MALTA
MEDICINES
AUTHORITY

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

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Licensing Directorate

Contents

1. Scope

This guideline applies to all the applications including supporting documentation submitted to the Malta Medicines Authority in relation to new product registration, up to and including all pre-authorisation and post-authorisation procedures under European, National and Centralised procedures of registration.

2. Abbreviations

ASMFs / DMFs	Active substance master files / drug master files
CESP	Common European Submission Portal
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human
CMS	Concerned Member states
CT	Clinical Trial
CTD	Common Technical Document
CTR	Clinical Trial Regulation
CTIS	Clinical Trial Information System
DCP	Decentralised Procedure
DTD	Document Type Definition: A DTD defines the structure and the legal elements and attributes of an XML document.
EU	European Union
eAF	electronic application forms
eCTD	electronic Common Technical Document
e-forms	Electronic forms
EMA	European Medicines Agency
esubmissions	electronic submissions
FUMs/SOs	Post Authorisation Follow-up Measures / Specific Obligations
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LAB	Labelling
MA / MAH	Market Authorisation / Market Authorisation Holder
MRP	Mutually Recognised Product
PI	Parallel Importation
PIL	Patient Information Leaflet
PL	Patient Leaflet
PMFs	Plasma master files
PSUR(s)	Periodic Safety Update Reports
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TIGes	Telematics Implementation Group for Electronic Submission and ICH Implementation
XML	Extensible Markup Language

3. Standards to streamline the business process

Standards for electronic submissions have been developed for human medicinal products, by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

The aim of electronic submissions (eSubmissions) 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 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.

CONTENT FORMAT	The electronic exchange standard is called electronic Common Technical Document (eCTD). This standard is based on "M4: The Common Technical Document (CTD)" in its various parts. https://www.ich.org/page/ctd All submissions of regulatory information concerning marketing authorisations application & lifecycle for medicinal products to National Competent Authorities are to be done using electronic Common Technical Document (eCTD). For further information on eCTD and the version implementation please refer to section 4.
E-FORMS	For applications where the eCTD format is not available, such as parallel import applications, and authorisations in accordance with article 126(a) of Directive 2001/83/EC, electronic submissions are still required (see section 3 and Appendix 1) and should still be submitted through CESP. Further information on electronic forms (e-forms) available can be found here: http://www.medicinesauthority.gov.mt/onlineapplications See Section 4.2.2 for details
EXCHANGE/ SUBMISSION	The Malta Medicines Authority requests that any submissions related to marketing authorisation applications and post-authorisation applications be submitted electronically through the Common European Portal (CESP) (https://cespportal.hma.eu). For further information refer to section 5
CLINICAL TRIAL APPLICATIONS	For applications where the eCTD format is not available, such as clinical trial applications refer to http://www.medicinesauthority.gov.mt/clinicaltrialsa#Application%20to%20conduct%20a%20clinical%20trial
CONTENT	Relevant CMDh documents referring to submission requirements should be referred to: http://www.hma.eu/277.html.

4. Electronic format for dossier submission

4.*1* *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 eCTD Specification is based on XML technology.

The specification for the XML structure is the DTD (https://admin.ich.org/sites/default/files/inline-files/ich-ectd-3-2_dtd_0.zip) . 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 1 January 2018, all submissions (new applications, variations, renewals, PSURs, etc) are required to be in eCTD. Please refer to the eSubmissions Roadmap (which can be found on the eSubmissions page) for other important deadlines. This includes submissions for all products with national marketing authorisations.
From July 2019 the Active Substance Master File (ASMF) from the ASMF holder is also required to be in eCTD format.
More information on eCTD submissions can be found on the eSubmissions page of the European Medicines Agency.

The current electronic version was developed by the eCTD Implementation Working Group and released as version 3.2 in February 2004. The European Union applies the eCTD Specification in the European region and has completed it with the European Module 1. Preparation of the version updates is ongoing within the ICH. For more information, please refer to the eCTD EU M1 specification and eCTD webpages to identify which version is currently valid and acceptable.

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 is available on:p
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.

4.2 Electronic applications (eAF) & Electronic forms (eForms)

4.2.1 For Mutual Recognition, Decentralised & National Procedures

The word-based application forms (AF) have been replaced by electronic application forms (eAF), with new possibilities like electronic data import/export, data population within the form, online access to standardised catalogue terms, built in business rule validation, and support for validation of form, etc. Implementation of mandatory use of the eAF is part of the HMA eSubmission roadmap http://esubmission.ema.europa.eu/tiges/cmbdocumentation.html.
This applies to all the application forms, i.e.
- New applications for national, decentralised, and mutual recognition procedures applications (eAF version implementation plan is important to note)

- Variations applications (eAF version implementation plan is important to note)
- Article 61(3) notification forms
- Line extension applications
- Responses to validation queries
- Responses to assessment questions
- Supplementary information
- Renewal applications
- PSURs
- Follow-up measures (FUMs)/Specific Obligations (SOs)
- Active substance master files (ASMFs)/drug master files (DMFs)
- Vaccine antigen master files (VAMFs)
- Plasma master files (PMFs)

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

Technical Validation is being performed in line with the eCTD version roadmap.

