Guidance for Industry on Providing Regulatory Information in Electronic Format

TIGes Harmonised Guidance for Non-eCTD electronic Submissions (NeeS) for human medicinal products in the EU

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1 Introduction

This Guidance Document is intended to assist pharmaceutical companies with the submission of regulatory information in electronic format to the National Competent Authorities in the EEA (hereafter referred to as NCAs). This document details the requirements for the submission of Non-eCTD electronic Submissions (NeeS). A separate EU guidance document covering eCTD submissions, which is regarded as the principal electronic submission format in EU, has also been published on the EMA eSubmission website.

Note: This guidance is not applicable for electronic submissions in NeeS format to the EMA as the EMA does not accept this type of electronic compilation.

This document has been created by the Harmonisation Group, a sub-group of the Telematics Implementation Group for electronic submissions (TIGes), and adopted for publication by the TIGes. It is strongly recommended that all National Competent Authorities adopt this guidance as the basis for their dealings with applicants when using a non-eCTD format for electronic submissions in case eCTD cannot be supported.

It should be stressed that this Guidance Document reflects the *current* situation and will be regularly updated in the light of changes in national and/or European legislation together with further experience gained within NCAs of using information submitted in electronic format. It should be emphasised that NeeS applications should be regarded as an interim format and that applicants should be actively planning their move to full eCTD submissions.

This document consists of three parts: Introduction, General Considerations, Module Specific Information and two associated annexes.

2 General considerations

2.1 Scope

2.1.1 Types of product

This guidance covers the submission of electronic regulatory information for all *human* medicinal products falling within the competence of NCAs in the EEA. This includes prescription, over the counter medicines, innovative and generic product submissions. The product types include small molecules, biotech products, herbals, vaccines, homeopathics and blood products.

2.1.2 Types of submission

This guidance applies to all submissions, regardless of size, related to the authorisation and maintenance of medicinal products, including, but not restricted to, new marketing authorisations, variations, renewals, PSURs, active substance master files.

2.1.3 Types of procedures

This guidance covers applications made in Community procedures falling within the competence of NCAs only: National, Mutual Recognition and Decentralised.

2.1.4 Exceptions

This guidance does not apply to the electronic submission of pre-MA information such as scientific advice, clinical trial applications, orphan drug designations, PIP submissions and related submission correspondence. This guidance is also not applicable for centralised procedures as the EMA does not accept submissions in NeeS format.

2.2 Structure of submissions

Regulatory information must be structured in accordance with the Common Technical Document (CTD), which for paper submissions became mandatory in the European Union with effect from 1 July 2003.

For NeeS applications the eCTD folder structure is used. The breakdown of the electronic submission should be in conformity with the ICH Granularity Document and the ICH and EU eCTD file naming conventions should be followed. (Links are found at EMA eSubmission website.)

The difference from an eCTD is that the two relevant XML files, the index.xml and eu-regional.xml for the backbone

of Modules 2 to 5 and Module 1 for the EU, respectively and the util folder are not present, so navigation through a NeeS is based on electronic Tables of Content, bookmarks and hypertext links.

2.2.1 Dossier Structure

Typically, a NeeS application should cover all dosage forms and strengths of a product with any one invented name. In MRP/DCP, a single NeeS application should preferably be used for each procedure (e.g. UK-H-1003). If applicants decide to have one NeeS dossier per strength or form, they should inform the agencies in the cover letter. Once a structure has been decided and submitted for a product (strengths or forms), applicants should continue to use this structure for all subsequent NeeS dossiers for the same product or communicate to authorities if a change is needed.

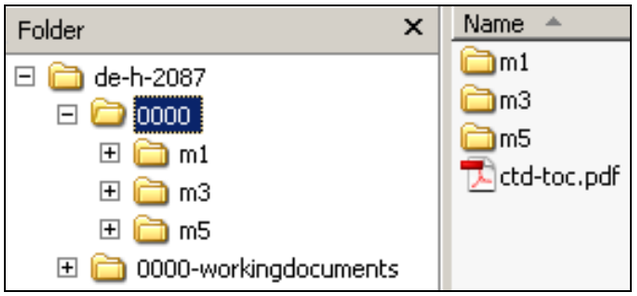
2.2.2 Table of Contents and bookmarks

Some NCAs have a tool with which they create their own TOCs. However, TOCs always need to be provided by the applicant and should always be submitted in PDF format.

All documents in the NeeS dossier should be referenced from a hyperlinked Table of Contents (TOC). Hyperlinks for each document should always be provided to the first page of the appropriate file.

In the case of small dossiers (e.g. for certain variations), especially when only one module beside module 1 is concerned, it should be acceptable to only include a main TOC referring directly to the content documents. However, for larger submissions, the main TOC should always be linked to module TOCs which are then further linked to the documents in each module. The module TOCs should not include hyperlinks to documents in other modules.

