European Medicines Agency
Evaluation of Medicines for Human Use

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EMEA IMPLEMENTATION OF ELECTRONIC-ONLY SUBMISSION AND eCTD SUBMISSION:

PRACTICAL GUIDELINES RELATING TO NON-eCTD ELECTRONIC SUBMISSIONS

According to EMEA's revised Statement of Intent on electronic-only submission and eCTD submission, from 1 January 2010, it will be mandatory to use the eCTD format for all submissions provided to EMEA in the context of Centralised Procedure applications. Until 1 January 2010, EMEA will continue to accept non-eCTD electronic submissions (eCTD is, however, the recommended format).

This document aims to address the EMEA's main requirements for the structure, format and presentation of all such non-eCTD electronic submissions. All non-eCTD electronic submissions sent to EMEA must adhere to the guidelines contained in this document, from 1 February 2009 until such time as the eCTD format is mandatory.

To further clarify, from 1 February 2009 until 1 January 2010, all submissions sent to EMEA in the context of the Centralised Procedure must either be formatted as eCTD (in which case the EMEA practical eCTD guidance http://www.emea.europa.eu/htms/human/genguidance/genreg.htm should be followed), or should be formatted according to the guidelines laid out in this document. No other electronic submission formats will be accepted.

The EMEA's non-eCTD electronic submission guidelines will therefore apply for a finite period of time (to 1 January 2010) and are intended as a transitory measure to improve the standardisation and quality of all non-eCTD electronic submissions provided in the context of the Centralised Procedure during this time period. Adherence to the guidelines is further intended to facilitate the transition to the eCTD format for all submissions. It is important to highlight that the non-eCTD electronic submission described here is considered to be a transition format, and applicants should actively plan to ultimately use the eCTD format.

These guidelines are the EMEA's interpretation of, and are complementary to, the 'European Guidance for Industry on Providing Regulatory Information in Electronic Format: Non-eCTD electronic Submissions (NeeS)' produced by the Telematics Implementation group for eSubmission (TIGes). The document aims to highlight the areas in the TIGes guidance that are of particular importance to EMEA, namely:

- Full adherence to the CTD file/directory structure for all non-eCTD electronic submissions
- Use of recommended file formats (PDF/Word) for all documents in non-eCTD electronic submissions
- Use of appropriate file-naming convention for all documents in non-eCTD electronic submissions
- Composition of standardised electronic submissions in such a way as to facilitate review and processing

From 1 February 2009 until 1 January 2010, any non-eCTD electronic submission provided in the context of the centralised procedure must comply with these specific guidelines from EMEA for non-eCTD electronic submissions. Any non-eCTD electronic submission *not* built in accordance with the guidelines contained in this document will be rejected by EMEA.

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GLOSSARY

A brief glossary of terms (for the purpose of this document only) is indicated below:

Term	***Definition***
Applicant	A pharmaceutical company or its agent that is submitting information in support of an ***application***.
Applicant's information	Regulatory information submitted by an ***applicant*** for or to maintain a marketing authorisation that falls within the scope of this guidance document
Application	A collection of documents compiled by a pharmaceutical company or its agent in compliance with European legislation and guidelines in order to seek a marketing authorisation or any amendments thereof. An **application** may comprise a number of **submissions**.
Procedure	A Community registration procedure for the authorisation of medicinal products in the European Community. There are 4 types of procedures that operate within the EC – the Centralised, Decentralised, Mutual Recognition and National Procedures.
Submission	A single set of information and/or documents supplied by the applicant as a part of, or the complete, Application. (In the context of eCTD, this is equivalent to '**sequence**').

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SUBMISSION TYPES

Every submission of information made in the context of a centralised marketing application procedure and the subsequent maintenance of the lifecycle of the application (e.g. initial application, supplementary information, variations, renewals, Follow-Up Measures (FUMs), Periodic Safety Update Reports (PSURs), Notifications etc) should be made in electronic-only format, and these guidelines followed if eCTD format is not used.

However, it should be clarified that these guidelines for non-eCTD electronic submissions do not extend to information submitted prior to the initial application, (e.g. scientific advice application) and certain information relating to pharmacovigilance and clinical trials.

