

Requirements on Electronic submissions for New Applications within National and European procedures

It was agreed by the Heads of Medicines Agencies (HMA) in Reykjavik on 28 February 2005 that by an agreed end-2009 deadline, the European Regulatory Agencies must have the infrastructure and processes in place to handle electronic-only eCTD to successfully support the related decision-making processes for medicinal products within the European Union. The Medicines Authority is in a position to accept electronic only submissions.

The transition to electronic submissions brings with it several advantages not only the obvious reduction in printing, archiving and transportation costs, but also facilitates consistency in information viewed across Medicines Agencies, the ability to manage the lifecycle of the product and improved navigation and assessment of documentation.

Electronic submissions will be accepted for these application types:

- National
- MRP (Malta CMS/RMS)
- DCP (Malta CMS/RMS)
- Centralised
- Article 45/46 Paediatric Study (MT rapporteur/non-rapporteur)
- Traditional Herbal Medicinal Product
- Homeopathic
- Variation applications
- Line extension applications
- Responses to validation queries
- Responses to assessment questions
- Supplementary information
- Renewal applications
- Batch-specific requests
- Active substance master files (ASMFs)/drug master files (DMFs)
- Vaccine antigen master files (VAMFs)
- Plasma master files (PMFs)
- Referrals

The number of copies to be submitted for Mutual Recognition and Decentralised procedures is outlined in the CMDh guideline on electronic submissions.

Electronic submissions will be accepted in both eCTD and NeeS (non eCTD Submission) format. eCTD format is preferred.

The **Cover letter** and the **Application form** have to also be submitted in paper (see below).

The Common Technical Document (CTD)

The CTD has five modules:

- Regional module: 1 (different for each region; i.e., country)
- Common modules: 2-5 (common to all the regions)

The CTD only defines the content of the common modules.

Both the [EMA](#) and [ICH](#) have published guidelines on electronic submissions.

The switch from paper-only to electronic can be made during any phase of the life cycle of a medicinal product. In fact, companies are being requested to submit electronic dossiers if these are now available for products previously submitted in paper format. Once the switch to electronic is made it is highly recommended to submit further correspondence on the particular medicinal product in electronic format. For those Marketing Authorisation Holders who did not have electronic CTD or NeeS dossiers in electronic format when submitting the dossier for initial authorisation, it is desirable that should the dossier be converted to eCTD, this is made available to the Medicines Authority. For Marketing Authorisation Holders wishing to move from a NeeS or paper format to an eCTD format an eCTD baseline must be submitted prior to an eCTD product submission. Prior notification of the intention to move to an eCTD format for an application should be emailed to prelicensing.mru@gov.mt.

Non eCTD electronic Submissions (NeeS)

A *non-eCTD* electronic submission is any submission of electronic information formatted as a simple set of electronic files and folders, organised into module folders containing PDF or MS Word files as per the CTD guidance. There is no ability to manage the lifecycle of the product in this format.

More information on **NeeS** submissions can be found on the EMA guideline: [Guidance for Industry on Providing Regulatory Information in Electronic Format: Non-eCTD electronic Submissions \(NeeS\)](#).

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 and eCTD file naming conventions should be followed. It is also recommended to submit PDF files that are searchable.

eCTD Submissions

The *electronic Common Technical Document (eCTD)* is an interface for the pharmaceutical industry to agency transfer of regulatory information. The content is based on the Common Technical Document (CTD) format. The structure, folder and file names correspond to those of the CTD.

The eCTD is an XML (Extensible Markup Language) catalogue with links to the actual files in the CTD submission. As the eCTD is based around an XML backbone the submission can be viewed via a web browser and can be loaded on to a web server. As a submission format, it contains additional technical components which enable the lifecycle of individual files in the application, and the lifecycle of the product itself, to be managed.

Data structure:

The Primary technical components are:

- A high level folder structure (required)
- An XML "backbone" file which provides metadata about content files and lifecycle instructions for the receiving system
- An optional lower level folder structure (recommended folder names are provided in Appendix 4 of the eCTD specification)
- Associated Document Type Definitions (DTDs) and stylesheets.

