Guideline for submission of applications and documents for medicinal product authorisation and post-authorisation activities

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This guideline applies to all the applications and all relevant documentation submitted to the Medicines Authority in relation to product registration, including authorisation and post-authorisation procedures.

1 Electronic submissions

The concept of eSubmission and the use of electronic format of files were firstly introduced by pharmaceutical companies in coordination with the EMA and "pioneer" National Competent Authorities, under the auspices of International Conference on Harmonisation (ICH). ICH has agreed on certain rules and requirements for a structured submission of electronic files. The aim of eSubmission is focused on the minimisation of paper use during the exchange of information between applicants and National Competent Authorities and facilitation of business process.

The Medicines Authority requests that any submissions related to marketing authorisation applications and post-authorisation applications be submitted electronically whenever possible.

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.

It is highly recommended that whenever possible all applications are submitted through the Common European Submission Portal (CESP). More information can be found on the CESP website at cesp.hma.eu/. Paper application forms are no longer accepted. If not using CESP please submit applications (signed) on CD/DVD.

Relevant CMDh documents referring to submission requirements should be referred to: http://www.hma.eu/277.html.

For applications where the CTD format is not applicable, such as parallel import applications, clinical trial applications and authorisations in accordance with article 126(a) of Directive 2001/83/EC, electronic submissions without paper copy of the application form are recommended (see section 3 and Appendix 1). These applications should also be submitted through CESP.

2 Electronic format for dossier submission

2.1 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 European Medicines Agency (EMA) and the International Conference on Harmonisation (ICH) have published guidelines on electronic submissions. It is strongly recommended to send applications electronically and reduce paper submissions as much as possible.

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/procedures 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. Marketing Authorisation Holders wishing to move from a NeeS or paper format to an eCTD format can do so at any time.

Prior notification of the intention to move to an eCTD format for an application should be emailed to prelicensing.mru@gov.mt.

2.2 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. (This type of submission will no longer be accepted after eCTD becomes mandatory as described in the eCTD section below).

More information on NeeS submissions can be found on the eSubmissions page of the European Medicines Agency.

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. Please note that NeeS submissions are only accepted in accordance with timelines included in the eSubmission Roadmap in Appendix 2 where Malta is acting as Reference Member State.

2.3 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 structure of the documentation associated with a medicinal product follows the modular division (M1-M5) defined in the CTD. The module containing administrative information, Module 1, contains regional information.

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.

From July 1 2015 the eCTD format is mandatory for applications for new medicinal products for human use in the decentralised procedure. Therefore companies are required to submit new DCP applications in eCTD format. Once a submission has been received in eCTD format, all subsequent submissions must be submitted in eCTD format. From 1 January 2017 all other application types in CP, DCP and MRP must be in eCTD format. From 1 January 2018, all other submissions (variations, renewals, PSURs, etc) will be required in eCTD. Please refer to the eSubmissions Roadmap (which can be found on the eSubmissions

page) for other important deadlines. More information is also available on the eSubmissions page of the European Medicines Agency.

The Medicines Authority also prefers receiving ASMFs from ASMF holders in electronic format. The applicant part of the ASMF must be in the eCTD format as part of the dossier.

More information on eCTD submissions can be found on the eSubmissions page of the European Medicines Agency.

Guidance on placement of documents within the eCTD structure for particular submission types can be found in:
Notice to Applicants EudraLex - Volume 2

The ICH CTD page:
http://www.ich.org/products/ctd.html

TIGes Harmonised eCTD and NeeS guidance as available on:
http://esubmission.ema.europa.eu/

ICH Guidance for Industry on Providing Regulatory Information in Electronic Format: eCTD electronic Submissions, available at the following link.

CMDh Guidance for companies on eSubmissions.

