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Guidance for submission of clinical trial applications, substantial amendment notifications and end of trial declarations to the Research and Development Division.

| Your letter from | Your reference | Our reference | Annex | Date |
|---|---|---|---|---|
| | | FAMHP/R&D | | 05.08.2021 |

## Guidance for submission of dossiers to the Research and Development Division

Dear Madam,
Dear Sir,

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

This guidance supersedes the former 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 indeed a clinical trial, thus falling within the scope of the Directive, please refer to the Decision tree to decide whether a trial is a "clinical trial" (algorithm can be found in the annex of the Q&A). Please also refer to the Regulation 1394/2007 on advanced therapy medicinal products.

This guidance does not apply to the submission of clinical trial applications selected for the CTR pilot project. Please consult the Guidance document for sponsors of CTR pilot projects, available on the FAMHP website, for more information on the submission of clinical trial applications according to the CTR pilot process.

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 section 2.1.3 on substantial amendments for the ethics committee. |
| 16.11.2018, V1.2 | §1.1.: clarification on the content of the CD-ROMs for the submission of GMO CTAs following deliberate release procedure.<br>§1.4.: with regard to the Investigator's brochure (IB): new procedure for handling new versions of the IBs. See text in bold. |
| 05.08.2021, V2 | Introduction page: addition of the link to the decision tree available in annex of the document "Questions & Answers", version 7, chapter 5, volume 10 of EudraLex<br>§1.1:<br>- with regard to the payment: no proof of payment is needed, an invoice will be sent afterwards<br>- additional updates than those requested in possible GNAs are not accepted<br>- submission via CESP is required, also for GMO deliberate release dossiers (CD-ROMs are no longer needed)<br>§1.2 indication of the relevant protocol section(s) with specific measures in case of RSI update<br>§1.3: additional information on protocol language<br>§1.4: clarification on when an SmPC may replace the IB and summary of changes needed upon IB update<br>§1.5: clarification on when an SmPC may replace the IMPD and need for a simplified IMPD and track changes/summary of changes document in case of IMPD updates<br>§2.1.1: additional information on substantial amendments<br>§2.1.2: timetables 15/28 + 30d also apply to substantial amendments for GMO deliberate release CTAs<br>§2.1.3: additional information on amendments for the EC<br>§2.2:<br>- a DSUR needs to be submitted separately from a substantial amendment + DSUR guidance<br>- additional information on timeframe for label updates<br>§3:<br>- clarification that a recruitment halt is also considered as a temporary halt<br>- the submission of a temporary halt and a substantial amendment needs to be done separately<br>- please inform us about quality OOS<br>§4: updated information on national and global End of Trial notification(s)<br>§5: new head of the R&D Division, new FAMHP address and payment information<br>§7: information on the need of a QP declaration for UK manufacturing activities<br>§9.2: submission via CESP is required from now on<br>§9.3: questions or problems related to the insertion of data in the XML file can be addressed to the EudraCT helpdesk<br>§9.4: the EC approval cannot be sent upon initial CTA submission, since the CTA needs to be submitted on the same day to the FAMHP and the EC. EC approval should be provided afterwards. |

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## 1. APPLICATIONS FOR CLINICAL TRIALS

### 1.1. General remarks

The processing time for clinical trial applications (CTA) is 15 days (for mono-centric phase 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 7 May 2004 on experiments on humans, this period may be extended depending on the nature of the Investigational Medicinal Product (IMP) being investigated.

This period is extended with 30 calendar days in the case of trials with medicinal products for gene therapy, somatic cell therapy or tissue engineering and for all trials with medicinal products containing genetically modified organisms. In addition, the period may be extended with 90 calendar days in the case of consultation of the Biosafety Advisory Council in accordance with article 2 of the Royal Decree of 18 December 1998 on the deliberate release into the environment and placing on the market of genetically modified organisms.

The procedure also provides a clock-stop system for a maximum period of one month after notification to the applicant of major comments (Grounds for Non Acceptance) raised by our experts.

Upon receipt of the CTA file by the Research and Development Division (R&D Division) of the FAMHP, the division will send a confirmation of receipt email (CoR email) to the applicant.

For commercial trials, an invoice will be sent with a structured message for payment.
For non-commercial trials, no fee is required.

The period to validate the CTA file remains three days.

**Three possible situations may occur.**

1. The CTA file is complete: in this case the file manager sends an email to the applicant to confirm the start date (T0) for the treatment/evaluation of the CTA. The T0 will therefore correspond to the date of the confirmation of receipt email previously sent 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 practice usually 15 or 28 days). In case of minor deficiencies, the start 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 deficiencies and to indicate the deadline for providing an adequate response 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 start date for the treatment/evaluation of the CTA (T0) = date of the confirmation of receipt email (CoR email).
- CTA file incomplete (minor): the start date for the treatment/evaluation of the CTA (T0) = CoR email + maximum of three days.
- CTA file incomplete (major): the start date for the treatment/evaluation of the CTA = date of the email confirming that the CTA file is complete.

It is accepted that the applicant adds some documentation (complementary/forgotten) to the file during the treatment period. However, if this addendum relates to 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). Updates or additional documents to any updates that have been requested in GNAs, will not be accepted. The applicant will need to await the approval before submitting the additional updates in a subsequent substantial amendment. In case this is not respected, a re-submission of the CTA is needed.

**Only CTA dossiers and substantial amendments that are submitted electronically via CESP (Common European Submission Portal, see annex 3) will be accepted.**
Please contact us if no confirmation of receipt has been received within five days after CESP submission.

The 'deliberate release' clinical trial applications with a GMO also need to be submitted via CESP. The applicant is requested to submit the complete dossier to the FAMHP: CTA part and Biosafety part (cfr the Royal Decree of 21 February 2005).

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.

### 1.2. Cover letter

The following elements should be included in the cover letter:
- EudraCT number;
- clinical trial title;
- protocol number;
- specific features of the clinical trial if applicable (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 Investigational Medical Product (IMP) and granted by a competent authority (if applicable);
- if the trial is part or is intended to be part of a Paediatric 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 Investigator's Brochure (IB) or the Summary of Product Characteristics (SmPC) where the Reference Safety Information (RSI) can be found in the CTA file for the assessment of expectedness of serious adverse reactions. If new Serious adverse reactions (SARs) are included in the RSI, the applicant should refer to specific sections or pages of the protocol where risk mitigation measures that cover these SARs can be found. A justification for the addition of new SARs can be added directly in the Investigator's brochure, in the section close to the Reference Safety Information;
- 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).
- labelling: request for a waiver, if applicable (see further in the current guidance) 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.
- possible radiopharmaceuticals and a copy of the Federal Agency for Nuclear Control (FANC) authorization.

[1] 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 as a separate document. The absence of a complete protocol and/or protocol summary will be considered as a major deficiency for validation of the CTA file. English versions are preferred, although not mandatory. Dutch and French versions will also be accepted.

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 European Union or any country of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and is used in accordance with the marketing authorization (MA), i.e. within the same indication, population, posology, treatment duration. In this case, the SmPC should be submitted as a separate document. If an SmPC is used as reference safety information for a clinical trial where the IMP is used off-label, the applicant should provide a justification for using that SmPC as RSI in this trial.

