Substantial amendments

An amendment is considered as substantial if the modification has a significant impact on:

- Security or physical or mental integrity of the subject
- Scientific value of the trial
- Organization and execution manner of the trial
- Quality and security of each IMP used in the trial

Annex 5 of '*Detailed guidance for the request for authorization of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial.*' Describes general situations that lead to substantial amendments.

→ Annex 1 of the present document gives a list of substantial and non-substantial amendments. However, this list is not limitative.

In Belgium, the legal framework shares out competencies related to clinical trials between the Competent Authority (CA) and the Leading Ethics Committee (LEC). The CA is competent for giving an advice on the elements related to the quality data and the pre-clinical data of the medicinal product for clinical trial. The LEC gives an advice on the other points of the dossier.

→ A substantial amendment has always to be submitted both to the CA and to the LEC. It is however possible that some modifications have only to be approved by the LEC (and are only sent to the CA for notification) and conversely.

Non-substantial amendments

The substantial amendments not related to the protocol shall not be submitted to the CA and the LEC. However, they have to be listed and incorporated the Investigator Brochure (IB) at the time of its annual update. The updated IB has to be sent annually to the CA and the LEC. The list of the non substantial amendments has also to be available on demand on the investigation site and by the promotor. The classification of an amendment as non-substantial remains promoter's responsibility.

Procedure

Submission

The following points have to be considered:

- An amendment (for LEC, for CA or for both) has always to be submitted in parallel to the LEC and the CA.

- Each amendment has to be identified with a reference number that only corresponds to this amendment and allows a clear distinction from the other modifications.

- The dossier must contain the following documents:

    - An appended letter with a description of the amendment (included the eudra-CT number (2), the protocol number, the title of the trial, the amendment code and the date) and the reasons of the submission of this amendment. The appended letter has to contain any information not mentioned in the "European amendment form" and could have an impact on the risk to which the participants of the trial are exposed.

    - The "European amendment form": (http://eudract.emea.europa.eu/document.html);

    - The modified documents/an overview of the modifications in a table (before/after)/the information that justifies the amendment (ex: if applicable: a summary of the data, the updated risks/benefit assessment, possible consequences for the already involved patients in the trial, possible consequences for the assessment of the trial results)

    - The "European application form" in paper version and electronic XML format in case of modification of the original form.

- It is very important to correctly complete the "European amendment form":

    - For a substantial amendment only for the CA (see annex 1), sections A.2 and A.4.2 will be ticked;
    - For a substantial amendment only for the LEC (see annex 1), sections A.3 and A.4.1 will be ticked;
    - For several modifications that have to be authorized both by the LEC and the CA, sections A.2 and A.3 will be ticked ;
    - Sections related to the promoter, the original dossier and the amendment have to be rigorously completed.

- When the amendment concerns several clinical trials in which the same medicinal product is used, the promoter may submit only one dossier to the CA and the LEC. However, the appended letter has to contain a list of all the concerned trials, included the corresponding eudra-CT numbers and the corresponding amendment codes.

- When **urgent security measures** are necessary to protect patients, these measures can be taken immediately. However, in every case, the promoter has to warn the CA and the LEC as soon as possible. Moreover, in the following 15 calendar days, it's essential that the promoter should submit a substantial amendment with a description of the events, the taken measures and the action plan.

- A change of the LEC may not be communicated with a substantial amendment. The consequence of this change is a new submission of the dossier with the same eudra-CT number followed by a letter A, B, C, … as it is a re-submission. This dossier will thus again in parallel to the LEC and the CA.

- The submission of an amendment before the approval of the original dossier will not be accepted.

Review

An amendment will be reviewed in the same dead line as for the original dossier.

Implementation of the modification

The amendment may only be implemented if the CA has not formulated motivated objections against this substantial modification at the end of the legal delay. If the approbation of the LEC is necessary, the modification can only be implemented if this authorization has been received.