It should then be noted that the following types of information submitted to EMEA and Regulatory Authorities are not explicitly covered by this guidance:

- **Individual Case Safety Reports** ("ICSRs"): This information is submitted to the National Competent Authorities (NCAs) and the EMEA in the context of the EudraVigilance system.
- **Clinical trials registration information**: This information is to be submitted to the NCAs in the format and manner prescribed by such Authorities for the territory in which the trial is conducted.
- **Suspected Unexpected Serious Adverse Reactions** ("SUSARs") encountered during clinical trials are reported to the central, Eudra Clinical Trials (EudraCT) database in support of the implementation of Directive 2001/20/EC.
- **Scientific Advice (formal), Protocol Assistance**
- **Orphan Drug Designations**
- **Other Processes (e.g. referrals)**

SUBMISSION STRUCTURE

The key requirement for non-eCTD electronic submissions provided to EMEA is that 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.
The structure of the non-eCTD electronic submission should be in line with the ICH CTD Granularity Document.

Furthermore, non-eCTD electronic submissions provided to EMEA must also fully comply with the precise file and directory structure (and file naming convention) as presented in the ICH eCTD Specification.

The only differences between an eCTD and a non-eCTD electronic submission in each case should therefore be that:

- **The index.xml and eu-regional.xml files, and the util folder containing other technical eCTD components, are omitted from a non-eCTD electronic submission;**
- **A non-eCTD electronic submission should contain dynamic table of content documents to facilitate navigation, (such ToCs do not form part of the eCTD as the function is provided by the eCTD XML backbone).**

Guidance on placement of documents within the CTD/eCTD structure for particular submission types can be found in:

The EU-CTD Notice to Applicants
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol2_en.htm;
The CTD question and answer document published by the Notice to Applicants
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/b/ctd_qa_05_2006.pdf;
The ICH CTD Q&A
http://www.ich.org/LOB/media/MEDIA1189.pdf;
The EMEA pre-submission guidance
http://www.emea.europa.eu/htms/human/presub/list.htm
The EMEA post-authorisation guidance
http://www.emea.europa.eu/htms/human/postguidance/index.htm.

The eCTD file and directory structure should not only be observed for initial applications where all sections of the dossier are populated – this structure should also be followed for every follow-up and post-authorisation submission.

The product invented name or INN should be used to name the root folder of the non-eCTD electronic submission. Below this level, the use of 4-digit sequence numbers as per the eCTD is recommended to contain the module folders e.g. WonderPil/0000. Non-eCTD electronic submissions should then be managed at product, not strength, level.

Navigation

Navigation through a non-eCTD electronic submission as described above is based on electronic tables of content, bookmarks and hypertext links.

The first level of detail should list the modules of the CTD according to the Notice to Applicants. These entries should be 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. 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.

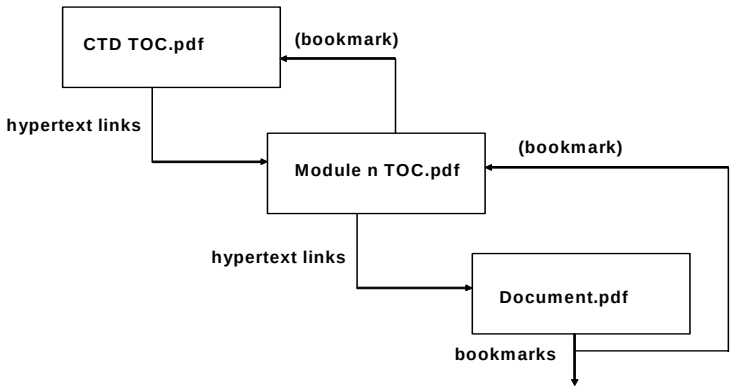
For new applications, detailed statements justifying absence of data or specific CTD sections should be provided, in the relevant Quality overall summary and/or non-clinical/clinical overviews.