Figure 1: Folder structure



The file containing the main Table of Contents for the CTD should be named *ctd-toc.pdf* and be located in the four digit number named folder for the NeeS submission. This folder comes next to the root or top level folder (see also section 2.4).

The files containing the module Tables of Content should be named *m1-toc.pdf*, *m2-toc.pdf*, *m3-toc.pdf*, *m4-toc.pdf* and *m5-toc.pdf* and be located in the corresponding top level module folder.

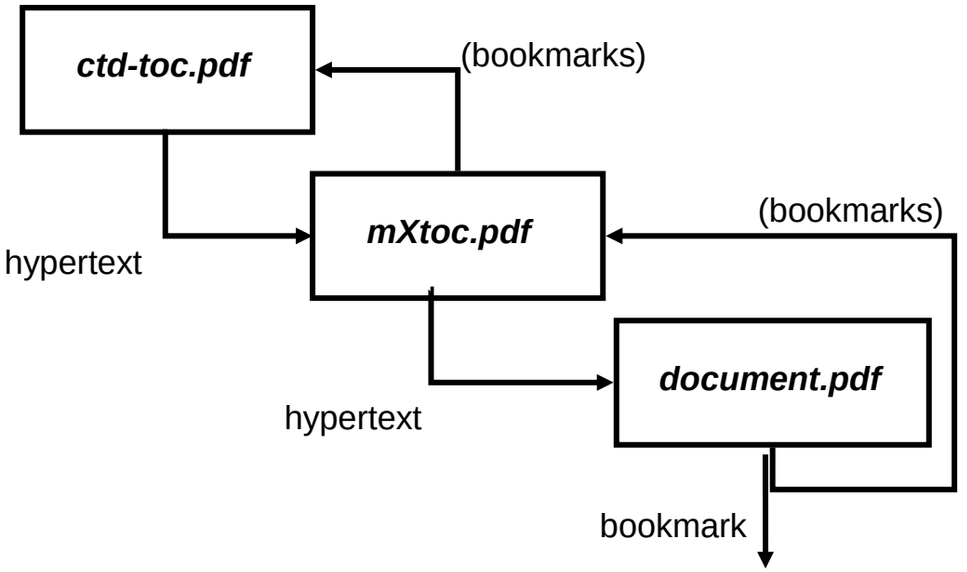
The top level folder will be part of the submitted NeeS. It is recommended but not required that the name of this folder is consistent from one NeeS submission to the next.

An example of the TOC structure is presented in Annex 2. It should be noted that these are just *examples* and are provided for guidance and illustrative purposes only.

An additional function might be provided to allow easy navigation back to the Table of Contents above. This can be achieved through the use of a bookmark linked back to the previous level. This additional function is not mandatory, but when provided it will facilitate the assessment.

The figure below describes diagrammatically this situation.

Figure 2: Principle for hypertext link use in TOC



2.3 Moving to NeeS format applications

A NeeS format application can normally be started with any initial, variation or renewal MA application. Once the switch to this electronic format is made it is expected that further applications and responses relating to the particular medicinal product are submitted in NeeS format. Applicants can switch from NeeS to eCTD at the start of any new regulatory activity. Applicants should however not change from eCTD back to NeeS. In exceptional circumstances, if this should be needed, please contact the concerned NCAs in advance.

There is no requirement to reformat the whole dossier into NeeS format when switching from paper to NeeS, but this could be done at the applicant's discretion. For example, at the time of a repeat use procedure, provision of an electronic copy to the existing CMSs (in addition to the new CMSs) could be beneficial. It should then be clearly stated in the cover letter of the reformatted dossier that the content has not been changed, but only its format.

For additional guidance on principles concerning change of format, please refer to the eCTD Guidance document section 2.4. .

2.4 General Submission Considerations

2.4.1 File and folder structure

A Submission is a collection of documents and each document should be provided as a separate file. The detailed structure of the NeeS should conform to the ICH Granularity Document and EU M1 specifications. For further guidance on file naming, please refer to the "File-Folder Structure & Names" work sheet included in the NeeS validation criteria. The root folder of the submission should preferably be named with an identification of the product concerned (e.g. an abbreviation of the product name in lower case or the procedure number, followed by the subfolder name of four digits, e.g. mydrug/0000/ or de-h-1234/0000/.

Total folder/file path should not exceed 180 characters. Counting starts from the first digit of the four digit folder name in which the ctd-toc.pdf is placed.

2.4.2 Submission numbering

The folder in which ctd-toc.pdf is placed should be named with a four digit number. This number is not required to be unique or sequential for the NeeS submission. However, it is recommended that a sequential number system is used where possible and if so, a tracking table would be helpful.

