eSubmission Guidelines

New ways of working at FAMHP

Version 2.13

Publication date: 30/10/2015

Implementation date: 01/01/2016

Federal **A**gency for **M**edicines and **H**ealth **P**roducts
Eurostation II
Place Victor Horta 40/40
1060 Brussels
www.fagg.be

DOCUMENT HISTORY

Date	Author	Version	Comments
14/05/07	André Lhoir	2.6	Updated version
xx/02/08	Ann Verhoye	2.7	Updated in order to add necessary information in view of the NeeS guideline
01/07/09	Ann Verhoye	2.8	Updated in order to comply to current European guidance and new mail size limit
01/05/2010	Ann Verhoye	2.9	Updated in order to comply to better regulation
07/07/2011	Ann Verhoye	2.10	Updated in order to comply to new eCTD and NeeS validation rules
14/11/2011	Ann Verhoye	2.11	Updated in order to reflect EU requirements and in order to reflect validation reports to be saved in the workingdocuments folder.
24/06/2013	Ann Verhoye	2.12	Updated in order to reflect the voluntary CESP pilot phase starting from 1/7/2013.
30/10/2015	Ann Verhoye	2.13	Updated in order to reflect the mandatory eAF from 1/1/2016

Table of Content

Federal Agency for Medicines and Health Products
Eurostation II
Place Victor Horta 40/40
1060 Brussels
www.fagg.be

1. Introduction

One of the conclusions of the Business Process Reengineering project that was conducted by the DGMP in 2003-2004, was to implement a new back-office and case management system with document and workflow management capabilities in order to:

- Automate administrative processes and improve the operational efficiency of the NCA
- Ameliorate case management and decision-making processes
- Eliminate paper handling (storage, copying, transportation, confidential shredding, etc.)
- Increase communication and knowledge transfer
- Enabling access to a centralized data model in line with European legislation
- Further improve the quality carried out by the NCA
- Build an electronic interface to industry stakeholders for electronic applications and communications

This document completes and clarifies the previous Guidelines Ver. 1.0 and all FAQs already published.

This document supersedes previous versions.

2. Important reminder

The applicant is fully responsible for the correctness and completeness of the submitted file within any type of e-dossier submitted to the FAMHP.

To this end the applicant must ensure that the submitted file will comply to the full compliance requirements as laid down in the full compliance road map, published on the FAMHP website and updated on regular basis.

(full compliance webpage link: http://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelen/procedures_vhb/esubmission/index.jsp)

Moreover, the applicant needs to submit the following two statements:

1. A declaration about the content of the proposed leaflets (SmPC, PIL) & Labelling
2. The conformity statement of translation.

(1) The applicant is responsible for the conformity of the national leaflets (SmPC and PIL) and the national labelling according to the file (registration or variation). As for the variations or files which cause change in the leaflets or labelling, the applicant has to declare that the content of the proposed leaflets and labelling is identical to the approved version and that the proposed changes only reflect the content of :

1. the previously submitted MRP variations type IA and IB, already "approved" by the RMS

   and/or

   the previously submitted national variations type IB for which the timeframes for implementation have passed, and the previously submitted type IA and administrative variations
2. if a MRP dossier is concerned: the previously submitted variations type II and notifications under Art. 61(3) (Directive 2001/83/EC) already approved by the RMS
3. if a NP dossier is concerned: the previously submitted variations type II and notifications under Art. 34§4 (RD 14.12.2006) already approved by the FAMHP (i.e. receipt of the "round up" mail) and notifications under Art. 34§4 (RD 14.12.2006) for which the timeframes for implementation have passed.
4. submitted file.

For European procedures, this declaration should either be submitted at the closing of the variation. It is recommended to include this declaration in the cover letter.

(2) The applicant should mention the intention to use the conformity statement on translation of SmPC into two national languages (Dutch and French), and PIL and labelling into the three national languages (Dutch, French, German) in the cover letter. A template of this conformity statement is available on the website. The conformity statement itself has to be submitted together with the translations at the end of the procedure.

Glossary

Please find below a list of abbreviations and key words used in this Guidelines document:

Key word or abbreviation	Explanation or definition
AC	Administrative Change
AMM	Autorisation de Mise sur le Marché (Marketing Authorisation)
CESP	Common European Submission Platform
CHMP	Committee on Human Medicinal Products of the EMA
CP	Centralised Procedure
CTD	Common Technical Document (Document standard developed by ICH and supported by EMA)
DCP	Decentralised Procedure
eAF	electronic Application Form
ECTD	The electronic CTD
EMA	European Medicines Agency (www.ema.europa.eu)
eSubmission system	The new document and workflow management system which is implemented at FAMHP that manages the electronically submitted applications for new drug registrations, variations, renewals, etc.
EUDRALINK	System developed by EMA for secure electronic transfer of files
FAMHP	Federal Agency for Medicines and Health Products
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation (www.ich.org). The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.
MRP	Mutual Recognition Procedure
NCA	National Competent Authority
NeeS	Non-eCTD electronic Submission
NP	National Procedure
Paper dossier	The hard copy (paper copy) of a drug application
PIL	Patient Information Leaflet
SmPC	Summary of Products Characteristics

Tree structure	The term ‘tree strcuture’ as used in this document indicates the sequence folder and all underlying folders and documents.
XML	Extensible Markup Language (XML) is a simple, very flexible text format derived from SGML (ISO 8879). Originally designed to meet the challenges of large-scale electronic publishing, XML is also playing an increasingly important role in the exchange of a wide variety of data on the Web and elsewhere.