The IB must be updated every year (before the end of the calendar year following the year of the current IB). An update of an IB with (urgent) safety information is possible at any moment, whereas the reference safety information should be updated only once per year, if necessary. A full track changes version must be submitted together with the updated IB version. A detailed summary of changes that highlights the substantial changes must be provided for the updated IB as well.

**Please note that comments/recommendations made upon the first submission of a new version of an IB will be applicable/valid for each submission of the same version of the IB (in an initial CTA dossier or a substantial amendment dossier).**
**These comments/recommendations will not be repeated for 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 (meaning that the product is not modified). In addition, a short simplified IMPD-document needs to be available, to state and conclude clearly that the commercial supply and the clinical supply do not differ from one another.

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 (apart from the active substance(s)) 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.

In case of IMPD updates, please provide a track-changes version together with the updated IMPD version. A detailed summary of changes that highlights the substantial changes must be provided for the updated IMPD as well.

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).

## 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) should be submitted to the competent authority (CA) or 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 clarifications in the CT-1 detailed guidance regarding amendments is clearly aimed at avoiding the excessive submission of substantial amendments. A substantial amendment is defined as an amendment that has an impact on safety or on physical or mental integrity of the participants to the trial and/or changes to the interpretation of the scientific data.

Upon submission of an IB in a substantial amendment application containing an update to the RSI, which is not accompanied by a protocol amendment, the sponsor should specify in the submission cover letter what risk mitigation measures are already in place in the protocol to manage any new safety issues and if these new safety issues are adequately covered in the subject information leaflet (informed consent form) or if it needs to be updated. If the protocol is going to be updated, a planned time of submission should be communicated.

Generally, substantial amendments shouldn't be submitted to us if the trial has ended (or never started) in Belgium and the change has no impact (any more) on Belgian participants. If there would still be an impact on the follow up of the patients/effect on the scientific interpretation of the study data, then a substantial amendment should still be submitted.

ICFs need to be submitted for approval to the EC only and purely quality information (IMPDs) needs to be submitted for approval to the FAMHP only.

For protocols and IBs, the distinction is not always clear.
For purely clinical changes in the protocol (e.g. update inclusion/exclusion criteria …), it could suffice to submit them to EC only, unless they have possible consequences e.g. on the trial design, dosages, contraception, B/R, safety …
Regarding the IBs, we consider that substantial changes should be submitted as a substantial amendment for approval to the FAMHP and EC.

A substantial amendment can be submitted while a previous one is still under evaluation. However, generally, if the two amendments would be linked e.g. protocol and IB amendment, we advise to submit them together.
We are also in favour to group as much as possible the amendments, e.g. to submit 1 substantial IB amendment that is applicable for several trials at the same time.

According to the Detailed guidance CT-1, art 120(f), a change in the number of participants in the Member State concerned is regarded non-substantial, if the total number of participants is identical or the increase/decrease is insignificant in view of the absolute number of participants.
The sponsor should analyse the impact of this variation on the safety, the physical and the mental integrity of the clinical trial participants and on the quality of the scientific results of the trial. It is a case by case analysis which depends on all parameters (indication, B/R, statistics … ) of the trial. However, in general, if there is more than 10% change in the total number of participants, a substantial amendment should be submitted.

#### 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 detailed summary of changes that highlight the substantial 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 (only one European amendment notification form and a single copy of the supporting documentation) needs to be submitted to the FAMHP. However a payment must be made for each EudraCT number.

The processing time of substantial amendments is the same as the one for the corresponding original CTA (15/28 days + 30 days for ATMPs/GMOs). Also substantial amendments for GMO deliberate release CTAs will be handled within these 15/28 + 30d timelines. However, the validation date is always the date of receipt of the substantial amendment (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 substantial amendments for review and approval of the EC only (and not for the FAMHP). The payment for the substantial amendment to be reviewed by the EC only should however be done to the EC and the FAMHP. You should wait for the invoice (or invitation to pay) with a structured message for payment.

Regarding these changes, for the FAMHP the notification form of a Substantial Amendment and cover letter need to be provided (for notification), as mentioned higher in this guidance ("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 (with the exception for non-commercial sponsors)").

Also the European application form and the XML (section G) and the list of sites in the protocol will need to be updated and provided in this case.
The substantial amendments concerning the informed consent forms 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 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 and should be submitted separately. However, if data require a substantial change in the CTA documentation, a substantial amendment should be submitted accordingly. For more information on DSURs, please consult the Q&A document for DSURs, prepared by CTFG, and the template and guidance on our website.

The submission of the annual updated IB is not necessarily considered as a substantial amendment unless the changes have an impact on the safety of the trial subjects or the interpretation of the scientific documents in support of the conduct of the trial or if the presented data require a substantial change in the CTA documentation.

The annual update of the IB (unless it is considered as substantial amendment) does not need to 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.

There is no legal deadline for implementing new labels after they have been updated, for example after a change of sponsor, but we recommend to keep this timeframe as short as possible. We also recommend

that the clinical trial participants are clearly and timely informed of the updates. If the implementation of the new labels is not possible within a short timeframe, the trial participants should be re-informed regularly.

## 3. TEMPORARY HALT AND URGENT SAFETY MEASURES

A temporary halt of the trial shall be submitted to the FAMHP within fifteen 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.2.6 and E.4.). A temporary halt of recruitment/enrolment (also at site level) is also seen as a temporary halt of a trial. 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.

A temporary halt should be submitted separately from substantial amendments. Both a temporary halt and a substantial amendment cannot be provided in one submission package.

Urgent safety measures may be taken without prior notification to the competent authority. However, the competent authority shall be informed afterwards. In addition, if these measures induce substantial modifications of the initial documentation, a substantial amendment should be submitted as soon as possible.

Please also inform us about any out-of-specifications regarding quality aspects.

## 4. END OF A CLINICAL TRIAL

With reference to the recently updated Declaration of the End of Trial form, we would like to receive this declaration form twice if the national and global end of trial dates are different.
If the national and global end dates coincide in Belgium, it suffices to send the form only once.

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. FAMHP Address

To the attention of Marleen Laloup, Head of Division a.i.
Federal Agency for Medicines and Health Products
Research and Development Division
Avenue Galilee 5 box 03
1210 Brussels

### 5.2. Fees

A separate payment should be made for each complete dossier and/or substantial amendment. For commercial trials, an invoice will be sent with a structured message for payment.
For non-commercial trials, no fee is required.

## 6. LABELLING OF MEDICINAL PRODUCTS FOR CLINICAL TRIALS

6.1. General rule

- In accordance with EudraLex Volume 4, annex 13
- Three national languages (Dutch, French and German) on the primary and secondary packaging

6.2. Exceptions

**Non Investigational Medical Products (NIMPs)**
For medicinal products authorized in Belgium used in an approved indication or not: no specific labelling.
Other medicinal products: general rule.

**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 labelling 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.

**Please note that no exception will be made in multinational clinical trials, the use of booklets may avoid this kind of problem.**

**If the subjects take the medicinal product(s) at home, no exception will be made for the rule of three languages.**

## 7. DECLARATION OF THE QUALIFIED PERSON

It is recommended to use the proposed template in EudraLex for the qualified person's declaration.

