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Guidance for submission of clinical trial applications, substantial amendment notifications and end of trial declarations to the R&D division.

To the applicants.

Your letter from	Your reference	Our reference	Annex	Date
		FAMHP/R&D		13/11/2018

Guidance for submission of dossiers to the R&D division

Dear Madam,

Dear Sir,

This document is intended to update the information on the submission of clinical trial applications, substantial amendment notifications and end of trial declarations to the competent authority in Belgium (FAMHP).

From now on this new guidance supersedes the circular letter 575.

The present guidance refers to clinical trials as defined in article 2(a) of Directive 2001/20/EC. To determine whether an experiment is effectively a clinical trial, thus falling within the scope of the Directive, please refer to the algorithm available in annex of the document “Questions & Answers”, version 7, chapter 5, volume 10 of Eudralex. Please also refer to regulation 1394/2007 on advanced therapy medicinal products.

This guidance is not applicable for the submission of clinical trial applications which are selected for the CTR pilot project. For the submission of clinical trial applications following the CTR pilot process, please consult the Guidance CTR pilot project for sponsors, available on the FAMHP website.

Document Revision History

Date of publication	Revision description
15/05/2018, V1.0	N/A
30/05/2018, V1.1	§2.1.3.: clarification of point 2.1.3 related to substantial amendments for the ethics committee.
25/10/2018, V1.2	§1.1.: clarification related to the content of the CD-ROMs for the submission of GMO CTAs following deliberate release procedure. §1.4.: related to the Investigator's brochure (IB): new way of working for handling of new versions of the IBs. See text in bold.

1. APPLICATIONS FOR CLINICAL TRIALS

1.1. General remarks

- The processing time for clinical trial applications (CTA) is 15 days (for mono-centric phases 1) or 28 days (for all the other phases) starting from the date of validation of the CTA file (T0). However, as described in Article 13 of the Law of 05.07.2004 concerning experiments on the human person, this period may be extended depending on the nature of the product studied.

- These delays are prolonged with 30 calendar days in case of trials with gene therapy medicinal products, somatic cell therapy medicinal products or tissue engineered products and for all trials with medicinal products containing genetically modified organisms. Moreover the delay may be prolonged with 90 calendar days in case of consultation of the Biosafety Advisory Council in accordance with article 2 of Royal Decree from 18 December 1998 concerning the deliberate release into the environment and placing on the market of genetically modified organisms.

- The procedure also foresees a clock-stop system not exceeding one month upon notification of major comments (Grounds for Non Acceptance) raised by our experts to the applicant.

- For commercial studies, upon reception by the R&D division of both the CTA file **and** the proof of the corresponding payment (confirmed by the bank to the R&D division), the R&D division sends a confirmation of receipt email (CoR email) to the applicant.

- For non-commercial studies, no fee is required.

- The period to validate the CTA file remains three days.

Three situations may then occur:

1) The CTA file is complete: in this case the file manager sends an email to the applicant to confirm the starting date (T0) for the treatment/evaluation of the CTA. The T0 will thus correspond to the date of the confirmation of receipt email sent previously by the administrative service of the R&D division (T0= date of CoR email).

2) The CTA file is incomplete but the deficiencies are considered as minor (see Annex 1: minor deficiencies for validation): the file manager sends an email to the applicant to notify the starting date (T0) for the treatment /evaluation of the CTA as well as to request the missing documents/information, which must be provided within the legal processing period for the application (in practical most of the time 15/28 days). In case of minor deficiencies, the starting date for the treatment/evaluation of the CTA (T0) corresponds to the date of the validation email sent by the file manager and not necessarily to the date of the confirmation of receipt email (CoR email).

3) The application is incomplete and the deficiencies are considered as major (see Annex 1: major deficiencies for validation): an email is sent by a R&D file manager to the applicant to detail the major shortcomings and to notify the deadline for providing an adequate answer to these major deficiencies. The T0 is not granted. The starting date for the treatment/evaluation of the CTA will remain pending until the missing documents/information are provided. A new submission will be required if major deficiencies persist or if the missing information/documents are not provided within deadline. Once having received the requested information/documents and the CTA file being complete, the file manager sends an email to the applicant to notify the starting date (T0) for the treatment/evaluation of the CTA.

In summary:

- CTA file complete: the starting date for the treatment/evaluation of the CTA (T0) = date of the confirmation of receipt email (CoR email)

- CTA file incomplete (minor): the starting date for the treatment/evaluation of the CTA (T0) = CoR email + max 3 days

- CTA file incomplete (major): the starting date for the treatment/evaluation of the CTA = date of the email confirming that the CTA file is complete

- Henceforth it is acceptable that some documentation (complementary/forgotten) is added to the file by the applicant during the treatment period. However, if this addendum concerns the scientific documentation that will be evaluated by our experts such as the Investigational Medicinal Product Dossier (IMPD), the brochure of the investigator (IB), the risk/benefit balance or the protocol, then the legal period for the treatment of the CTA starts again (new T0)

- From May 15th until September 30th 2018, in addition to the submission by post (CD-ROM + signed cover letter), **a new option is available for the submission of CTA dossiers and substantial amendments : the dossier may be entirely electronically submitted via CESP (Common European Submission Portal).**

  These are the 2 possible options for submission during this transition period :

  1) By post : only the cover letter is to be submitted in hard copy together with a CD-ROM containing the CTA file in format as specified in Annex 2 of this document. The practical arrangements (transition period) are also presented in Annex 2.

  2) Via CESP: electronically only and following the process as described in Annex 3 of the present document.

  However we ask the applicants to only use one of the 2 possibilities for the submission.

  From October 1st 2018 only the submission via CESP will be accepted.

- Only for 'deliberate release' clinical trial applications with a GMO, we still request to perform the submission by post (CD-ROM/USB + signed cover letter), also after October 1st 2018. The applicant is requested to submit 3 identical CDROMs/USBs containing the complete dossier (CTA part + Biosafety part (cfr the RD of 21/02/2005)) to the FAMHP. Please provide those CDROMs/USBs 'unblocked', so the FAMHP still has the option to add certain documents for the Ministers regarding the trial if needed, such as updated documents that may need to be provided by the applicant following possible validation questions.

- For any submission of an application for a clinical trial with a GMO medicinal product please consult and follow the guidance document "Overview of procedures for submitting an application for clinical trials with GMO-medicinal products for human and veterinary use in Belgium" available on our website : https://www.famhp.be/sites/default/files/overview_of_procedures_for_submitting_an_application_for_a_clinical_trial_with_gmo_products_-_vs_10-07-2015_1.pdf. Regarding 'deliberate release' clinical trial applications with a GMO, please also consult the Royal Decree of February 21nd 2005: https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/ar_ogm_21_02_2005_0.pdf

1.2. Covering letter:

As a reminder, according to the detailed guidance, here are the elements to be included in the cover letter:

- EudraCT number
- Clinical Trial Title
- Protocol Number
- Specific features of the clinical trial where appropriate (e.g. unusual and particular IMP's such as GMOs, clinical trial with unusual design)
- Clinical trial with special population (if applicable)
- First-in-man administration of a new active substance (if applicable)
- Scientific advice related to the IMP and granted by a competent authority (if applicable)
- If the trial is part or is intended to be part of a "Pediatric Investigation Plan" (PIP)
- If the IMP or the Non Investigational Medicinal Product (NIMP) is a narcotic or a psychotropic substance
- Reference to the section/page of the IB or the SmPC where the reference safety information can be found in the CTA file for the assessment of expectedness of serious adverse reactions
- In the case of a re-submission, the changes as compared with the previous submission must be highlighted

To facilitate and accelerate the validation of the file, it is recommended to mention the following information in the cover letter, if applicable:

- Manufacturing sites in Belgium: which operations and where?
- NIMP(s): which ones and why the sponsor considers them as NIMPs[1]?
- Exploratory trial (as defined in the Belgian guideline of exploratory trial)
- Labeling: request for a waiver, if applicable (see end of the current circular) or reminder of a waiver obtained for phase 1 units
- Answers to possible minor objections formulated at the occasion of the approval of a previous application with the same IMP: if present in the file
- Possible radiopharmaceuticals and a copy of the Federal Agency for Nuclear Control (FANC) authorization.

[1]See: « Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials » (volume 10)

1.3. Protocol:

- The protocol must be accompanied by a summary of the protocol. It is recommended to provide this summary l as a separate document. The absence of this summary will be considered as a major deficiency for validation of the CTA file.

1.4. Investigator's Brochure (IB):

- The Summary of Product Characteristics (SmPC) may replace the IB if the IMP is authorized in a member state of the EU or any ICH country and is used in accordance with the marketing authorization (MA).

- The IB must be updated every year (before the end of the calendar year following the year of the current IB). A full track-changes version must be submitted together with the updated IB version.