4. Different types of e-Submission dossiers identified by the FAMHP

The FAMHP has defined two types of dossiers for electronic submission.

A. eCTD or electronic Common Technical Document

This is a standard agreed by the ICH and endorsed by the CHMP. Regarding Module I EU specifications are requested. It consists of 3 main elements:

- The electronic Application Form (eAF) in PDF.
- The directory structure, a tree structure with all the required documents for registration based on the CTD structure standard.
- an XML file ('XML backbone') containing valuable and structured information on all documents in the dossier (e.g. meta data such as versioning information, check sum, table of contents, etc.).

This format allows the FAMHP to import and classify the registration dossier. As it contains versioning data on the documents, it enables the FAMHP to manage different document versions (modified documents, unmodified documents, deleted documents, etc.).

Please also check the eSubmission road map: it contains the dates on which eCTD becomes mandatory for the different procedures and dossier types (http://esubmission.ema.europa.eu/tiges/cmbdocumentation.html)

The eCTD specification is available on www.ich.org (CTD modules 2 to 5) and http://esubmission.ema.europa.eu for the European specifications (CTD Module 1) and more specifically for the application forms at

http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

There are eCTD software tools on the market that can help the pharmaceutical industry to view and/or create eCTD dossiers.

Please pay attention to the following remarks:

As the eCTD format evolves it is important that the pharmaceutical industry respects the last eCTD specification.

The applicable eCTD specifications version is always the current version. The XML versions applicable are:

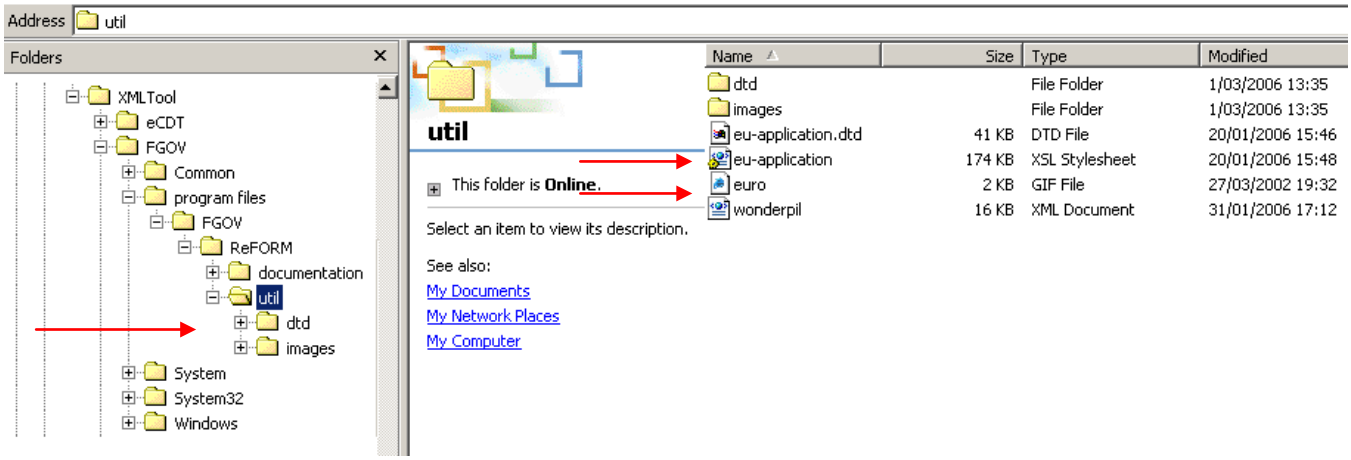
- For Modules 2 to 5: ich-eCTD- DTD (current version)
- For EU Module 1: EU-index. DTD (current version)
- For the new application form: EU-application. DTD (current version) and XSL version

- For the variation form: DTD current version

Attention points when submitting an XML file

When submitting an XML file (Application form) please be sure to add the DTD and the XSL properly linked to the XML file.

Both DTD and XSL file are to be present in the UTIL directory. To be sure to have the correct information which help us when downloading the XML Form, please copy either the complete "Util" directory or the both mentioned files within an "Util" directory.



Please also read point 4 described below for NeeS, this is applicable for eCTD submissions as well!!!!

B. Non-eCTD electronic Submission (NeeS)

When an eCTD is submitted , please assure that the eCTD is backwards compatible with the NeeS format, meaning adherence to folder and filenaming convention which is still Best Practice.

This type of electronic submission should comply to the recommendations as listed in the 'Guidance for Industry on Providing Regulatory Information in Electronic Format: Non-eCTD electronic Submissions (NeeS)' current version.

Notes:

1. the NeeS submission may not contain word documents. All documents requested by the FAMHP in word format (product information related documents and AMMs) are to be submitted at time of dossier submission /dossier closing (this is after the European phase for MRP and DCP procedures). At submission of the file PDF format of PI documents and AMMs need to be included in the NeeS. If you submit word documents (cfr translations of PI in case of IA or IB variation), please gather them in a folder named '*sequence number*-workingdocuments'(no hyphen), separated from the tree structure and mention this clearly in your cover letter. *(see also 'nice to know' point 5)*. The word documents required for the closing of files falling within the scope of the project 'change MAH' (see circular letter 542, annex 7) have to be present at time of the original submission in this workingdocuments folder.