As from 1 January 2021, the United Kingdom withdrew from the European Union and became a 'third country'.
From that date, the batch release of IMPs produced in the UK will no longer be insured by the qualified person of an importer based in the UK (except for manufacturers situated in Northern Ireland who are recognized as EU manufacturers). More information is available in the Questions and Answers document of the EMA to Stakeholders on the implementation of the Protocol on Ireland/Northern Ireland.

The batch release must be done by the qualified person of an importer based in another European member state. The same applies to IMPs produced outside the EU. The importer and qualified person must be changed via a substantial amendment revising section D.9.2 of the European application form, with a new QP declaration and a manufacturing authorization of the new importer and a revision of the section "manufacturers of the drug product" of the investigational medicinal product dossier (IMPD).

If the IMP is shipped to Belgium from another EU country, this is considered as being distribution and not as import, so no import requirements apply.
On the other hand, if IMPs are shipped to Belgium from a non-EU country, an import license and a QP declaration are required.

## 8. ANY QUESTIONS?

Please contact the general email address of the R&D Division (CT.RD@fagg-afmps.be) for any questions about this document.

## 9. ANNEX 1: VALIDATION QUESTIONS

9.1. Major deficiencies for the validation

- Protocol: missing
- Summary of the protocol: missing
- Investigator's 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 that highlights the substantial 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)

9.2. Minor deficiencies for the validation

- Cover letter: incomplete (Detailed Guidance)
- labelling: not complying
- IMPD: TSE certificates missing
- FANC authorizations (missing): for radiopharmaceuticals
- 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)

## 10. ANNEX 2: FORMAT OF THE SUBMISSION FILE

### 10.1. General remarks

All clinical trial applications, substantial amendment notifications and end of trial declarations should be submitted electronically to the FAMHP, in order to facilitate the processing and archiving of these dossiers.

### 10.2. Support

Only CTA dossiers and substantial amendments that are submitted electronically via CESP (Common European Submission Portal, see annex 3) will be accepted.
Please contact us if you have not received any confirmation of receipt within five days after CESP submission.

### 10.3. Format

All electronically provided documents must be in PDF format.
The EU Application Form should be provided in PDF format and XML format.
Questions or problems related to the insertion of data in the XML file can be addressed to the EudraCT helpdesk.

To facilitate further processing, these PDF files should be easy to handle (e.g. copy-paste, keyword search).

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 quickly find specific sections of text.
4. Files should not be locked by a password.
5. Each part of the application dossier for a clinical trial should be a separate file.
6. The names of these files must follow the syntax described below (see section 10.4.)
7. The PDF version of the European application form should be saved twice: a first part corresponding to the entire form and the second part only containing the signed page. The same applies to the European substantial amendment notification form.

### 10.4. Names of the files

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

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

**Special cases**

- Add "signature" to the file name for all documents containing signatures.
  Example: 2010-090094-00_Application-Form-Signature.pdf

- Add the name of the medicinal product in the file name for all documents referring to a particular medicinal product (investigational medicinal product or authorized medicinal product).
  Example: EudraCT Number-Manufacturing-Authorisation-Name of the medicinal product.pdf

List of file names (non-exhaustive)

**Initial CTA files**

| **Information** | **Name of the PDF file** |
|---|---|
| Cover letter | Cover-Letter.pdf |
| EU application form (PDF)<br>EU application form (XML)<br>Signature | Application-Form.pdf<br>Application-Form.xml<br>Application-Form-Signature.pdf |
| List of the European competent authorities to which the application has been submitted | Competent-Authorities.pdf |
| Copy/Summary of scientific advice | Scientific-Advice.pdf |
| Protocol | Protocol.pdf |
| Investigator's brochure | Investigators-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 |
| Labelling examples in the national languages | Labels.pdf |

Since the CTA needs to be submitted on the same day to the FAMHP and the Ethics Committee, please provide us with the opinion of the Ethics Committee as soon as it is available.

**Substantial Amendments**

| **Information** | **Name of the PDF file** |
|---|---|
| Cover letter | Cover-Letter.pdf |
| Substantial Amendment notification form (PDF)<br>Signature | Amendment-Notification-Form.pdf<br>Amendment-Notification-Form-Signature.pdf |
| List of the modified documents | *See names in previous table* |
| EU application form (PDF)<br>EU application form (XML)<br>Signature | Application-Form.pdf<br>Application-Form.xml<br>Application-Form_Signature.pdf |

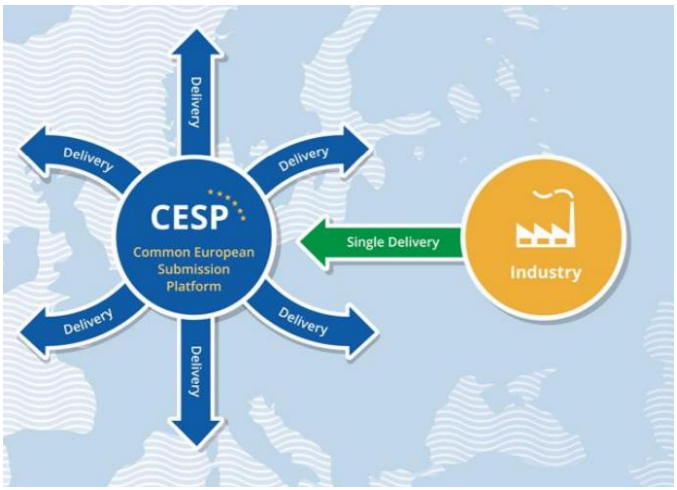
## 11. ANNEX 3 : E-SUBMISSION THROUGH THE COMMON EUROPEAN PORTAL (CESP)

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 the Health Products Regulatory Authority (HPRA) of 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.




