European Medicines Agency
*Evaluation of Medicines for Human Use*

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# PRACTICAL GUIDELINES ON THE USE OF THE eCTD FORMAT FOR:

## PLASMA MASTER FILE HOLDERS[1] (PMF-H)

## ALSO FOR MARKETING AUTHORISATION APPLICANTS/HOLDERS

***(for plasma derived medicinal products and medical devices that include a PMF certificate)*:**

## PLASMA MASTER FILE (PMF) PMF 2ND STEP PROCEDURE

[1] Whenever an MAH/applicant does not use the PMF certificate system, this guidance should also be used to prepare the plasma source part of the MAA dossier

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## Introduction/Background

From 1 January 2010, according to EMEA's revised Statement of Intent on electronic-only submission and eCTD submission, (see http://www.emea.europa.eu/htms/human/raguidelines/dossier_format.htm), it will be mandatory to use the eCTD format for all electronic submissions provided to EMEA in the context of Centralised Procedure marketing authorisation applications[2]. Until 1 January 2010, although EMEA will accept non-eCTD electronic submissions, eCTD remains the highly recommended format.

It is the intention that the eCTD format supports all marketing applications sent to EMEA, and related procedures. By analogy this is applicable also to submission of the Plasma Master File, meaning that it is in January 2010 that this guidance comes into force (although the eCTD format can, of course, be used for PMF submissions before this point and is indeed recommended).

For further practical information on the EMEA general requirements for eCTD and general guidance as to how to build an eCTD, Plasma Master File Holders and Applicants should refer to:

- EMEA Practical eCTD Question/Answer document: http://www.emea.europa.eu/htms/human/raguidelines/dossier_format.htm);
- The ICH eCTD specification (http://estri.ich.org/eCTD/index.htm); and
- The EU M1 eCTD Specification (http://esubmission.emea.europa.eu/eumodule1/index.htm).

Plasma Master File Holders and Applicants should treat this guidance as complementary to the 'Guideline on the Scientific Data Requirements for a Plasma Master File' issued by the CHMP (http://www.emea.europa.eu/pdfs/human/bwp/379403enfin.pdf).

## General Principle

Although the prescribed eCTD structure can accommodate the submission of data required for the PMF, it should be clarified that the eCTD PMF dossier remains a *stand alone* dossier and is distinct from the marketing authorisation eCTD dossier and lifecycle.
The PMF information should therefore *not* be additionally included/integrated into section 3.2.s.2.3 of the product-specific eCTD dossiers.

The PMF will be updated at least annually with the submission of the Annual update.
For the affected MAs, the PMF 2nd step will follow each PMF re-certification/variation. By logical extension, when there is a certification, re-certification or variation of the PMF, it is *not* required to send eCTD sequences containing the full updated PMF data for all existing concerned MA dossiers.

*(The 2nd step procedure should not involve a re-assessment of the information in the PMF (2001/83/EC as amended), and the inclusion of the full PMF package in the product dossier might trigger such a reassessment.).*

It is expected that the 2nd step procedure as reflected in the MAA dossier will normally be of a purely administrative nature. If a variation to the PMF has an impact on any part of the MAA dossier, then this should be reflected in the eCTD MAA dossier as a consequential variation application as appropriate.

[2] This does not apply for ongoing procedures. For the initial eCTD submission, PMF Holders and MAHs are advised to contact the responsible EMEA PMF project manager.

## Objectives of this Guideline

This guidance merely intends to indicate the specificities of using the eCTD format to present a PMF dossier in accordance with the CHMP PMF guideline

This guidance document therefore aims to address the specific requirements for the structure, format and presentation of an eCTD used to submit a Plasma Master File (PMF), or to present changes to a PMF within the certification procedure.

This guidance also intends to address the practical requirements for the use of the eCTD format for a 2nd step procedure after a PMF (re)certification/variation.

## 1. Structure of the eCTD Dossier for the PMF

The complete PMF scientific data package is made up of multiple files. The PMF data should be placed in module 3 under 3-2-s-2-3 control-of-materials within the eCTD structure.

Documentation should be included as per the CHMP guideline on the scientific requirements for the PMF (http://www.emea.europa.eu/pdfs/human/bwp/379403enfin.pdf), including the respective sub-sections described in the scientific guideline.