.

2. the TOCs as mentioned in the NeeS guideline are not required by the FAMHP. When the TOCs are included in the submission, they are accepted provided the naming convention is followed.

3. the sequence folder of the NeeS should be named '0000'.

4. The folder on top of the sequence folder ('0000') should state the product specific variation procedure number prefix which is defined as follows:

cc-h-xxxx-yy

cc: country code or 'nat' for national procedures

xxxx: group counter

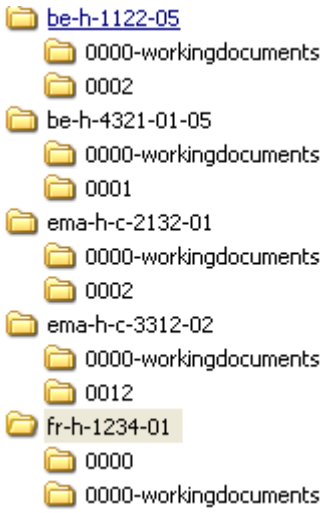
yy: product counter

Below this folder level one tree structure can be submitted.

!!!Always use '-' instead of '/' when indicating the procedurenumber in the intermediate level folder. No spaces are allowed in the procedurenumber! Caps cannot be used, the TIGes Harmonised Guidance for Non-eCTD electronic Submissions (NeeS) for human medicinal products in the EU version 3.0 mentions small letters for the procedure number in it's examples.

Example Worksharing

fr-h-1234-01	ema-h-c-3312-02	ema-h-c-2132-01	be-h-4321-01-05	be-h-1122-05
0000	0012	0002	0001	0002



In this example the submission concerns a worksharing procedure concerning different medicinal products:

Top folder: prefix product specific variation procedure number: e.g. if be-h-4321-01-05.

NeeS: the only tree structure allowed in the intermediate folder is applicable to all strengths/pharmaceutical forms of the specifc medicinal product. In this case, the one tree structure contained in it should concern products 01, 02, 03, 04 and 05 belonging to the medicinal group 4321.

eCTD: If an eCTD submission is concerned, and lifecycle management allows to create one top folder for all strengths/pharmaceutical forms of a specifc medicnal product, then this is to be followed. Only in the cases where the lifecycle management requires one tree structure per strength/pharmaceutical form of a medicinal product, the top level folders are to be defined on that level.

For example: if an eCTD lifecycle exists for the x mg strength of Product P and a separate eCTD exists for the y mg strength of product P then for each strength a seperate intermediate folder and corresponding eCTD sequence is to be submitted.

be-h-4321-01

0001

be-h-4321-02

0002

It is recommended to clearly mention in the cover letter which product data can be found in the different submitted tree structures. It is evident that the cover letter should mention that a worksharing or a grouping is concerned.

Medicinal product (name +strength+form) 1: all info in fr-h-1234-01 – 0000

Medicinal product (name +strength+form)2: all info in ema-h-c-3312-02 – 0012

Medicinal product (name +strength+form) 3: all info in ema-h-c- 2132-01 – 0002

Medicinal product (name +strength+form) 4 (= product counter 01): all info in be-h-4321-01-05 - 0002

Medicinal product (name +strength+form) 5 (= product counter 02): all info in be-h-4321-01-05 - 0002

Medicinal product (name +strength+form) 6 (= product counter 03): all info in be-h-4321-01-05 - 0002

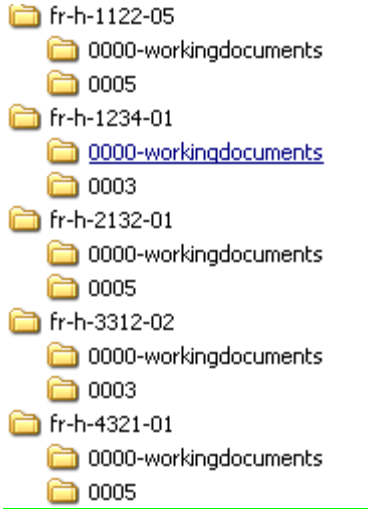
Medicinal product (name +strength+form) 7 (= product counter 04): all info in be-h-4321-01-05 - 0002

Medicinal product (name +strength+form) 8 (= product counter 05): all info in be-h-4321-01-05 – 0002

Medicinal product (name +strength+form) 9: all info in be-h-1122-05 – 0002

Example grouping

fr-h-1234-01	fr-h-3312-02	fr-h- 2132-01	fr-h-4321-01-05	fr-h-1122-05
0005	0003	0003	0005	0005



The explanation as mentioned under the example worksharing is valid for the grouping example as well.

Please note that one CD/DVD/mail/CESP should be used per submission, if seperate variations and groupings are submitted simultaneously different CD/DVD/mail/CESP are required.

Nice to know

1. Where to download the application form and get information on how to fill it?

For **new registrations, variations** and **Renewals**:

http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

For **Art. 61(3) notifications** and **Art. 34§4 notifications**:

http://www.hma.eu/101.html

2. Are all non- volume based PDF formats accepted?

No, only those which comply with section 2.8.1 and annex I of the 'Guidance for Industry on Providing Regulatory Information in Electronic Format: Non-eCTD electronic Submissions (NeeS)'.

