European Medicines Agency
Evaluation of Medicines for Human Use

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With PPTA comments

PRACTICAL GUIDELINES FOR

PLASMA MASTER FILE HOLDERS[1] (PMF-H)
ON THE
eCTD FORMAT:

PLASMA MASTER FILE (PMF)

PPTA General comments:

The intention of the PMF system is that the PMF dossier is a stand alone dossier. If it is the aim to additionally include the documentation into section 3.2.S.2.3. of an approved Marketing Authorisation dossier, this would contradict the philosophy of the PMF being a stand alone dossier. This point should be clarified.
It should be indicated, where the Annexes should be placed in the eCTD-PMF? Specifically a. Annex A b. Annex 1: Checklist on the Annual Update c. Annex II: Information on Centers d. Annex III: Information on Test Labs e. Annex IV: Information on Storage Establishments f. Annex V: Information on Transport Establishments The Annexes should only be submitted once in one defined position in the eCTD.
Currently, PMF holders have to submit the Annexes in pdf- and word-format, as well as in clean and track-changes versions. Guidance should be provided on how the word-files (and the additional track-changes versions) of the annexes should be submitted with the eCTD.
It would be appreciated to get exact instructions about the pdf file name and the corresponding directory (folder name). Reference is made to page 4-12 of the ICH eCTD specification, version 3.2.2. The examples given in the draft guidelines cannot be used for pdf file names and directory as they are far too long and include special characters (e.g.: /).For the submission of the 2nd step, please advise how to fulfil the requirements of the Belgium eCTD requirements. The required pdf file name is 'control-of-materials VAR'.pdf
It should be specified where the epidemiology data report tables have to be presented, for example in the Appendices chapter or in Section 3.2.S.2.3.2.1.2
Filename suggestions should be clearly visible in the guidance and not "hidden" in hyperlinks.

[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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 16
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Sequence information for the PMF is missing in the guidance. Are PMF holders to start with 0000, when they submit a PMF application in the eCTD format for the first time – regardless of the actual current submission tracking? Are references to previously submitted PMF versions possible, e.g. if the first eCTD submission would be a variation to the PMF?
Guidance on other submission attributes and how to use the attributes in the context of the PMF would be helpful.
Current PMF guideline asks for the complete dossier/data package of the PMF to be resubmitted at the time of the annual update. That would not make a whole lot of sense with the eCTD. In the sense of the eCTD only those sections that have changed from the previous lifecycle would be submitted. Clarification is needed.
Is it anticipated that the vendors/tools accommodate the listed node extensions as part of new a DTD [as in provided TOC] or is the expectation that the applicant build in the folder structure, like current DTD?
In addition it seems that the specific second step documents are missing: a. The PMF certificate of compliance with Community legislation, together with the b. evaluation report attached. c. An Expert statement, outlining the applicant's view of the impact (or non-impact) d. Of the PMF to each concerned medicinal product(s). e. A signed declaration stating that the PMF data package and certificate of Compliance are fully applicable to the concerned medicinal product(s).

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/genguidance/genreg.htm), it will be mandatory to use the eCTD format for all submissions provided to EMEA in the context of Centralised Procedure applications. 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 PMF application submissions.

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

- EMEA Question/Answer document: http://www.emea.europa.eu/htms/human/genguidance/genreg.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).

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

Objective of this 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.

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 an eCTD Implementation Working Group. 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 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)

Term	*Definition*
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. 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. (Use of node extensions is, however, generally discouraged and should only be done when there is no other feasible means to submit information in the correct regulatory structure).
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.

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1. USE OF THE eCTD TO SUPPORT THE PMF LIFECYCLE

PPTA comment:

Regarding the structure given in the draft guidelines, a substructure for chapter 1, General Information is missing. The guideline on the scientific data requirements for a plasma master file (PMF) Revision 1 lists 3 subchapters, which in our experience are necessary and are covered by the lifecycle. We would propose to introduce a substructure for chapter 1 on general information.

1.1 Structure of eCTD

Structure and Location of the PMF Package in the eCTD

The complete PMF scientific data package is made up of multiple files (see chapter 1.2 in this doc.).
The PMF should be placed in module 3 of the eCTD, under m3-2-s-2-3-control-of-materials, including the documentation structure as required by the CHMP guideline (http://www.emea.europa.eu/pdfs/human/bwp/379403enfin.pdf), and the respective sub-sections should be created using the same numbering and order.
Node extensions can be used as necessary, although are generally discouraged unless absolutely necessary.
PPTA Comment:
Node extension should be allowed, especially for PMF chapters in which a lot of information is presented in multiple documents, e.g. 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". In this chapter the testing information including validation reports is to be presented. Combining all the different documents into one pdf-file for this chapter is not feasible.