Documentation for the 2nd step should be in accordance with the EC guideline:
http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2004/july/vamfpmf.pdf

Other eCTD relevant modules (M1 and M2) and respective sections should be populated as appropriate with supporting documentation for the PMF itself (e.g. Cover Letter and Application Form in M1 (sections 1.0 and 1.2 respectively), and the Expert Statement (Quality Overall Summary) in M2).

### 1.1. File/Directory Structure vs. XML Backbone and Stylesheet/eCTD Review Tool

As described in the eCTD specification, the file/directory structure is the structure of folders and files that forms the eCTD submission, and which underlies the presentation of the files afforded by the use of the XML backbone and stylesheet. The file/directory structure used to submit the PMF data should be in accordance with the eCTD specification and beyond this should be logical, easily navigable and should group files into country-specific folders where appropriate. There are no specific recommendations/requirements for folder/directory names. These should merely be logical, succinct and indicative of contents.

It should be noted that, although the file/directory structure can be used directly to navigate through the submission, the more common method of navigation will be, at a minimum, via the XML backbone and the stylesheet which displays links to the files, or via a dedicated eCTD review tool.

### 1.2. Applicable/Non-Applicable Documents

Files listed in examples in this guidance should only be submitted if applicable to the submission in question.
As detailed in the EMEA's general eCTD guidance EMEA/596881/2007, blank placeholder documents for non-applicable files should *not* be included in the eCTD. If a scientific justification for a missing document is required, this should be included in the Quality Overall Summary or clinical/non-clinical overview.

### 1.3. Node Extensions

Node extensions and nested node extensions are allowed and should be used as necessary in the eCTD to achieve the required structure.

### 1.4. Granularity

In general, a lower level of granularity is preferred and information should be split into separate files as necessary (e.g. in chapter 2.2.2 "Testing of blood/plasma donations and pools for infectious agents, including information on test methods and, in the case of plasma pools, validation data on the tests used", the information can be split to a lower level of granularity into several PDF files). This approach facilitates the ongoing lifecycle management of the PMF.

### 1.5. Re-use of Content

In line with the eCTD principle of re-use of data, where the same file is applicable in more than one PMF dossier location (e.g. the Plasma Derived Product list in 1.1 of the PMF, and Annex A), a single document should be included in the underlying file/directory structure of the eCTD, and a hyperlink (xlink href) should be included in the XML backbone to the file for both relevant ToC locations.

### 1.6. Example eCTD Structure for the PMF

The example below shows a possible stylesheet view of an eCTD PMF submission:

- DTD nodes (e.g. m3-2-body-of-data) appear in **black** as in the official stylesheet. (Note that all module 1 section titles are displayed by the m1 stylesheet, whether the section is populated or not; in other modules, the section title is only displayed if the section is populated with file(s));
- Leaves are references to files in the eCTD, and each leaf has a leaf title which is not the same as the underlying PDF file name. Leaves appear in blue (because of the hyperlink to a PDF file). It is the suggested eCTD leaf title attributed to the file, *not* the underlying PDF filename, which is displayed in the example. The leaf titles displayed in the examples are intended as a guide only – other leaf titles can be used as appropriate.
- Node extensions (grouping of files, with a title) appear in brown (for information). Please note that in the current eCTD stylesheet, no dedicated colour for node extensions is defined; brown is used here in the example stylesheet view for instruction and clarification purposes only.
- Some leaves illustrated may not be applicable for all PMF submissions.
- Appendices illustrated are examples only.

### Module 1 EU

1.0 Cover Letter

Cover Letter (EMEA) [new]

1.2 Application Form[3]

Application Form (EMEA) [new]
Annex – Variation Application Form (EMEA) [new]
Annex – Letter of Authorisation (EMEA) [new]

1.3 Product Information

[3] Please note that *only* the application form and LoA are required to be placed in 1.2; all other annexes should be placed in M3 as shown in this guideline.