Hyperlinks

In general, hypertext links are encouraged within the non-eCTD electronic submission, to facilitate swift navigation around the dossier, but should not be overused. The non-eCTD electronic submission should be structured and links provided in such a way as to ensure that the reviewer is constantly aware of the overall structure and narrative flow of the dossier. For example, Module 3 is highly structured and therefore, only minimal use of hyperlinks should be necessary.

When the same citation appears on a page more than once, it is recommended that a link only to the first instance of the citation per page is provided.

Figure 1.



FILE FORMATS

Currently the following file formats support the goals of e-working, are compliant with national archiving regulations, and are accepted by EMEA for non-eCTD electronic submissions:

- For narratives: Portable Document Format (PDF), 1.4 only (with some exceptions – see further details of PDF files below)
- 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)
- (SAS data files are currently not accepted by EMEA)

(There are also initiatives within the European Union to enable the submission of structured data using XML. These initiatives relate to the Application Form, and Product Information (i.e. PIM). Both initiatives are under development.)

The EMEA also requires RTF/Word documents (Word being the preferred format) for Product Information (SPC, Package Leaflet and labelling documents) and M2.2 – 2.5 in addition to the PDF copies, for the purposes of review and document manipulation, whilst in a transition period to exclusive use of PDF. The Module 2 summaries (2.6, 2.7) are **not** required in RTF/Word format. RTF/Word documents are considered as an aid to review and are not a formal part of the non-eCTD electronic submission.

PDF Files

Portable Document Format (PDF) is an electronic format that is open, de facto, and published and created by Adobe Systems Incorporated (http://www.adobe.com). No specific products from Adobe or any other company are necessary to produce PDF documents.

The following points can be made in relation to PDF files:

- files should be PDF v1.4 (except for documents that must be submitted in another PDF version (e.g. Paediatric Investigation Plan), and should be legible with the Acrobat Reader search plug in or any other freeware viewer
- PDF files should be saved as 'Optimized' to reduce the size and allow faster opening when viewed via an internet connection

- the use of additional software to navigate and work with the files is not acceptable, unless agreed upon with the Agency
- PDF files produced from an electronic source document are much preferred to PDF files generated from scanned paper since those 'electronic' PDF files provide the maximum functionality to the reviewers in terms of search capabilities and copy & paste functionality
- Expert Reports and the Overviews/summaries in the CTD Module 2 should always be generated from an electronic source document
- if scanning is unavoidable, readability and file size should 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
- the maximum individual acceptable file size is approximately 100 MB. The main consideration is to format in such a way as to ensure clarity, speed of download and ease of review. Further guidance should be sought from the EMEA regarding individual larger files as to their acceptability
- fonts should be chosen of a type, colour and size such that they allow easy reading of documents on screen (1024 x 768 pixels) or after printing; examples of such font-types are:
    - Times New Roman, 12-point, black
    - Arial, 10-point, black
- all fonts used in a document (except Times New Roman, Arial and Courier) should be embedded, including all the characters for the font; in other words, limit the number of fonts used in a document and avoid customised fonts
- if colours other than black are used, colour reproduction after printing should be tested before submission
- print area for pages should fit on an A4 sheet of paper; margins should allow binding in multi-ring binders without affecting readability.

Additional details on PDF can be found in the ICH eCTD Specification Document, Appendix 7.

Please also refer to the recent EMEA announcement regarding PDF requirements for product information: http://www.emea.europa.eu/htms/human/qrd/docs/43183607en.pdf and the related documents (please see further information related to this guidance in section 'File Naming' below).

FILE NAMING

All files in a non-eCTD electronic submission provided to EMEA should follow the highly recommended file naming convention laid out in the eCTD specification*. File names in all modules have fixed and variable components, and should be indicative of the content of the file. Components are separated by a hyphen. No hyphens or spaces should be used within each component.

The file name should allow the reviewer to infer the file's content relative to other files, and differentiation should be provided between file names to enable unambiguous concurrent review of files. The file and path name together should be less than or equal to a maximum of 230 characters including the appropriate file extension. Only letters (lower case), numbers, or hyphens should be used in the name. Please refer to the current EU eCTD M1 specification for further information on file naming: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm.