### 11.1. When to use CESP?

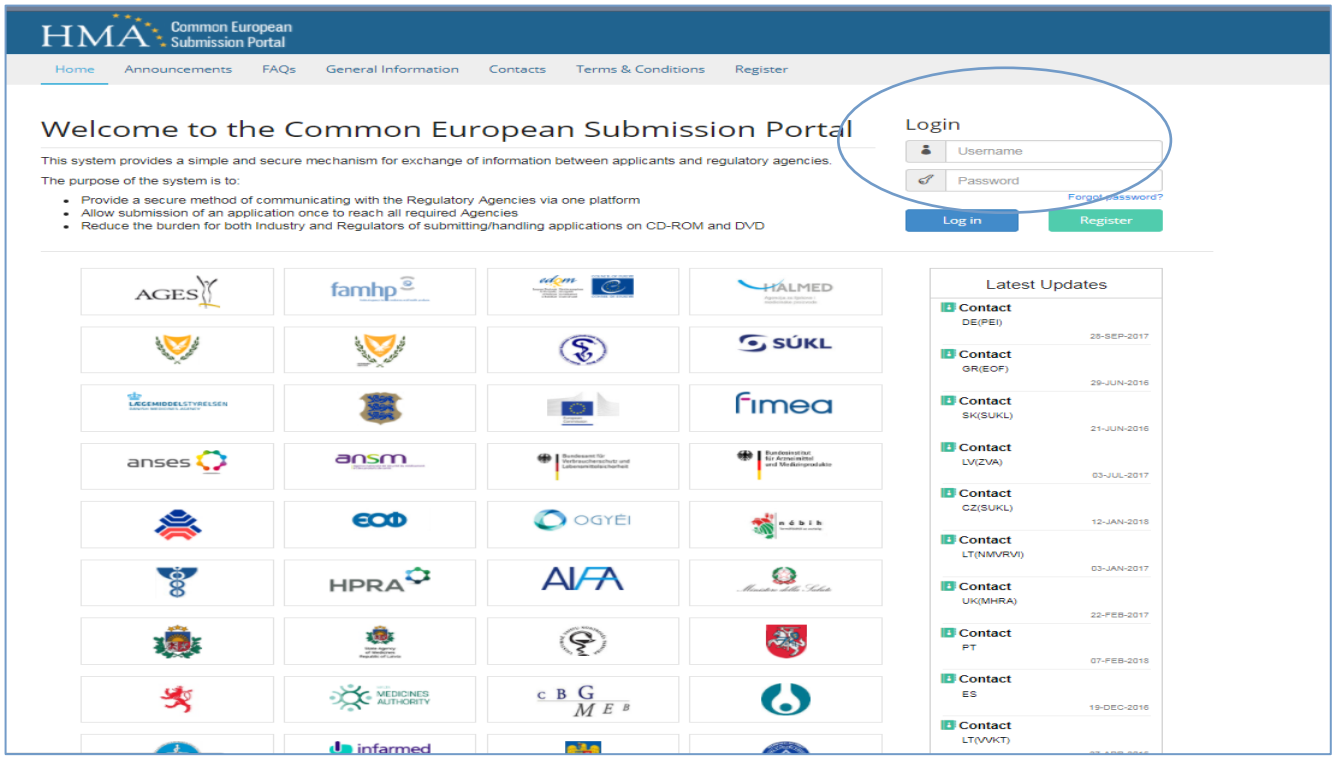
| | |
|---|---|
| Clinical trials (medicinal products) | Initial application for a clinical trial |
| | Substantial amendment for a clinical trial |
| | ASR/DSUR submission |
| | Urgent safety measure |
| | Temporary halt notification |
| | End of trial declaration |
| | CTR Pilot – initial application 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 Re-evaluation for a CUP/MNP |
| | Substantial Amendment for a CUP/MNP |
| Clinical trials, clinical investigations and Unmet Medical Needs | Approval of the ethics committee |