4.2.2 For other purely national applications

The electronic method of submission/transmission of the applications falling under the purely national licensing requirements*, i.e. where the eAF is not applicable, are to be done using the Online Applications e-Forms functionality as present on the Malta Medicines Authority website link here http://www.medicinesauthority.gov.mt/onlineapplications.

For the list of e-forms present therein, wherever a signature is required to be inserted, the separate Declaration form available from http://www.medicinesauthority.gov.mt/onlineapplications. is to be filled in and attached to the e-form and submitted online, through CESP. ***After clicking the print button, save form to PDF and send via CESP. This applies to Licensing forms ONLY.***

*Licensing e-forms:

- 126a new application
- 126a notification of variation
- Parallel import new application/ Parallel import renewal
- Parallel import notification of variation
- Request for sunset clause exemption
- Article 61(3) notification (as applicable to MT only)
- Batch specific request
- Borderline classification request form
- Withdrawal of MA/licence
- Transfer of MA during procedure
- Transfer of MA after MA is issued
- Scientific Advice Request (SAR) or Protocol Assistance (PA)
- Sunset Clause request

^ *refer to Appendix 1 for mode of transmission for this e-form.*

5. Exchange / Submissions

Since 2013, the Malta Medicines Authority has been accepting online submissions through the Common European Submission Portal (CESP).This mode of submission is mandatory from January 2022. This system provides a simple and secure mechanism for exchange of information between applicants and regulatory agencies.

The purpose of the system is to:

- Provide a secure method of communicating with the Regulatory Agencies via one platform
- Allow submission of an application once to reach all required Agencies
- Reduce the burden for both Industry and Regulators of submitting/handling applications on CD-ROM and DVD

Submission through the portal is required 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 mandatory for national applications utilising e-forms, (see section 3.2.2).
No applications are to be sent to personal mailboxes - these will not be accepted and will delay the process.

Please be aware of the following while submitting through CESP:

- Do not drop over the delivery file until the entire submission has fully uploaded to CESP.

- Please refer to our National Requirements which are indicated on the Contacts tab of the
- CESP Platform prior to submitting documentation.
- CESP supports the upload of zip files using the following software only: Winzip and Microsoft Compressed File Format.

Delivery file:

- Must not be renamed or re-used.
- Ensure the type of submission is correctly identified.
- Ensure the appropriate category on the dropdown list is selected.
- For variations the full MRP/DCP procedure number must be provided.
- Specify the zip software used for compression.
- Where possible please provide the Maltese product authorisation number (MA).

All documents requiring signatory should present with a signature. A scanned signature is acceptable.

For European Procedures, more information on submission requirements for new applications and variations can be found on the CMDh website https://www.hma.eu/27.html .

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

6. Specific documents and application types – how and where to submit

6.1 General considerations Module 1

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 Malta Medicines Authority website. Please also refer to Appendix 1.

The eCTD technical validation report showing the submitted sequence has passed technical validation (with the name and version number of the validation software).
- Tracking table for eCTD sequences, including a description of each submission type.
- Statement that the submission is checked with an up-to-date and state-of-the-art virus checker (name and version of the anti-virus programme must be mentioned).

Note: The MMA does not accept password protected submissions

6.2 Module 1.3.1: Product Information

Product information (PI) including the Summary of product characteristics (SmPC), package leaflet (PL) and labelling (LAB) should be included in the submission via the portal. Where changes to the product information are being proposed, a clean and track changed version in word format is to be submitted during the application process. The Product information texts should be submitted as working documents in word format. The SmPC, PIL and LAB are to be separate as three working documents.

The End of Procedure product information for National & European procedures and following variations where there are changes to the Product Information 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. It is important to ensure that the Malta specific details (e.g. license number, authorisation dates, MAH, ADR reporting details) are included.

Product information for National Phase submissions should be received in word format on mrp-dcp.adm@gov.mt.

6.3 Module 2

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

6.4 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.

Draft responses to questions are to be submitted only once –through CESP and are to be sent to the Reference Member State only. The final Day 106 responses are sent as a sequence when requested to do so by the RMS to the Reference Member States and Concerned Member States.