2.4.3 File Naming

The eCTD file naming conventions described in the ICH M2 eCTD Specification and EU Module 1 Specification must be adhered to for files in Modules 1-3 and are highly recommended for files in Modules 4-5. If an applicant wishes to submit multiple files in one section, where only one highly recommended name is available, this can be achieved using a suffix to the filename, using the file name-*var*.pdf convention as described in the EU Module 1 Specification, (e.g. pharmaceutical-development-*container*.pdf). For further guidance on file naming, please refer to the "File-Folder Structure & Names" work sheet included in the NeeS validation criteria.version 2.1
File names, including the extension, must not exceed 64 characters. Folder names must not exceed 64 characters.

2.4.4 Placement of Documents

Guidance on the placement of documents within the CTD structure for particular submission types can be found in the EU-CTD Notice to Applicants.

Please note that where document TOCs are included they should be located within the document itself. For each document, provide bookmarks for every entry in the document's Table of Contents to the appropriate location, or where a Table of Contents does not exist, provide bookmarks to a sufficiently detailed level, typically to Level 3 or 4 headings, as considered appropriate.

2.5 Correspondence

Similar to eCTD NeeS will support that users have a compiled view of the information submitted in the appropriate place in the dossier over time. Therefore, formal responses to questions should always be submitted in NeeS format, as well as any correspondence that relates directly to the content of the dossier.
In addition to the NeeS application, information may need to be exchanged to assist the processing or handling of the application. Not all such correspondence need to be included in the NeeS dossier. This additional, other correspondence should be exchanged outside the NeeS via the usual electronic means (email, Eudralink etc), and is not subject to the requirements in this document.

2.6 Paper requirements

In general, electronic submissions should be accompanied by a signed application form and cover letter. Detailed information on each NCA's specific requirements can be found at the CMDh website, or websites of the individual NCA.

Although most NCAs now accept electronic only applications, on rare occasions paper can be required (refer to CMDh website), Guidance on the minimum requirements to produce a paper submission from a NeeS has also been published see - "Practical Guidance For the Paper Submission of Regulatory Information in Support of a Marketing Authorisation Application When Using an eCTD or a NeeS as the Source Submission."

2.7 Hardware

NCAs will not accept any hardware (laptops, desktops, zip drives, etc.) from applicants in connection with the submission of information in electronic format. The electronic information should be directly readable and usable on NCAs hardware and software.

2.8 File formats

In general terms the majority of documents included in electronic submissions should be in PDF format (see next section on the use of PDF file versions). Files that might be requested by NCAs in MS Word or RTF format should *not* be included in the NeeS structure.

The use of XML for application forms in particular is likely to increase as agency systems develop the functionality to handle it in their own business processes.

Further detailed guidance on the specific file formats can be found in the ICH eCTD specification document and EU Module 1 specifications.

2.8.1 PDF

Portable Document Format (PDF) is an open, de facto, electronic publishing standard. Although created by Adobe Systems Incorporated there are several alternative suppliers of PDF software. Applicants need to check that their PDF documents meet the following key requirements:

- Files should be legible with Acrobat Reader, version 5.0 or higher.
- PDF file version 1.4 or 1.7 should normally be used, except where there is an agency specific requirement for a another version for example for application forms.
- PDF 1.3 or earlier versions are not acceptable for technical reasons. No exceptions will be made. For example, if a literature reference is received in PDF 1.3 or earlier, then the applicant must convert it to PDF 1.4 or 1.7.
- If the use of other versions of PDF is unavoidable then the applicant should explain the reason for it in the cover letter/explanation note as it is not in line with the Best Practice validation.
- Documents generated by the applicant should be created from electronic source documents and not from scanned material. Where access to the source electronic file is unavailable please refer to Annex 2.
- Normally, for the application form and cover letter, there is no requirement to scan wet signatures. The signature could in these cases appear only on the paper copy. However, some NCAs do require that wet signatures are scanned – for details refer to national guidance.

Additional details on PDF, including those relating to the good presentation of tables, can be found in the ICH eCTD Specification, Appendix 7.

2.8.2 Extensible Mark-up Language (XML)

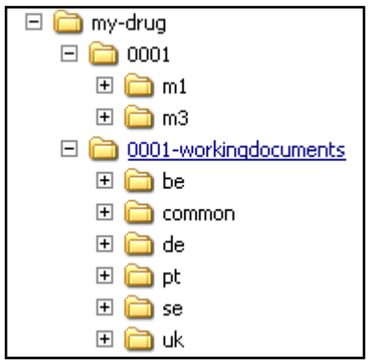
Initiatives on the use of XML structured information are supported for e-application forms. Please refer to EMA eSubmission website for further details.

2.8.3 Other File Formats

Other file formats such as rich text (RTF) or MS Word formats may be required in addition to the PDF requirement of the NeeS by some NCAs, especially for the provision of product information documents. Please refer to the CMDh website for further details.

The files referred to above should not be added as folder / documents within the NeeS structure. When submitted with an NeeS, they should always be provided in a separate folder called “xxxx-workingdocuments” on the same CD/DVD containing the NeeS, where the number (xxxx) matches the four digit named NeeS folder. It is recommended that the file names of these working documents follows the general convention for documents contained within the NeeS structure. (e.g. qos-var.doc and qos-var.pdf).

