

FINAL DRAFT

**Guidance for Industry on Providing Regulatory
Information in Electronic Format:
Non-eCTD electronic Submissions (NeeS)**

Part I General Considerations

***Part II Requirements for specific submission
types***

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Part I General considerations

1. Introduction

In 2005 the Heads of Medicines Agencies agreed that all Member States would be able to accept electronic-only submissions by the end of 2009. The benefits of moving to e-working were seen as:

- reduction of (internal) paper-flow (logistics and administrative burden),
- reduction of physical archiving space,
- facilitation of the review process:

- easy to view and legible on screen
- easy to print, maintaining a paper outlook as far as possible
- easy to navigate, e.g. through a directory structure, Table of Contents (ToC), bookmarks and/or hyperlinks
- provides search capabilities
- simplifies the preparation of assessment reports (copy & paste, etc).

This Guidance Document is intended to assist pharmaceutical companies with the submission of regulatory information in electronic format to the National Competent Authorities (hereafter referred to as NCAs) and the European Medicines Agency (hereafter referred to as EMEA). This document details the requirements for the submission of Non-eCTD electronic Submissions ([NeeS](#)) as currently these form the majority of electronic applications in the EEA. A further document will be issued later to cover full [eCTD](#) submissions.

This document has been created by the eGuidance Topic Group, a sub-group of the Telematics Implementation Group – Electronic Submissions (TIGes) consisting of agency representatives from, Belgium, Denmark, France, EMEA, Germany, Hungary, The Netherlands, Portugal, Sweden and the United Kingdom, together with industry representatives from EFPIA and EGA. It is recommended that all National Competent Authorities adopt this guidance as the basis for their dealings with applicants.

In preparing this Guidance Document, experience gained with the electronic submission of full dossiers, Product Information and Periodic Safety Update Reports (PSURs), national legislation, current ICH and EU standards in the area of electronic submissions and several international documents, has been taken into consideration.

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 and EMEA of using information submitted in electronic format. It should be emphasised that NeeS applications should only be regarded as an **interim** format and that applicants should be actively planning their move to full eCTD submissions.

This Guidance Document consists of two parts: the first part contains some general considerations with respect to the submission of electronic regulatory information, whilst the second part contains specific requirements for different types of submissions. Please refer to Chapter 7 of the [Notice to Applicants](#) for specific NCA requirements.

2. Scope

2.1 Type of product

Submission of electronic regulatory information is considered acceptable under the terms of this Guidance Document for all *human* medicinal products falling within the competence of the NCAs and EMEA.

2.2 Type of submission

Regulatory information can be submitted in electronic format for every type of submission, ranging from new applications, (e.g. full, abridged), variations, etc. for National, Mutual Recognition, Decentralised and Centralised procedures, to PSUR, Drug Master Files, in accordance with this Guidance Document.

2.3 Format and structure of submissions

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

For NeeS applications it is highly recommended that the eCTD structure is used so that all sections of the CTD are in the right order. The breakdown of the electronic submission should be in conformity with the [ICH Granularity Document](#) and eCTD file naming conventions should be followed.

3. Paper requirements

Submission of paper copies is no longer required in some NCAs. An overview of the requirements for paper and electronic copies is specified for each NCA and EMEA in Chapter 7 of the [Notice to Applicants](#). A [guidance document](#) on the preparation of paper copies from eCTD applications has also been produced by the EMEA.

If NeeS applications are being used as a source, consideration has to be given to the provision of appropriate tables of contents for each module together with one for the overall submission. Please see Annex 2 for example tables of contents.

The switch from paper to electronic-only can be made at the start of any phase in the life cycle of a medicinal product, initial application or a later variation. Once the switch to electronic-only is made it is highly recommended that further applications and responses relating to the particular medicinal product are submitted in electronic format.

4. Hardware

NCAs and EMEA 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 and EMEA hardware and software. Although it is the policy of the NCA and EMEA to maintain 'state-of-the-art' desktop configurations and IT infrastructure in line with common office standards, the electronic information should not only be readable on the latest operating system (OS), but support a reasonable number of previous OS versions. The general IT consensus in this area requires that OS systems should be no more than two versions behind the current standard.

5. File formats

5.1 General

Currently the following file formats support the goals of e-working, are compliant with national archiving regulations, ICH and EU eCTD specifications and are accepted by NCAs and EMEA:

- For narratives: Portable Document Format (PDF), 1.4 only
- For graphics: PDF or when appropriate or when PDF is not possible, use Joint Photographic Experts Group (JPEG), Portable Network Graphics (PNG), Scalable Vector Graphics (SVG) or Graphics Interchange Format (GIF)
- In accordance with EU Module 1 specifications NCAs and EMEA accept RTF file format but always in addition to the PDF files of the same documents. In general these files should be located outside the main submission but with the same filenames as the PDF files.
- SAS data files by arrangement.