6.5 Parallel import applications

Submission of parallel import licence applications renewals and variations should be submitted through CESP. For queries related to Parallel Importation please send emails to the mailbox: parallel.medicinesauthority@gov.mt.

6.6 Withdrawal applications

Withdrawal applications should also be submitted through CESP, as a sequence, where relevant

6.7 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.

- From now until the new CTR comes into force the current system applies; see website http://www.medicinesauthority.gov.mt/clinicaltrialsa?l=1 ; Once the CTR comes into force [31 January 2022]. The Regulation harmonises the assessment and supervision processes for clinical trials throughout the EU, via a Clinical Trials Information System (CTIS). CTIS will contain the centralised EU portal and database for clinical trials foreseen by the Regulation. CT applications, amendments and Annual safety reports will go through the CTIS
- Until further notice PSURs are **not** to be sent through the CESP. From 13 June 2016, it is mandatory for all MAHs in the European Union (EU) to submit PSURs for human medicines directly to the PSUR repository. This means that companies must use the repository as a single point for all submissions and should no longer submit PSURs to NCAs directly. The PSUR repository is mandatory for both centrally and nationally authorised medicines whether they follow the EU single assessment or a purely national assessment procedure. The PSUR repository is intended for PSURs for human medicines only.

- PSURs that have not been sent to the PSUR repository are considered as not submitted and will not be assessed. PSURs not sent to the PSUR repository will not fulfil the MAH's legal obligation to submit PSURs.

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.

7. Samples & Mock-ups

Product samples must be submitted at the start of the procedure only for procedures where Malta is Reference Member State in the DCP and MRP and for National marketing authorisation applications. One unit of each presentation being proposed is required to be submitted. This unit should not necessarily be in the final livery. In the case of Duplicate procedures, where the lead procedure is assessed by MT, samples are not required.

Samples are also required for centralised procedures where Malta is rapporteur. Unless otherwise requested, these samples are normally not required for testing but for assessment purposes.

For procedures where Malta is Reference Member state and for National applications, mock-ups are to be submitted before marketing/launch to the e-mail address licensing.medicinesauthority@gov.mt copying miau.medicinesauthority@gov.mt.

For procedures where Malta is Concerned Member State samples, mock-ups should be submitted upon request by the Malta Medicines Authority only.

Samples of re-packaged/re-labelled products are to be submitted for parallel imported products with the application form. One unit of each presentation being proposed is required to be submitted. If samples are not submitted with the application, processing of the application cannot resume. Please refer to the Parallel importation section of the Malta Medicines Authority website and in particular the Guide to Parallel importation and the Guidelines on re-packaging.

8. Contact point for general queries

Should you require more general information please send email to licensing.medicinesauthority@gov.mt.

9. References

EMA esubmissions general page
EMA esubmissions CMB page
EMA esubmissions CMB documentation
Regulatory information – eSubmission Gateway for centralised procedures
CMDh eSubmissions page
https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/eSubmissions/CMDh_085_2008_Rev_25_04_2021_clean_eSubmission_for_new_MA.pdf
https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/eSubmissions/CMDh_006_2008_Rev_25_2021_04_clean_eSubmission_for_Variations_and_Renewals.pdf

Signature on file

Appendices

Appendix 1 – Acceptable submission routes

Appendix 1

ACCEPTABLE SUBMISSION ROUTES

	CESP portal submission	Email submission	**eAF**	**eforms**	**EU Repository**
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 / National Phase	✓	✓mrp-dcp.adm@gov.mt			
PSURs					✓
Clinical Trials		✓info.medicinesauthority@gov.mt			✓ (from Jan 2022)
Follow up measures	✓	✓mrp-dcp.adm@gov.mt			
126a new application	✓				
126a notification of variation	✓				
Parallel import new application/ Parallel import renewal	✓				
Parallel import notification of variation	✓				
Request for sunset clause exemption	✓				
Article 61(3) notification (as applicable to MT only)	✓				
Batch specific request	✓				
Borderline classification request form		✓			
Withdrawal of MA/licence	✓				
Transfer of MA during procedure	✓				
Transfer of MA after MA is issued	✓				
Scientific Advice Request (SAR) or Protocol Assistance (PA)	✓				
Sunset Clause request	✓				
New applications for - National MAs - DCP - MRP	✓		✓		
Variations applications for - National MAs	✓		✓		

- DCP - MRP					
- Article 61(3) notification forms	✓		✓		
- Line extension applications	✓		✓		
- Responses to validation queries	✓		✓		
- Responses to assessment questions	✓		✓		
- Supplementary information	✓		✓		
-Renewal applications	✓		✓		