Figure 3: Proposed structure for “workingdocuments” containing country specific product information documents



If working documents for more than one NCA are submitted on the same CD, sub folders with the country code should be used.

For information on translations being provided outside of the NeeS refer to section 3.3.

If, at any stage in a procedure, an e-mail or Eudralink message is used to send information, this does not change the format requirement. The subject line of the message should always include as a minimum the product name and procedure number for identification purposes.

2.9 Bookmarks and hypertext links

Navigation through an electronic submission is greatly enhanced by the appropriate use of bookmarks and hypertext links. ICH guidance states “It is expected that any document that has a Table of Contents (TOC) will have bookmarks (see the eCTD specification for details). Documents without TOCs should have bookmarks included

where it aids in the navigation around the document content. For example, a 4 page document summarising findings could require bookmarks to aid navigation. However, a 300 page file containing a single data listing might not require bookmarks as there is no further internal structure. Please consult regional guidance documents for further details."

In general terms, bookmarks and hyperlinks should be used to aid navigation.

Additional details on creating bookmarks and hypertext links in PDF documents can be found in the ICH eCTD Specification, Appendix 7.

See section 2.2.2 for details of hypertext links in Tables of Contents.

2.10 Technical validation of NeeS submissions

The technical validation of a NeeS is a separate activity to the content validation of a submission and takes place irrespective of the type of the submission. NCAs have adopted a common set of technical validation criteria against which all NeeS can be checked using NeeS review and validation tools.

From September 1st 2011, two categories of validation rules apply: "Pass/Fail", and "Best Practice".

- **Pass/Fail Criteria**
  These are validation criteria that can either be passed or failed. NeeSs that fail to meet one or more of these criteria will be returned to the applicant for fixing and resubmission, using the same four digit folder name.
  The pass/fail category has been introduced for the possibility of future automation of NeeS validation.

- **Best Practice Criteria**
  Any deviation from the criterion should always be reported by the validating tool.
  These are validation criteria that it is considered good practice to ensure are correct in the submitted NeeS. The applicant should make every effort to address these areas before the NeeS is submitted to the agency. The applicant should be prepared to include justification for any Best Practice criteria not met in the submission cover letter, the reviewer's guide in an added note to the submission.
  NeeS that fail to meet one or more of these criteria will still be accepted by the agency during technical validation and it is possible that agencies may not even check these criteria during technical validation.
  These criteria assess factors that affect the overall ease of use of the NeeS.

Note: Errors found during the regulatory administrative validation should be resolved through the submission of a new NeeS. If using a sequential numbering system, this submission containing the required documents should have the next number.

2.11 Other Technical Information

2.11.1 Security Issues

The physical security of the submission during transportation is the responsibility of the applicant. Once received by NCAs, security and submission integrity is the sole responsibility of the NCA.

2.11.2 Security Settings

Submission or file level security is not permitted. If one-time security settings or password protection of an electronic submission is used this could constitute grounds for the rejection of the submission.

There must be no security setting to open any individual file. This includes passwords, certificate security, adobe policy server settings, etc. There must be no further security settings applied to any individual file (except for files in Modules 3.3, 4.3 and 5.4). For example, in Adobe Acrobat, all "restrictions" should be "allowed" when viewing the Document Preferences > Security settings>.

2.11.3 Protection Against Malware

The applicant is responsible for checking the submission for malware such as viruses. Checking should be performed with an up-to-date virus checker and be confirmed in the cover letter. After receipt at NCAs, a similar internal virus check will be performed. If a virus is detected it will constitute grounds for rejection of the electronic submission.

2.11.4 Electronic Signatures

Although electronic signatures are currently accepted in the EU as being legally equivalent to handwritten signatures (Directive 1999/93/EC), the majority of NCAs do not have a system for that yet and therefore require that certain specific documents (covering letters, Application Forms), where needed, are authenticated by separate signed paper copies.

2.11.5 Transmission Media

Currently CD-R and DVD-R are the generally accepted media standards. However, some NCAs may accept NeeS or working documents over Eudralink/e-mail or via portals. However, this would of course not be possible where signed cover letters and/or application forms are required. See CMDh website for further details.

2.11.6 Procedure for sending electronic information

Electronic media sets should be submitted at the same time as any required paper documentation. The electronic media should be packed adequately to prevent damage and the package should include a cover letter. See CMDh website for further details.

Eudralink/e-Mail (where applicable)

In order to send the NeeS over Eudralink the entire submission has to be zipped first. Some zip formats are not widely readable and therefore a submission could be rejected if the zipped format cannot be read by the agency. Please note there is a size limit of 80 MB per file. It is not recommended to split a NeeS. Therefore initial submissions will not be possible over Eudralink as the file size will be usually over 80 MB.