Please see [EU M1 Specification](#) for further details.

5.2 Portable Document Format (PDF)

Portable Document Format (PDF) is an open, de facto, electronic publishing standard, created by Adobe Systems Incorporated (<http://www.adobe.com>). There are several alternative suppliers of PDF software apart from Adobe Systems. Applicants need to check that the PDF documents produced meet all the requirements listed below:

- Files should be legible with Acrobat Reader, version 5.0 or higher.
- PDF file version 1.4 only should be used.
- Documents should be generated from electronic source documents and not from scanned material, except where access to the source electronic file is unavailable or where a signature is required. See Annex 1 for further guidance on text searchable documents.

- PDF files produced from an electronic source document are highly preferred over PDF files produced from scanned paper since those 'electronic' PDF files provide the maximum functionality to reviewers in terms of search capabilities and copy and paste functionality;
- Overviews in the CTD Module 2 **must always** be generated from an electronic source document
- Product information may be required to be submitted additionally in rtf format as detailed in the [Notice to Applicants](#)
- If scanning is unavoidable, readability and file sizes of less than 100MB need to be balanced. The following is recommended: resolution 300 dpi (photographs up to 600 dpi), avoid greyscale or colour where possible, use only lossless compression techniques
- Fonts should be chosen of a type, colour and size that allow easy reading of documents on screen (1024x768 points) and after printing; examples of strongly recommended font-types are Times New Roman, 12-point, black; Arial, 10-point, black (coloured fonts are discouraged).
- Try to avoid the use of colour. If colours other than black are used, legibility after printing should be tested pre-submission
- Print area for pages should fit on an A4 sheet of paper.
- Landscape-oriented tables should automatically appear in landscape on screen

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

6. Security

There are various aspects related to security. The physical security of the submission during transportation is the responsibility of the applicant. Once received by NCAs and EMEA, security and submission integrity is the sole responsibility of the NCA and EMEA.

6.1 Password protection

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

6.2 Virus protection

The applicant is responsible for checking the submission for viruses. Checking should be performed with an up-to-date virus checker and be confirmed in the cover letter. After receipt at NCAs and EMEA, a similar internal virus check will be performed. If a virus is detected it will constitute grounds for rejection of the electronic submission. If submissions are uploaded via a portal no data corruption should occur as a result of the process.

6.3 Electronic signatures

Although electronic signatures are currently accepted in the EU as being legally equivalent to handwritten signatures (Directive 1999/93/EC), some NCAs and EMEA require that certain specific documents (covering letters, Application Forms) are authenticated by separate signed paper copies. Please refer to each NCA for detailed guidance on this matter.

7. Technical validation of electronic submissions

The following items may be checked during validation:

- Virus check at the NCA and EMEA,
- Compliance with general requirements (e.g. PDF file properties, see section 5.2),
- Compliance with the eCTD structure templates and naming convention (see Part II of this Guidance Document for details),

- Compliance with specific details of pure PDF submissions (see Part II of this Guidance Document for details) with special attention to bookmarks,
- Security settings or password protection,
- Any other serious defect, incident, etc. associated with the initial processing of the electronic submission.

If during the administrative processing or the actual review of an electronic submission serious defects are found, NCAs and EMEA will normally contact the applicant in the first instance. If these defects cannot be remedied quickly, the submission will normally be returned to the applicant. Examples of such defects would be a substantial number of non-functioning hyperlinks, hyperlinks to non-existing documents or an over-reliance on scanned documents.

8. Procedure for sending electronic information

8.1 Address

The electronic submission should be submitted to the address referred to in the [Notice to Applicants](#), Chapter 7.

8.2 Packaging and labelling

The sets of physical media for electronic information 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 section 8.3 below).

The CD or DVD discs should be labelled with:

Procedure number (if avail) e.g.	DE/H/512/01/001/DC
Applicant	PharmaCompany
ATC-Code	L01CA01
Type of submission	initial-maa
Invented name	WonderPill
Drug substance (INN)	Pioglitazone hydrochloride
Date sent	12.01.2006

8.3 Cover letter

The cover letter should include as a minimum, the information specified in the [CMDh Guidance](#) document which also includes a template that can be used. Please see Chapter 7 of the [Notice to Applicants](#) for details on the provision of signed paper documents.

8.4 Media

Applicants should provide the electronic information on the smallest number of discs possible, taking into consideration the size of the submission. Currently CD-ROM, CD-R, DVD-R are considered acceptable media standards. If more than one CD or DVD is needed, avoid spanning the contents of a Part or a Module of the dossier over two CDs or DVDs.

8.5 Archiving and working copies

Please refer to Chapter 7 of the [Notice to Applicants](#) for details of the number of copies of electronic submissions required for archiving and review purposes.