- **Please note that from October 15th 2018 comments/recommendations sent at the occasion of the first submission of a new version of an Investigator's Brochure will be applicable/valid for each submission of the same version of the Investigator's Brochure (in an initial CTA dossier or a substantial amendment dossier). These comments/recommendations will not be repeated at each submission by the same applicant.**

1.5. Investigational Medicinal Product Dossier (IMPD):

- The CTD format (Common Technical Document) must be applied.
- It is recommended to present data in tabular form accompanied by brief explanations of crucial points.
- The SmPC (or equivalent documentation) may replace the IMPD if the IMP is registered in a member state (or an ICH country) and is used according to its marketing authorisation.
- No GMP documentation should be submitted if the IMP has a marketing authorization in the EU or an ICH country, if it is not modified as compared to its marketing authorization and if it is manufactured in the EU.
- The content of a simplified IMPD is mentioned in point 87 table 1 of the CT-1 detailed guidance
- on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial.
- No IMPD should be provided if:

    - The IMP is a placebo and the placebo has the same composition as the test product, is manufactured by the same manufacturer and is not sterile.
    - The IMP is a placebo whose IMPD has already been approved in a CTA in the Member State concerned.

1.6. Additional documents:

- The content of the label for each IMP.
- The copy of the approval of the leading Ethics Committee (hereafter referred as EC) must be submitted as soon as available (as the CTA dossier must be submitted concomitantly to the EC and to the FAMHP).
- A copy of any scientific advice on any aspect of the CTA file, if available.
- A copy of the decision of the European Medicinal products Agency (EMA) and of the Paediatric Committee's opinion if the trial is part of an approved PIP (unless if available on internet).
- It is recommended to include the proof of payment of the fee in order to link the payment to the CTA file (the confirmation by the bank to the FAHMPS is nevertheless indispensable before the treatment of the CTA can start).

2. AMENDMENTS

2.1. Substantial amendments:

2.1.1. General remarks

- It is the responsibility of the sponsor to determine if a substantial amendment (SA) is for the competent authority (CA) or for the EC. A modification of the documentation to be reviewed by the EC shall be submitted to the EC only. However the Royal Degree of 15th July 2004 states that the fee related to a SA evaluated by the EC must be paid once directly to the EC (art.2§3) and once to the FAMHP (art.1§3). This is the reason why, the fee for a substantial amendment must still be paid to both the EC **AND** the FAMHP. With the exception for non-commercial clinical trials we ask that the notification form of a substantial amendment (but not the related documentation) is still sent to the FAMHP in order to make the link with the payment of the amendment.
- The purpose of clarifications in the CT-1 detailed guidance concerning the amendments is clearly to avoid excessive submission of substantial amendments.
- A substantial amendment is defined as having an impact on safety or on physical or mental integrity of the participants to the trial and / or changing the interpretation of the scientific data.

2.1.2. Competent authority

- The updated XML file must be provided for each submission of an amendment, even if no changes are made to this document compared with the previous submission.
- Each substantial amendment must be designated by a unique reference number which clearly allows to distinguish it from other changes in the file.
- A track-changes version or a detailed overview (comparative table) with the modified words/text and a summary of changes must be provided for the updated documents (protocol, IB, IMPD,…).
- A substantial amendment can contain multiple changes.
- If the modification affects multiple trials of the same sponsor with the same IMP, only one file needs to be submitted to the FAMHP (only one European amendment notification form and a single copy of the supporting documentation). However a payment must be made for each EudraCT number.
- The processing time of for substantial amendments is the same as the one for the corresponding original CTA (15/28 days + 30 days for ATMPs/GMOs). However, the validation date is always the date of receipt of the substantial amendment and the corresponding payment (T0= date of CoR email)), unless there are missing documents. A T0 email will then be sent when the dossier is complete.

2.1.3. Ethics Committee

- The substantial amendments concerning the investigator (e.g. change of an investigator) and the Clinical Investigation sites (e.g. adding a site) are evaluated by the EC. The European application form and the XML form must be updated and submitted to the FAMHP at the occasion of the submission of the next substantial amendment.
- The substantial amendments concerning the informed consent are evaluated by the EC.

2.2. Non-substantial Amendments

- Non-substantial amendments should be registered (not submitted) and added to the documentation submitted with the next substantial amendment. The sponsor is responsible for the decision to submit an amendment to the CTA documentation as a substantial amendment or not. It is a decision on case-by-case basis. Examples of substantial amendments and non-substantial amendments are presented in the new version of the detailed guidance (see Section 3.4. of the CT1).
- The submission of the annual safety report (ASR/DSUR) is not considered as a substantial amendment. However, if data require a substantial change in the CTA documentation, a substantial amendment should be submitted accordingly.
- The submission of the updated IB is not considered as a substantial amendment unless the presented data require a substantial change in the CTA documentation.
- The annual update of the IB (unless it is considered as substantial amendment) must not be submitted to the FAMHP.
- A change in the name or in the coordinates of the contact person (e.g. email address, post address) is not a substantial amendment as long as the sponsor and the legal representative remain unchanged. However the sponsor must ensure that the FAMHP is informed as soon as possible and at least at the time of the next substantial amendment. If the sponsor believes that the time limit before submission of the next substantial amendment is too long, it is its responsibility to communicate the information separately to the FAMHP.

3. Temporary halt and urgent safety measures:

- A temporary halt of the trial shall be submitted to the FAMHP within 15 days of the decision. A temporary halt is not a substantial amendment but it is communicated to the FAMHP through the Substantial Amendment Notification Form (Section E.4.). A request for restarting the trial must be submitted as substantial amendment. The trial can only restart upon approval by the EC and if no motivated objections have been raised by the FAMHP within legal deadline.
- Urgent safety measures may be taken without prior notification to the competent authority. However, the competent authority shall be informed ex post. Moreover, if these measures induce substantial modifications of the initial documentation, a substantial amendment should be submitted as soon as possible.

4. End of a clinical trial:

- The Declaration of End of Trial Form should only be submitted to the FAMHP when the trial is completed in all concerned countries.
- Concerning the Clinical Trial Study Report/Synopsis, it is not necessary to submit it to the FAMHP when the document has been uploaded on the EudraCT-EU Clinical Trial Register. In Belgium it is sufficient to follow the European requirements on this topic (Guidance on posting and publication of result-related information on clinical trials (2012/C 302/03)).

5. PRACTICALITIES

5.1. Address where to submit CTA applications and amendments (from October 1st 2018 only for 'deliberate release' clinical trial applications with a GMO):

Federal Agency for Medicinal and Health Products

Division Research and Development

To the attention of Pieter Vankeerberghen

Eurostation Building, 8th floor (8C005)

Victor Horta Place 40 box 40

1060 Brussels

5.2. Fees

For an initial trial the amount applicable at the date of this circular must be paid to the following account indicating in the communication box: first the mention "EudraCT", followed by the correct EudraCT number (It is acceptable to have also in the reference the number of the study after the EudraCT number):

679-0001514-59

Details of the bank:

Poste financière
Chaussée d'Anvers 59
B-1100, Bruxelles (Belgique)

SWIFT code: PCHQBEBB
IBAN code: BE84 6790 0015 1459

For substantial amendments, a similar rule is applicable. The payment communication must indicate the EudraCT number, followed by "amendment" + the specific amendment code.

For each complete dossier and /or substantial amendment a separate payment must be done.

There is no fee to be paid for the submission of non-commercial clinical trials.

6. LABELING OF MEDICINAL PRODUCTS FOR CLINICAL TRIALS

6.1. General rule:

- Conform to Annex 13 Eudralex Volume 4
- 3 national languages on the primary and secondary packaging

6.2. Exceptions:

1) NIMPs:

- For medicinal products authorized in Belgium, used in an approved indication or not: no specific labeling
- Other medicinal products: general rule

2) Languages:

- Phase 1 units: a general waiver can be obtained if the IMPs are administered at the unit, if the clinical team understands the language used and if the subjects do not handle the product. In this case labeling in a single language can be accepted (including English). A copy of the general waiver must always be attached to the cover letter of the CTA.

- Other phases: the general rule is applied unless the four following conditions are met:
  • IMP is administered on site.
  • The subjects do not handle the product.
  • The clinical team understands the national language(s) used.
  • The reason for the difficulty in applying the general rule is clearly justified.
  In these conditions a specific waiver, only valid for this particular trial, may be granted if the justification has been deemed sufficient.

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Attention: in case of multinational clinical trials, no exception will be accepted, the use of booklets allowing to prevent this type of difficulty.

In any case, if the subjects take the medicinal product(s) back at home, no exception to the rule of three languages will be tolerated.

7. DECLARATION OF THE QUALIFIED PERSON

It is recommended to use the template proposed in Eudralex with the aim of harmonization: (https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2013-12_qp_template_imp.pdf).

Thank you for the attention you paid to this guidance. Please contact the general e-mail address of the General Division R & D (CT.RD@afmps.be) for any questions.

8. ANNEX 1 : VALIDATION QUESTIONS

8.1. Major deficiencies for the validation:

- Protocol: missing

- Summary of the protocol: missing

- Investigator brochure: missing

- For medicinal products with marketing authorization: SmPC missing

- GMP: EU manufacturing authorization missing / unauthorized operation

- GMP: “Declaration of GMP compliance” of the EU qualified person missing for IMPs manufactured in a third country, or incomplete

- IMPD: missing

- IMPD: no information on the « blinding »

- IMPD: no information on encapsulation (bioequivalence)

- IMPD: no information on the placebo

- IMPD: inconsistent with the CTD structure

- IMPD: sites missing in the section P.3

- EU application form: PDF version missing or inconsistent with the XML file

- EU application form: not signed by the applicant (a scanned version is sufficient)

- CE’s: incorrect choice of ECPSO (Principal Ethics Committee) (see circular 619)

- Track-changes version or detailed overview (comparative table) with the modified words/text and a summary of changes for the updated documents (protocol, IB, IMPD,…) in the submission package for a substantial amendment.