* EMEA is aware that a discrepancy currently exists between the eCTD file naming convention, and the EMEA PDF file naming requirements for EPAR documents (http://www.emea.europa.eu/htms/human/qrd/docs/43183607en.pdf). The eCTD file naming convention dictates that a country code, document type and variable part that should be applied to each file name (cc-spcdoc-var.ext) , whereas the EMEA requirements dictate that the EMEA product number and language code should be applied to each PDF document to be used for the EPAR (**H**-[EMEA product number]-**PI**-[2 letter language code]).

Until such time as the requirements are aligned, the EMEA PDF file naming requirements should be met for the EPAR documents rather than following the eCTD filenaming convention in the non-eCTD electronic submission, at the time of finalisation of the EPAR.[1]

TEXT SEARCHABLE DOCUMENTS

Applicants are requested to ensure that all non-eCTD electronic 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.

PDF files with searchable text can be created by all PDF tools from a source file in a text format (e.g. MS Word, MS Powerpoint, RTF, etc.).

If the only version of a document available is in paper, then scanning to PDF and using an Optical Character Recognition (OCR) process is the only way to create searchable text. PDF files created in this way will be larger in size, and the quality of the text that is created will be inferior to the original. For these reasons, applicants are recommended to use scanning/OCR only if strictly necessary.

The following documents should always be text-searchable:

- Key administrative documents in Module 1 including, the cover letter, application form, product information documents
- Any document in Module 2 of the MAA (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 of the MAA
- 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)

The following documents do not need to be text searchable:

- 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

[1] The approach is different for an eCTD format submission, since eCTD builder tools will generally not allow inclusion of documents within an eCTD that do not respect the eCTD filenaming convention (see the EMEA practical Q&A on eCTD for further information on this).

SUBMISSION MEDIA

The 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 the EMEA's hardware (e.g. CD/DVD drive) using its own software. It is the policy of EMEA to maintain desktop configurations and IT infrastructure in line with common, office standards.

Hard media (e.g. CD, DVD) must be used for all non-eCTD electronic submissions. Eudralink *can* be used in addition to hard media, but *not* as the *sole* medium for submission. It is appreciated that it may be necessary, at certain key milestones in the procedure (e.g. for the provision of the translation documents post-Opinion), to submit documents via Eudralink in the first instance in order to ensure that the documents are received in a timely manner by EMEA and work can commence. It is expected, however, that this interim 'working' submission or documents will be followed as soon as reasonably possible by an exact copy of the same non-eCTD electronic submission on hard media, the submission that will become the formal EMEA record. Advance submission via Eudralink should only be used in situations where a requirement to submit on hard media would impact submission deadlines.
Please note that the requirement for hard media applies to EMEA as an agency, and may not be reflected in all National Competent Authorities involved in the Centralised Procedure – individual guidance from NCAs should be sought if necessary.

DVD-R/DVD-ROM (including dual layer) is accepted. In fact the provision of DVD over multiple CDs is strongly recommended by EMEA. CD-R conforming to ISO 9660 can be accepted; however, if an individual non-eCTD electronic submission is of such a size as to span several CDs, the provision of DVD is much preferred as this allows the processing of the submission directly from the hard media, without the need to first recompile the submission on a server.

The electronic media should be packed adequately to prevent damage. Each CD or DVD submitted with a non-eCTD electronic submission should include the following label information, clearly presented and printed on the media:

- The applicant name
- The product (invented) name(s)
- The International Non-proprietary Name (INN) of the product
- The full application number (if known)
- The submission date (YYYY-MM)
- Number of media units per full set and an indication of the place of the individual CD/DVD within this set
- The submission type contained on the CD/DVD (e.g. Initial Application, Variation Type II)

ELECTRONIC SIGNATURE

'Advanced electronic signatures' are currently accepted in the EU as being legally equivalent to handwritten signatures (Directive 1999/93/EC2).

