analyt-proc
                analytical procedures-general method-1.pdf
                analytical procedures-general method-2.pdf
                analytical procedures-general method-3.pdf
                analytical procedures-general methods.pdf
              32s43-val-analyt-proc
                validation-analyt-procedure-1.pdf
                validation-analyt-procedure-2.pdf
                validation-analyt-procedure-3.pdf
              32s44-batch-analys
                batch-analyses.pdf
              32s45-justif-spec
                justification-of-specification.pdf
            32s5-ref-stand
              reference-standards.pdf
            32s6-cont-closure-sys
              container-closure-system.pdf
            32s7-stab
              postapproval-stability.pdf
              stability data.pdf
              stability-summary.pdf
    util
      dtd
      style
```

**EDQM Application form for a first submission including declarations**

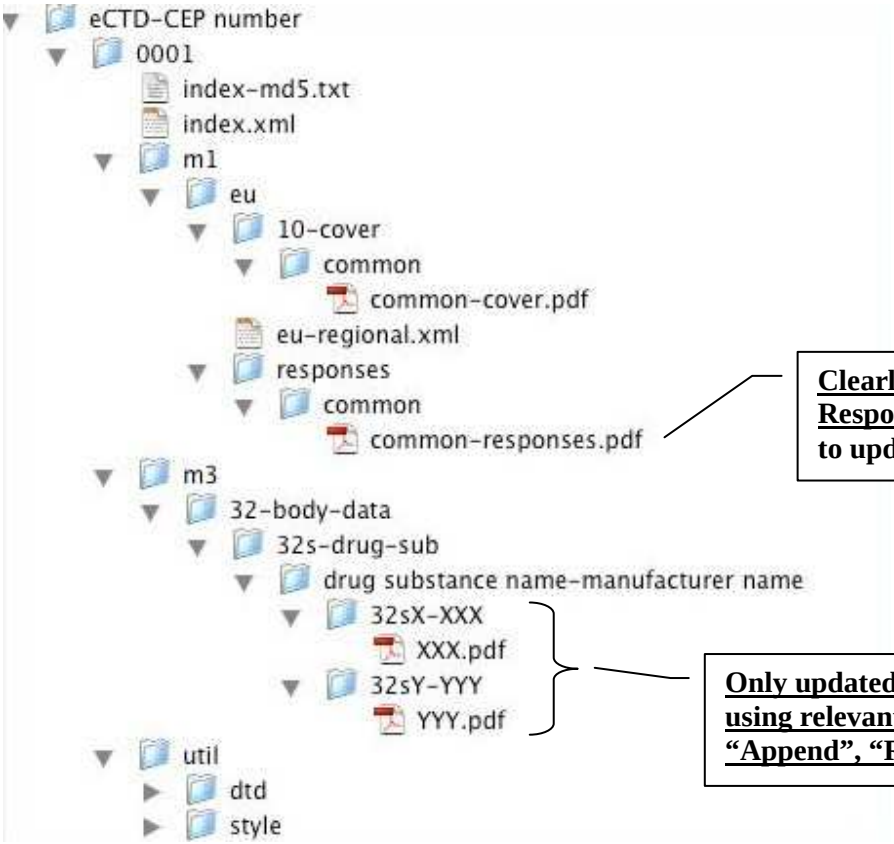
**CV of quality Expert**

**If relevant should contain 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, catalyst…)**

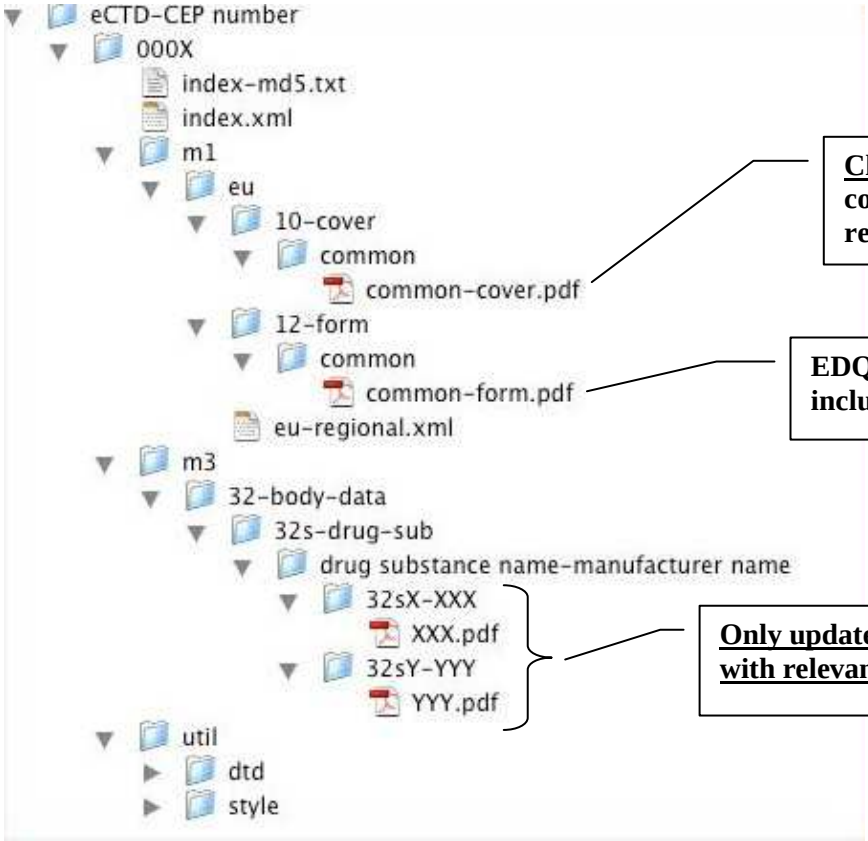
- **Additional information (responses to EDQM questions) sequence 0001**




**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)**

```
NeES-substance name-manufacturer name
    ctd-toc.pdf
    m1
        eu
            10-cover
                common
                    common-cover.pdf
            12-form
                common
                    common-form.pdf
            14-expert
                141-quality
                    quality.pdf
            additional data
                common-additionaldata.pdf
    m2
        23-qos
            qos.pdf
    m3
        32-body-data
            32s-drug-sub
                drug substance name-manufacturer name
                    32s1-gen-info