Only PDF format 1.4 or higher will be allowed. As soon as the submission contains one pdf file of a lower version, the submission is rejected.

3. What about dossiers concerning several strengths/pharmaceutical forms of 1 medicinal product?

eCTD

It is encouraged to submit one eCTD for several strengths, all application forms can be listed in the 12-form/cc folder. The top folder, indicating the product specific procedure number is required. This foldernaming should clearly indicate if different forms or strength of a medicinal product are concerned by the submission.
Please also check the eSubmission road map: it contains the dates on which eCTD becomes mandatory for the different procedures and dossier types (http://esubmission.ema.europa.eu/tiges/cmbdocumentation.html)

NeeS

When submitting a dossier for different strengths/pharmaceutical forms of a medicinal product, 2 options are available :

Option 1: applicable for new registrations

Top folder: indicating the product specific procedure number.

One tree structure for all concerned strengths/pharmaceutical forms of the concerned medicinal product.

- Cover Letter should clearly specify the different forms or strengths of the concerned medicinal product.

- The tree structure contains an overall retribution form.

- The tree structure contains all information which is valid for all strengths and forms of the concerned medicinal product.

- Empty folders can be deleted.

- All application forms are to be in the 12-form/cc folder of the tree structure.

Option 2: applicable for variations concerning different strengths/pharmaceutical of a specific medicinal products (grouping and work sharing excluded for this option)

One tree structure is submitted including all information for all concerned strengths/pharmaceutical forms of the medicinal product. The top folder indicates the product specific variation number. The cover letter clearly states the strengths and pharmaceutical forms of the medicinal product involved by the dossier. The option of complex cannot be used in combination with the option grouping or worksharing.

4. What about the need for signatures on the eSubmitted dossier?

A. Signature on cover letter:

Each submitted dossier needs to be foreseen of a handwritten signature (signed AND printed/scanned+OCR'd cover letter) when submitted by mail/eudralink/CD-ROM/DVD/CESP.

! It is allowed to submit the cover letter in two-fold, as follows, if necessary:

- *0000\m1\eu\10-cover\be-cover.pdf* = scanned image of the cover letter
- *0000\m1\eu\10-cover\be-cover-**text**.pdf* = pdf text searchable document build directly from the initial Word document (without company header and signature)

B. Signature on the application form:

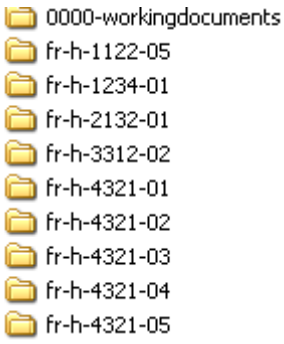
A signature on the application form is required for all dossiers where Belgium acts as RMS.

Please see Q10 here:
http://esubmission.ema.europa.eu/eaf/eaf_9.1/eAF%20Questions%20and%20Answers.pdf

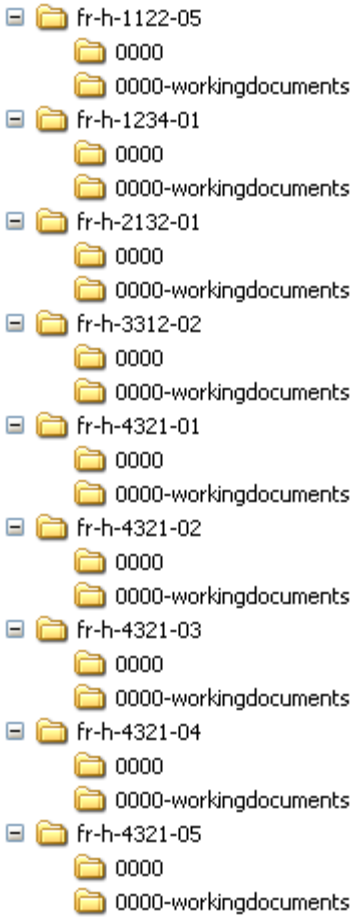
5. What about the submission of word files?

If word files are to be submitted, please submit them out of the CTD-tree structure, within a separate folder, and mention the fact of submitting a separate word file folder in the cover letter of your submission. The folder should be named 'sequence number - workingdocuments' (sequence number = 4 digits; no hyphen) in accordance with NeeS requirements. One such folder per submission (one full application, one grouping, …. ! Several single variations are not considered to be one submission.) is allowed. For new registrations it has to be submitted out of all tree structures. For groupings and worksharings, and complex dossier it needs to be submitted out of the intermediate folders indicating the procedurenumbers, as indicated in the example below (option 1 – 1 overall working document folder, next to the folders above the sequencefolders, for the complete submission. Please use descriptive filenames! In case of groupings or different procedurenumbers involved the filename '0000-workingdocuments will be allowed.). However in order to comply to EU validation rules for NeeS submissions, the working document folder might also be a subfolder of the procedurenumber folder (option 2 – 1 working document folder next to each submitted sequencefolder):

Option 1 (one submission concerned):



Option 2 (one submission concerned):



6. What about esubmission in view of the better regulation

(http://esubmission.ema.europa.eu/eumodule1/index.htm)

A. The eCTD submissions should follow the implementation timeline for the EU M1 eCTD specifications:

From the date of 01.SEPT 2013 :