Other eCTD relevant modules (M1 or M2) and respective sections should be populated as appropriate with supporting documentation for the PMF (e.g. Cover Letter and Application Form in M1 (section 1.0 and 1.2 respectively), and the Expert Statement (overall summary) in M2).
PPTA comment:
What does the expert statement refer to? – to the expert statement required according to the 2nd step guideline or to the QOS of the product dossier (implying this would have to be updated with each 2nd step procedure)?

File Operation Attributes

All files should have file operation attributes as appropriate: “New”, “Replace”, “Append”, etc. (*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.
PPTA comment:
Please confirm: Regarding the procedure type: For the submission and the answer to a LoQ we believe that this is CP, for the submission of the 2nd step this will be national – at least as long as the eCTD EU M1 specification has not been changed.

Sub-Section Names

Names should all be in accordance with the PMF Guideline.

1.2 File Naming and Leaf Titles

Both the PDF filename and the leaf title are used to identify and describe the file in the eCTD (these are separate elements). EMEA will view the eCTD using a dedicated review tool that displays only the leaf titles for documents, not the underlying PDF filenames.
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**.

Filenames

PPTA comment:

The filenames as suggested in the guidance only cover the nodes as listed. Furthermore, filename suggestions are missing for some chapters.

Filename suggestions should be clearly visible in the guidance and not "hidden" in hyperlinks. Some filenames could be shortened using certain commonly accepted acronyms instead of complete words. Are there plans to further clarify the element level eCTD titles /filenames? What about the files in the respective chapters, especially in Section 2.2.2.?

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, such as 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.
It is important the convention is followed to avoid technical validation issues and truncation of the link/path to the actual documentation.

Leaf Titles

PPTA comment:

Additional leaf titles may be needed to present meaningful information to the (re)viewer, especially for chapters that contain multiple files (also refer to comment on node extensions above).

There is no limitation on the length of naming of leaf titles, meaning that required can be accommodated. For this reason, the eCTD leaf titles should be used to label the PMF “section/subsection titles” rather than the filenames assigned to the PDF files,
The names to Leaf titles should be in accordance with the PMF guideline (http://www.emea.europa.eu/pdfs/human/bwp/379403enfin.pdf).

Suggested leaf titles applied to additional files submitted with the PMF in modules 1 and 2 are as follows:
PPTA comment:
Up to now we do not have an application form for the 2nd step procedure. Application form for the 2nd step procedure needs to be provided.

M1:

- m1.0-cover letter
    - 1.0 Cover Letter [new]
- m1.2-application form

PPTA comment:

Add the missing (and required) country code in the structure of the relevant sections in Module 1 (cover letter, application form, additional data).

- 1.2 Application Form [new]

PPTA comment:

Please clarify which format should be used for the Application Form – pdf or xml? Will the currently available Application Form for the PMF be adjusted? What about signatures? Filename suggestion is

missing in guidance.

In general: all Annexes should be attached to the specific section e.g. Annex II attached to 3.2.S.2.3.1.1

- 1.2.1 Annex I [new]

PPTA comment:

Is that meant to be "Annex I: Checklist on the Annual Update" or the Annex to the Application Form? Filename suggestion is missing in guidance. Please clarify and add filename suggestions.

- 1.2.2 Annex II [new]

PPTA comment:

Which Annex II is specifically referenced here? What about Annex A & Annexes III, IV & V? Please clarify and add filename suggestions.

- m1.4-information about the experts
  - 1.4.1 Quality [new]

PPTA comment:

Not required according to relevant CHMP guideline.

- additional data
  - Letter of Authorisation [new]

PPTA comment:

"Where applicable" should be added in the guidance, since an LoA may not be needed in all cases. Add filename suggestions.

M2:

- M2-3-quality-overall-summary3-
  - Quality Overall Summary [new]

PPTA comment:

Is this to be what is currently called the "Expert Statement"?

Should the information that is currently presented in chapter 1.3 "Overall Safety Strategy" also be included in this chapter?

Not required according to CHMP Guideline.

Please clarify and add file name suggestions

Below is shown the relevant M3 table of contents for a new PMF dossier, when viewed in HTML via the style sheet. All the titles below are the Leaf titles. Filename refers to the actual name of the PDF file.