- GLP – OECD statement missing (following CTFG guideline: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/QAs_document_on_GLP_-_2017.pdf)

8.2. Minor deficiencies for the validation:

- Cover letter: incomplete (Detailed Guidance)

- labeling: not complying

- IMPD: TSE certificates missing

- FANC authorizations (missing): for radiopharmaceutics

- EU application form: inconsistencies

- NIMP's: information on NIMP(s) missing or incomplete

- Absence in the cover letter of the information on where the Reference Safety Information (RSI) can be found in the CTA dossier (IB or SmPC)

- EU application form not signed by the applicant (a scanned version is accepted)

9. ANNEX 2 : FORMAT OF THE SUBMISSION FILE

9.1. General remarks:

For ease of processing and archiving we decided to adopt the electronic submission of clinical trial applications, substantial amendment notifications and end of trial declarations.

9.2. Support:

During the transition period (until the end of September 2018), the submission of the dossier on a CD-ROM with a signed cover letter appended, will still be accepted.

In this case, the electronic data must be saved on a compact disc (CD or DVD).
We do not accept the following DVD formats:
- DVD-ROM
- DVD-RAM

Dossiers submitted on non-standard discs will not be accepted.

From October 1st 2018, all submissions must be performed via CESP (see how to submit via CESP in annex 3) and CD-ROM submissions will not be accepted any more (unless for 'deliberate release' clinical trial applications with a GMO).

The format as described in point 3. must be respected whatever the chosen option for the submission.

9.3. Format:

All the documents provided electronically must be in PDF format except the EU Application Form, which, in addition to PDF format, must also be provided in XML format.
To facilitate subsequent processing these PDF files should be easy to handle (e.g. copy-paste, keyword search etc ... ..)

Some requirements for the preparation of these PDF files:

1. The files must allow "copy/paste" and other changes. If the source file is no longer available the applicant can provide a scanned copy. However he must provide readable documents.
2. Certificates, licenses, authorizations and other documents with a signature must be scanned.
3. The layout should be as clear as possible. If possible a detailed table of contents must be included in order to find quickly specific sections of text.
4. Files should not be locked by a password.
5. Each part of the application dossier for clinical trial should be a separate file.
6. The names of these files must follow the syntax described below (see section 4.)
7. The PDF version of the European application form must be saved twice: a first part corresponding to the entire form and the second part with only the signed page that has been scanned. The same principle applies to the European substantial amendment notification form.

9.4. Names of the files:

To name the different files we ask you to respect a defined syntax: EudraCT number first, followed by the file name in English (see list below):

Example:
EudraCT Number_Name of file.pdf
2010-090094-00_Covering-Letter.pdf-

Special cases:

1) To name the scanned pages of the documents with signatures we ask you to add "signature" in the name.
Example: 2010-090094-00_Application-Form-Signature.pdf

2) In case the document refers to a particular medicinal product (investigational medicinal product or authorized medicinal product) we ask you to add the name of this medicinal product in the filename.
Example: EudraCT Number-Manufacturing-Authorisation-Name of the medicinal product.pdf

Hereafter list of file names (non-exhaustive)

Initial CTA files

INFORMATION	NAME OF THE PDF FILE
Cover letter	Covering-Letter.pdf
EU application form (PDF) EU application form (XML) Signature	Application-Form.pdf Application-Form.xml Application-Form-Signature.pdf
List of the European competent Authorities to which the application has been submitted	Competent-Authorities.pdf
Opinion of the Ethics Committee	Ethics-Committee-Opinion.pdf
Copy/Summary of Scientific Advice	Scientific-Advice.pdf
Protocol	Protocol.pdf
Investigator brochure	Investigator-Brochure.pdf
Dossier of the investigational medicinal product (IMPD)	Impd.pdf
Simplified dossier of the investigational medicinal product	Simplified-Impd.pdf
Summary of Product Characteristics (SmPC)	Smpc.pdf
Copy of the manufacturing authorization	Manufacturing-Authorization.pdf
Declaration of the Qualified Person	QP-Declaration.pdf
GMP certificate for biological active substance	GMP-Active-Substance.pdf
Copy of the import authorization	Importer-Authorization.pdf
Viral safety studies	Viral-Study.pdf
TSE certificates	TSE-Certificate.pdf
Labeling examples in the national languages	Labels.pdf

Substantial Amendments

INFORMATION	NAME OF THE PDF FILE
Covering letter	Covering-Letter.pdf
Substantial Amendment notification form (PDF) Signature	Amendment-Notification -Form.pdf Amendment-Notification -Form-Signature.pdf
List of the modified documents	*See names in previous table*
EU application form (PDF) EU application form (XML) Signature	Application-Form.pdf Application-Form.xml Application-Form_Signature.pdf

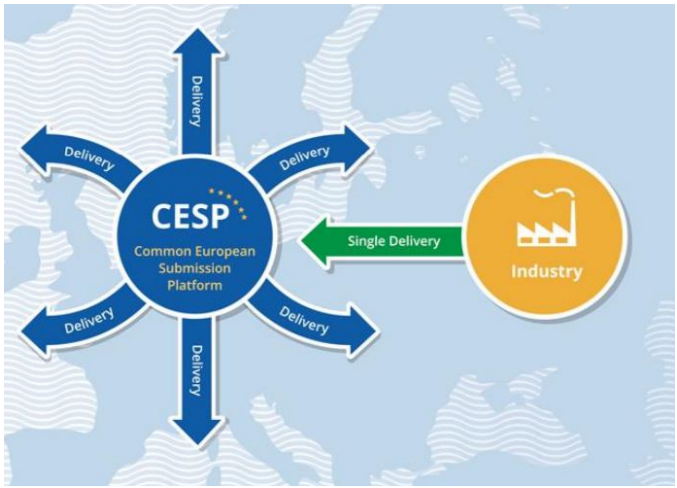
10. ANNEX 3 : E-SUBMISSION THROUGH THE COMMON EUROPEAN PORTAL (CESP)

The Common European Submission Portal is a simple and secure mechanism for the exchange of information on submissions between applicants and competent authorities in Europe.

CESP is a secure web platform developed by HPRA (Ireland) under the supervision of the Heads of Medicines Agencies.

The main advantages of this portal include:

- A multipurpose delivery system that can be used for any type of digital information transfer
- Tracking system
- Automatic notification by the application
- Simple, fast and efficient delivery system for information
- Allow easier and faster submission of updates / responses to information requests from the Agencies
- Provide a secure method of communication with the Regulatory Agencies via one platform
- Reduce the burden for both Industry and Regulators of submitting/handling applications on CD-ROM and DVD



10.1. For which application CESP must be used ?

Clinical trials (medicines)	Initial application for a clinical trial
	Substantial amendment for a clinical trial
	ASR/DSUR submission
	Urgent safety measure
	Temporary halt notification
	End of trial declaration
	CTR Pilot – initial application for a clinical trial
	CTR Pilot – Substantial modification for a clinical trial
Clinical investigations (medical devices)	Initial application for a clinical investigation
	Serious Adverse Events Notification
	Notification of end of clinical investigation / performance study
Unmet Medical Needs	Initial application for a CUP/MNP
	Periodic Reevaluation for a CUP/MNP
	Substantial Amendment for a CUP/MNP
Clinical trials, clinical investigations and Unmet Medical Needs	Approval of the ethics committee

