EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA eSubmission Gateway: Questions and answers relating to practical and technical aspects of the implementation

This question and answer document aims to address the commonly-asked questions and provide guidance regarding technical and practical aspects of the European Medicines Agency's eSubmission Gateway for electronic submissions as part of the Centralised Procedure.

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1. Objectives of eSubmissions via the Gateway

Q1. What is the eSubmission Gateway?

The EMA eSubmission Gateway enables applicants to submit via a secure Internet connection all eCTD format Centralised Procedure applications related to the authorisation and maintenance of medicinal products, e.g. new marketing authorisations, variations, renewals, PSURs, active substance master files (ASMF) and Plasma Master Files (PMF). It is based on the ESTRI (Electronic Standards for the Transfer of Regulatory Information) gateway standard, which defines a secure data exchange service for regulatory information. The eSubmission Gateway accepts only electronic submissions in eCTD format in the context of the Centralised Procedure.

Q2. What is the objective of electronic Submissions via the EMA eSubmission Gateway?

Currently electronic submissions are received by the European Medicines Agency via CD-ROMs and DVDs from the Applicants. The Gateway offers Applicants an easier and quicker way of submitting eCTD submissions securely over the Internet. The service is already offered by the European Medicines Agency for Eudravigilance and is now available for the Centralised Procedure covering all eCTD submissions related to the authorisation and maintenance of medicinal products, including new marketing authorisations, variations, renewals, PSURs, active substance master files (ASMF) and Plasma Master Files (PMF).
The use of the Gateway improves the Agency's efficiency in handling the submissions received and in making them available quickly within the European Review System (EURS).

Q3. Which types of applications can I submit via the EMA eSubmission Gateway?

The eSubmissions Gateway service is offered for all Centralised Procedure applications for Human Products, submitted in eCTD format only e.g. new marketing authorisations, variations, renewals, PSURs, active substance master files (ASMF) and Plasma Master Files (PMF). Currently all other submission types such as Referrals, Scientific Advice and Paediatrics are outside the scope of the eSubmissions Gateway.

Q4. Is there another solution if our organisation has no access to the eSubmission Gateway Installation?

The Agency is also developing a web-based eSubmission Gateway client, which is more suitable for low transmission volumes and which could be used by small and medium-sized pharmaceutical companies. This solution is under development and it is expected that a pilot phase will start in the 1st quarter of 2013.

2. Archival file formats and maximum size

Q5. What archival file formats are available for submission via the Gateway?

The eCTD submission should be archived as a zip file (Encryption and Password should be disabled on the zip file). As soon as the eCTD submission is received by the Gateway, it is encrypted. Other archival file formats are not allowed. The compressed application file must comply with the ZIP open format.

Q6. Is there a maximum size for a submission made via the Gateway?

The maximum size for a single eSubmission transmission is 12GB Unzipped. The system has not been extensively tested beyond this maximum size, so if a submission exceeds the maximum allowable size, successful transmission may not be guaranteed.

3. File naming conventions

Q7. What is the file naming format for submitting electronic Submissions via the EMA eSubmission Gateway?

The filename is used as a means of identifying specific information, allowing the Agency to automate processing of the submission once received.

The filename is broken down into different parts as described in the table below:

Data	Remarks	Case sensitive	Example
SenderRoutingId_	Routing ID for Sender as registered by the Gateway for identification & MDN message. This will be supplied to the Applicant by Gateway support	Upper	XYZ
ReceiverRoutingId_	Gateway routing ID to differentiate this eSubmission from other application transmissions.	Upper	ESUBPROD
EMEA Product No_	e.g. EMEA/H/C/000000	Upper	EMEAHC000000 or Hxxxxxx (Initial application)
Product Name	maximum 30 characters	Upper / Lower	Wonderpill
Submission Type	See list of Submission types below	Upper / Lower	initial-maa
Sequence Number	0000-9999	N/A (should be numeric)	0020
.zip	.zip	Lower	.zip

Filename Example:

XYZ_ESUBPROD_HC000xxx_Wonderpill_initial-maa_0020.zip

List of Submission Types See link:
http://esubmission.ema.europa.eu/eumodule1/index.htm

EU Module 1 Specifications 1.4 (Appendix 1: The EU Module 1 XML Submission) – see "Type". e.g. initial-maa, var-type1a, etc.