EU M1 v 2.0 : for all eCTD submissions

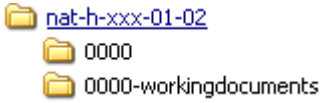
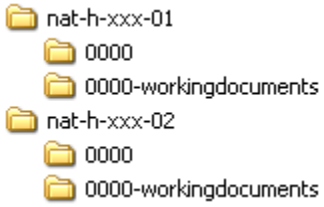
From 1st July 2016:

EU M1 v 3.0 for all eCTD submissions

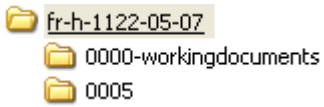
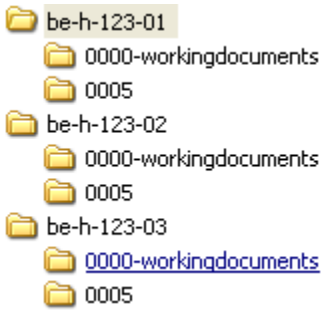
B. NEES submissions:

For submission of grouped variations or variation in view of worksharing, one NEES tree structure per medicinal product group (= all strengths and forms of a specific medicinal product) is requested. This means that when introducing a group variations concerning different strengths or forms of a specifc medicinal product only one tree structure needs to be prepared. Create the necessary top folders on medicinal product level indicating the procedure number.

For grouping and worksharing an overall, retribution form and application form is used, and should be present in each tree structure of the submission. It is recommended to detail the way of proceeding used to calculate the total fee.

NeeS	eCTD
New application concerning more than one strength/pharmaceutical form of a medicinal product: One Top folder: Always use one folder for all strengths/pharmaceutical forms of the medicinal product indicating the procedure number. Example: NeeS new registration for three strengths of a specifc medicinal product. 	**New application concerning more than one strength/pharmaceutical form of a medicinal product:** (1) One top folder. Indicating the procedure number for all strengths/forms of the concerned medicinal product. One overall tree structure for the concerned strengths/pharmaceutical forms of the medicinal product. Example see left side. (2) Several top folders: one top folder per strength/pharmaceutical form of a specific medicinal product indicating the procedure number. One tree structure per strength/pharmaceutical form of the medicinal product per top folder. Example for eCTD if life cycle management requires strength/pharmaceutical form specific tree structures. 

Federal Agency for Medicines and Health Products
Eurostation II
Place Victor Horta 40/40
1060 Brussels
www.fagg.be

NeeS: Variations concerning more than one strengths/pharmaceutical form of a medicinal product:	eCTD: Variations concerning more than one strength/pharmaceutical form of a medicinal product:
1. No grouping or worksharing is concerned ***Is more than one medicinal product concerned?*** YES: not accepted NO: Top folder: product specific variation number One tree structure covering all concerned strengths/pharmaceutical forms of the medicinal product. Example below:  	**1. No grouping or worksharing is concerned** ***Is more than one medicinal product concerned?*** YES: not accepted NO: Top folder: product specific variation number. One tree structure covering all strengths/pharmaceutical forms of the concerned medicinal product. Example see left side. OR *(2)Top folder per strength/pharmaceutical form indicating the Procedure number. One tree structure per strength/pharmaceutical form of the medicinal product. Example below: 

Federal Agency for Medicines and Health Products
Eurostation II
Place Victor Horta 40/40
1060 Brussels
www.fagg.be

1.2. NeeS: A grouping or worksharing is concerned One top folder for all strengths/pharmaceutical forms of each concerned medicinal product indicating the product specific variation procedure number One tree structure per the top folder. Example: grouping submission valid for five medicinal products, mention the concerned strengths/pharmaceutical forms of the medicinal product in the top folder name. Example see next page.	**1.2. eCTD: A grouping or worksharing is concerned** *(1) One top folder for all strengths/pharmaceutical forms of each concerned medicinal product indicating the product specific variation procedure number : e.g. be-h-123-02-06. One tree structure per top folder. Example see left side. *(2) One top folder per strength/pharmaceutical form of each concerned medicinal product indicating the product specific variation procedure number prefix. One tree structure per top folder. (* The choice is based on the LCM: if sequence '0000' was started with different tree structures per strength/pharmaceutical form, then option (2) is to be used, if it was started with one overall tree structure for all strengths/pharmaceutical forms of the medicinal product the option (1) is to be chosen.) Example below: Example see next page.

fr-h-2132-01 0000-workingdocuments 0005 fr-h-3312-02 0000-workingdocuments 0003 fr-h-4321-01-05 0000-workingdocuments 0005	fr-h-2132-01 0000-workingdocuments 0005 fr-h-3312-02 0000-workingdocuments 0003 fr-h-4321-01 0000-workingdocuments 0005 fr-h-4321-02 0000-workingdocuments 0005 fr-h-4321-03 0000-workingdocuments 0005 fr-h-4321-04 0000-workingdocuments 0005 fr-h-4321-05 0000-workingdocuments 0005

Note concerning annual reports: In an eCTD, delaying the submission of type IA's for the annual report might seriously affect the life cycle management of further sequences. As type IA's are issued in the FAMHP with an automated email, applicants who prepare their submissions in the eCTD format may be advised to submit the type IA's as soon as they are ready and not to collect them in an annual report. However this decision is left to the applicant.