                        general-properties.pdf
                        nomenclature.pdf
                        structure.pdf
                    32s2-manuf
                        control-critical-steps.pdf
                        control-of-materials.pdf
                        manuf-process-and-controls.pdf
                        manuf-process-development.pdf
                        manufacturer.pdf
                        process-validation.pdf
                    32s3-charac
                        elucidation-of-structure.pdf
                        impurities.pdf
                    32s4-contr-drug-sub
                        32s41-spec
                            specification.pdf
                        32s42-analyt-proc
                            analytical procedures-general method-1.pdf
                            analytical procedures-general method-2.pdf
                            analytical procedures-general method-3.pdf
                            analytical procedures-general methods.pdf
                        32s43-val-analyt-proc
                            validation-analyt-procedure-1.pdf
                            validation-analyt-procedure-2.pdf
                            validation-analyt-procedure-3.pdf
                        32s44-batch-analys
                            batch-analyses.pdf
                        32s45-justif-spec
                            justification-of-specification.pdf
                    32s5-ref-stand
                        reference-standards.pdf
                    32s6-cont-closure-sys
                        container-closure-system.pdf
                    32s7-stab
                        postapproval-stability.pdf
                        stability data.pdf
                        stability-summary.pdf
```

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

**EDQM Application form for a first submission including declarations**

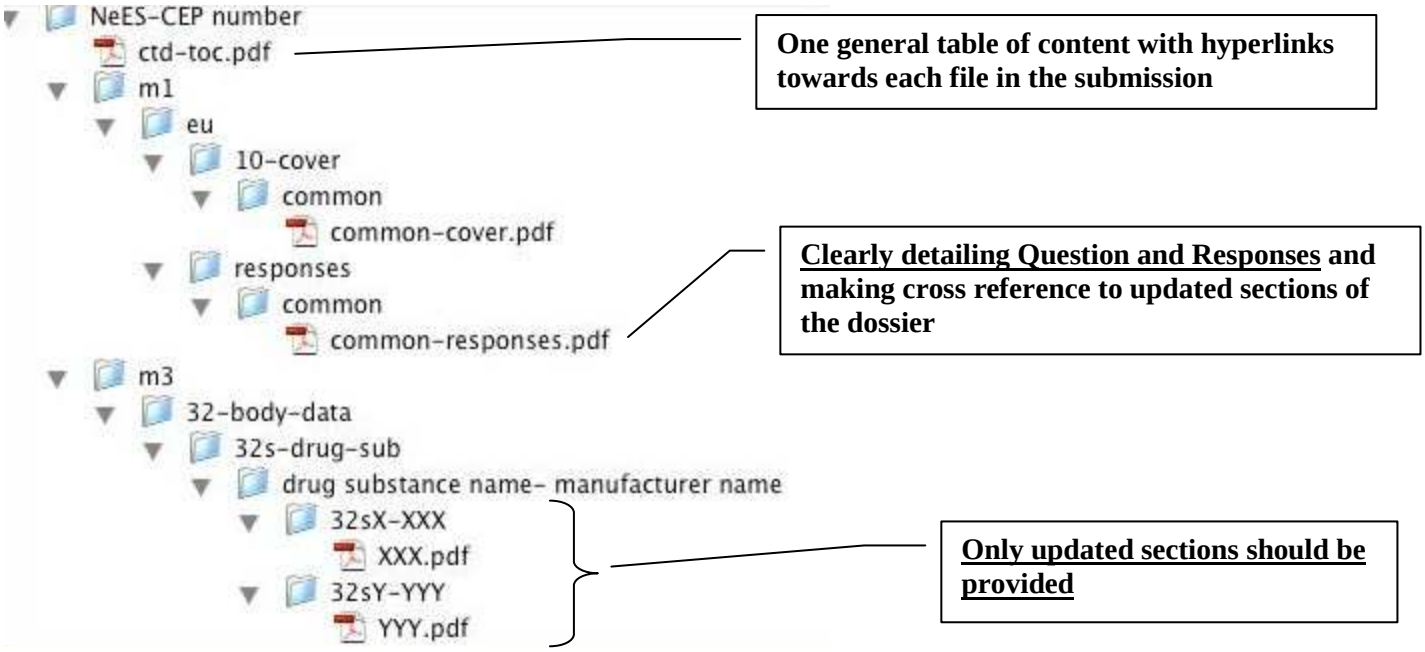