1.3.1 SPC, Labelling and Package Leaflet
1.3.2 Mockup
1.3.3 Specimen
1.3.4 Consultation with Target Patient Groups
1.3.5 Product Information already approved in the Member States
1.3.6 Braille

1.4 Information about the Experts

1.4.1 Quality

Information about the Expert – Quality [new]

1.4.2 Non-clinical
1.4.3 Clinical

1.5 Specific Requirements for Different Types of Applications

1.5.1 Information for Bibliographical Applications
1.5.2 Information for Generic, 'Hybrid' or Bio-similar Applications
1.5.3 (Extended) Data/Market Exclusivity
1.5.4 Exceptional Circumstances
1.5.5 Conditional Marketing Authorisation

1.6 Environmental Risk Assessment

1.6.1 Non-GMO
1.6.2 GMO

1.7 Information relating to Orphan Market Exclusivity

1.7.1 Similarity
1.7.2 Market Exclusivity

1.8 Information relating to Pharmacovigilance

1.8.1 Pharmacovigilance System
1.8.2 Risk Management System

1.9 Information relating to Clinical Trials

1.10 Information relating to Paediatrics

Reponses to Questions[4]

Responses to Questions - EMEA [new]

Additional Data[5]

Additional Data – EMEA - Commitment [new]

[4] The section 'Responses to Questions' is to be used for the answers to LoQs, including attachments.
[5] The section 'Additional Data' is to be used for responses to FUMs, including attachments.

## Module 2

- m2-3-quality-overall-summary

  Quality Overall Summary [new] [6]

## Module 3

- m3-quality
  - m3-2-body-of-data
    - m3-2-s-drug-substance [manufacturer: manuf] [substance: subst]
      - m3-2-s-2-manufacture
        - m3-2-s-2-3-control-of-materials
        - PMF Annual update module

          1. Annex I - Summary of all changes *(link to section annexes)*

          2. List including cases, over previous year, for which it was retrospectively found there were indications that a donation contributing to a plasma pool was infected with HIV or hepatitis, A, B, or C

          3. List including number of positive donations that have been identified per viral marker by NAT testing at the fractionator level including minipool testing. (If NAT testing of minipools is performed by PMF holder, results of the NAT testing should be provided, including the number of minipools tested and positive donations identified)

        - PMF Dossier Integrated[7] - (in accordance with Sc. Requirements guideline)
          - 1. General Information (Summary)
            - 1.1 Plasma Derived Product list [new] [8]
            - 1.2 Overall Safety Strategy [new]
            - 1.3 General Logistics (flow chart) [new][9]
          - 2. Technical Information on Starting Materials
            - 2.1 Plasma Origin
              - 2.1.1 Information on centres in which collection is Carried Out [new]
              - a) Blood establishments and centres[10] [new]

[6] Expert Statement, (applicable to initial applications for certification and type II variations, including The Annual Update whenever thisincludes changes/type II variations. Link to 1.2 Overall Safety Strategy in Module 3
[7] This applies for all submissions; initial certifications and recertifications (variations, annual updates)
[8] See Annex A
[9] Descriptive file, linked to actual flow chart in Appendix I

- b) Characteristics of donations [new]
- c) Epidemiological data on blood transmissible infections[11] [new]
- 2.1.2 Centres Testing Donations and Plasma Pools [new] [12]
- 2.1.3 Selection/Exclusion Criteria for Blood/Plasma Donors [new]
- 2.1.4 Traceability [new]

- 2.2 Plasma Quality and Safety
  - 2.2.1 Compliance with Ph. Eur. Monographs [new]
  - 2.2.2 Testing of Blood/Plasma Donations and Pools [new]
  - 2.2.3 Characteristics of bags for blood and plasma collection [new]
  - 2.2.4 Conditions of Storage and Transport of Plasma [new] [13]
  - 2.2.5 Procedures for any Inventory Hold Period [new]
  - 2.2.6 Characterisation of the Plasma Pool [new]
- 2.3 Contractual Arrangements with Plasma Suppliers [new]

- Annexes
  - Annex A – List of plasma Derived Products [new]
  - Annex II – Information on Centres [new]
  - Annex III – Information on Test Labs [new]
  - Annex IV – Information on Storage Establishments [new]
  - Annex V – Information on Transport Establishments [new]

- Appendices [14]
  - Appendix 1 – Flow Chart of Supply Chain [new]