When using Eudralink, it is important that the expiry date is set to the maximum of 90 days to ensure that it can be opened during the process at the receiving authority. In addition, all information relating to the submission must be contained within the zipped submission; no formal information should be included in the body of the Eudralink message.

Please note, in order to re-obtain the correct NeeS structure, unpack or extract the zip-file and save the content on your local path system. Otherwise the NeeS structure is not displayed in the correct way. When using Eudralink, some NCAs require an additional copy on hard media, check individual NCA web sites for details.

Portals

Generally only small (<100MB) applications can be handled this way. Applicants should check with individual agencies for details of this process. If submissions are uploaded via a portal no data corruption should occur as a result of the process.

CD/DVD

Zipped files should not be used when sending CDs or DVDs.

Applicants should provide the electronic information on the smallest number of discs possible, taking into consideration the size of the submission.

If an individual NeeS is of such a size as to span several CDs, the provision of a DVD is recommended. However, if CD-R must be used, when large applications are submitted it is inevitable that the application will necessarily span multiple CDs. Where possible, individual modules should not be split over multiple CDs (e.g. if possible, a single CD should contain Module 1, Module 2, if too large to fit on the same CD should then go onto the next CD even if this requires CD 1 not to be filled to capacity and so on). If, in the case of larger modules, where a split over multiple CDs is inevitably necessary, subfolders should be distributed in sequence, and these subfolders should not be split between CDs, even if this requires a CD to be sent not full to capacity.

Submissions for workshare/grouping variations across MAs are recommended to be supplied together on a single CD/DVD. The CD/ DVD should contain a top level folder called either grouping or worksharing and clearly marked subfolders for each product that takes part in a worksharing or grouping procedure (see example below)

Figure 4: Proposal of folder structure in case of grouping using sequential four digit folders

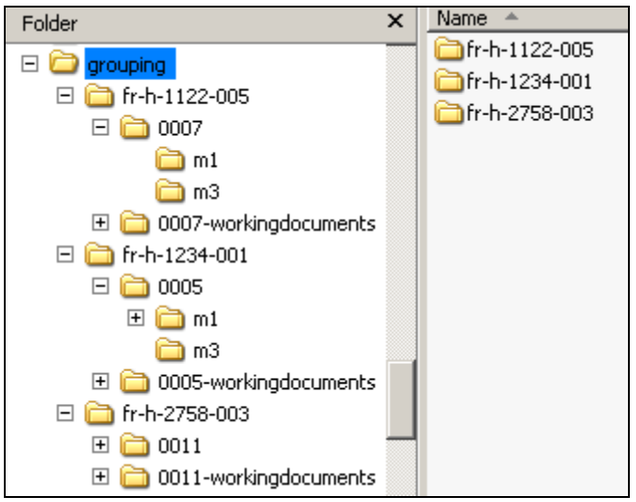
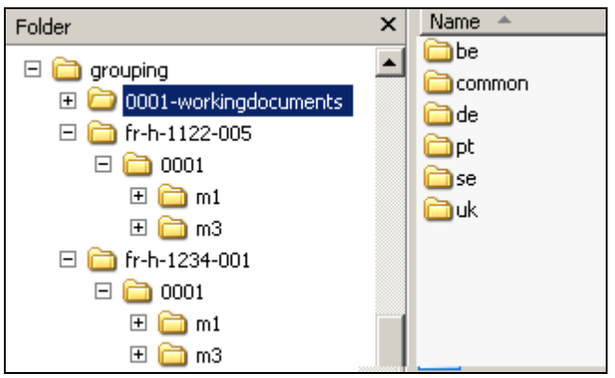


Figure 5: Proposal of folder structure in case of grouping using non-sequential four digit folders



Note: In this case it will be identical for all products.

It is the choice of the applicant if a separate CD/DVD is provided for each new submission or if several submissions (e.g. concerning several variations) for the same medicinal product (same NeeS) is provided on the same CD/DVD. This should be clearly described in the cover letter and indicated on the disc (see 2.12.6).

It is, however not recommended to include previously submitted submissions to the same agency on a CD that contains a new NeeS.

Generally, it is recommended to only submit once in one transmission format. If an additional transmission type is used (for example, a submission is sent via Eudralink and followed up with another copy of the same submission on CD), then this should be explained with a note or hard copy letter such that the receiving agency can easily identify that it is a re-submission.

2.11.7 Labelling of Media:

Each CD or DVD submitted with a NeeS should include the following label information, clearly presented and printed on the media:

- Format: NeeS
- The applicant's name
- The product (invented) name(s)
- The International Non-proprietary Name (INN) of the active substance(s)
- The full application number(s) (if known)
- The four digit number(s) used for NeeS contained on the CD/DVD (0000, or a sequential number)

- If there are too many submissions to list on the CD/DVD label itself, a separate list should be provided in the cover letter.
- Number of media units per full set and an indication of the place of the individual CD/DVD within this set (e.g. 1(5), 2(5), etc.
- The submission type(s) of each NeeS submission(s) contained on the CD/DVD (e.g. Initial Application, Variation Type II)

2.11.8 Number of Media Requested

Please refer to the CMDh website for details of the number of copies of electronic submissions required for archiving and review purposes. Many NCAs destroy discs after data has been uploaded into their systems. Where an NCA requires the disc to be archived they may have additional requirements. Note: The current standard to burn CDs/DVDs is Universal Disk Format (UDF), which has replaced the former ISO standard 9660.