5How to submit your dossier: eCTD Directory structure and naming conventions

From 05/02/07, each electronic dossier concerning a human medicinal product and submitted to the FAMHP, is subject to two technical verifications.

From September 2011, the technical validation rules which will be applicable are:

(1) compliance towards the eCTD tree structure for both NeeS and eCTD submissions

(2) compliance towards folder and file naming for NeeS submissions

! Please remark that respect of folder and filenames is considered to be 'best practice' for eCTD submissions meaning that the applicant should be prepared to include justification for any Best Practice criteria, such as folder and filenaming, which are not met in the submission cover letter/reviewer's guide.

This is called 'full compliance'.

NeeS submissions

1) For NeeS submission for which BE acts as RMS: instead of the Belgian checker NeeS report the Extedo actual version or the Lorenz NeeS actual version report needs to be included in the submission, this allows a 100% compliance check which will be valid in all concerned MS.

Please file this validation report in the working documents folder. Even if you need to submit no word files, you still need to create the 'sequencenumber-workingdocuments'folder in order to save the validation report within. If you choose option 1 as mentioned on page 15 of this guideline please use descriptive filenames for the validation reports of the different tree structures submitted, so the FAMHP can easily identify the tree structure reflected within each validation report.

2) For other submissions (where BE do not acts as RMS):

Note that the Best report is now called NeeS report.

Both technical verifications are based on the requirements described in the Notice to Applicants for module 1, and modules 2 to 5 (ICH requirements).

For both technical verifications, a score is given to the dossier. This score will be included in the so-called 'NeeS report', which will be included in the mail sent to you after the dossier is uploaded in our system. This NeeS report will provide details on the errors concerning both the eCTD structure and the folder/file naming.

"full compliance" has been implemented in three stages :

1. adaptation stage (1/2/2007-27/3/2007)

2. self-testing stage (27/3/2007 – end june 2007)

3. start (September 2007)

The score to which your dossier must comply, as far as both technical verifications are concerned, is determined by a road map. (http://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelen/procedures_vhb/esubmission/index.jsp)

It is available on our website. It mentions the minimum score for each technical verification, to which your dossier must comply to be accepted by the FAMHP.

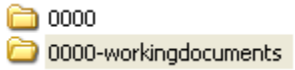
If one of the minimum scores is not obtained for your dossier, the NeeS report will be returned to you mentioning the rejection of your dossier. In that case, the dossier need to be resubmitted to the FAMHP and an administrative fee needs to be paid for the rejected dossier.

If both minimum scores were obtained for your dossier, the NeeS report will be returned mentioning that the submission of your dossier was accepted by the FAMHP.

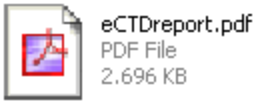
Please consult the road map regularly before submitting your dossier in order to be aware of the latest updated information regarding minimumscores. If you use the checker available on our website before submitting the dossier, the NeeS report will automatically be placed outside/besides the NeeS structure.

(*) eCTD submissions

For each eCTD tree structure contained in the submission the Lorenz actual version, or Extedo actual versions of a valid eCTD validation report must be included in your submission. A valid eCTD validation report means that **all Pass/Fail criteria are met**. **Absence of a valid validation report with all Pass/Fail criteria which are met means invalidation of the submission.** The validation report must be made in presence of all preceding sequences and the new sequence you are to submit (*). Please name these reports 'eCTD report' and store them in the working documents folder. The Belgian NeeS checker will not be used for eCTD's by the agency. The applicant should provide one eCTD report per submitted eCTD sequence.



When clicking on sequencenumber-workingdocuments folder:



The Extedo PDF version report or the Lorenz main html report should always be saved in the working documents folder. Even if you need to submit no word files, you still need to create the 'sequencenumber-workingdocuments'folder in order to save the validation report within.

There is no technical validation on the filename of the report.

(*)When launching the technical validation within Extedo or Lorenz be sure that the sequence to be submitted and all previous sequences are present within the eCTD validator.

On 27 March 2007 the FAMHP gave an infosession regarding full compliance, during which the CTD tree structure (NeeS Report) was discussed as well. The CTD structure including naming conventions can be consulted via our website:

http://www.fagg-afmps.be/nl/binaries/best%20verification%20report_tcm290-26694.doc

The full compliance webpage offers all necessary information for a correct esubmission:

http://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelen/procedures_vhb/esubmission/index.jsp

Which type of dossier is included in the eSubmission full compliance (see further) requirement?

All dossiers (new applications, variations, renewals) concerning human products (including products derived from herbals, excluding homeopathic products and parallel import) as far as they follow the national procedure, the MRP or DCP are included in the eSubmission full compliance requirement. Dossiers concerning human products submitted by CP need to be submitted in eCTD format as well, and should comply to the requirements mentioned here above (*) on the same page.

Dossiers concerning veterinary products are excluded at this moment.

PSURs are excluded.

Response files are excluded as well except for response files for BE RMS dossiers submitted after 1/1/2012, these are to be fully compliant in compliance with EU requirements.

ASMF can be submitted in electronic format, either in eCTD or in NeeS. ASMF is out of scope of the technical validation.

The content of module I such as it should be submitted including the FAMHP good practice remarks (in italics) is given below.

Module 1 from 1/6/2016 EU M1 v3.0 (http://esubmission.ema.europa.eu/eumodule1/index.htm) will be applicable!