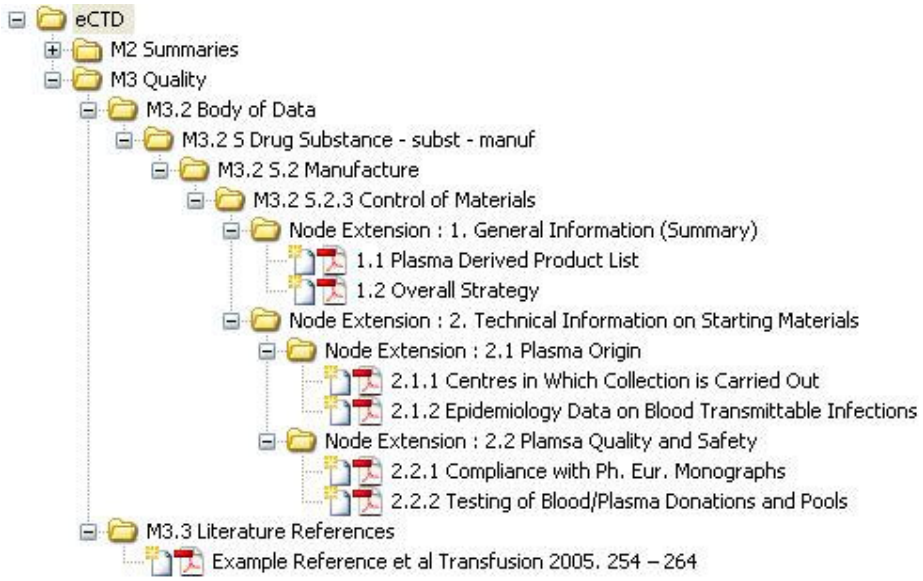
[10] See EMEA/CHMP/BWP/3794/03 (current version) also, include link to Annex II
[11] See EMEA/CPMP/125/04 (current version) also include links to relevant appendices
[12] See Annex III
[13] See Annexes IV and V
[14] Appendices listed are examples only

- Appendix 2 – Epidemiological Data FTD [new]
- Appendix 3 – Epidemiological Data RTD [new]
- Appendix 4 – List of Test Kits: Serological Testing Kits [new]
- Appendix 5 – List of Test Kits: NAT Testing Kits [new]
- Appendix 6 – List of blood bags and bottles [new]
- Appendix 7 – Minipools NAT [new]
- Appendix 8 – Pool Testing[15] – serology [new]
- Appendix 9 – Pool Testing – NAT [new]

- m3-3-literature-references
  - Example Reference et al Transfusion 2005. 254 – 264 [new]

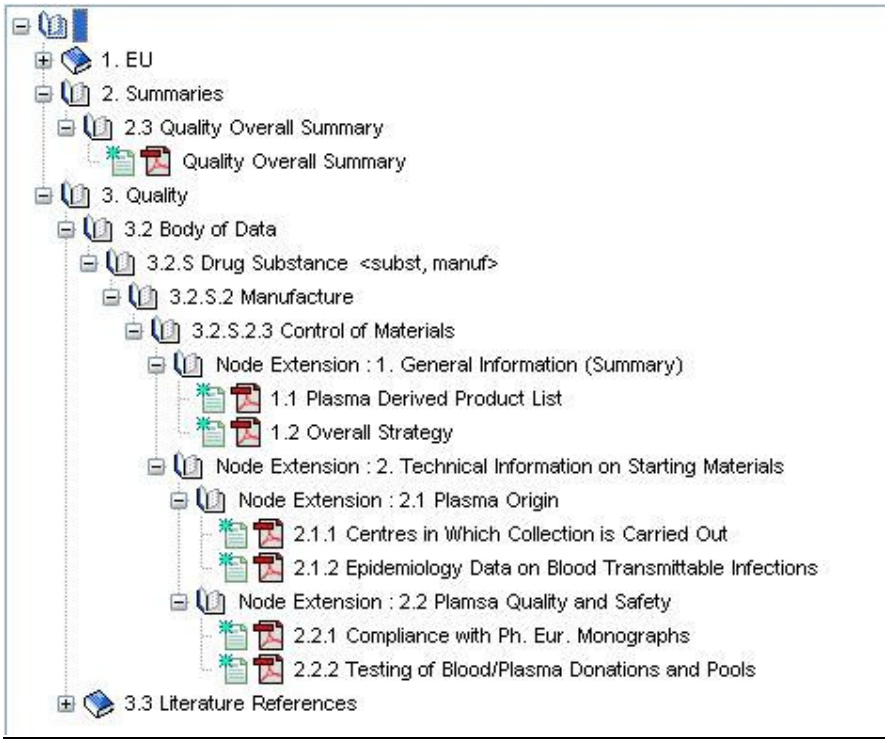
Two examples of how the structure may be displayed within eCTD tools are shown in figures 1 and 2 below (please note not all files required are displayed in these examples – they are intended to indicate basic structure only)