2.11.9 Technical Baseline Applications

A baseline submission is a compiled submission of the current status of the dossier, i.e. resubmission of currently valid documents that have already been provided to an agency but in another format. The sections provided to make up a baseline can be defined by the applicant, but any omissions should not render the submitted content misleading. A baseline would typically consist of the module 3 documents that tend to change over time during the lifecycle of the product. Preferably it should be text source documents included, but good quality scanned images would also be acceptable in these cases, preferably with Optical Character Recognition (OCR) to facilitate text searching.

Baselines could be provided at the beginning of a regulatory activity as a separate submission, at the applicant's discretion, and may assist in referencing to historical information.

It should be clearly stated in the cover letter of the "baseline NeeS" that the content of the current dossier has not been changed but only the dossier format and consequently, there should be no need for the NCAs to assess baseline submissions and hyperlinks between documents are therefore not needed in baseline submissions.

3 Module specific information

3.1 Module 1.0 Cover Letter and Tracking Table

A cover letter should always be provided.

Please see also the CMDh website for requirements of signed paper copies of the cover letter and application form to each NCA.

If a sequential numbering system is used, a tracking table would be helpful.

3.2 Module 1.2: Administrative Information (Application Forms)

The application form should always be provided as a PDF file within the NeeS structure and for some NCAs also be provided as a signed paper copy or submitted through a portal. Please refer to the CMDh website (eSubmissions) for details.
For this specific PDF file a newer version than PDF version 1.4 may be appropriate and acceptable in accordance with the NeeS validation criteria.

3.3 Module 1.3.1: Product Information

Product information should be supplied as PDF files but some NCAs require an RTF or Word file in addition to facilitate assessment. Those additional files should be provided in the separate folder <four digit number>-workingdocuments on the same CD / DVD (see also section 2.9.3).

It is not required to provide the tracked changes version in PDF format, if it is submitted as Word document in the workingdocuments folder.

National translations in MRP/DCP should be managed outside of the NeeS (in analogy to CMDh BPG for eCTD in MRP/DCP). This is also applicable for Type IA or IB variations, when translations of the product information are required already with the first submission. In such cases, the translations should be provided with descriptive

filenames in the same working documents folder, in MS Word format only. If working documents for more than one NCA are submitted on the same CD, sub folders with the country code should be used (see figure 3).

3.4 Module 1-responses

The submission of electronic information in response to a list of questions from NCAs should follow the same basic principles as the first submission. The written response should be submitted following the EU recommended response folder and file structure. Please note that all data related documents are aligned with the CTD structure, refer to EU CTD Implementation as appropriate.

To help in the management of responses it is recommended:

- To use the variable part of the filename to indicate what responses are being provided
- The responses be split up into separate files for each major section of the submission (e.g. Quality, Non-clinical and Clinical). For example, Responses to Questions for the Initial Application – *cc-responses-day106-quality.pdf*, Responses to Questions for Type II Variation 028 - *cc-responses-var028-clinical.pdf* etc.
- Provide a full copy of the list of questions received from the agencies as the first document in this section (eg cc-responses-questions.pdf).

In MRP/DCP, all of the files for the response documents should be placed in the folder m1/eu/responses/common, regardless which member state raised the question.

If responses to more than one question are submitted in a single file bookmarks should be used within the PDF file to clearly identify each response.

3.5 ASMF

The ASMF can be submitted as a NeeS regardless if an application for Marketing Authorisation for a medicinal product referring to the ASMF is submitted in eCTD format or paper. Also, the other way around is acceptable, i.e. even if an application for Marketing Authorisation for a medicinal product is submitted in NeeS format and there is a reference to an ASMF, the ASMF submitted by the ASMF holder could be provided in another format.

Applicants using NeeS for ASMF or for MAAs including an ASMF are recommended to add "ap" or "rp" as a suffix to the file name for content in the applicant's part and restricted part, respectively.
Note that this is not the same recommendation as given in the current version 1.0 of the "Practical guidance for the use of eCTD format for ASMF" published on the EMA eSubmission website, but is acceptable under the NeeS file naming as it is part of the variable portion of the file name.

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Annex 1 Guidance on Text Searchable Documents

A1-1. General

Applicants are requested to ensure that all submissions contain the maximum amount of text searchable content. Documents with searchable text will aid the assessor, or any other user, in searching for specific terms and also in copying and pasting information into another document, such as an assessment report.