2.4 Electronic applications (eAF)

For marketing authorisation applications the current Word based application forms (AF) have been replaced by electronic application forms (eAF), using different technologies to capture and transfer information. The content is the same but new possibilities such as electronic data import/export, data population within the form, and others, have been introduced. This will eventually apply to all the application forms, i.e. initial, renewals and variations. A stepwise approach has been developed to deliver the vision, as follows:

Step 1: 1 July 2015 – use of e AFs compulsory for centralised procedures

Step 2: 1 January 2016 – eAFs are to be used for all EU procedures. The eAF will be the only published version of the AF.

If you have any questions regarding these electronic application forms, please contact the eAF service desk with your query on eaf@ema.europa.eu.

3 Where and how to submit applications

For all applications, it is encouraged to limit the submission of paper applications as much as possible to exceptional circumstances. The Medicines Authority has changed all the information received to electronic format. Submitting paper may cause delays in review of the application due to the administrative process to change to electronic format.

Since 2013, the Medicines Authority has been accepting online submissions through the Common European Submission Portal (CESP). Submission through the portal is strongly recommended for all types of applications (new and post-authorisation procedures) – it is a secure way of sending electronic submissions, receiving an immediate acknowledgement of receipt with the possibility of sending outside of working hours and without any additional fees. Please refer to the CESP website on http://cesp.hma.eu/Home for more information and registration with the system. This is also strongly recommended for national applications (as well as parallel import applications and applications in accordance with article 126a).

If applications are submitted through the portal, no additional paper copies or other media (e.g. paper, CD/DVD, email and Eudralink packages) should be sent. Applications and documents should only be sent through one medium of submission, which should be stated in the cover letter. All documents should be signed, including the cover letter. Cover letters and application forms sent through the portal or through CESP will be considered invalid if they are not signed (scanned signature is acceptable until further notice). Notifications for CESP submissions are to be sent to the mailbox prelicensing.mru@gov.mt.
No applications are to be sent to personal mailboxes - these will not be accepted and will delay the process.

For European Procedures, more information on submission requirements for new applications and variations can be found on the CMDh website.

Applications for the centralised procedure shall be submitted via the EMA's eGateway and Common Repository.

3.2 Specific documents and application types – how and where to submit

3.2.1 Cover letter

For European procedures, the signed cover letter should include as a minimum, the information specified in the CMDh Guidance document and template for European procedures. Please refer the CMDh website and specific documents related to electronic submissions.

For other procedures please refer to any relevant procedural guidance in the specific section of the Medicines Authority website. Please also refer to Appendix 1.

The signed cover letter should form part of the electronic submission, whether this is being carried out through CESP or other electronic media such as CD/DVD. No additional paper copies of cover letters are required to be sent with electronic media. Cover letters are to be signed before being scanned for submission through electronic means.

3.2.2 Module 1.3.1: product information (SmPC, PL and labelling)

Product information (PI) including the Summary of product characteristics (SmPC), package leaflet (PL) and labelling) should also be submitted through the portal or on CD-ROM, CD-R or DVD-R in editable word format together with the application. Where changes to the product information are being proposed, a clean and track changed version in word format are to be submitted.

The End of Procedure product information for European procedures and following variations where there are changes to the PI should be sent ONLY to the mrp-dcp.adm@gov.mt mailbox. Sending to personal mailboxes or other mailboxes may cause delays in the finalisation process.

3.2.3 Module 2

Module 2 should be additionally sent in word format as part of the working documents.

3.3 Variations

Variation applications should ONLY be sent via CESP or on electronic media (CD/DVD). Variation applications should follow the same format as the original submission in terms of eCTD or NeeS.

3.4 Renewals

It is desirable that renewal applications are also received in electronic format, with no additional paper copies, including of the (signed) cover letter.. Please refer to the relevant CMDh guidance.

Renewal applications should ONLY be sent via CESP or on electronic media (CD/DVD) and NOT via personal or generic mailboxes.

3.5 Responses

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.
Responses to questions are to be submitted only once – either through CESP, on CD/DVD or through the mrp-dcp.adm@gov.mt mailbox or the appropriate Eudra mailboxes. Multiple submissions through different methods are to be avoided i.e. responses are to be submitted once through the preferred medium.