Notes:
Please use an underscore between each data item within the filename.

Do not use an underscore anywhere else other than between each data item of the filename.

Do not use special characters or spaces in the individual data items of the filename. Acceptable characters are: a to z (upper or lower case), 0 to 9 and "-"(hyphen).

The maximum number of characters of the filename should be 180.

The "Type" (see above) should be selected from the list (link) provided.

Q8. What is the file naming format for submitting Worksharing and Type IA (IG) Grouping applications? How should I submit Worksharing applications?

For Worksharing and Type IA Grouping applications, applicants are required to obtain a "EMEA/H/C/WSxxxx" or "EMEA/H/C/IGxxxx" number (via email to PA-BUS@ema.europa.eu) in advance of submitting their Work-sharing or IA Grouping.

Filename Example:

In this case the following file naming convention is to be used:

MAH_ESUBPROD_HCWSxxxx_ProductName_TypeII_00xx.zip or

MAH_ESUBPROD_HCIGxxxx_ProductName_TypeIA_00xx.zip

When there is a combination of different types of variations (Grouping), the variation Type should be the 'highest type' in the group.

Applicants are required to ensure that each product for the Worksharing is sent in separate zips. The Worksharing number and application type should be always correctly referred to. Additionally, it is imperative that all products within Worksharing /IA Grouping are sent at the same time to ensure that they arrive together.

If one product in the Worksharing/IA Grouping fails during the transmission, only this part of the Worksharing /IA Grouping has to be re-sent. Content validation will only start when ALL parts of the Worksharing / IA Grouping has reached the Agency. The submission date of the Worksharing / IA Grouping will be the date of the last submitted product.

4. Connection and registration process

Q9. What is the connection and registration process required for submitting eSubmissions via the European Medicines Agency Gateway?

First-time trading partners must use the Registration process and test files for initial testing of connectivity against the External Compliancy Test environment before being registered for Production.

Once testing against the External Compliancy Test environment is successful, the European Medicines Agency will register the trading partner for Production and live eSubmission eCTD sequences may be transmitted in the Production environment.

Please refer to the following documents on the eSubmission website:
- How to register for the eSubmission Gateway
- How to connect to the eSubmission Gateway

The documents can be found under: http://esubmission.ema.europa.eu/esubmission.html

Q10. My company has multiple names (i.e. Pharma Company and Pharma Company Europe) – do I need to register both as separate companies?

Each affiliate company should be registered; however there is no need to register them as separate companies and the same gateway identifier can be used for all companies from the same group.

Q11. We are a consultancy representing multiple Marketing Authorisation Holders (MAHs). Does each MAH need to register to use the eSubmission Gateway?

It is not necessary for each MAH to register. We only require registration for the consultancy.

Q12. Can we have multiple users after the registration is complete?

Once the registration is complete and testing has been verified you do not need to register multiple users.

Q13. How long does it take to register?

The registration process is likely to take approximately 2-5 working days to be completed. It is crucial that the relevant technical information is provided to the EMA in order to complete the process.

5. Technical questions

Q14. Which Gateway solution is used by the EMA?

At the EMA we are using a product called Axway Synchrony Gateway Interchange (version 5.8).

Q15. Which protocols should I use when transmitting eSubmissions via the European Medicines Agency Gateway?

For information on Protocol types, please refer to the document 'How to register for the eSubmission Gateway' which can be found on the eSubmission website (http://esubmission.ema.europa.eu/esubmission.html).

An automated Gateway MDN (Message Disposal Notification) message is sent to the applicant acknowledging receipt of the transmission.