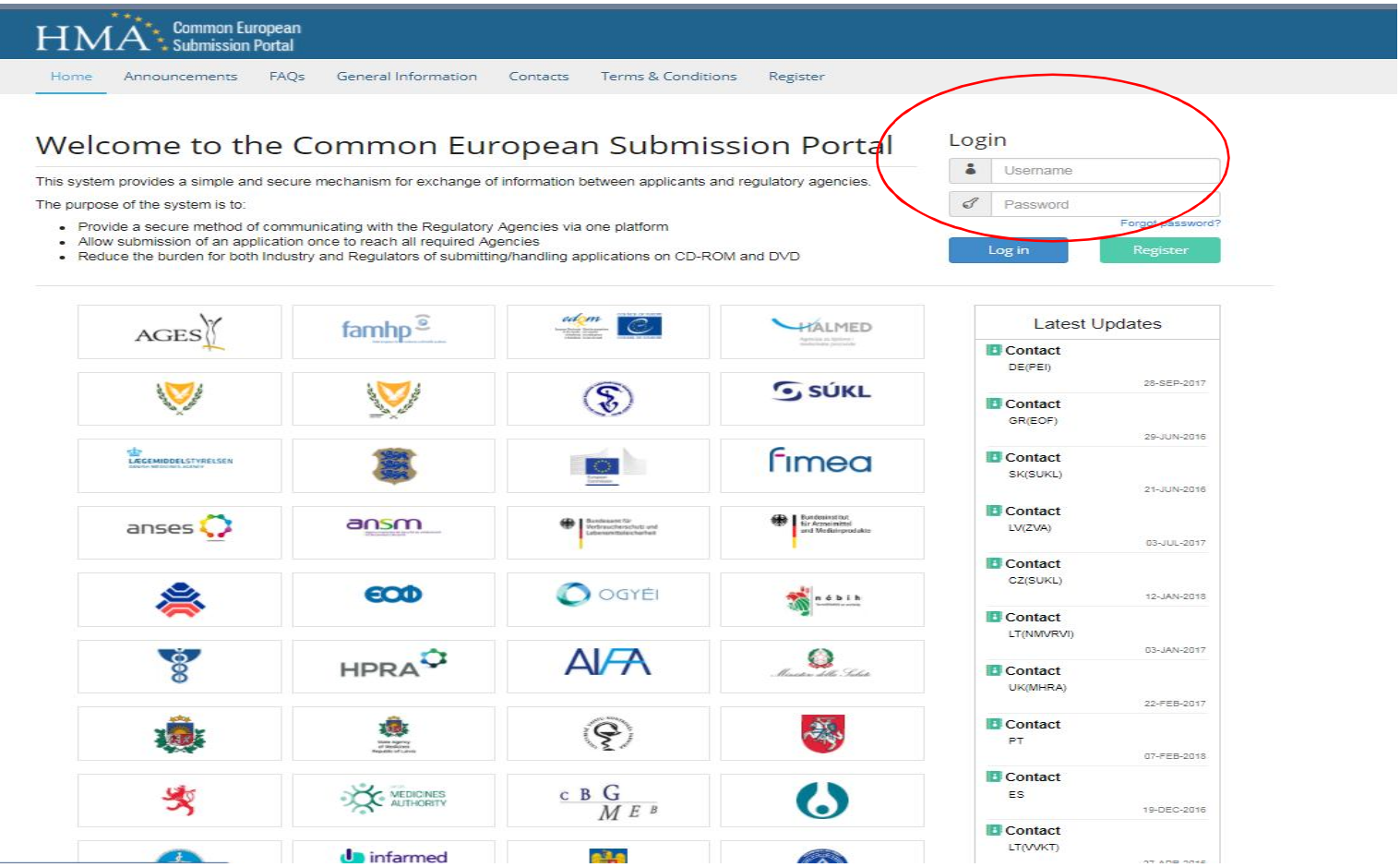
When using CESP, please do not send the same dossier via other ways to the Agency.

10.2. How to submit an application through CESP?

10.2.1. Account and connection

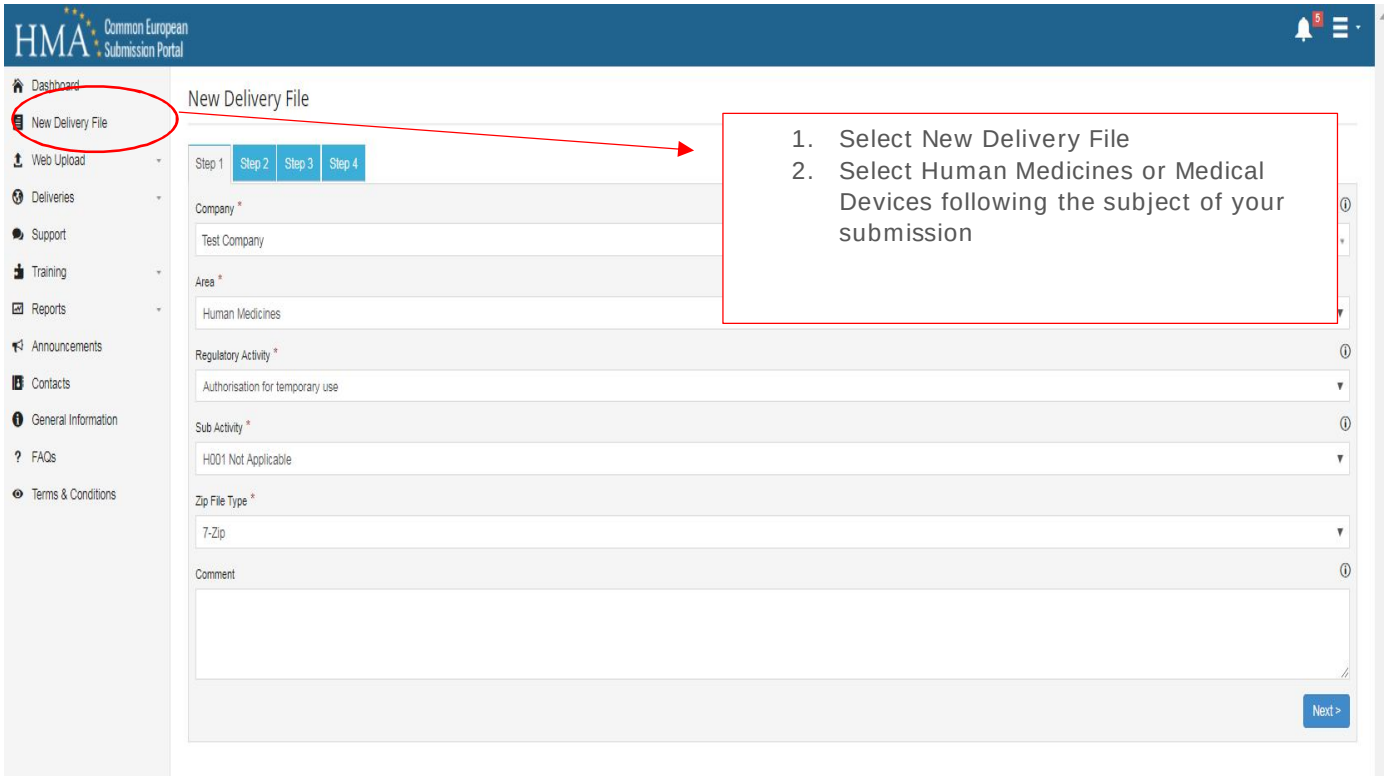
Link to the website : https://cespportal.hma.eu/Account/Login

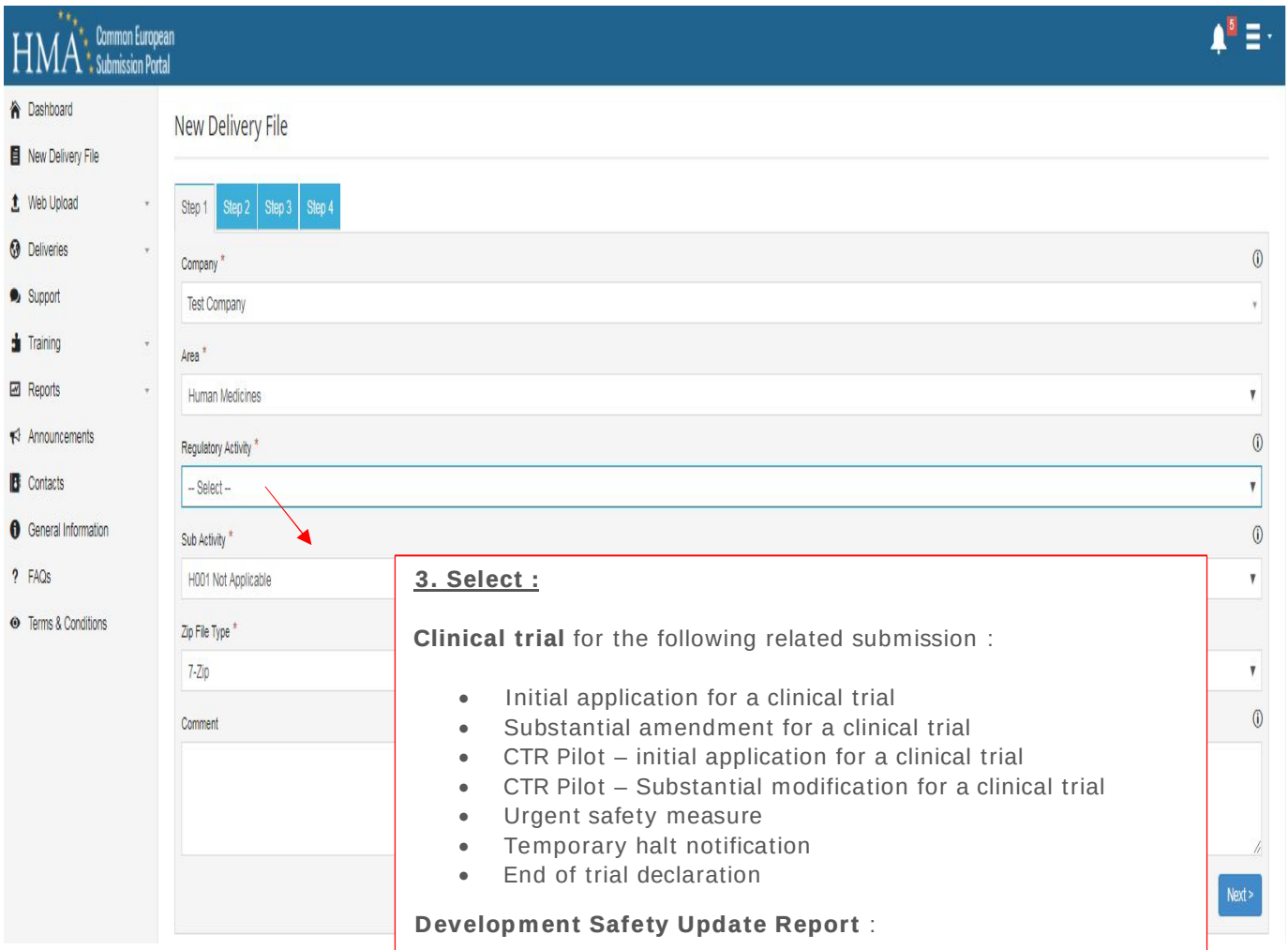
If you don't already have an account, please select "register" or follow this link https://cespportal.hma.eu/delivery/create



10.2.2. E-submission

First create a delivery file: A new delivery file has to be made for each submission.