3.6 Other application types (National)

Applications for parallel importation, authorisations in accordance with article 126a of Directive 2001/83/EC, article 61(3) notifications and transfer applications are also to be submitted in electronic format, through the portal or on electronic media. It is acknowledged that these applications cannot follow the NeeS or eCTD format and for these types of applications these requirements are not relevant.

Parallel import applications

Submission of parallel import licence applications – specific parallel import applications mailbox.

For parallel import new applications, renewals and variations the specific Parallel import mailbox can also be used - parallel.medicinesauthority@gov.mt. No paper application forms are required. If applications are sent on CD/DVD, application forms and annexes must be signed before being scanned and included in the electronic submission. Applications can also be sent via CESP. Paper submissions may delay the review process of the applications and are not encouraged.

Withdrawal applications

Withdrawal applications can also be submitted through CESP or electronically on CD/DVD.

3.7 Other procedures

Periodic Safety Update Reports

Follow-up measures

Clinical Trials

- These submissions are also required to be completely paperless. No additional paper should be submitted. Refer to the relevant sections on our website for more information on each of these procedures.
- Until further notice PSURs are not to be sent through the CESP.

For submission of centralised procedures please refer to the relevant EMA guidance. Applications for the centralised procedure are to be submitted via the EMA's eGateway and Common Repository.

3.8 Label information for submissions on electronic media

There must be only one regulatory activity per medicinal product, per CD/DVD for all types of procedures.
Each CD/DVD must include this information on the label:
Format: eCTD/NeeS (where relevant)
Applicant's name
Product name
EU procedure number (where relevant)
MA/AA/PI number (in case of renewals)
Sequence number(s) of the eCTD and NeeS submissions
Type of procedure (e.g. New DCP, MRP, PI, Variation type 2, etc)
If this information is not present, it may delay the start of the procedure.

4 Samples

Product samples should be submitted at start of the procedure only for procedures where Malta is Reference Member State in the DCP and MRP and for National marketing authorisation applications on the basis of articles 8 and 10. They will also be requested for centralised procedures where Malta is rapporteur. For procedures where Malta is Concerned Member State samples should be submitted upon request by the Medicines Authority.
Samples of re-packaged/re-labelled products are to be submitted for parallel imported products with the application form. If samples are not submitted with the application, a delay in review is to be expected. Please refer to the Parallel importation section of the Medicines Authority website and in particular the Guide to Parallel importation and the Guidelines on re-packaging.

5 Contact point for queries

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

6 Read more

EMA esubmissions general page

EMA esubmissions CMB page

EMA esubmissions CMB documentation

Regulatory information – eSubmission Gateway for centralised procedures

CMDh eSubmissions page

7. APPENDICES

7.1 Appendix 1 – Acceptable submission routes

TABLE 1	**Acceptable routes for submission – ONLY one medium to be used for each submission**				
Document/s for submission	**CESP portal**	**CD/DVD**	mrp-dcp.adm@gov.mt	**Eudralink account holders to** mrp-dcp.adm@gov.mt or Eudra mailboxes	parallel.medicinesauthority@gov.mt
New applications – MRP and DCP	✓	✓			
Module 1.3.1 product information – in editable word version, clean and track-changed if applicable	✓	✓	✓		
End of Procedure product information for European variations where there are changes to the PI	✓	✓	✓		
Variation applications	✓	✓			✓*
Renewal applications	✓	✓			✓*
Responses to list of questions in national and European procedures	✓	✓	✓	✓	
Parallel import licence applications/renewals/ variations and related documents	✓	✓			✓*
Applications of the withdrawal of product authorisation/licence applications	✓	✓			

Other national application types (acc. to article126(a), article 61(3) notifications, transfer of Marketing Authorisation Holder)	✓	✓			
PSURs Follow-up measures Clinical Trials		✓			

* Parallel import mailbox to be used only for applications related to parallel import applications – new, renewal, variation.