**Please do not send the same dossier simultaneously to the agency through other means.**

11.2. How to submit an application through CESP?

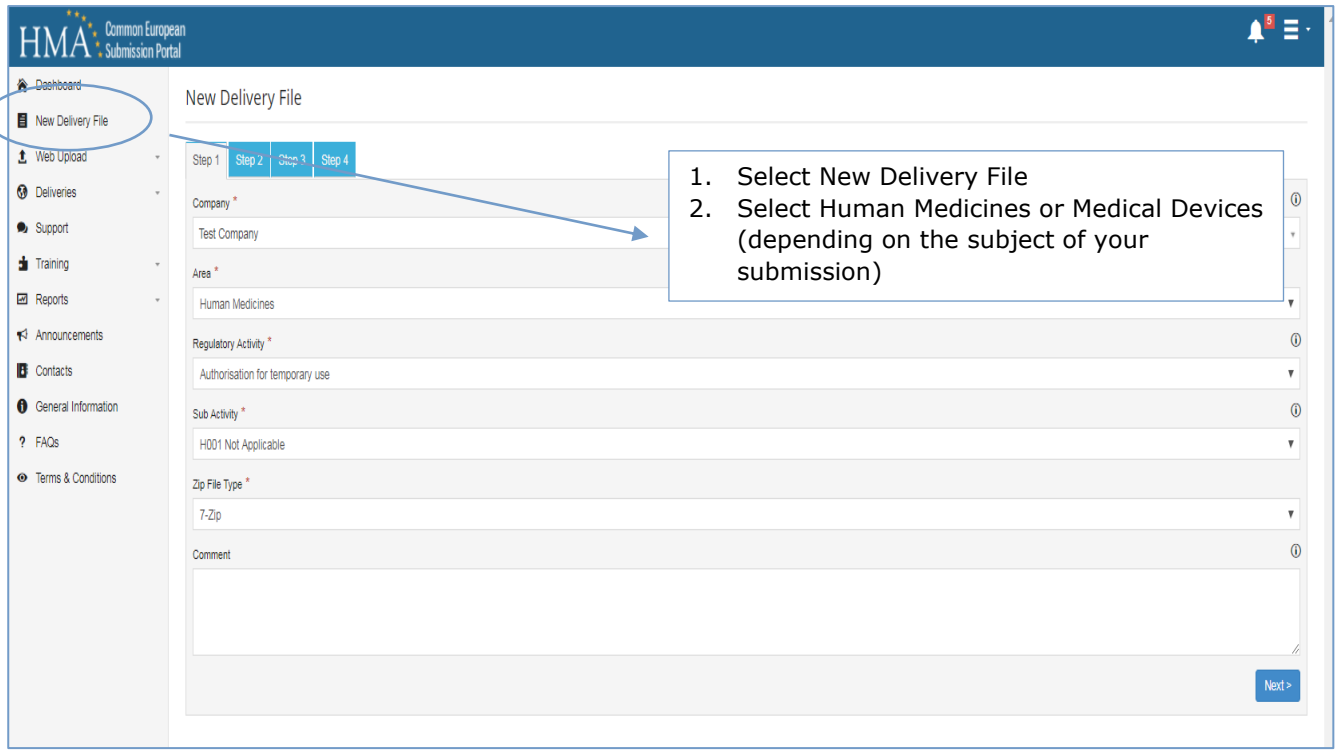
11.2.1. Account and connection

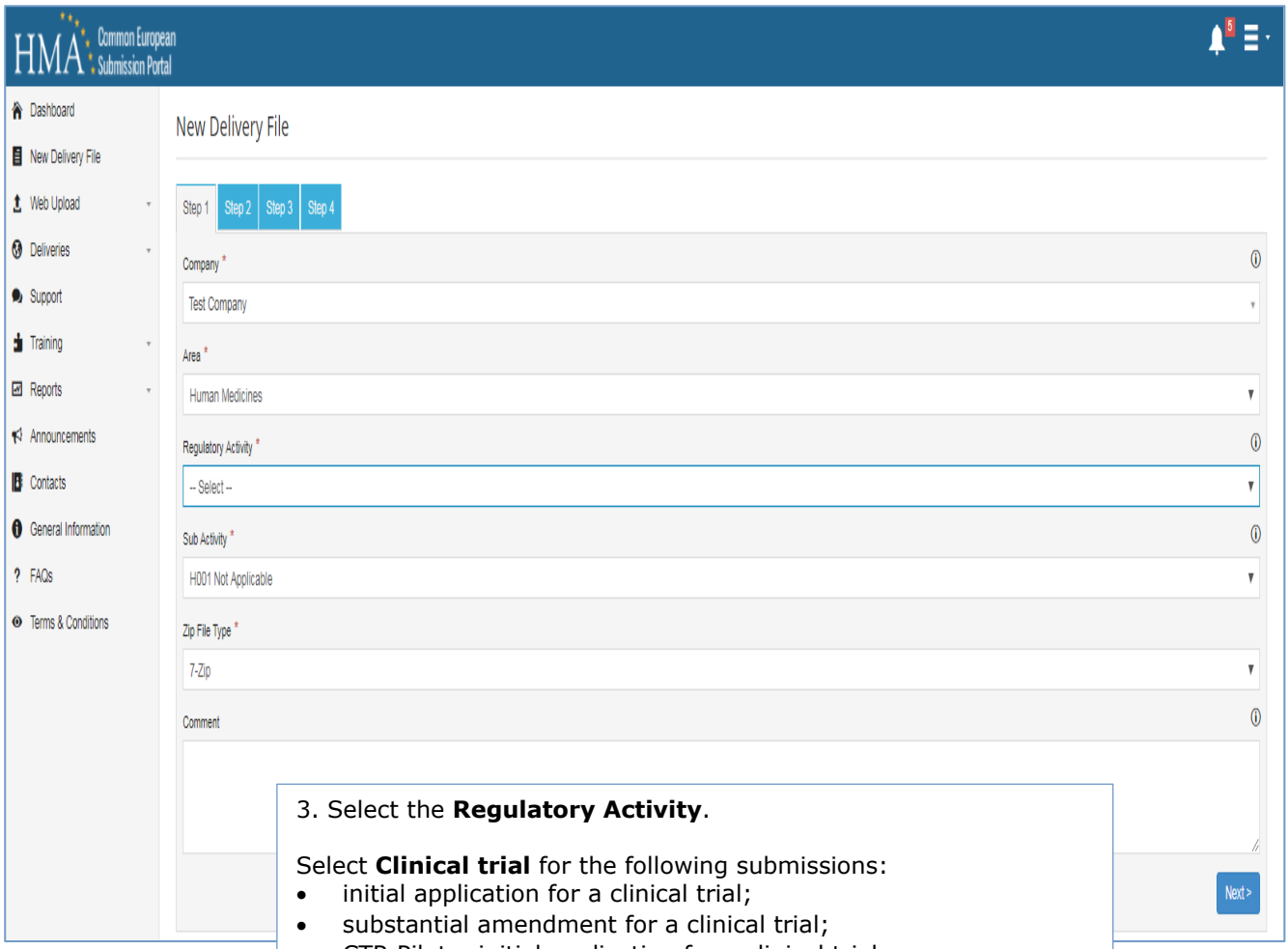
Create an account or log into the application if you already have an account.




11.2.2. E-submission

Create a "New Delivery File" for each submission.






3. Select the **Regulatory Activity**.

Select **Clinical trial** for the following submissions:

- 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.

Select **Development Safety Update Report** for:

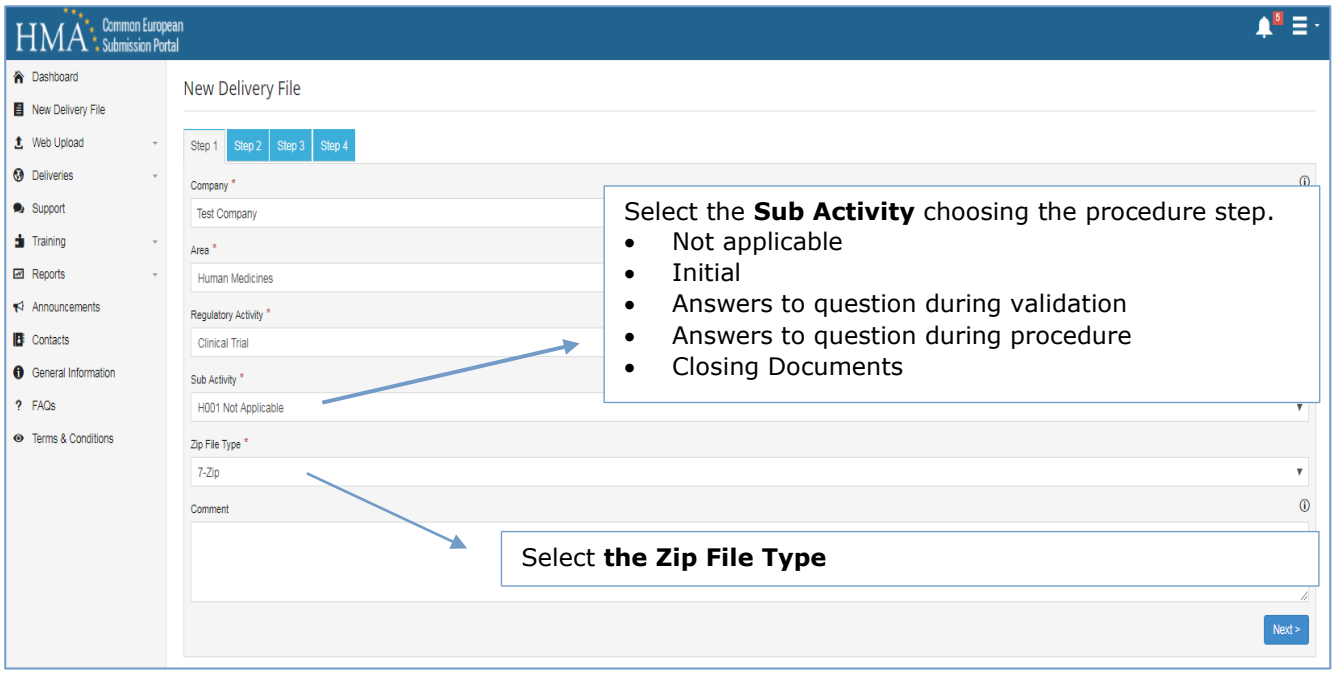
- ASR/DSUR submission

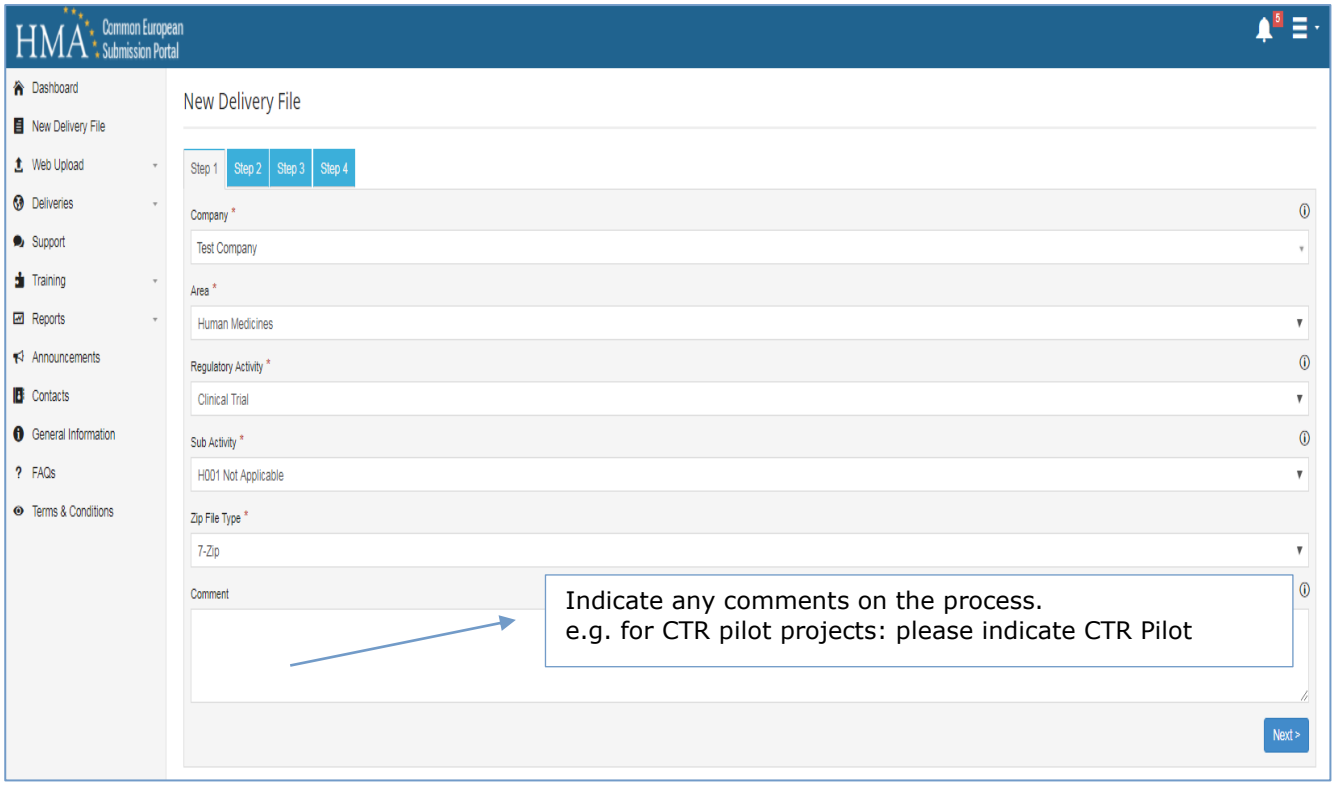
Select **Authorization for temporary use** for:

- initial application for a CUP/MNP;
- periodic reevaluation for a CUP/MNP;
- substantial amendment for a CUP/MNP.

Select **medical device** for:

- 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** choosing 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
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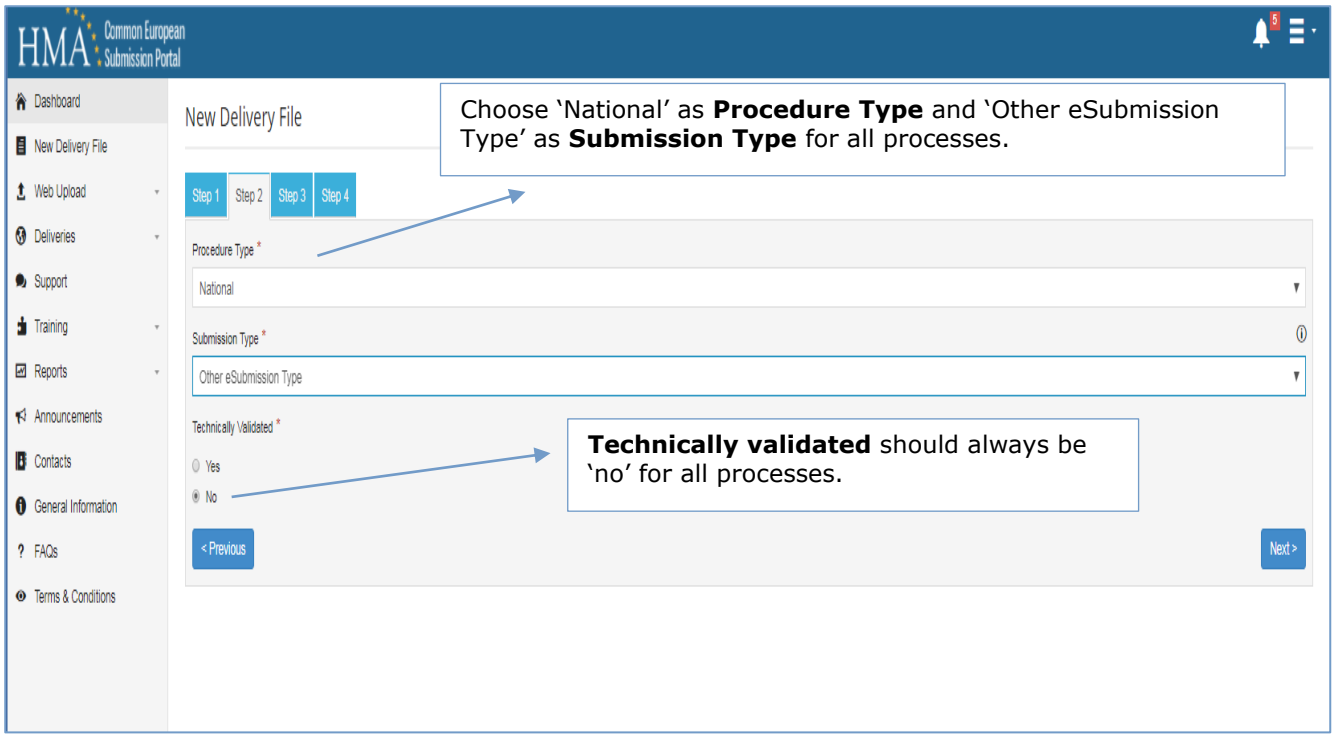
Contacts
General Information
FAQs
Terms & Conditions
New Delivery File
Step 1
Step 2
Step 3
Step 4
Company *
Test Company
Area *
Human Medicines
Regulatory Activity *
Clinical Trial
Sub Activity *
H001 Not Applicable
Zip File Type *
7-Zip
Comment
Next >
Indicate any comments on the process.
e.g. for CTR pilot projects: please indicate CTR Pilot


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
Choose 'National' as **Procedure Type** and 'Other eSubmission Type' as **Submission Type** for all processes.
Step 1
Step 2
Step 3
Step 4
Procedure Type *
National
Submission Type *
Other eSubmission Type
Technically Validated *
Yes
No
**Technically validated** should always be 'no' for all processes.
< Previous
Next >


