THIS IS AN UNOFFICIAL TRANSLATION OF CIRCULAR LETTER XXX PUBLISHED IN DUTCH / FRENCH.

Dear Madame,
Dear Sir,

This document is intended to update information about submission of applications for clinical trials, 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 new circular supersedes circulars 493 and 528 as from 1st November 2010.

APPLICATIONS FOR CLINICAL TRIALS

General remarks

- The processing time for authorizing applications for clinical trials (Clinical Trial applications-CTA) is 15 days (mono-centric phases 1) or 28 days (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, submission of a CTA or an amendment is only acceptable if the two following conditions are met:
  1° the R&D division has received the dossier
  AND
  2° the corresponding fee has been paid (as confirmed by the bank to the R&D division)[2].

  For non commercial studies, no fee is required.

  As soon as these conditions are met (dossier + payment for commercial studies; dossier alone for non-commercial studies), the administrative service of the R&D division sends an email to the applicant to notify the confirmation of receipt (CoR email).

- The period to validate a CTA dossier remains three days.

[1] http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm
[2] http://www.fagg-afmps.be/en/human_use/medicines/Medicines/research_development/clinical_trials/index.jsp

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During the validation period, three situations may therefore occur:

1) The application is complete: An email is sent by a R&D file manager to the applicant in order to notify the starting date (T0) for the treatment/evaluation of the application. In this case, the T0 will 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 application is incomplete but the shortcomings are considered as minor (see Annex 1: minor shortcomings for validation). An email is sent by a R&D file manager to the applicant:

- to notify the starting date (T0) for the treatment/evaluation of the application.

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 this case the start date (T0) is thus the day of sending of the validation email by the file manager and not necessarily the date of confirmation of reception of the dossier.

3) The application is incomplete and the shortcomings 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 dossier 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,

- The following documents are no longer required when submitting a CTA dossier to the Federal Agency for Medicinal products 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 dossier 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) or the protocol, then the legal period starts again (new T0)

- As from 1st January 2011 the dossier shall be submitted electronically. Only the cover letter is to be submitted in hard copy together with a CD-ROM containing the CTA dossier 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 letter:

- EudraCT number
- Trial Title
- Protocol Number

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- Specific features of the trial where appropriate (e.g. unusual and particular IMP's such as GMOs, trial with unusual design)
- Trial with special population (if applicable)
- First 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 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.
- The place where the reference security information is put in the dossier CTA to facilitate the evaluation when a side effect is a SUSAR (Suspected Unexpected Serious Adverse Reaction).
- In the case of a letter of re-submission, the changes compared with the previous submission must be highlighted

To facilitate and accelerate the validation of the dossier we recommend to mention the following information in the letter, if applicable:

- Manufacturing sites in Belgium: which operations and where?
- NIMP(s): which ones and why the sponsor considers them as NIMPs?
- Other trials in Belgium (in progress or not) with the same IMP (with mention of the correspondent EudraCT numbers)
- Exploratory trial
- Labeling: application for a waiver if applicable (see end of this circular) or a reminder of the waiver obtained for Phase 1 units.
- Responses to possible minor objections formulated at the occasion of the approval of a precedent application with the same IMP: if present in the dossier
- 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. The absence of this summary will be considered as a major deficiency for validation of the dossier.

Investigator's Brochure:

- 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 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).

Investigational Medicinal Product Dossier:

- 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).

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- 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 and if it is manufactured in the EU.
- 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 submitted 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 principal Ethics Committee (hereafter referred as EC) if it is available (unless the EC informed the applicant that it has itself sent a copy of its opinion to the FAMHP).
- A copy of any scientific advice on any aspect of the dossier, 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).
- Proof of payment of the fee.

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 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 the modification of the Belgian law related to fees for clinical trials, the fee must still be paid to both the EC **AND** the FAMHP. We also ask the applicant to continue to send the notification form of an SA (Substantial Amendment Notification Form) to the FAMHP in order to make the link between the modification and the payment.
- The purpose of clarifications to CT1 concerning the amendments is clearly to avoid excessive submission of substantial amendments.
- SA is defined as having an impact on patient safety and / or changing the interpretation of the scientific data.