We recognize that not all documents need to be text searchable. This short document provides some guidance about what must be text searchable and the ways to ensure that files are created appropriately.

A1-1.1 Creating Text Searchable Files

PDF files with searchable text can be created by all PDF tools from a source file in a text format (e.g. MS Word, SAS, MS PowerPoint, Rich Text Files, etc.). When created in this way, the file will usually be the smallest in size (measured in kilobytes or megabytes) that they can be.

If the only version of a document available is in paper, then scanning to PDF and using an Optical Character Recognition (OCR) routine is the only way to create searchable text. PDF files created in this way tend to be much larger in size, for the same number of pages (from 10 to 100 times as large), and the quality of the text that is created will almost certainly not be a 100% match to the original text. It is noted that tools for checking and correcting this text tend to be somewhat cumbersome. For these reasons, applicants are recommended to use scanning/OCR only as a last resort.

Applicants are reminded that the text produced by the OCR routine should be “hidden” behind the image of the original page so that the user can refer to the picture of the page and the text on it as final verification of the data. As a result, the applicant should ensure that, as a minimum, the text on the scanned image is legible to the user. Poor quality images should not be provided and you should note that these can only inevitably lead to poor quality OCR text.

A1-2. Documents that must always be text searchable

(i.e. the PDF should be produced wherever possible from a text source, such as MS Word, but if sourced from a scanned original then they **must be** OCR’d.)

- Key administrative documents in Module 1 including, the cover letter, application form, product information documents
    - Applicants are reminded that some NCAs regard logging in through a portal as sufficient to establish a users identity and do not require handwritten signatures on Cover Letters and Application Forms submitted this way.
- Any document in Module 2 (QOS, Preclinical Overview and Summaries, Clinical Overview and Summaries).
- The main body of text and main tables in any preclinical or clinical report required to support the main claim of the application.
- The main body of text in any reports, methods, analytical procedures, etc. supplied in Module 3 The main body of text of Periodic Safety Update Reports (PSURs)
- The main body of text of Risk Management Plans
- The main body of text of Environmental Risk Assessment
- Any English translation of a document originally written in a foreign language (see also below)

A1-3. Documents that do not need to be text searchable

(i.e. the PDF should be produced wherever possible from a text source, such as MS Word, but if sourced from a scanned original then there is no need for OCR.)

- Any original GMP certificate
- Any original certificate of analysis
- Any manufacturer's licences
- Any certificate's of suitability
- Any Manufacturing Authorisation
- Any document written in a foreign language where a translation is provided in English (however, the translation should be text searchable, see above)
- Any literature references sourced from journals, periodicals and books (except when these are used in a bibliographic application to support the main claims of the application).
- The blank CRF in a Clinical Study Report
- Patient data listings (when supplied)
- CRFs (when supplied)
- Any page with a signature that does not contain other information key to the understanding of the submission
- Applicants should consider providing signatures on separate pages from key text in reports, overviews, etc.

A1-4. Further Information

If applicants are uncertain whether or not a particular document should be text searchable, they should contact their NCA for guidance.

Annex 2 Example Tables of Contents

These Tables of Contents are *examples* and are provided for illustrative and guidance purposes only. The blue underlined text illustrates where hyperlinks to the individual documents may be added.
In these examples there are some “Not applicable” documents shown. “Not applicable” documents should not appear in the dossier and nor should they be included in the TOCs.

The following is an example of a CTD TOC (main TOC)

Module 1	Administrative Information and Prescribing Information	Module 1
Module 2	Common Technical Document Summaries	Module 2
Module 4	Nonclinical Study Reports	Module 4
Module 5	Clinical Study Reports	Module 5

The following are examples of module TOCs.

Module 1	Administrative Information and Prescribing Information	
1.0	Cover Letter	1.0
1.2	Application form	1.2
	Annex 5.3 Proof of establishment of the applicant in the EEA.	Annex 5.3
	Annex 5.4 Letter of authorisation for communication on behalf of the applicant/MAH	Annex 5.4
	Annex 5.5 Curriculum Vitae of the Qualified Person for Pharmacovigilance	Annex 5.5
	Annex 5.6 Manufacturing Authorisation required under Article 40 of Directive 2001/83/EC	Annex 5.6
	Annex 5.8 Flow-chart indicating all sites involved in the manufacturing process of the medicinal product or active substance	Annex 5.8
	Annex 5.9 GMP certificate(s) or other GMP statement(s); Where applicable a summary of other GMP inspections performed.	Annex 5.9
	Annex 5.12 Ph. Eur. Certificate(s) of suitability for TSE	Annex 5.12
	Annex 5.17 List of Mock-ups or Samples/specimens sent with the application, as appropriate	Annex 5.17
	Annex 5.22 declaration from the Qualified Person of the manufacturing authorisation holder	Annex 5.22
1.3.	Product information	1.3.
1.3.1	SPC, Labelling and Package Leaflet	1.3.1
	common - combined SPC	1.3.1
	be - de - intermediate packaging 10 mg	1.3.1
	be - de - outer packaging 10 mg	1.3.1
	be - de - package leaflet 10 mg	1.3.1