Figure 1




[15] CE/Non CE

Figure 2




## 1.7. Documents required for the PMF 2nd Step Submission within the Product eCTD Structure

For a 2nd step PMF submission within a Marketing Authorisation, only, the following documents should be provided for the corresponding eCTD:

### Module 1 EU

- 1.0 Cover letter
- 1.2 Application form
- 1.2 Certificate of Compliance

### Module 2

- 2.3 Expert Statement regarding the impact (if any) of the PMF on the concerned medicinal product(s)[16]

Submissions should otherwise be built in line with the eCTD guideline for MAAs as regards structure/placement, envelope elements and metadata.

[16] This is the Quality Overall Summary.

## 2.0. Envelope Elements and Metadata for the PMF Certification/Recertification Dossiers

This section describes how the envelope elements (*see glossary*) and leaf metadata should be used in the eCTD when submitting PMF dossiers.

The relevant administrative particulars (e.g. application number, applicant name) for the submitted eCTD dossier are filled in/populated in the eCTD using the envelope elements. Generic information on the eCTD envelope and the mandatory/optional elements is provided in the EU eCTD module 1 specification. (http://esubmission.emea.europa.eu/eumodule1/index.htm)

The information provided in the envelope is very important and is used to identify, display and group the individual eCTD submission dossiers, and is also automatically extracted by the review tools (software) for dossier display.

The particular envelope elements used by the EMEA's eCTD review tool for the display and management of submissions, and that *must* be populated by the PMF Holder, are: <sequence number[17]>; <application number>; <applicant>; <submission type>; and <submission description>.

Some of the key envelope elements must be populated using a pre-defined pick-list of values. Others allow the inclusion of free-text. It is acknowledged that at present, for those envelope elements where the value must be chosen form a pre-defined list (most notably the envelope element <submission type>), the eCTD EU M1 specification pick list *does not currently include values specific to the Plasma Master File*. The existing available values should therefore be used to identify the submission type, as indicated below.

### 2.1. Notes on PMF dossier Particular Envelope Elements:

1. <Submission Type>

| Type of Submission | eCTD <Submission Type> Value to be Selected: |
|---|---|
| ○ Initial PMF Certification submission | 'initial-maa' |
| ○ Annual Update of the PMF re-certification | 'annual-reassessment' |
| ○ Other Subsequent recertifications: | |
| ▪ Type IA Variation | 'var-type1a' |
| ▪ Type IB Variation | 'var-type1b' |
| ▪ Type II Variation | 'var-type2' |
| ▪ Transfer of PMF Holder | 'transfer-ma' |
| ○ PMF 2nd Step | 'supplemental-info' |

[17] Indicates "versioning" for a dossier indicating from the initial submissions how many times has been updated. (one dossier application or one procedure can comprise several sequences.)

2. <Submission Description>

   In all cases, the free-text envelope element <submission description> should be used to describe the scope related to the PMF and to further identify the submission as relating to a Plasma Master File, or a PMF 2nd Step. The contents of the <submission description> envelope element should be concise but clearly indicative of the exact content of the submission. The submission description should not exceed 200 characters.

3. <Application Number>

   This is key envelope element which identifies and allows sorting of the PMF certification submissions/application procedures. The <Application Number> envelope should always be filled in/populated to indicate that the submission relates to the PMF.

   The <Application Number> should follow this convention:

   <EMEA>/<H>/<PMF holder ref. number>/<initial submission year[18]>/<type of change for variations or transfers>/<procedure number (if applicable)>, all separated by slashes e.g.:

   EMEA/H/PMF/000123/08
   EMEA/H/PMF/000123/08/I/01

4. <ATC>

   This envelope element is not applicable for the PMF dossier.
   Where an envelope element is not applicable, please indicate 'Not Applicable' rather than leaving the element blank.