Each submission message constitutes one "sequence". A cumulative eCTD consists of one or more sequences. While a single sequence may be viewed with web browser and the [ICH stylesheet](#), viewing a cumulative eCTD requires specialized eCTD viewers.

More information on eCTD submissions can be found in the EMA guideline: [Guidance for Industry on Providing Regulatory Information in Electronic Format - eCTD electronic submissions](#).

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

- The EU-CTD Notice to Applicants
 - [EU Legislation - Eudralex - Pharmaceuticals - Enterprise and Industry](#)
- The CTD question and answer document published by the Notice to Applicants
 - [EudraLex - Volume 2 - Pharmaceutical Legislation Notice to applicants and regulatory guidelines medicinal products for human use. - Pharmaceuticals - Enterprise and Industry](#)
- The ICH CTD Q&A
 - <http://www.ich.org/LOB/media/MEDIA1189.pdf>

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 refer to Chapter 7 of the [Notice to Applicants](#) for details on the provision of signed paper documents. The cover letter should have an original signature (see also below – Signatures).

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.

Module 1.2: administrative information (application forms)

Some competent authorities request that applicants create an application form on their own portals. Currently it is still not possible for the Medicines Authority to accept applications through a portal. The Medicines Authority requires the application form to be provided as a PDF file together with one signed paper copy (scanned signature is also acceptable). Please refer to [CMDh Guidance](#) for details.

Module 1.3.1: product information

For Nees applications product information should be supplied as PDF files but a Word file should also be submitted to facilitate assessment. Please refer to Chapter 7 of the [Notice to Applicants](#) for details. The product information text (SmPC, Labelling, and Package Leaflet) should be submitted in editable

word format in a separate CD/DVD along with the PDF file.

Responses to questions

The organisation of the submission of electronic information in response to a list of questions should follow the same basic principles as the first submission. The written responses should be submitted following the ICH recommended response folder and file structure. Appropriate navigation in the submission should be allowed and should follow the same concepts as described under 1.1.

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](#).

Renewals

It is desirable that renewal applications are also received in electronic format, i.e. as PDF files with no additional paper copies (except for the application form). Please refer to Chapter 7 of the [Notice to Applicants](#) for details.

Packaging / Labelling and Security of the submission

The physical security of the submission during transmission is the responsibility of the applicant. The electronic information (on media described above) should be submitted at the same time as the paper documentation (cover letter and application form where applicable). One-time security settings or password protection of electronic submissions is acceptable for security purposes during transportation/transmission from the applicant to the Medicines Authority. This protection is only accepted when one password is used to protect the complete submission. It is not allowed to protect the submission on file level. Once received by the Medicines Authority, these settings should be removable.

Please label the actual disk not the case (as the two can become separated) with the below information:

1. The applicant's name
2. The product's (invented) name(s)
3. The International Nonproprietary Name (INN) of the product
4. The full application number (if known)
5. The sequence number(s) of the eCTD submissions contained on the CD/DVD
6. The submission date
7. The application type of each eCTD submission(s) contained on the CD/DVD (e.g. Initial Application, Variation Type II), as per the eCTD envelope information.

Signatures

The authenticity of certain documents (covering letters) should be guaranteed by paper copies with a handwritten signature. Until the proper system is in place at the Medicines Authority for the use, tracking and maintenance of electronic signatures, the signed cover letter (original signature) and application form (scanned or original signature) should be submitted both electronically and in paper for procedures.

Technical validation

Until further notice, technical validation of the application will not take place.

Samples

Product samples should be submitted at start of the procedure only for procedures where Malta is Reference Member State and for National procedures. For procedures where Malta is Concerned Member State samples should be submitted upon request by the Medicines Authority.

Other application types (national)

Applications for parallel importation, authorisations in accordance with article 126a, withdrawal applications, article 61(3) notification and transfer applications have to be submitted also in paper, with original signatures. Summary of product characteristics, package leaflet and labelling should also be submitted in electronic editable word format on CD-ROM, CD-R or DVD-R.

Other procedures

- PSURs
- Follow-up measures
- Clinical Trials

These submissions are required to be completely paperless. No additional paper should be submitted. Refer to the appropriate sections on our website for more information on each of these procedures.

Contact point for queries

Should you require more information please send email to prelicensing.mru@gov.mt.