Module 2	Common Technical Document Summaries	
2.4	Nonclinical Overview	2.4
2.5	Clinical Overview	2.5
2.6	Nonclinical Written and Tabulated Summary	2.6
2.7	Clinical Summary	2.7

Module 4	Nonclinical Study Reports	
4.2	Study Reports	4.2
4.2.1	Pharmacology	4.2.1
4.2.1.1	Primary Pharmacodynamics	4.2.1.1
	study report 1	4.2.1.1
	study report 2	4.2.1.1
	study report 3	4.2.1.1
4.3	Literature References	4.3
	Reference 1	4.3
	Reference 2	4.3
	Reference 3	4.3

Module 5	Clinical Study Reports	
5.2	Tabular Listing of All Clinical Studies	5.2
5.3	Clinical Study Reports	5.3
5.3.1	Reports of Biopharmaceutic Studies	5.3.1
5.3.1.1	Bioavailability (BA) Study Reports	5.3.1.1
	study report 1	5.3.1.1

Document Control

Change Record

Version	Author(s)	Comments
0.1 June 2007	Ricco van den Hoorn	First draft
0.2 June 2007	Alison Davis	With suggested changes from BfARM accepted
1.0 August 2007	David Wheeler	Following comments from Topic Group Members, removal of references to eCTD
1.1 October 2007	David Wheeler	Following comments at Topic Group meeting 29 August
1.2 November 2007	David Wheeler	Following comments at Topic Group meeting 16/17 October
1.3 December 2007	David Wheeler	Following review comments at TIGes et al
1.4 January 2008	David Wheeler	Following review/comments at Topic Group 19 December
1.41 December 2009 -	Karin Gröndahl	New draft version for comments; updated in accordance with the eCTD guidance and CRs received to MHRA
1.42 December 2009	Karin Gröndahl	Following review comments at subgroup TC meeting 9 December
1.43 December 2009	Karin Gröndahl	Following review comments at subgroup TC meeting 22 December
1.44 January 2010	Klaus Menges	Commented draft 1.43 for subgroup TC meeting 14 January
1.45 January 2010	Karin Gröndahl	Following review comments at subgroup TC meeting 14 January
1.46 February 2010	Karin Gröndahl/ Geoff Williams	Following review comments at subgroup TC meeting 12 February
1.47 February 2010	Karin Gröndahl	Minor changed new version after e-mails within the subgroup
1.48 March 2010	Karin Gröndahl	Final draft version after subgroup meeting at EMA 2 March
2.0 March 2010	Klaus Menges	Final version to be published
2.1 June 2011 -	Klaus Menges	New draft for revision in line with updated validation criteria, experience gained and alignment with eCTD guidance changes
2.2 July 2011	Alastair Nixon/ Karin Gröndahl	Incorporating comments from the group and further alignment with eCTD Guidance
2.3 July 2011	Klaus Menges / Karin Gröndahl	Following review comments at subgroup TC meeting 12 July
2.4 July 2011	Alastair Nixon/ Karin Gröndahl	Following review comments at subgroup TC meeting 21 July
2.5 July 2011	Nixon/ Gröndahl/ Menges	Following review comments at subgroup TC meeting 26 July and tidying the document for final draft for TIGes
3.0 August 2011	Alastair Nixon/ Karin Gröndahl	Following review of TIGes comments and final updates at subgroup TC meeting 22 August 2011. Final document for TIGes adoption and publication.

Reviewers

Version	Name	Organisation
1.41 – 1.46	Members of the subgroup	TIGes Harmonisation group
1.47	Members of the subgroup	TIGes Harmonisation group
1.48	Members of the TIGes	TIGes
2.1-2.4	Members of the subgroup	TIGes Harmonisation group
2.5	Members of the subgroup and the TIGes	TIGes Harmonisation group/TIGes
3.0	Members of the subgroup and the TIGes	TIGes Harmonisation group/ TIGes

Distribution

Version	Distributed to	Way of distribution
1.41 – 1.46	Members of the subgroup	E-mail December 2009-February 2010
1.47	Members of TIGes	E-mail 26 February 2010
1.48	Members of TIGes	E-mail 2 March 2010 and presented at the meeting
2.0	General public	Published on EMA e-submission website March 2010
2.1-2.4	Members of the subgroup	E-mail June-July 2011
2.5	Members of the subgroup and TIGes	E-mail 1 August 2011 for comments
3.0	Members of the subgroup and TIGes	E-mail 24 August 2011 for adoption by TIGes

Coming into Operation

Version	Date in operation	Comment
1.4	January 2008	Draft for publication for use
2.0	March 2010	Publication for use
3.0	August 2011	Published for use