Please delete empty folders.

1.0 Cover Letter

- *The cover letter should be the original signed Cover Letter. The cover letter should be printed AND scanned+OCR'd. The cover letter should be text searchable as indicated in the 'Guidance for Industry in Electronic Format: Non-eCTD electronic Submissions (NeeS)'.*

- *Mention the dossier ID if known.*

- *The 2 statements as listed on page 5 are to be retaken.*

- The cover letter (for both national and European procedures) should be in compliance with the 'Member States recommendation on the Cover Letter for new applications submitted through the MRP/DCP' as published on the CMD website:

http://www.hma.eu/91.html (the document can be found at the bottom of the page)

Moreover, the templates for the cover letter for new applications in MR and DC procedures as published on the same web pages are to be used.

For variations a template for the cover letter is now available on: http://www.hma.eu/96.html. Be sure to mention related variations. It is highly recommended to use the template of the variation cover letter since the template includes all necessary information to identify the application correctly and to support the validation

The cover letter may be edited in English for national procedures as well.

1.1 Comprehensive Table of Contents

The table of contents is allowed but is not required for the agency. If you decide to submit a ToC anyway, please take into account the following issues:

- *Include a Table of Contents with hyperlinks, if possible, to the related document in the respective eCTD modules.* ***When submitting a NeeS ensure that all the paths in the links are relative when building the hyperlink, ie: use '/m1' instead of '/0001/m1'***
- *Make sure all filenames are clear and logical and respect the eCTD nomenclature*

1.2 Application Form

- Application form should be stored in the "be" folder.

- Annexes should be stored in the "Common" folder if applicable to more than one country for MRP. The annexes should be stored in the BE folder for NP. Annexes are: e.g ticked guideline, GMP-certificate, proof of establishment,dossier description, justification of type IA, other… . For the application form itself the naming convention is to be followed (ex be-form.pdf), for the annexes a descriptive filename without hyphens or spaces should be added as a variable component (ex be-form-proofofpayment.pdf, common-form-pheurcertificate.pdf, common-form-tickedguideline)

- Always use the AF annex for the proof of payment (5.1 in case of new MAA).

- *For new registrations, one application form per medicinal product strength is expected*
- *For grouping and worksharing one overall application form should be used. All tree structures involved by the grouping or worksharing should include the overall application form.*
- *Signature on the application form is mandatory in case Belgium acts as RMS.*

- *The Application form refers to any form (new applications, applications for variations or renewals). Always use the country directory at this level for all procedures even when only one file is submitted to only one country during the life cycle of the submission.*
- *Delete empty folders.*
- *The application form should be text searchable as recommended in the 'Guidance for Industry in Electronic Format: Non-eCTD electronic Submissions (NeeS)'.*

Applicable from 1/1/2016:*The use of the eAF is mandatory for all procedures !*

1.3 Product Information

1.3.1 **SmPC, Labelling and Package Leaflet**

- *The proposed European SmPC, PIL and labelling are to be included in the 'common' subfolder for European dossiers. The proposed national SmPC, package leaflet and labelling are to be included in the 'be'subfolder.*
- *Please note that for type IA, IB and administrative variations affecting the Product Information all national translations should be present at the initial variation application, but the national proposals (European dossier)/translations (national dossier) for type II variations and renewals may be submitted at the end of the procedure. Word versions of translations at submission are to be included in the' sequence number- workingdocument's folder.*
- *The proposed labeling text should include braille in normal text format (this is in compliance with NtA requirements).*
- *Please also check the file 'Note to finalise SPC-PIL-labelling (.WORD) as published on our website:*

  http://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelen/procedures_vhb/procedures/index.jsp
- *The submitted electronic file should only contain pdf versions of the PI documents. The word versions of these documents are to be submitted at time of dossier closing (this is after the European phase for MRP and DCP procedures).If your word files are submitted at time of submission of your dossier please submit them in a separate word file folder, next to the tree structure.(see also 'nice to know' point 5)*

1.3.2 Mock-up

- *The proposed mock-up should visualise braille using dots (this is in compliance with NtA requirements).*

1.3.3 Specimen

1.3.4 Consultation with Target Patient Groups

- *Subfolder: "be" for national procedures, include here readability testing results.*
- *Subfolder "common": for European procedures include here readability testing results*

1.3.5 Product Information already approved in the Member States

- *For applications in a Mutual Recognition Procedure copies of the approved Product Information of the relevant medicinal product, as approved by Member States, need to be included here. This section only has to be provided for initial applications, not for post-authorisation procedures.* (http://ec.europa.eu/health/files/eudralex/vol-2/b/ctd-qa-updatev3_2008-02_en.pdf)

1.3.6 Braille

1.4 Information about the Experts

1.4.1 Quality

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

Responses to Questions

- *This folder is divided in CC folders. !Be aware that the 'Guidance for Industry on Providing Regulatory Information in Electronic Format: Non-eCTD electronic Submissions (NeeS)' requests responses to be introduced respecting the CTD tree structure of the original submission.*
- *Currently, the FAMHP will not perform full compliance testing on responses to questions.*

Additional Data

- Besides AMM and derogation forms the 'additional folder' can be used for other documents that do not really fit in any other section (ex: list of dispatch dates for BE RMS files, transfer agreement, declaration of conformity of translations (The declaration of conformity is always to be submitted given that the SmPC is needed in Dutch and French and the PIL/labeling is needed in Dutch, French and German at the end of the procedure), …).