HMA Common European Submission Portal
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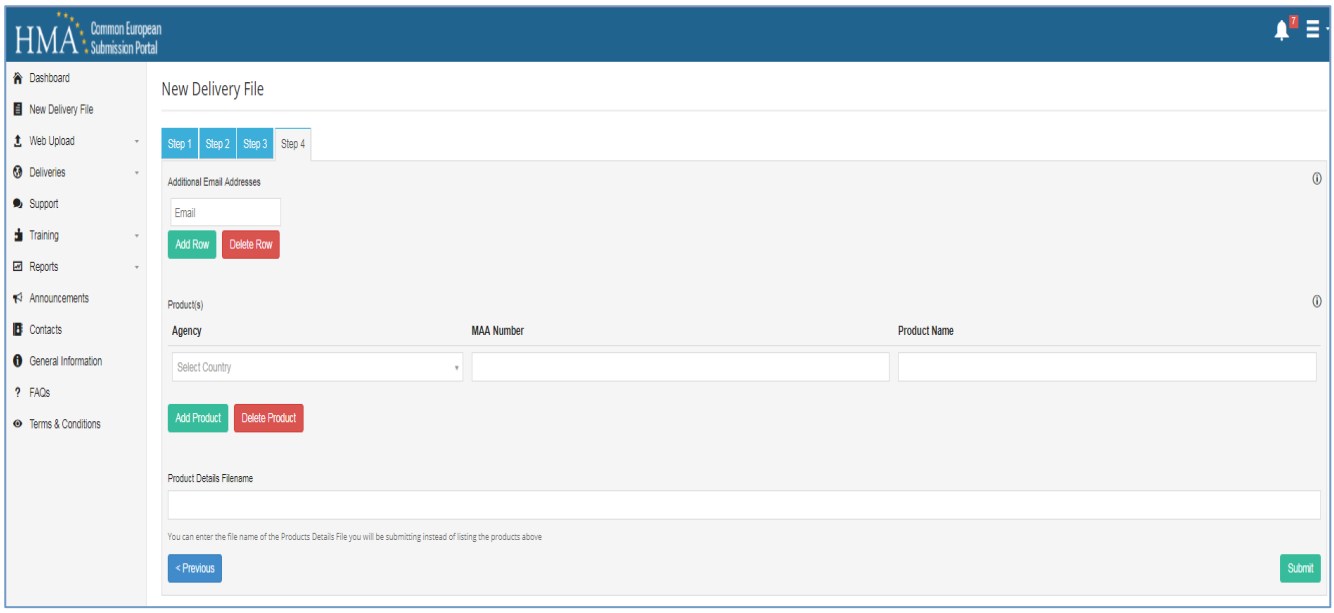
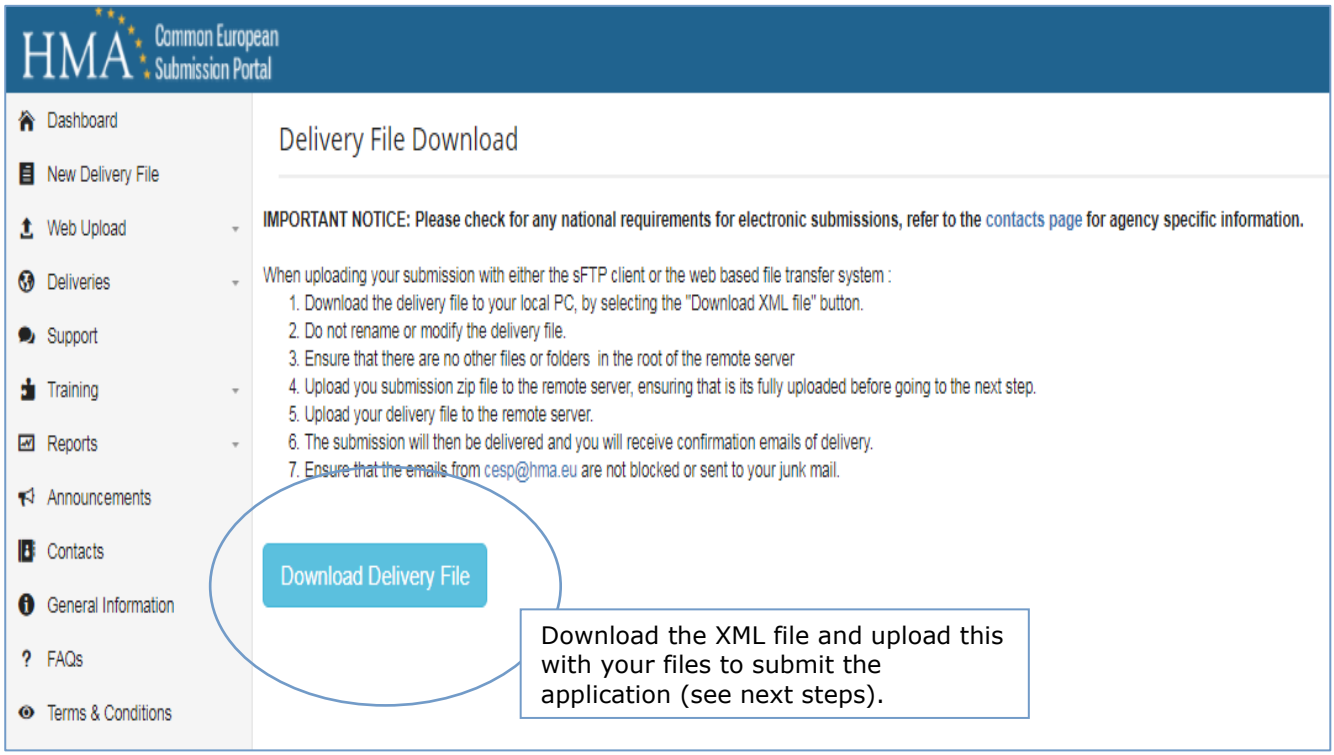
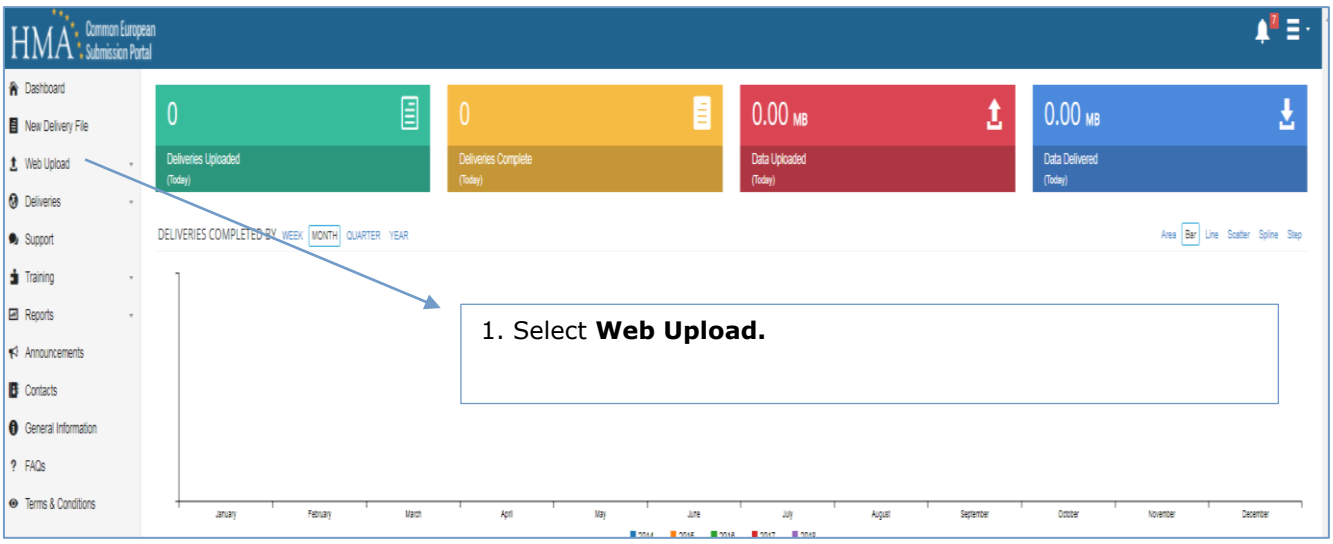
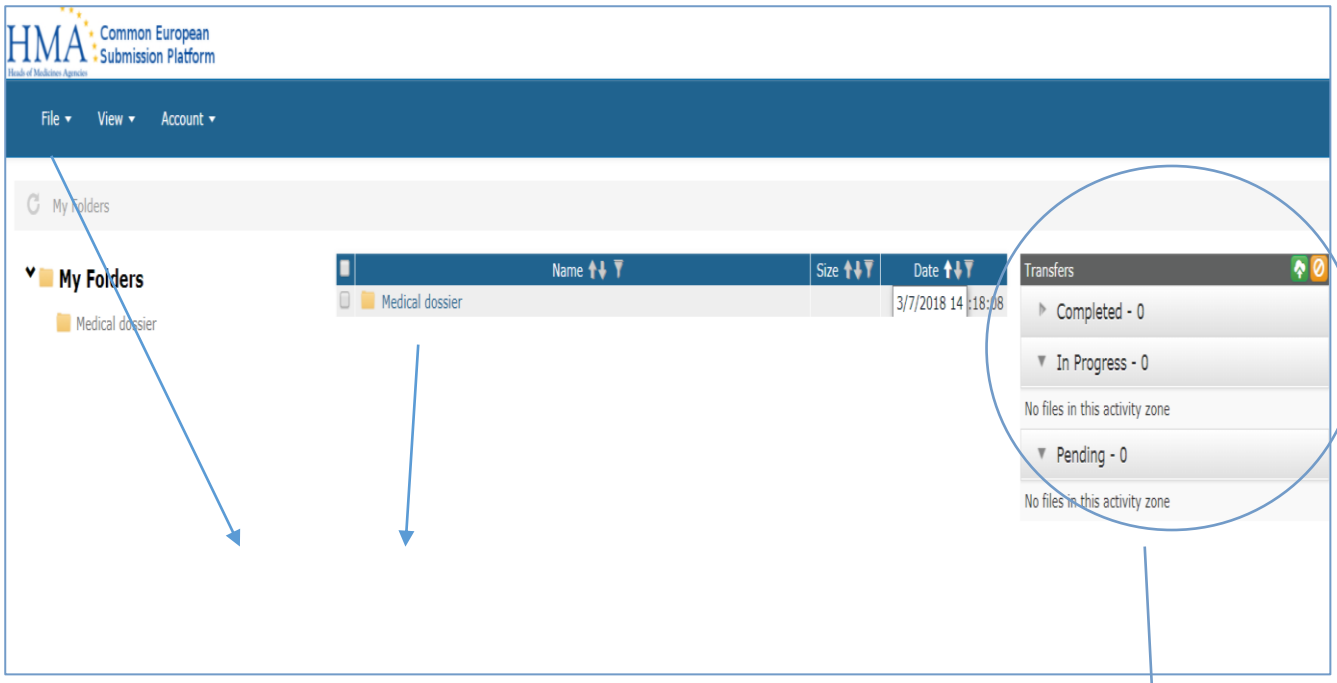
Reports
Announcements
Contacts
General Information
FAQs
Terms & Conditions
New Delivery File
Step 1
Step 2
Step 3
Step 4
National Agency (mouseover flag for National Requirements) *
Choose Belgium – famhp to send your submission.
AT
BE
HR
CY
CZ(SUKL)
DK
EE
FI
FR(ANSM)
DE(BfArM)
DE(PEI)
GR(EOF)
HU(OGYEI)
IS
IE
IT(AIFA)
LV(ZVA)
LT(VVKT)
LU
MT
NL
NO
PL(URPL)
PT
RO(ANMDM)
SK(SUKL)
SI(JAZMP)
ES
SE
UK(MHRA)