3. Select :

Clinical trial for the following related submission :

- Initial application for a clinical trial
- Substantial amendment for a clinical trial
- CTR Pilot – initial application for a clinical trial
- CTR Pilot – Substantial modification for a clinical trial
- Urgent safety measure
- Temporary halt notification
- End of trial declaration

Development Safety Update Report :

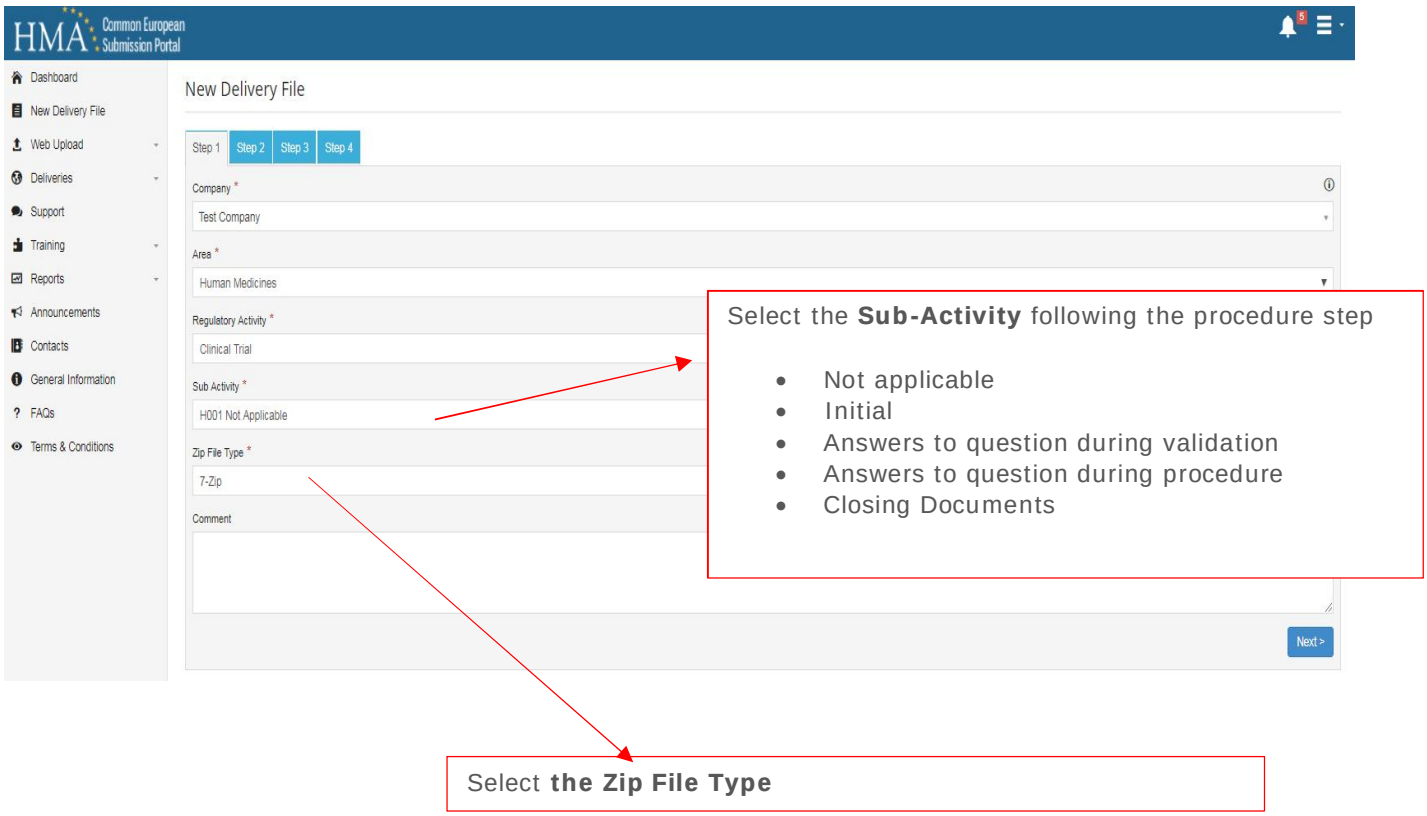
- ASR/DSUR submission

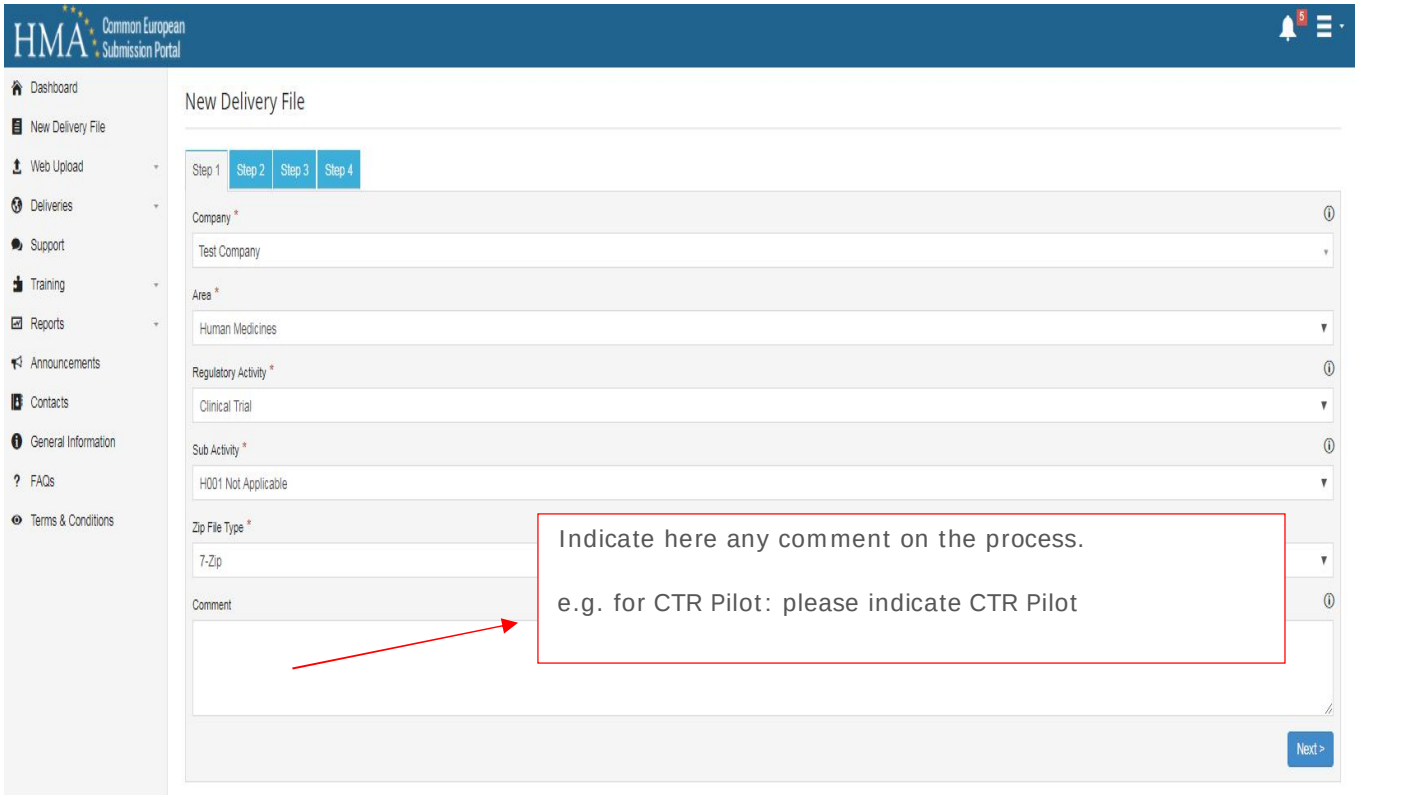
Authorization for temporary use for the following related submission :