Part II Requirements for specific submission types

1. New applications

1.1 Acceptable dossier formats and file formats

Please refer to Part I of this Guidance Document for general information on the submission of a dossier in electronic format.

NeeS electronic submissions comply fully with the folder and file organisation as presented in the ICH eCTD Specification Document (including naming conventions). The only difference 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.

Navigation through such an electronic submission is based on electronic tables of content, bookmarks and hypertext links.

The first level of detail should simply list the modules of the CTD according to the Notice to Applicants. These entries are linked to the lower level tables of contents or documents as relevant. This level of the comprehensive table of contents should be a single page and should be provided as a single PDF file. The file containing the table of contents for the CTD should be named *ctd-toc.pdf*.

The second level of detail should contain the table of contents for each Module of the CTD. Hyperlinks for each document should be provided to the first page of the appropriate file. In general, this table of contents should consist of only a few pages. The files containing the 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.

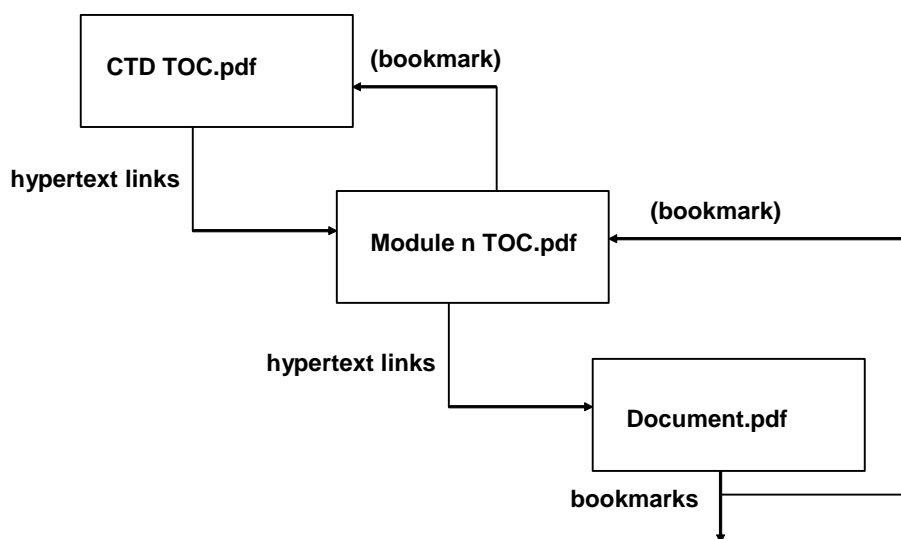
The third level of detail is the table of contents for each document, where such a table of contents is provided. Ideally the table of contents should be included within the same file as the rest of the document. For each document, provide bookmarks for every entry in the document's table of contents 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. It is not necessary to add hypertext links within the document's table of contents although this can act as an additional means of navigation.

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 isn't mandatory but when provided it will facilitate the assessment.

However, in order to improve clarity in extremely complex submissions it may be appropriate to provide intermediate level tables of contents between the Module and the document table of contents. Similarly, for a small submission (e.g. abridged) it may be appropriate to provide only the *ctd-toc.pdf* which links directly to the documents.

Figure 1 describes diagrammatically the above situation.

Figure 1.



It should be noted that some NCAs, e.g Belgium, do not require TOC files as their checking tools create them.

Please see Annex 2 for example tables of contents. It should be noted that these are **examples** and are provided for guidance and illustrative purposes only.

1.2 Module 1.2: administrative information (application forms)

Some NCAs request that applicants create an application form on their own portals. The majority of NCAs and EMEA require the application form to be provided as a PDF file together with signed paper copies. Please refer to [CMDh Guidance](#) for details.

1.3 Module 1.3.1: product information

For Nees applications product information should be supplied as PDF files but many NCAs require an RTF/Word file in addition to facilitate assessment. Please refer to Chapter 7 of the [Notice to Applicants](#) for details.

2. Responses to questions

The organisation of the submission of electronic information in response to a list of questions from NCAs and EMEA should follow the same basic principles as the first submission. The written response should be submitted following the ICH recommended response folder and file structure. In this case the written response document should be placed in the folder [name e.g mydrug/m1/eu/responses]. Appropriate navigation in the submission should be allowed and should follow the same concepts as described under 1.1.

3. Variations

The same technical approach used for written responses can be used for the submission of variations and is relevant for any combination of dossier format and file format. The content of

such submissions should follow the normal recommendations given in the Notice to Applicants. NCAs and EMEA have a distinct preference for naming the root folder of the submission with the product (invented) name in lower case followed by the subfolder, name, e.g. mydrug/.