---

(1) The term "notification", as mentioned in annex 5 of the 'Detailed guidance for the request for authorization of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial', corresponds to the term "submission" as mentioned in the present document and can absolutely not be considered as a « notification » as we mention it in the text above.

(2) As a new eudra-CT number has to be asked for every new clinical trial, amendments submitted for a clinical trial have to use the same eudra-CT number as for the original trial. In consequences, amendments related to trials submitted before the law of 7 May 2004 have no eudra-CT number, as the original trials. The above-mentioned procedure is thus not applicable for this kind of amendment. Amendments related to trials authorized by an EC before 7 May 2004 have to be sent by the applicant only for notification to the R&D department.

ANNEX 1

List of substantial and non-substantial amendments (non restrictive list)

1) Substantial amendments for CA and LEC

- Each modification of the contact data of the promoter, applicant or legal representative. As soon as this amendment is implemented, these new data have to be mentioned in all documents related to the trial. Documents which are already on the investigation site (as inform consent, labeling, etc…) have not to be amended;
- Change of promoter or legal representative (e.g.: transfer of responsibilities from the promoter to another person or organization);
- Change of the (or one of the) investigation center(s) or adding of new investigation centers;
- Modification of the IB if there is a modification of the risks/benefits ratio;
- Substantial modifications of the non-clinical pharmacology and toxicological data When the assessment of the risks/benefit ratio is modified by:
  - Results of new pharmacological tests;
  - New interpretation of existing pharmacological tests;
  - New toxicological tests;
  - New interpretation of existing toxicological tests;
  - Results of new interaction tests;

2) Substantial amendments for the CA

- Modifications related to the IMP:

  - Modification related to import of an IMP (e.g.: change of the import site)
  - Change of name or code of an IMP (e.g.: change of the company code to an INN or a trade mark during the trial: modification of labeling)
  - Change of primary packaging material;
  - Change of manufacturer(s) of an active substance (AS): e.g.: change to a new manufacturer;
  - Change of the manufacturing process of an AS: e.g.:
    - Modified synthesis ways (in the final steps of synthesis);
    - Supplementary impurities or new impurities (e.g.: widening of the acceptance criteria for individual impurities has to be justified from toxicological point of view);
    - Modification of physicochemical properties with influence on the quality of the IMP (e.g.: distribution of particle height, polymorphism, etc…);

- Modification of AS spécifications: e.g:
  - Widening of acceptance criteria;
  - Deletion of tests related to quality control of the AS;
- Modification of manufacturing of an IMP;
- Modification of (release or end of shelf life) specifications of an IMP:
  - Widening of the acceptance criteria with clinical pertinence (e.g.: change of hardness of the IMP with influence on disintegration and of in-vitro dissolution);
  - Deletion of tests related to quality control of the IMP;
  - Modification of excipients specifications with a change in the medicinal product activity, e.g. modification of particle height with influence on in-vitro dissolution;
  - Modification in the IMP formulation:
    E.g.: modification of IMP composition (included change of excipients by others with same functional characteristics);
  - Modification control procedures of an AS: e.g.: replacement of an existing procedure by a new one;
  - Modification control procedures of an IMP;
  - Modification control procedures of an excipient not described in the pharmacopoeia;
  - Reduction of the shelf life (including after first opening and reconstitution);
  - Modification (e.g.: restriction) of keeping conditions of the AS of the IMP;
  - Modification of reconstitution procedure and/of administration of the IMP;
  - Canceling of temporary suspension of the marketing authorization (MA) of the IMP or substantial modifications of this MA.

Remark:

Each amendment related to an IMP and that leads to a new potential risk for the patient/subject must be considered as a substantial amendment. That is the case for modifications related to impurities, microbial contamination, viral security, BSE and for modification of the IMP stability in particular when toxic degradation products can be formed.

