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Federal Agency for Medicines and Health Products

DG pré
Division R&D

YOUR LETTER FROM
YOUR REF.

OUR REF. FAMHP/R&D
DATE

ANNEX

CONTACT
TEL. 02/524.80.00
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Circular n° 575
To the attention of sponsors of clinical trials

SUBJECT Applications for clinical trials and submissions of substantial amendments-new version of the detailed guidance 'CT1'

This document is a translation of the official and signed versions in Dutch and French

Dear Madame,
Dear Sir,

This document is intended to update information about submission of applications for clinical trials, notification of substantial amendments and declarations of end of trials to competent authority in Belgium (named FAMHP) following the publication of the new version of the « Detailed guidance on the request to the competent authorities for authorization 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 »[1] (hereafter called CT1 or detailed guidance) in the Official Journal of the European Union of 30th March 2010.

This document clarifies the implementation by the Belgian competent authority of the new version of the guidance CT1.
This document is neither a translation nor an explanation of the entire guidance. Indeed, some aspects are clearly presented in the detailed guidance and do not need further explanations; others concern the Ehics Committee. Both documents (the guidance CT1 and the present circular) must be taken into consideration

From now on this new circular supersedes circulars 493 and 528. However, a transition period is foreseen until 31 January 2011.

Both the detailed guidance and the present circular concern 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[2]. Please also refer to regulation 1394/2007 on advanced therapy medicinal products[3].

1 http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm
2 http://ec.europa.eu/health/files/eudralex/vol-10/v10_chap5_qa_v7.pdf
3 http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF

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APPLICATIONS FOR CLINICAL TRIALS

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. The procedure also foresees a clock-stop system not exceeding one month upon notification of major comments 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[4]), 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:

- **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).**
- 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).
- 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 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

- The following documents are no longer required when submitting a CTA file to the Federal Agency for Medicines and Health Products (FAMHP):
    - The sponsor's letter authorizing the applicant to act on his behalf
    - The Proof of receipt of the EudraCT number
    - The list of the on-going clinical trials with the same Investigational Medicinal Product (IMP)

- 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)

- The file must be submitted electronically. 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.

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)

In accordance with the new version of the CT1 new points should also appear in the cover letter:

- 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 protocol, IB or any other document where the reference security information can be found in the CTA file in order to facilitate the evaluation when a side effect is a SUSAR (Suspected Unexpected Serious Adverse Reaction).
- 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[5]?
- 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.

Protocol:

- The protocol must be accompanied by a summary of the protocol. This summary can be a separate document and written in English (or in one of the national languages). The absence of this summary will be considered as a major deficiency for validation of the CTA file.
- The different points of the detailed guidance concerning the protocol must be taken into account (e.g. definition of the end of trial...)

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).

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

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 simplified IMPD is mentioned in point 87 table 1 of the detailed guidance.
- 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.

Additional documents:

- The content of the label for each IMP (**a concrete example is no longer required**).
- The copy of the approval of the leading Ethics Committee (hereafter referred as EC) if it is available at the moment of the submission. If not, the applicant must submit this approval as soon as available.
- 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 included 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).

AMENDMENTS

Substantial amendments:

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, awaiting a modification of the Belgian law related to fees for clinical trials, 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 to CT1 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.

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 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). However, the validation date is always the date of receipt of the substantial amendment and the corresponding payment (T0= date of CoR email).

Ethics Committee

- The substantial amendments concerning the investigator are evaluated by the EC (e.g. change of an investigator).
- The substantial amendments concerning Clinical Investigation sites are evaluated by the EC (e.g. adding a site): upon modification of the legislation related to fees for clinical trials this change shall not longer be submitted to FAMHP. However 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.

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) 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 FAHMPS.
- These two documents (ASR + update of the IB) should be submitted exclusively on CD-ROM. Only the cover letter needs to be submitted in paper format.
- 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.

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.

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.

ADDRESS WHERE TO SUBMIT CTA APPLICATIONS AND AMENDMENTS

Federal Agency for Medicinal and Health Products
Division Research and Development
To the attention of Kristof Bonnarens
Eurostation Building, 8th floor
Victor Horta Place 40 box 40
1060 Brussels

- **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):

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.

LABELING OF MEDICINAL PRODUCTS FOR CLINICAL TRIALS

General rule:

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

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.

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.

DECLARATION OF THE QUALIFIED PERSON

You will find in Annex 3 an example of a declaration form to be completed by the European Qualified Person of the importer in the case of medicinal products manufactured outside EU / EEA. This is an example: the form may vary but the content shown in annex 3 must appear on the statement.

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

Annex 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: Belgian marketing authorization missing
- GMP: "Declaration of GMP compliance" of the EU qualified person missing for IMPs manufactured in a third country, or incomplete (see annex 3)
- GMP: "Declaration of GMP status" for biological substance missing
- 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 543)

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

Annex 2

1. GENERAL REMARKS

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

From now on only electronic submissions will be considered.
During the transition period, and until 28/02/2011, the submission may be performed electronically or on paper. However it is strongly advised to submit as from now on the entire file electronically.

2. SUPPORT

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.

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.

4. NAMES OF 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

Annex 3

QUALIFIED PERSON DECLARATION
CONCERNING INVESTIGATIONAL MEDICINAL PRODUCTS
MANUFACTURED IN THIRD COUNTRIES.

THIS MUST BE PROVIDED IN SUPPORT OF A
REQUEST FOR AUTHORISATION OF A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE WHERE THE PRODUCT IS IMPORTED FROM OUTSIDE THE EEA.

MANUFACTURING AUTHORISATION NUMBER – under which product(s) are to be imported.....

INVESTIGATIONAL MEDICINAL PRODUCT(s) .....

SITE(S) OF MANUFACTURE OUTSIDE THE EEA
(Please list others on a separate sheet if more than 2 manufacturing sites are involved)
1.....
.....
.....
Activities carried out at this site.....

2.....
.....
.....
Activities carried out at this site.....

I certify that I am a EU Qualified Person and that the Investigational Medicinal Product(s) imported into the EU/EEA and used in this clinical trial, has/have been/will be manufactured at the named site(s) in accordance with standards of Good Manufacturing Practice equivalent to those applied in the EU

Signature.....

Name .....

Date.....