Please note: If the MDN message is not received the Applicant should stop transmitting and immediately contact the EMA Gateway support. The eSubmission should not be sent repeatedly and automated repeated transmission must be avoided.

Q16. Where can I purchase the right 1024 bit Triple DES encryption key? Is there a recommendation by the EMA?

The EMA provides its public key to the companies, and the company provides its public key to the EMA. The company can purchase a certificate from any provider, such as VeriSign, Thawte, Globalsign, etc. Most gateways provide the ability to generate a certificate which can also be used. The EMA's certificate is generated by the Axway Gateway. The private key should never be made available to anyone.

Q17.What is the recommended Triple DES encryption key length?

1024 or 2048 are excellent choices in encryption key length.

Q18. If an MDN has been received does it mean that the EMA can open the submission successfully?

No, applicants must wait until they receive a letter from the EMA as confirmation that the submission is valid. In the next release of the eSubmission Gateway an acknowledgement will confirm that the submission has been successfully transmitted and uploaded to our review system according to the current eCTD specification.

Q19. Where do I obtain an encryption certificate from?

External Compliance Testing Environment:

An encryption certificate will need to be added to completed forms. Please download the information from the Public Website of the European Medicines Agency (http://esubmission.ema.europa.eu/esubmission.html).

Production Environment:

An encryption certificate will need to be added to the completed forms. Please download the information from the Public Website of the European Medicines Agency (http://esubmission.ema.europa.eu/esubmission.html).

Q20. What happens if the EMA eSubmission Gateway is not responding? Is there a plan how to deal with downtime of the eSubmission Gateway service?

The EMA eSubmission Gateway has been implemented as high availability system. All its components are redundant and the eSubmission Gateway service is included in the Agency's business continuity plan which foresees the recovery of the service in case of a disaster in less than 24 hours.

Downtime caused by planned maintenance periods will be announced 2 weeks before the planned maintenance for the production environment and 1 week before for the external compliancy test environment.

Q21. How will applicants know if there is a technical issue with their submission?

As mentioned in Q15, an automated Gateway MDN (Message Disposal Notification) message is sent to the applicant acknowledging receipt of the transmission.

In the unlikely event of an incomplete transmission, the EMA inform applicants within 1-2 working days.

6. Cover letter and registration form

Q22. Do I need to include a hard copy Cover Letter / Registration form with submission sequences sent via the European Medicines Agency Gateway?

There is no need for applicants to send an additional signed cover letter / Registration form in paper form as the transmitted dossier already contains an electronic cover letter and relevant data (e.g. date and time). Date and time are stored on the Gateway server and the eCTD submission is loaded into EURS, where all the information can be retrieved at a later stage as required.

7. General questions

Q23. What is the cost of the eSubmission Gateway for industry partners?

The cost depends on the complexity of the configuration but usually starts at €10-15'000. Included in this cost is the software licence for the Gateway and a number of days of consultancy for the installation/configuration of the Gateway. There may be additional costs purchasing and setting up the necessary hardware/servers. A list of suppliers is available upon request.

Q24.What is the difference between the ESTRI Gateway and planned Web-based client?

The Gateway allows multiple submissions to be sent concurrently with an optimum transmission speed.

The Web-based client requires manual uploading of submissions and is more suitable for lower transmission volumes.

Q25.What is the criteria used to define small and medium sized companies?

The Agency applies the definition of micro, small and medium-sized enterprises provided in Commission Recommendation 2003/361/EC. Therefore companies must:

- be established in the EEA, and
- employ less than 250 employees, and
- have an annual turnover of not more than €50 million or an annual balance sheet total of not more than €43 million. Further details can be found here.

Q26. Do I need to send additional Media (CD, DVD) along with my Gateway submissions?

There is no need to send additional media along with the Gateway submission. Applicants must **not** send a duplicate submission electronically or via hard copy as this might lead to delays in the handling of applications.

Q27. How do I ensure that I do not miss a submission deadline?