5. <Invented Name>

   This envelope element is not applicable for the PMF dossier.
   Where an envelope element is not applicable, please indicate 'Not Applicable' rather than leaving the element blank (particularly as this element is mandatory so cannot be left blank).

6. <INN>

   This envelope element is not applicable for the PMF dossier.
   Where an envelope element is not applicable, please indicate 'Not Applicable' rather than leaving the element blank

A typical envelope for a PMF submission may therefore look similar to the example below:

| **Envelope for EMEA** | |
|---|---|
| Application Number: | EMEA/H/PMF/000123/04/AU/006 |
| Applicant: | PMF Pharmaceuticals Ltd. |
| Agency: | EMEA - European Medicines Agency (EU-EMEA) |

[18] Date format should be YY

| | |
|---|---|
| ATC: | Not Applicable |
| Submission: | Annual Reassessment |
| Procedure: | Centralised Procedure (CP) |
| Invented Name: | Not Applicable |
| INN: | Not applicable |
| Sequence: | 0007 |
| Related Sequence: | 0005 |
| Submission Description: | *Brief listing of the Annual Update 2009 plasma master file changes* |

### 2.2. Leaf Attribute Meta Data

Regarding other eCTD attributes, it is recommended that the substance and manufacturer leaf attributes are utilised and indicated at the level of m3.2.s.2.3-control of materials. The substance will normally be 'human plasma'.

## 3.0. File Formats

The EMEA accepts file formats in compliance with the current ICH eCTD specification document http://estri.ich.org/eCTD/index.htm and the current EU Module 1 specification document http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm.

It is expected that the vast majority of the PMF dossier files will be PDF.

However, Word copies of Annexes A and II – V are required in addition to the PDF for the purposes of review.
Word documents are considered as an aid to review and are not a formal part of the eCTD submission. The following principles apply to the submission of Word documents in parallel to the eCTD:

- Word documents should *not* be included in the eCTD backbone, as they are provided merely as an aid to review. Inclusion within the eCTD would require unnecessary management of the lifecycle of these documents in addition to the PDF documents.
- Word documents required for review should be located in a separate folder to the eCTD (named 'Word documents') and not referenced in the XML backbone, but made available on the same hard media (CD/DVD).
- For submissions made in support of the product lifecycle, both 'clean' and 'track changes' copies should be provided where applicable. These 'track changes' copies should be located at the end of the PMF together with the annexes/appendices and/or throughout the PMF text, where relevant.
- An indication should also be given in the filename as to whether the document is 'clean' or 'highlighted', if applicable. (This indication should also be given for PDF files in the eCTD leaf title).

Application Form Specifics

The application form should be submitted in PDF format. A scanned embedded handwritten signature, or a flattened electronic signature, is required in the form (in accordance with EMEA's general practical eCTD guidance EMEA/596881/2007)

## 4.0. Filenaming

An important distinction should be made between the use of *PDF file names* in the eCTD, and the use of *leaf titles* to identify files and sections of the submission. This is further explained in the eCTD specification.

The eCTD submission content is made up of multiple files (usually PDF) and folders. Each file and folder has its own name as well as being linked to a corresponding eCTD "<leaf> element. Each <leaf> element, with its associated attributes, provides important information on the file. One of these Leaf elements or attributes is the **leaf title**.

Both the PDF filename *and* the leaf title are used to identify and describe each file in the eCTD, but the leaf title does not have to be the same as the PDF filename given to the file. It is the PDF filename that is seen if navigation through the dossier is done via a direct view of the files and folders, but it is the leaf title that is displayed/ seen if the XML backbone and stylesheet or a dedicated eCTD review tool is used to navigate through the submission.

Usually, a dedicated review tool that displays only the leaf titles for documents, not the underlying PDF filenames, will be used for assessment of the PMF and lifecycle.

### 4.1. PDF Filenames

The PMF eCTD PDF file naming convention must be in accordance with the eCTD specification. (See http://estri.ich.org/eCTD/eCTD_Specification_v3_2.pdf, page 6-1)

There are certain limitations to the PDF file/directory names, such as the forbidden use of special characters (e.g. '/'), the name length of a single folder or file cannot exceed 64 characters (including the extension) and only lower-case font should be used in all file and directory (folder) names. The maximum length of a path is 230 characters, including file name, and extension. All parts of the file name should be separated by hyphens.
It is important the convention is followed to avoid technical validation issues and truncation of the link/path to the actual documentation.
Specific recommendations on the use of particular PDF file (and folder) names are not provided in this guidance. PDF file and folder names should simply be succinct, descriptive to allow easy identification of files/folders and differentiation between various files, and should contain an indication of country if applicable.