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






There are two ways to upload files.

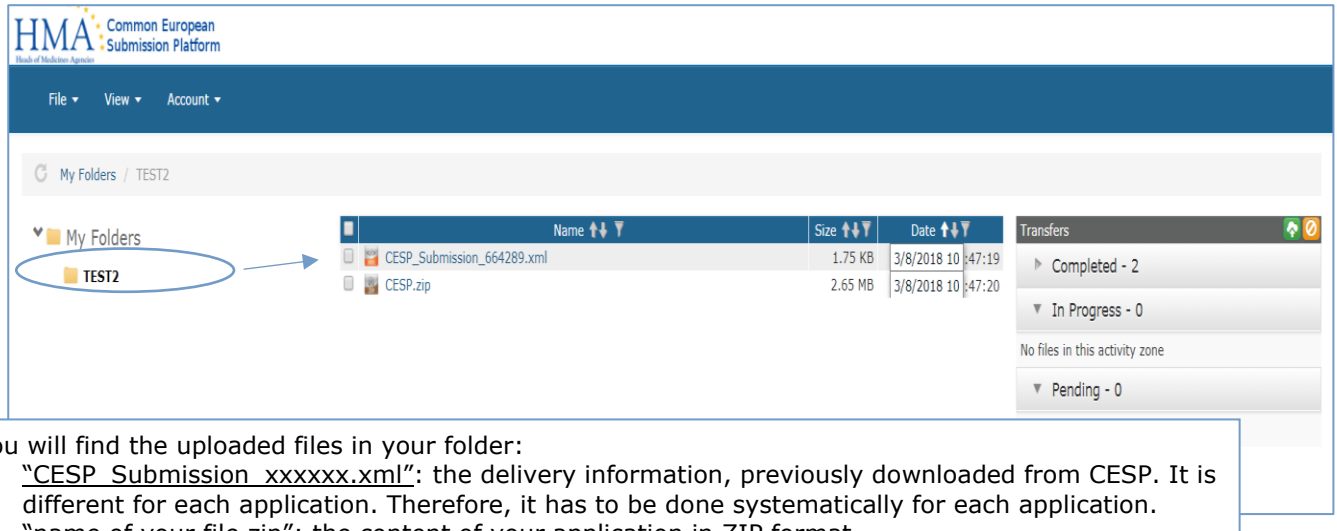
- Select "file" and "upload", select the file that you want to upload.
- Select the file that is saved on your computer and slide it into the webpage.

You can create several folders for each application.

Transferred files are detailed as:

- completed upload;
- upload in progress;
- pending upload.

**Important note**: 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, previously downloaded from CESP. It is different for each application. Therefore, it has to be done systematically for each application.
- "name of your file.zip": the content of your application in ZIP format.

Important

- Reminder: first upload your dossier in ZIP format on the website. When fully uploaded, 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.

### 11.3. Training and support

- An On Demand Training module is available for all CESP users. It contains the Latest Video Guides and Training documentation.
- The FAQ answers the most common questions on CESP.
- Support: the CESP Group can provide support to authorised users during normal working hours from Monday to Friday (not on public holidays). Contact details for the CESP Group support are available on the Portal.