The EMA eSubmission Gateway sends an automatic acknowledgement to the applicant as soon as the gateway has received the entire electronic submission file in eCTD format. The timestamp of the automatic acknowledgement has to show that the eCTD file has been entirely and correctly received by the EMA before the expiration of the submission deadline (midnight).

Therefore it is recommended that the applicant sends the electronic submission file well in advance of the actual deadline. This is particularly relevant for very large submission files given that the maximum supported file size is 12 Gigabytes.

Q28. How should I provide PI and working documents?

Working documents (with track changes) in Word format should be provided within the same submission outside the eCTD backbone in a separate folder and clean version of the PI should be provided within the eCTD structure.

When working documents are submitted together with the eCTD sequence, they should always be provided in a separate folder called "xxxx-workingdocuments" where the number (xxxx) equals the number of the eCTD sequence being submitted.

If in previous eCTD sequences the PI has been provided with track changes within the eCTD structure it is not necessary to continue providing updates on these documents. A 'delete' operation can be performed for these documents and from there on only provide the clean versions in PDF inside eCTD and track versions in Word outside eCTD.

Q29. Is it still required to send eCTD sequences on hard media (CD/DVD) to the Rapporteur, Co-Rapporteur and all CHMP members for eCTD submissions in the Centralized Procedure when at the same time eSubmission Gateway is used for submission to the Agency? Or do all CHMP members have access to the Gateway?

Yes, you should continue to send all hard media in accordance with the submission requirements of each National Competent Authority. There is guidance on post-authorisation procedures and initial authorisation procedures on the EMA website.

The EMA is working on the development of a Central Repository which will enable member states to view submissions electronically. This solution is expected to be ready within the first half of 2013.

Q30. Do we have to use the Gateway for all submissions or is it possible to submit some via the Gateway and some via the current CD media process?

It is possible for applicants to still use the former method of sending CDs / DVDs for different products after they have registered for the Gateway, however, the EMA would like to encourage use of the Gateway as much as possible.

Q31. We are already set up as we have used the Gateway before – do we still need to register?

Registration is required as e-Submissions is its own community, and is not a part of EVTEST or any other existing community. The eSubmission Gateway has its own transport URL and certificate.

Q32. I registered to use the eSubmission Gateway during the pilot phase, will I have to re-register if I want to continue using the eSubmission Gateway in full production?

There is no need to re-register for the production phase if you have already registered for the pilot.

Q33. What happens if the EMA receive submissions before NCAs?

This issue can only occur if the correct process is not followed. Individual NCAs can be contacted in order to establish which methods of submission they accept.

8. Glossary

Term	*Definition*
Applicant	A pharmaceutical company or its agent that is submitting information in support of an ***application***
ESTRI Gateway	Electronic Standards for the Transfer of Regulatory Information
Procedure	The centralised registration procedure for the authorisation and maintenance of medicinal products in the European Union. There are 4 types of procedures that operate within the EU – The eSubmissions via the Gateway is only dealing with the Centralised Procedure
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**'
External Compliance Test Environment	External Compliance Test Environment is used to test the compliance of a new trading partner from pharmaceutical industry with the EMA's eSubmission Gateway system
Production environment	Production environment is used for live production
Web-based client	A Web-based client/server network is a computer communication system, in which client computers send requests to the server computer for data from its database, and the server returns the results to the clients via Internet/WWW

9. Document revision history

Version	**Date**	**Details**
1.0	23rd November 2011	Documentation for pilot phase
1.2	15th March 2012	Updated Documentation for pilot phase
2.0	18th April 2012	Documentation for full production
2.1	22nd June 2012	Updated Documentation for production

10. Contact us

To register:

esubregistration@ema.europa.eu

For technical queries and failures you might encounter in the production environment:

gatewaysupport@ema.europa.eu

If any further non-technical questions that are not adequately addressed by this document, please forward your query or comment to eCTD@ema.europa.eu