### 4.2. eCTD Leaf Titles

There is no limitation on the length of eCTD leaf titles, meaning that information required to label the PMF sections/subsections/files according to scientific requirements (http://www.emea.europa.eu/pdfs/human/bwp/379403enfin.pdf) can be accommodated.

Although the full section title listed in the scientific guidelines need not be applied using the leaf title (many titles would then be too long to easily navigate), the leaf titles should be used to ensure that the leaf can easily be identified as relating to a particular part of the scientific guideline. Country should be indicated in the leaf title where appropriate, at least for the cover letter, application form and additional data.

eCTD Leaf titles should be succinct, clear and indicative of content.
Suggested leaf titles for PMF data required are provided in the example in section 1.5 of this guideline.

Additional leaf titles may be required to present meaningful information to the reviewer, particularly for chapters of the PMF that can contain multiple files.

## 5.0. Lifecycle and Sequencing

It is intended that the PMF will exist as a standalone dossier, separate from the marketing authorisation applications that are affected by it. The lifecycle of the PMF should therefore be managed independently.

### 5.1. eCTD Baseline Submission

The eCTD baseline submission is the first officially submitted dossier in eCTD format, for applications previously managed in paper or other electronic formats.

Although there is no obligation to do so, it is highly recommended that PMF Holders converting the PMF dossier to the eCTD format first submit such a 'baseline' eCTD dossier to all MS as well as to the MAH, when applicable.

Such a baseline is not directly associated with any procedure to the PMF; instead it is merely a conversion of the current certified PMF into the eCTD format, with no change in content.

When a PMF holder wishes to submit the CTD baseline, it is advisable that this is submitted at least 3 weeks in advance of a PMF procedure.

In the case of submission of a baseline, a signed declaration from the PMF Holder must be provided as an annex to the Cover Letter, stating that the content/data of the submitted modules in eCTD format is identical to the currently approved PMF, and that there have been no changes to the dossier content as a result of the provision of an eCTD submission. (Similar principles apply as when changing from the 'old' EU-format (NTA, Volume 2B, 1998) into the new EU-CTD-format (NTA, Volume 2B, 2001). Reference is made to the "Questions and Answers on the Presentation and Content of the Common Technical Document (CTD)", published on the European Commission website: (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm#2b).

The reformatted PMF eCTD submission will not be assessed. It will merely be loaded into eCTD review tools to serve as a baseline as the name suggests, to facilitate future eCTD lifecycle management of the PMF.

The baseline eCTD submission should be sequence 0000[19], regardless of the current submission tracking, as this marks the beginning of the tracking of the lifecycle in the eCTD. The Cover Letter should clearly indicate that the baseline submission does not form part of a procedure as such and is not for review, but is merely provided as an eCTD 'baseline' and an aid to lifecycle management. The envelope element <submission type> chosen for this reformatted submission should be '**reformat**' (available in current EU M1 v1.3). The <submission description> envelope element should be used to clearly indicate the baseline nature of the submission.

The baseline should contain the current full PMF certified data.

[19] In the exceptional circumstances the sequence number may not be 0000, PMF-H need to liaise with the Agency in such cases.

## 5.2 Updates to the PMF Dossier Sections

When there is any change to the PMF data, in line with general eCTD principles, only changed sections should be submitted, not the entire PMF (with the exception of the first submitted eCTD baseline sequence).

If the PMF-Holder wishes to covert to eCTD at the time of a variation, it is recommended that before the actual variation is submitted, a full baseline eCTD sequence 0000 is first submitted as described above, which will not be assessed, Any updated sections for review associated with the variation should be subsequently sent as a following sequence 0001, including the envelope metadata appropriate to the type of submission).

If the first eCTD submission to be sent is an Annual Update, then the full PMF should simply be sent as sequence 0000 (no need for a baseline in addition).