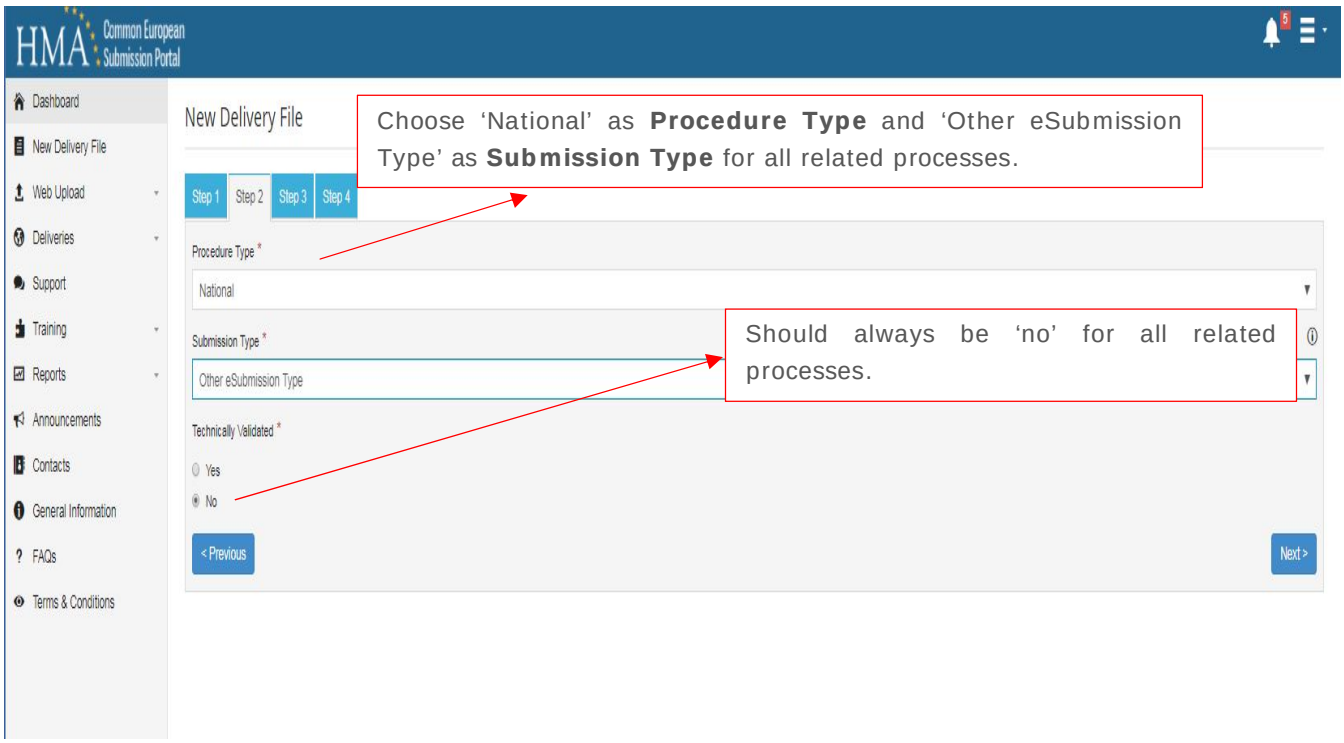
- Initial application for a CUP/MNP
- Periodic Reevaluation for a CUP/MNP
- Substantial Amendment for a CUP/MNP

Medical device for the following related submission :

- Initial application for a clinical investigation
- Substantial amendment for a clinical investigation / performance study
- Notification of end of clinical investigation / performance study


HMA Common European Submission Portal
Dashboard
New Delivery File
Web Upload
Deliveries
Support
Training
Reports
Announcements
Contacts
General Information
FAQs
Terms & Conditions
New Delivery File
Step 1
Step 2
Step 3
Step 4
Company *
Test Company
Area *
Human Medicines
Regulatory Activity *
Clinical Trial
Sub Activity *
H001 Not Applicable
Zip File Type *
7-Zip
Comment
Next >
Select the Sub-Activity following the procedure step
Not applicable
Initial
Answers to question during validation
Answers to question during procedure
Closing Documents
Select the Zip File Type


HMA Common European Submission Portal
Dashboard
New Delivery File
Web Upload
Deliveries
Support
Training
Reports
Announcements
Contacts
General Information
FAQs
Terms & Conditions
New Delivery File
Step 1
Step 2
Step 3
Step 4
Company *
Test Company
Area *
Human Medicines
Regulatory Activity *
Clinical Trial
Sub Activity *
H001 Not Applicable
Zip File Type *
7-Zip
Comment
Next >
Indicate here any comment on the process.
e.g. for CTR Pilot: please indicate CTR Pilot


HMA Common European Submission Portal
Dashboard
New Delivery File
Web Upload
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Contacts
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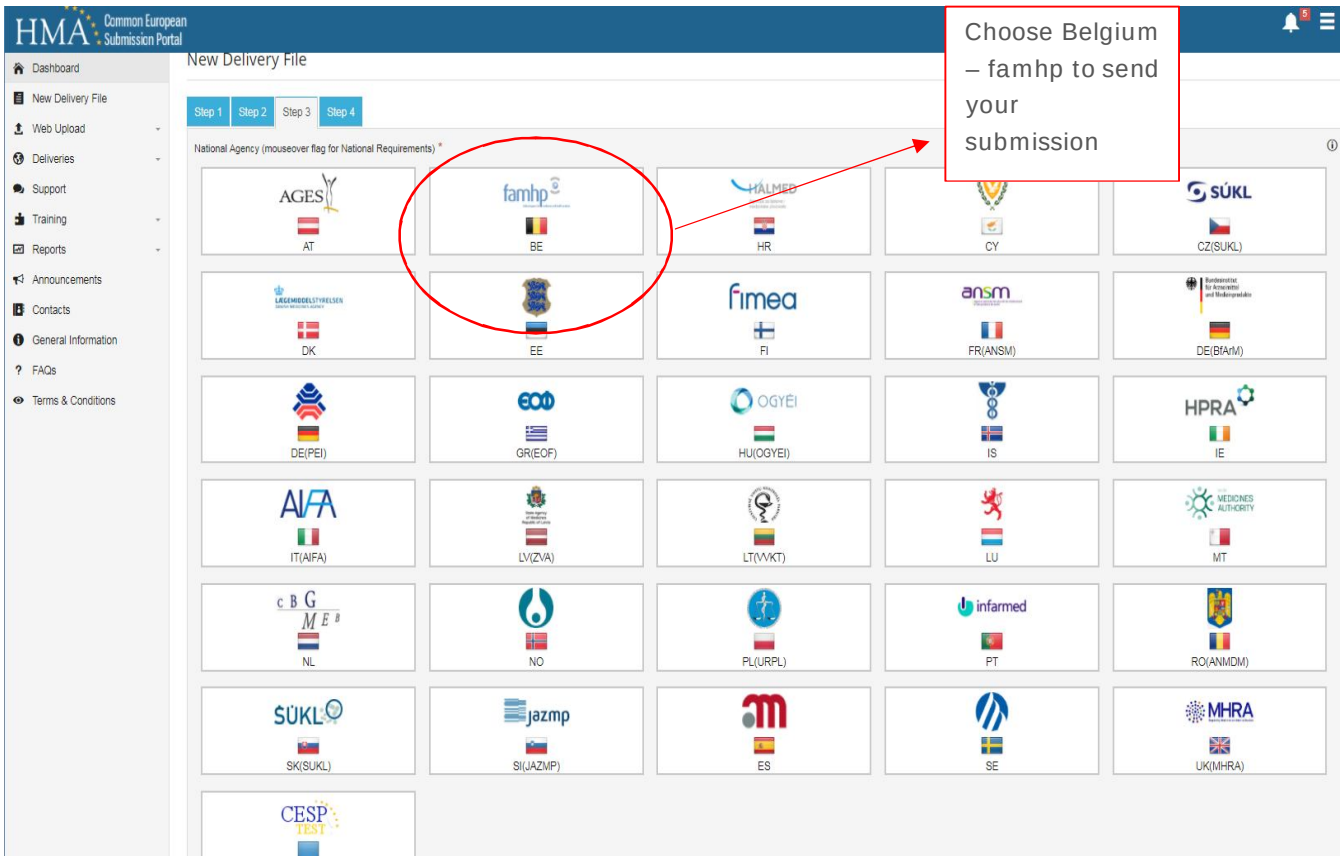
Terms & Conditions
New Delivery File
Choose 'National' as Procedure Type and 'Other eSubmission Type' as Submission Type for all related processes.
Step 1
Step 2
Step 3
Step 4
Procedure Type *
National
Submission Type *
Other eSubmission Type
Should always be 'no' for all related processes.
Technically Validated *
Yes
No
< Previous
Next >