- Include both the approved AMM and the proposal AMM. Note that submission of an AMM proposal is mandatory, if changes to the AMM are a consequence of the submitted dossier.

- This folder is divided in CC folders.

- Please make sure that this folder only contains pdf format. The word format of these documents if requested by the FAMHP (e.g. word version of AMM is required) needs to be submitted at time of dossier closing (this is after the European phase for MRP and DCP procedures). If your word files are submitted at time of submission of your dossier please submit them corresponding to the requirements mentioned 'nice to know' point 5.

! For the project change MAH the following documents should be given within the folder 'additional data': AMM, transfer agreement, declaration of conformity of translations, declaration that no other changes have been included in the SmPC/PIL/labeling (if not already included in the cover letter)

General remark regarding the use of CC and common subfolders:

NP: always use BE folder

MRP: use national country code folder for country specific documents, and use common folder for documents valid for ALL involved countries

DCP: use the common folder only

6Which communication channel is most appropriate for my eSubmission?

Please be aware that from the first of July 2013 **CESP** is highly encouraged as submission channel - for all details check the CESP communication on the famhp website esubmission webpage.

Never use several parallel communication channels for the electronic submission of your dossier!

The following older communication channels will still be allowed for submitting electronic registration dossiers to the FAHMP:

A. E-mail

For NP, DCP, MRP registration dossiers as well as any type of correspondence related to the dossiers, emails up to a size of 5,00 MB will be allowed. Please compress or 'zip' the file.

The general e-mail address for electronic dossier submission is dispatching@fagg-afmps.be except for

- PSUR for which the general e-mail address for electronic dossier submission is psurh@fagg-afmps.be

  (PSUR is not concerned by the FAHMP full compliance

The general e-mail address for correspondence/additional data/post-approval commitments concerning an (ongoing) dossier is prelicensing@fagg.be for new applications and gestion.fagg-afmps@fagg-afmps.be for variations and renewals.

National documents (word version of PI documents in national languages, final AMM proposals) need to be submitted to prelicensing@fagg.be for new applications and FAGG_CLOSING_FILE@fagg-afmps.be for variations and renewals.

!!! Pay attention to the following:

1. The **mail subject** always needs to mention at least: (all fields should be separated by "-")
   1. Type of procedure (MRP, DCP, NP)
   2. Type of dossier (type IA, IB, AC, IInc, IIc, R (renewal), new, E (repeat-use), PSUR, P (notification))
   3. The name of the medicinal product in Belgium
   4. Dossier ID (if known)

2. The **content** of the cover letter should be in the body of the mail.

3. **Dossiers** in a CTD directory structure that are sent via e-mail need to be **compressed** [1]("zipped" with WinZip) so that the relative eCTD folder structure is respected.
    - If you are using a different compression software than WinZip, please mention it in the Cover Letter.
    - Do not use password protection, in line with the 'Guidance for Industry on Providing Regulatory Information in Electronic Format: Non-eCTD electronic Submissions (NeeS)'

Please use the eCTD directory structure as it is defined in our empty folder structure tool.

(published on the FAMHP website: Wonderpil CTD boomstructuur (.ZIP) on http://www.fagg-afmps.be/nl/MENSELIJK_gebruik/geneesmiddelen/geneesmiddelen/procedures_vhb/esubmission/index.jsp)

A compressed or zipped folder can keep its directory structure thanks to a function of WinZip (see below):

a. First compress ('zip') the dossier folder by using the WinZip program (see below)

b. Then check the Option "Save full path info". This will store the whole folder structure information.

c. Verify the result in the compressed ('zipped') archive

d. Send the compressed archive via email to FAMHP (only NeeS and size smaller than 5,00MB)

4. **Eudralink (EMA):** This option could be used to submit electronic dossiers to the FAMHP (the same e-mail addresses as listed earlier can be used). This solution is a secure solution and allows to submit larger files. This option may also be used to submit additional info to the gestion team. As mentioned earlier, eCTD submissions cannot be sent as en email attachment as the email filter does not allow it. Please use Eudralink in these cases – always use the 90 day expiry date.

The use of systems as 'YouSendIt' will not be refused by the FAMHP on condition (i) that their use does not require a password and (ii) all responsibility is declined.

B. CD-ROM/DVD:

When CESP is not used and the size of the dossier exceeds 5.00 MB and is lower then 40,00 MB submission via mail is not supported, but Eudralink is still an option. When the size of the registration dossier exceeds the size of 40,00 MB, the pharmaceutical company needs to submit the dossier on a CD-ROM or DVD which needs to be shipped to the FAHMP (for DVD's all standards are accepted).

Federal Agency for Medicines and Health Products

1

VHB PRE (for new applications) or VHB POST (for variations/renewals)

Eurostation II

Place Victor Horta 40/40

1060 Brussels

!!! Pay attention to the following:

1. Please don't forget to print the signed cover letter and put it in the envelop when mailing the CD/DVD.

2. Do not use password protection, in line with the 'Guidance for Industry on Providing Regulatory Information in Electronic Format: Non-eCTD electronic Submissions (NeeS)'

3. Do not send parts of dossiers by email and parts on CD/DVD.