With the conversion to eCTD or any subsequent eCTD update submission (recertification procedure), it is important to ensure that all NCAs/MAHs receive the same eCTD sequences to allow the full PMF dossier to be displayed. The initial PMF (sequence 0000) and all subsequent sequences (sequences 0001 – xxxx) with updated sections should therefore be submitted to EMEA, MAHs and all NCAs to allow the loading into eCTD review tools and full local lifecycle management by all parties, and thus ensure that the PMF dossier (eCTD) is updated throughout.

## 5.3. File Operation Attributes

All files should have file operation attributes as appropriate: “New”, “Replace”, “Append”, or “Delete”. (*see glossary*).
In the case of the initial PMF certification submission, all file operation attributes should be ‘New’, and for the subsequent (re)certifications, these should change as appropriate during the lifecycle of the PMF.

## 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***. |
| Application | A collection of documents compiled by a pharmaceutical company or its contractor in compliance with European legislation and guidelines in order to seek a marketing authorisation or any amendments thereof. The entire lifecycle of an application may be represented by a number of submissions/sequences. |
| eCTD | eCTD stands for 'Electronic Common Technical Document'. This standard has been developed by the ICH M2 Expert Working Group and is maintained by the eCTD Implementation Working Group.<br>The eCTD includes, amongst other components, an XML backbone describing the submission structure and linking to individual files, an 'envelope' containing metadata describing the submission, operation attributes describing the lifecycle status of each file, and a leaf title for each file that is another way of identifying the file (in addition to the filename). |
| Submission (or Sequence) | Refers to a single set of information and/or documents supplied/submitted by the applicant as a part of, or as the complete, Application. (In the context of eCTD, this is equivalent to 'sequence'). |
| Envelope | The 'envelope' is a component of the eCTD submission which contains metadata (see below) concerning the submission. The envelope information (e.g. name of product, name of PMF Holder/applicant), can facilitate processing of the eCTD submission. |
| Envelope Metadata | A set of key values describing the overall eCTD contents upon submission. Metadata includes particulars in relation to the dossier submission. (Meta data on a document level is also included within the eCTD - examples for metadata on a document level include versioning information, language, descriptive information such as document names manufacturer, the type of submission, and related data items |

| *Term* | *Definition* |
|---|---|
| | etc). |
| Submission Type | This is an element in the eCTD envelope metadata, and describes the type of submission material sent to the regulatory agency. There is a pre-defined pick-list of valid values for submission type. (e.g. variation types) |
| File Operation Attributes | These are a set of values that describe the lifecycle status of each file in any eCTD submission. There are 4 operation attributes: 'New' (no effect on any file previously submitted in an eCTD); 'Append' (information in the file is submitted in addition to information previously submitted in an eCTD file); 'Replace' (the file replaces a file previously submitted in an eCTD), and 'Delete' (the file in question should no longer be considered in the assessment) |
| Leaf Title | The eCTD content is made up of multiple files. The eCTD contains a "<leaf>" element for each of these files.<br>The leaf title is used to easily identify the file when using a dynamic table of contents or eCTD review tool. Each <leaf> element has associated attributes that provide important information on the file to which the leaf element relates, including the location of the file in the folder structure, its unique ID, version number and a meaningful title. |
| Node Extension | Node extensions are a way of providing extended organisational information in the eCTD. The node extension should be visualised as an extra heading in the CTD structure and should be displayed as such when the XML backbone is viewed. |
| Procedure | Refers to the types of Community registration procedure for the authorisation of medicinal products in the European Community, which are: the Centralised, Decentralised, Mutual Recognition and National Procedures. |

If your questions are not adequately addressed by this document, please forward your query or comment to **eCTD@emea.europa.eu.**

Based on ongoing experience with the eCTD PMF and 2nd step submission, this guideline will be revised as necessary following publication.

Document Revision History:

| Version | Date | Details |
|---|---|---|
| 0.1 | December 2008 | Intial Draft |
| 0.2 | January 2009 | Revision following comments from SD, KB (EMEA) |
| 0.3 | May 2009 | Proposed final version following industry comments |
| 0.4 | June 2009 | Revision following final industry comments |
| 0.5 | July 2009 | Final revision following further industry and PMF group comments |
| 1.0 | August 2009 | All comments implemented for publication |