HMA Common European Submission Portal
Dashboard
New Delivery File
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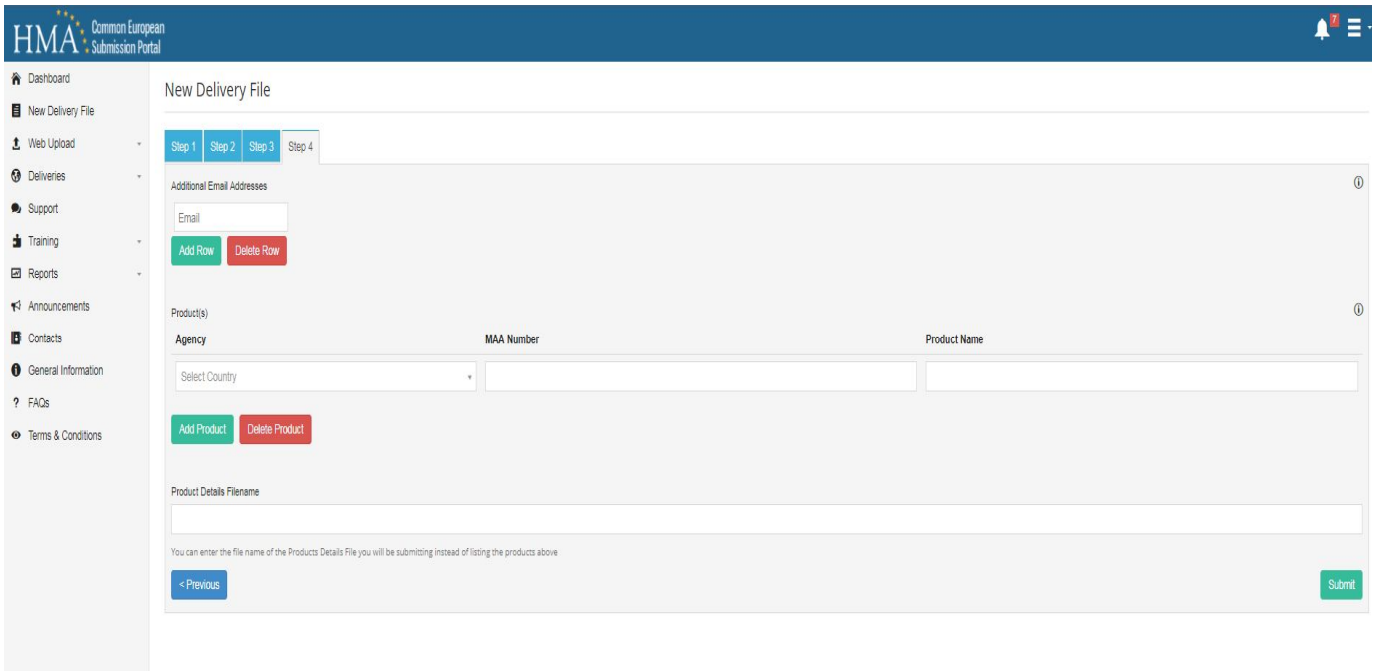
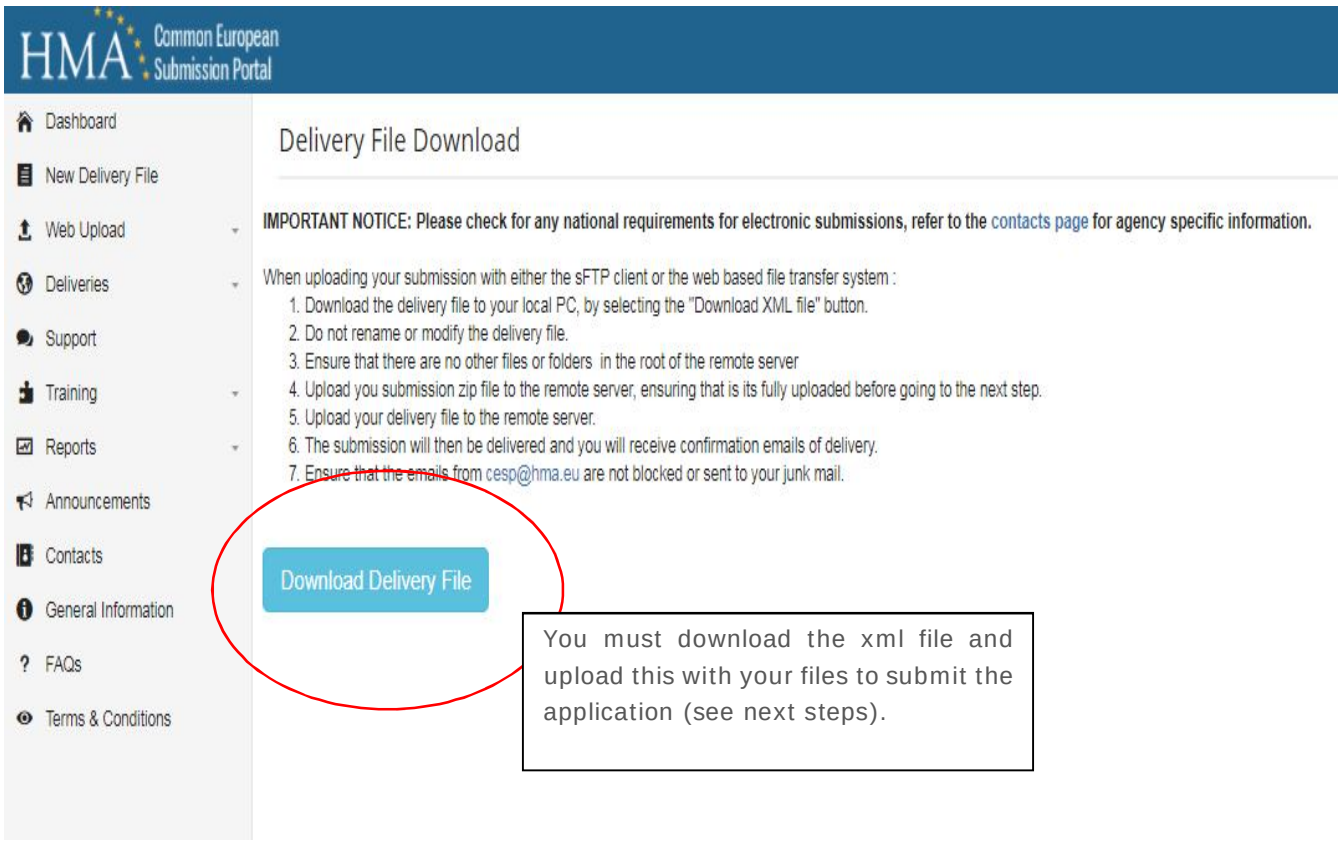
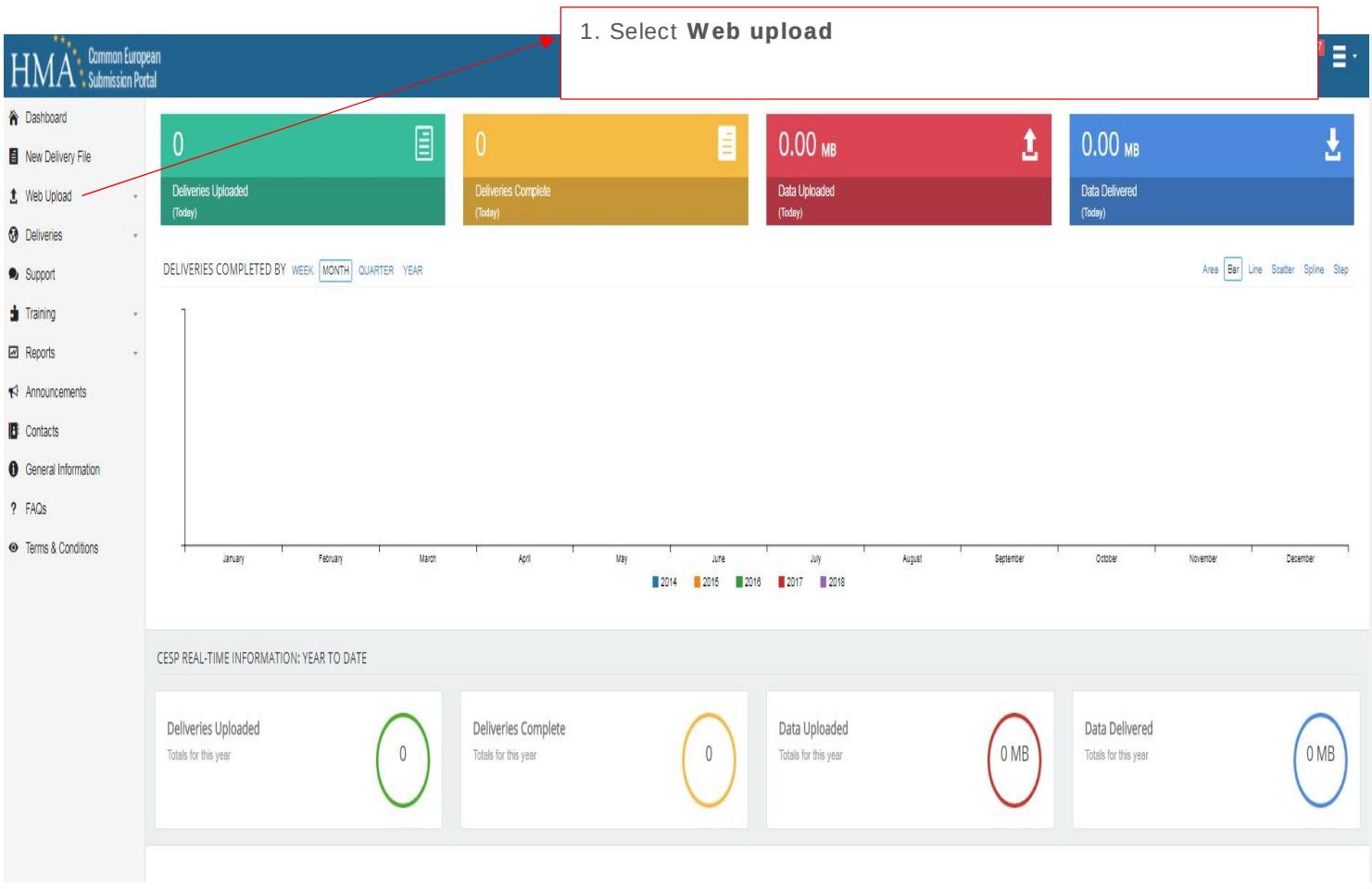
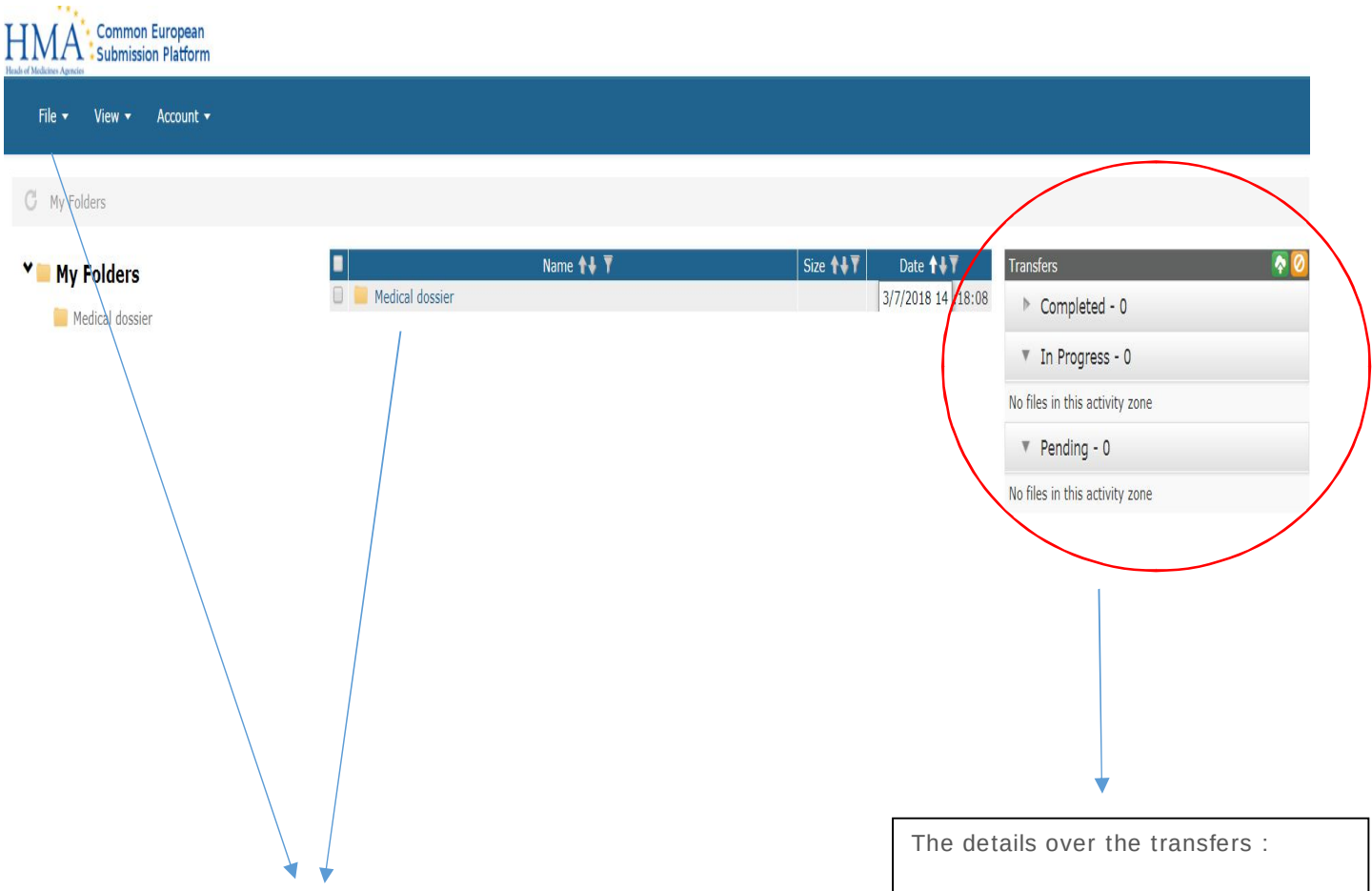
Terms & Conditions
New Delivery File
Step 1
Step 2
Step 3
Step 4
National Agency (mouseover flag for National Requirements) *
AGES AT
famhp BE
HALMED HR
CY
SÚKL CZ(SUKL)
DK
EE
fimea FI
ansm FR(ANSM)
DE(BfArM)
DE(PEI)
EOF GR(EOF)
OGYÉI HU(OGYEI)
IS
HPRA IE
AIFA IT(AIFA)
LV(ZVA)
LT(VVKT)
LU
MEDICINES AUTHORITY MT
CBG MEB NL
NO
PL(URPL)
infarmed PT
RO(ANMDM)
SÚKL SK(SUKL)
jazmp SI(JAZMP)
ES
SE
MHRA UK(MHRA)
CESP TEST
Choose Belgium – famhp to send your submission