An advanced electronic signature is a symbol an individual includes in an electronic document with the intention of identifying himself or herself. An electronic signature is generally defined as any letters, characters, or symbols manifested by electronic or similar means and executed or adopted by a party with an intent to authenticate a writing. Examples include:

- A PIN number or a code that the sender of the message uses to identify him/herself

Digital signatures are a subset of electronic signatures. It is important to differentiate between digital signatures and other forms of electronic signatures as digital signature technology serves a much more

[2] See http://europa.eu.int/comm/dg15/en/media/sign/index.htm

specialized market than electronic signatures and poses particular legal issues. Digital signatures will be accepted by EMEA in a non-eCTD electronic submission in the context of the Centralised Procedure provided that they are compliant with the European Electronic Signature Directive (e.g.'SAFE'), but the necessary software to 'read' these signatures is not available widely within the Agency, and EMEA does not currently have the necessary software components to validate these digital signatures. 'Flattened' or embedded digital signatures are preferred.

EMEA will also accept, for applicable documents within the non-eCTD electronic submission, (covering letters, Application Forms, export reports, certificates etc), a handwritten signature that is scanned or embedded as a graphic file in the electronic (PDF) document.

VALIDATION OF NON-eCTD ELECTRONIC SUBMISSIONS

The following checks may be made during validation by EMEA prior to the business validation of the content of the submission:

- Compliance with the file/folder structure and naming convention described in this document
- Compliance with general requirements (e.g. PDF file properties)
- Virus protection
- Security settings or password protection

If during the administrative processing or the actual review of a non-eCTD electronic submission, serious defects are found, EMEA will normally contact the applicant in the first instance. If these defects cannot be resolved quickly, the submission will normally be returned to the applicant.

SUBMISSION MILESTONES

The provision of information by the applicant during a procedure depends of course on the nature of the procedure and the specificities of the application and the assessment. All information, whether it be required deliverables/responses or supplemental information, should be provided according to the requirements laid out in this document.

There are, however, in any typical procedure, key milestones when a non-eCTD electronic submission with relevant updated files/information is expected in order to maintain a meaningful lifecycle for the application and reflect the procedure. The number of additional individual submissions provided within these milestones depends on the factors mentioned above.
The key milestones for e.g., an initial marketing authorisation procedure when the submission of information is expected are as follows:

1. Initial submission (Day 0 of procedure)
2. Response to business validation issues (if required)
3. Response to List of Questions (i.e. Day 121 for a new application)
4. Response to List of Outstanding Issues (i.e. Day 181, if required)
5. Application as agreed at Opinion (inc. agreed EN product information if changed at CHMP)
6. Provision of translations (i.e. Day 215 for a new application)*
7. Provision of final agreed translations following linguistic review (*it is not also required to send interim working versions of the product information before this point as formal submissions)*
8. Decision (i.e. final amended documentation if any changes occur during the Standing Committee phase)

By analogy, the same principle applies for all post-authorisation procedures, i.e., a submission is expected at day 0 of the application procedure, and subsequent sequences should then be provided in accordance with the corresponding milestones for that procedure, through to approval.

* Note that, in accordance with the information given under the section 'Submission Media', it is appreciated that it may be necessary, at certain key milestones in the procedure (e.g. for the provision of the translation documents post-Opinion), to submit an electronic submission or documents via Eudralink in the first instance in order to ensure that the submission is received in a timely manner by EMEA and so that work on the documents can commence. It is expected, however, that this interim 'working' submission or documents will be followed as soon as reasonably possible by an exact copy of the same submission on hard media, and it is this submission that will become the formal EMEA record of the documentation applicable at a certain point in the procedure.

CONVERSION OF EXISTING NON eCTD APPLICATIONS TO eCTD

After 1 January 2010, it will be mandatory to submit eCTD, even for post-authorisation submissions where the original application is in non-eCTD format.

If Marketing Authorisation Holders wish at this point, they may provide the EMEA with baseline approved information reformatted as eCTD for their already authorised products, although in order to move from non-eCTD electronic submission to eCTD mid-lifecycle, there is no obligation to submit a full, reformatted eCTD for already authorised products.

For further information on how to convert to eCTD from non-eCTD electronic submission and/or provide an eCTD baseline submission to EMEA, please refer to the EMEA's Question and Answer document on Practical and Technical Aspects of eCTD Implementation

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

Document Revision History:

Version	Date	Details
0.1	November 2008	Intial Draft
V1.0	December 2008	Final version following review by EMEA business