Competent authority

- The updated XML file must be provided for each submission of a SA, even if no changes are made to this document compared with the previous submission.
- Each amendment shall be designated by a reference number corresponding only to this amendment and which allows to distinguish it clearly from other changes in the dossier.
- An AS can contain multiple changes.
- If the modification affects multiple trials of the same sponsor with the same IMP, only one documentation needs to be submitted to the FAMHP (only one European application form

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and a single copy of the supporting documentation). However a payment must be made for each EudraCT number.
- The processing time of a SA 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 SA and the corresponding payment (T0= date of CoR email).

Ethics Committee

- SA's concerning the investigator are evaluated by the EC.
- SA's concerning Clinical Investigation sites are evaluated by the EC (e.g. adding a 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 next SA. The EC is therefore the single point of contact for keeping the correct information concerning the participating sites in Belgium.
- SA's relating to the informed consent are assessed by the EC.

Non-substantial Amendments

- Non-substantial amendments should be registered (not submitted) and added to the documentation submitted with the following SA (and not submitted any more at the same time as the annual update of the IB). The sponsor is responsible for the decision to submit an amendment to the CTA documentation as a SA or not. It is a decision on case-by-case basis. Examples of SA's 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 SA (but if data require a substantial change in the CTA documentation, a SA should be submitted accordingly).
- The submission of the updated IB is not considered as a SA (but if data require a substantial change in the CTA documentation, a SA should be submitted accordingly).
- 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 is not an SA 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 SA. If the sponsor believes that the time before the next SA submission might be too long, it is its responsibility to provide the information separately to 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 an SA 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 of the EC and / or if no motivated objections have been raised by 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.

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End of a clinical trial:

- The Declaration of End of Trial Form should only be submitted to FAMHP when the trial is completed in all countries concerned.

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The following reminders (described in circulars 493 and 528) remain applicable :

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

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

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

Labeling of medicinal products for clinical trials

General rule:

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

Exceptions:

1) NIMPs:

- For medicinal products authorized in Belgium, manufactured and used in accordance with their authorization: no specific labeling
- For unauthorized medicinal products or authorized medicinal products, modified from their authorization or used in an unapproved indication: general rule

2) Medicinal products used in commercial clinical trials:

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

- Phase 1 units: a general waiver can be obtained if the IMP is 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 letter of the CTA.
- Other phases: the general rule is applied unless these 4 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 the case of multinational trials, no exceptions will be accepted, the system of the booklet allowing to solve this type of difficulty.

In any case, if the subjects also 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.

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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" missing for biological substance
- GMP: "Declaration of GMP status" missing 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 circulars 472 and 515)

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: not complying

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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 2/1/2012 only electronic submissions will be considered.
During the transition period, and until 01/01/2012, the submission may be performed electronically or on paper. However it is strongly advised to submit as from now on the entire dossier 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 Amendment European Form.

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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) When the document refers to a particular medicinal product (investigational medicinal product or authorized medicinal product) we ask you to add the name of the medicinal product in the filename.
Example: EudraCT Number_ Manufacturing_Authorisation_Name of the medicinal product.pdf

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Hereafter list of file names (non exhaustive) .

Initial dossiers

INFORMATION	NAME OF THE PDF FILE
Cover letter	Covering_Letter.pdf
Application form (PDF) 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 authorizations	Importers_Authorization.pdf
Viral safety studies	Viral_Study.pdf
TSE certificates	Tse_Certificate.pdf
Labeling examples in the national languages	Labels.pdf

Amendments

INFORMATION	NAME OF THE PDF FILE
Covering letter	Covering_Letter.pdf
Amendment application form (PDF) Amendment application form (XML) Signature	Amendment_Application_Form.pdf Amendment_Application_Form.xml Amendment_Application_Form_Signature.pdf
List of the modified documents	*See previous table*
Application form (PDF) Application form (XML) Signature	Application_Form.pdf Application_Form.xml Application_Form_Signature.pdf

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