HMA Common European Submission Portal
Dashboard
New Delivery File
Web Upload
Deliveries
Support
Training
Reports
Announcements
Contacts
General Information
FAQs
Terms & Conditions
New Delivery File
Step 1
Step 2
Step 3
Step 4
Additional Email Addresses
Email
Add Row
Delete Row
Product(s)
Agency
MAA Number
Product Name
Select Country
Add Product
Delete Product
Product Details Filename
You can enter the file name of the Products Details File you will be submitting instead of listing the products above
< Previous
Submit



10.2.3. Upload your files (i.e. the dossier) on CESP





Two ways to upload files :

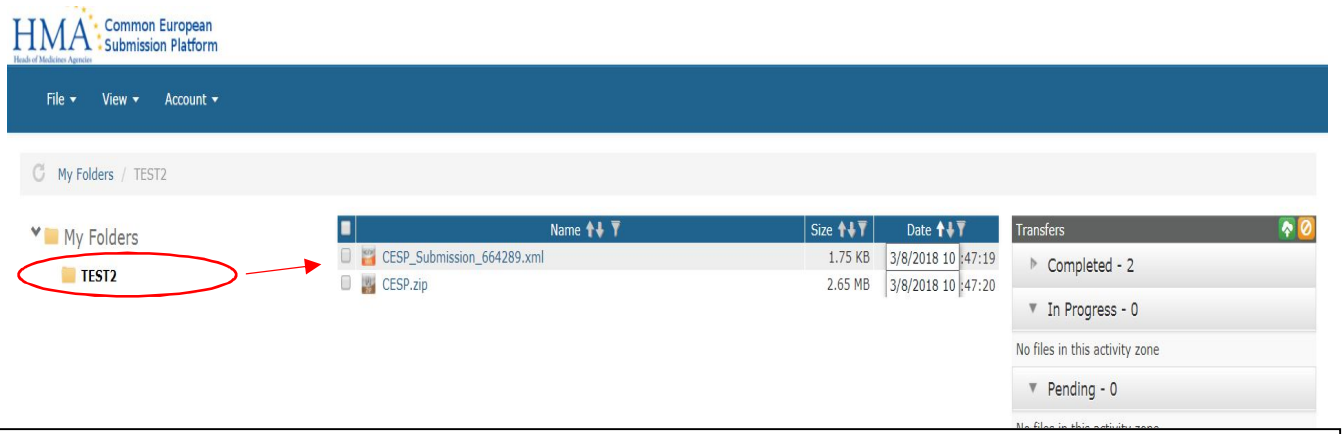
- Select “file” and “upload”, select your file that you want to upload.
- You can also directly select your file from your windows explorer, and slip it up to the webpage.

You can create several folders for each application

The details over the transfers :

- Completed upload
- Upload in progress
- Pending upload

Very Important: First upload your dossier – as a zip. When the zip is fully uploaded, then upload your delivery file previously downloaded (i.e. the file ending with xml). Also important – do not include a zip inside the zip as cesp does not allow this.



You will find the uploaded files in your folder:

- "CESP_Submission_xxxxxx.xml" : the delivery information, downloaded previously from CESP. It is different for each applications. It has thus to be systematically done for each application (whatever it is).
- "name of your file.zip" : the content of your application in zip format.

NB :

- Reminder : first upload your dossier in ZIP format on the website. When fully uploaded, then add the XML file.
- No further action is requested, the portal will send it to the selected Agency and will send you an e-mail regarding the notification. You can check it in the "deliveries" section on CESP.

10.3. Training and support

- An On Demand Training module is available for all CESP users. This contains the Latest Video Guides and Training documentation.
- Support : the CESP Group shall provide support in respect of the Portal to authorised users during normal working hours on Monday to Friday (other than public holidays listed below). Contact details for accessing CESP Group support are available on the Portal.
- FAQ is available for your common questions regarding the system : https://cespportal.hma.eu/Public/FAQs