4. Renewals

EMA and many NCAs would like to receive renewal applications in electronic format, i.e. as PDF files with no additional paper copies. Please refer to Chapter 7 of the [Notice to Applicants](#) for details.

Annex 1 Guidance on Text Searchable Documents

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.

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.

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
 - This also covers similar documents provided in non-MAA submissions.
- Any document in Module 2 of the MAA (QOS, Preclinical Overview and Summaries, Clinical Overview and Summaries).
 - This also covers similar documents provided in non-MAA submissions.
- The main body of text and main tables in any preclinical or clinical report required to support the main claim of the application.
 - This also covers similar documents provided in non-MAA submissions.
- The main body of text in any reports, methods, analytical procedures, etc. supplied in Module 3 of the MAA
 - This also covers similar documents provided in non-MAA submissions.
- The main body of text of Periodic Safety Update Reports (PSURs)
- The main body of text of Risk Management Plans
- Any English translation of a document originally written in a foreign language (see also below)

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.

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 for Each Module

Module 1	EU Module 1	Module 1
Module 2	Common Technical Document Summaries	Module 2
Module 3	Quality	Module 3
Module 4	Nonclinical Study Reports	Module 4
Module 5	Clinical Study Reports	Module 5

These Tables of Contents are **examples** and are provided for illustrative and guidance purposes only.

Module 1	EU Module 1	
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1.2	Application form	1.2
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	Annex 6.4 Letter of authorisation for communication on behalf of the applicant/MAH	Annex 6.4
	Annex 6.5 Curriculum Vitae of the Qualified Person for Pharmacovigilance	Annex 6.5
	Annex 6.6 Manufacturing Authorisation required under Article 40 of Directive 2001/83/EC	Annex 6.6
	Annex 6.8 Flow-chart indicating all sites involved in the manufacturing process of the medicinal product or active substance	Annex 6.8
	Annex 6.9 Statement (or GMP Certificate issued by an EEA inspectorate, when available) from the competent authority which carried out the inspection of the manufacturing site(s)	Annex 6.9
	Annex 6.12 Ph. Eur. Certificate(s) of suitability for TSE	Annex 6.12
	Annex 6.17 List of Mock-ups or Samples/specimens sent with the application, as appropriate	Annex 6.17
	Annex 6.22 declaration from the Qualified Person of the manufacturing authorisation holder	Annex 6.22
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	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
	be - fr - immediate packaging 10 mg	1.3.1
	be - fr - intermediate packaging 10 mg	1.3.1
	be - fr - outer packaging 10 mg	1.3.1
	be - fr - package leaflet 10 mg	1.3.1
	be - fr - combined SPC	1.3.1

	be - nl - immediate packaging 10 mg	1.3.1
	be - nl - intermediate packaging 10 mg	1.3.1
	be - nl - outer packaging 10 mg	1.3.1
	be - nl - package leaflet 10 mg	1.3.1
	be - nl - combined SPC	1.3.1
1.3.2	Mock-up	1.3.2
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	common - intermediate packaging 10 mg	1.3.2
	common - outer packaging 10 mg	1.3.2
	common - package leaflet 10 mg	1.3.2
	be - immediate packaging 10 mg	1.3.2
	be - intermediate packaging 10 mg	1.3.2
	be - outer packaging 10 mg	1.3.2
	be - package leaflet 10 mg	1.3.2
1.3.3	Specimen	1.3.3
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1.3.4	Consultation with target patient groups	1.3.4
	common - consultation with target patient groups	1.3.4
	be - consultation with target patient groups	1.3.4
1.3.5	Product Information already approved in the Member States	1.3.5
	common - approved package leaflet 10 mg	1.3.5

	common - approved combined SPC	1.3.5
	be - approved package leaflet 10 mg	1.3.5
	be - approved combined SPC	1.3.5
1.3.6	Braille	1.3.6
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1.4.3	Clinical	1.4.3
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1.5.1	Information about bibliographical applications	1.5.1
1.5.2	Information for Generic, `Hybrid` or Bio-similar Applications	Not Applicable
1.5.3	(Extended) Data/Market Exclusivity	Not Applicable
1.5.4	Exceptional Circumstances	Not Applicable
1.5.5	Conditional Marketing Authorisation	Not Applicable
1.6	Environmental Risk Assessment	1.6
1.6.1	Non-GMO	1.6.1
1.6.2	GMO	Not Applicable
1.7	Information on Orphan Market Exclusivity	1.7
1.7.1	Similarity	1.7.1
1.7.2	Market Exclusivity	Not Applicable
1.8	Information on Pharmacovigilanc	1.8
1.8.1	Pharmacovigilance System	1.8.1
1.8.2	Risk-management System	1.8.2
1.9	Information Relating to Clinical Trials	1.9
Responses to Questions		Not Applicable
Additional Data		Not Applicable

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