- m3-2-s-2-3-control-of-materials
  - 3.2.S.2.3 Control of Materials [new]

PPTA comment:
What kind of information is expected in this file? PMF Cover page (and/or TOC)?

Annexes: Plasma Derived Product List etc should be attached to this file.

- 3.2.S.2.3.1 General information (Summary) [new]

PPTA comment:

Should this chapter contain all three chapters currently included in the PMF – i.e. 1.1 General Information; 1.2 Plasma Derived Products List; and 1.3 Overall Safety Strategy?

- 3.2.S.2.3.2 Technical Information on Starting Material
  - 3.2.S.2.3.2.1 Plasma origin
    - 3.2.S.2.3.2.1.1 Information on centers or establishments in which plasma collection is carried out, including inspection and approval, and epidemiological data on blood transmissible infections [new]

PPTA comment:

Should this chapter include the narrative text sections/explanation regarding the list of collection centers?
Should the epidemiology data also be presented here?
All in one file or multiple files?
What is the difference between 3.2.S.2.3.2.1.1 and 3.2.S.2.3.4.1, both referring to the "information on centers or establishments in which plasma collection is carried out"?

    - 3.2.S.2.3.2.1.2 Information on centers or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status [new]

PPTA comment:

This chapter currently contains multiple (partly large) files, e.g. validation information on pool tests etc. How should this be handled in particular?

Additional nodes may be needed to present meaningful information. Combining multiple documents about different methods into one pdf-file for this chapter is not feasible (also see comment above).

    - 3.2.S.2.3.2.1.3 Selection/Exclusion criteria for blood/plasma donors [new]
    - 3.2.S.2.3.2.1.4 System in place which enables the path taken by each donation to be traced from the blood/plasma collection establishment through to finished product and vice versa [new]
  - 3.2.S.2.3.2.2 Plasma quality and safety
    - 3.2.S.2.3.2.2.1 Compliance with European Pharmacopoeia monographs [new]
    - 3.2.S.2.3.2.2.2 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 [new]
    - 3.2.S.2.3.2.2.3 Technical characteristics of bags for blood and plasma collection, including information on anticoagulant solutions used [new]
    - 3.2.S.2.3.2.2.4 Conditions of storage and transport of plasma [new]
    - 3.2.S.2.3.2.2.5 Procedures for any inventory hold period [new]
    - 3.2.S.2.3.2.2.6 Characteristics of the plasma pool [new]
- 3.2.S.2.3.3 Contractual Arrangements with Plasma Suppliers [new]
- 3.2.S.2.3.4 Appendices

Appendix 3.2.S.2.3.4.1 Information on centers or establishments in which blood/plasma collection is carried out [new]

PPTA comment:
What is the difference between 3.2.S.2.3.2.1.1 and 3.2.S.2.3.4.1, both referring to the "information on centers or establishments in which plasma collection is carried out"?

This seems to be Annex II.
Are the all PMF Annexes to be placed in this Chapter?
Information on Annex A, Annex 1, Annex III, IV and V is missing in the guidance.
Please clarify and add file names.

1.3 Envelope Elements and Metadata

The relevant administrative particulars/elements (e.g. application number, applicant) for the submitted dossier are filled in/populated in eCTD using the so-called "Envelope elements".
The information provided in the envelopes 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.

This section describes how the envelope elements (*see glossary*) should be used in eCTD. This information also indicates the relationships between individual submissions/sequences for effective lifecycle management of the application.

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[2]>; <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 include values specific to the Plasma Master File. The existing available values should therefore be used to identify the submission type.

Envelope Elements:

1. <Submission Type>

Type of Submission	eCTD <Submission Type> Value to be Selected:
o Initial PMF Certification submission	'initial-maa'
o Re-certification/Annual Update of the PMF	'annual-reassessment'
o Other Subsequent Submissions:	
▪ Type IA Variation	'var-type1a'

[2] 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.)

- Type IB Variation ‘var-type1b’
- Type II Variation ‘var-type2’
- Transfer of PMF Holder ‘transfer-ma’

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. 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> (e.g. PMF/000015/08/II) follows this convention:
   <PMF>/<PMF number><initial submission year>, <type of change for variations or transfers> and the PMF Holder name, all separated by slashes
   e.g.: PMF/000011/08/PmfholderX , PMF/000012/07/IA/004/PmfholderX
   If your questions are not adequately addressed by this document, please forward your query or comment to **eCTD@emea.europa.eu.**

Figure 1.

CTD TOC

Document Revision History:

Version	Date	Details
0.1	December 2008	Intial Draft
0.2	January 2009	Revision following comments from SD, KB (EMEA)