**CV of quality Expert**

**If relevant should contain copy of CEP, Toxicological report…**

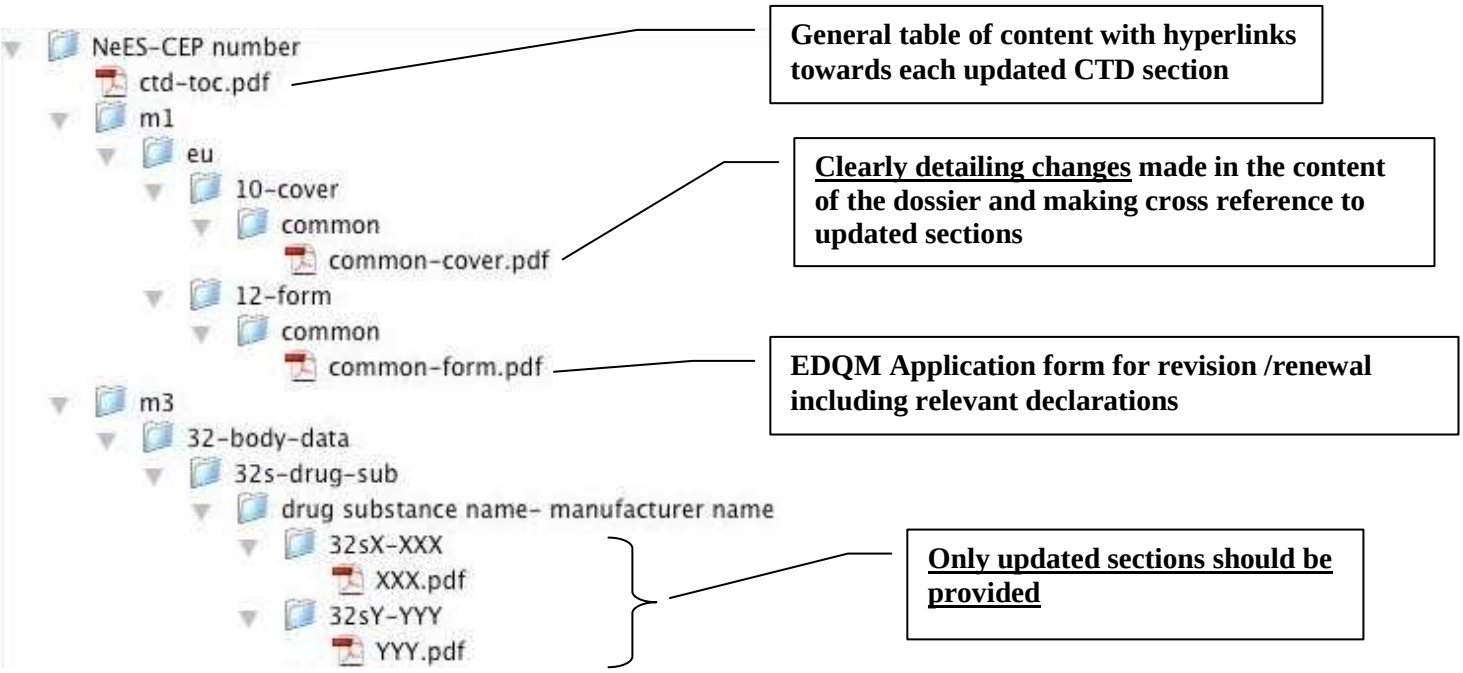
**Quality Overall Summary using EDQM template**

**As far as possible, relevant analytical procedures and validations should be separated (i.e. for Related substances, Residual solvents, catalyst…)**

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

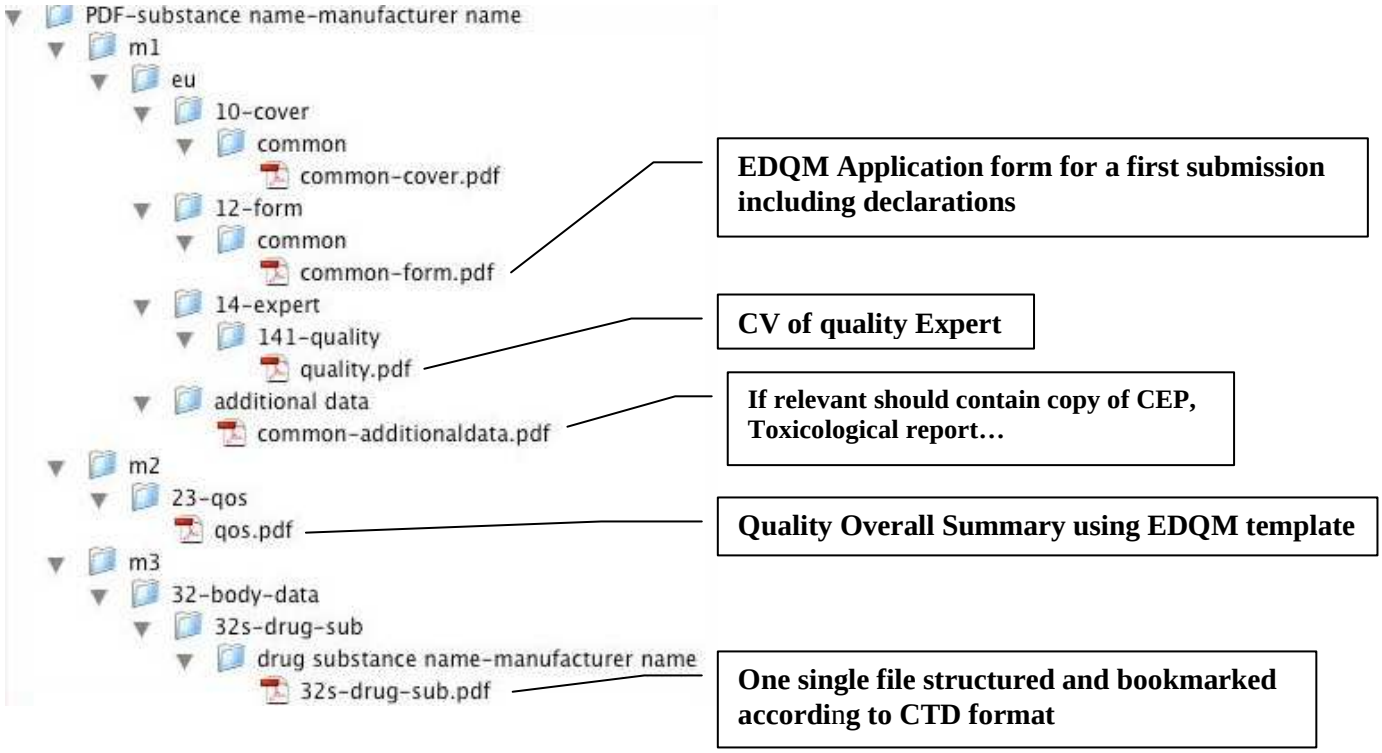



- **For revisions/renewal submissions**

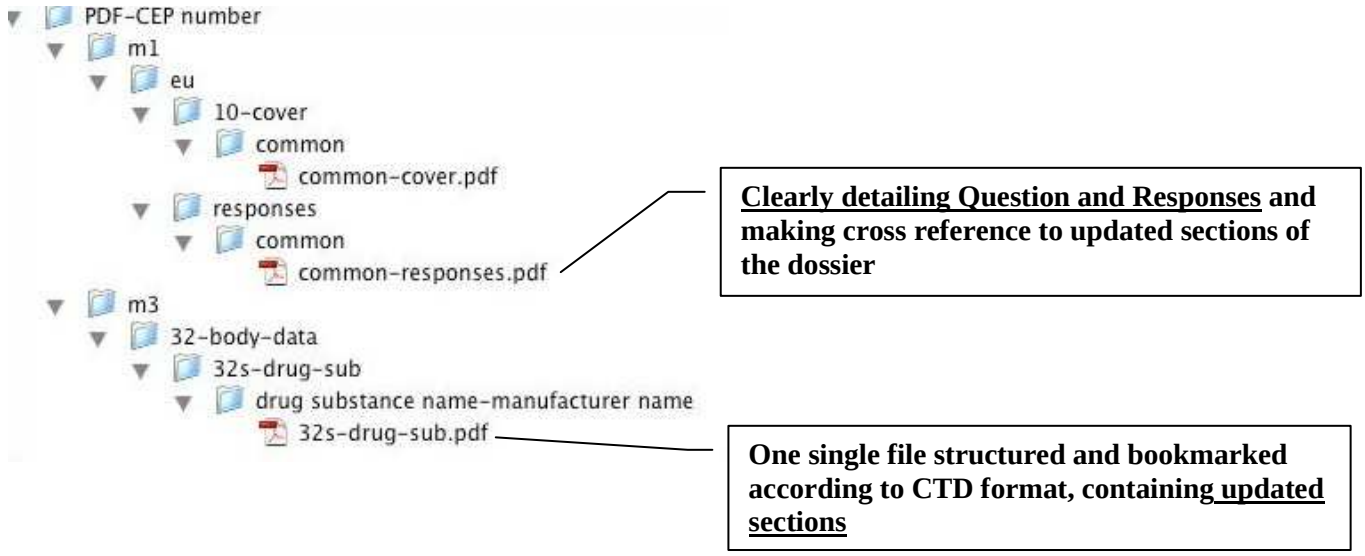


# ANNEX 3
## Single PDF structure, granularity and format

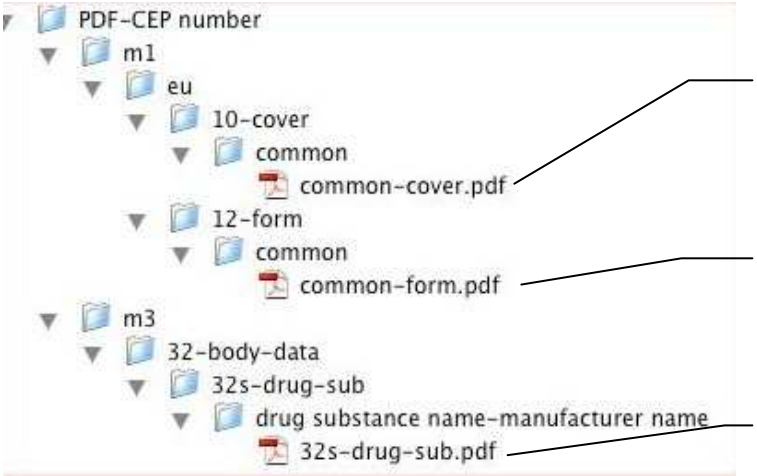
- **For the first submission (New Application)**




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



- **<u>For revisions/renewal submissions</u>**




**<u>Clearly detailing changes</u> 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 <u>updated sections</u>**