3) Substantial modifications for LEC

- Substantial modifications of clinical data

When the assessment of the risks/benefits ratio is modified by:

- Security problems related during trials with the same IMP;
- Results of new clinical pharmacology tests;
- New interpretation of existing clinical pharmacology tests;
- Results of new clinical trials;
- New interpretation of existing data further to clinical trials.

- Protocol modifications:

    - Trial objective;
    - Trial subject;
    - Informed consent;
    - Recruitment procedure;
    - Measure of efficacy of the investigational medicinal product;
    - Samples scheme (e.g.: additional blood samplings for security reasons or to measure the efficacy, new sampling rules for pharmacokinetic data);
    - Adding or change of tests or measures (e.g.: introduction of new monitoring procedures; new measures for determination of primary end of trial);
    - Number of participants to the trial;
    - Reduction of number of visits of the patients to the investigator;
    - Category of age of participants;
    - Inclusion criteria;
    - Exclusion criteria;
    - New definition of the high risk group;
    - Safety monitoring;
    - Duration of exposition to the investigational medicinal product (e.g.: continuation of treatment after the end of the trial);
    - Modification of the administrated dose for investigation (e.g.: upgrading of maximum tolerated dose);
    - End of the phase 1 part of a trial with definition of the recommended dose for the phase 2 part;
    - Extension of the duration of the blinded treatment;
    - Modification of comparator;
    - Statistical analysis;
    - Modification of the reconstitution procedure and/of administration of the IMP;
    - Addition of an open label extension of the trial;
    - Addition of optional pharmacogenetics;
    - Motivation material for patients;
    - New training material for self-administration of medicinal product.
    -

- Modification of the Investigation Brochure:

    - Each modification of the IB that changes the security profile of the IMP in such a way that pharmacovigilance reports are modified;
    - Modification of the IB leading to a modification of the inform consent;

- Modifications of the trial arrangements:

    - Change of the principal investigator or adding of new ones (even in an already approved site);
    - Change of the coordinating investigator;
    - Modification of the principal tasks allocated to the CRO;
    - Change of the definition of the end of the trial.

4) Non-substantial amendments

- Modifications related to the IMP:

    - Replacement of primary packaging material by an alternative packaging already mentioned in the IMPD;
    - Use of a new manufacturer of the AS within the same mother company and without change of specifications;
    - Change of manufacturing process of the AS: e.g.:
        - Modification of the first synthesis steps (prior to the starting GMP material);
        - Modification of process parameters without modification of the synthesis process and of the reagents;
        - Manufacturing on a higher scale on condition that specifications of the AS are not widened.
    - Modification of test procedures of the AS of the IMP: e.g.: variations on existing test procedures and already described in a precedent IMP. The new test conditions have to be validated and have to produce comparable or superior validation results. In the opposite case, the modification must be considered as a substantial amendment;
    - Modification of manufacturing of an IMP: e.g.:
        - Modification of process if the manufacturing process remains unchanged;
        - Manufacturing on a higher scale on condition that specifications of the IMP are not widened.
    - Narrowing of the acceptance criteria (release and end of shelf life) in the specifications of the IMP;
    - Extension of shelf life and/of extension of keeping conditions based on supplementary data on condition that shelf life specifications are not modified.
    - Modification of IMP formulation: e.g.:
        - Non functional coatings of tablets with identical qualitative composition but with a different quantitative composition;
        - Modification of shape of immediate liberation tablets.

- Other changes:

    - Deletion of typing errors;
    - Administrative changes (e.g.: change of name or address of the manufacturer of the IMP);
    - Minor clarifications in protocol;
    - Update of IB (except if there is a modification of the assessment of the risks/benefit ratio);
    - Modification of documentation used for data collection (e.g.: case report file);
    - Communication of a FDA approval.

Remark:
The list of substantial and non-substantial amendments describes the most important amendments and the most frequent amendments. For amendments to clinical trials not described in the above-mentioned list and for which there could be hesitations on the amendment nature, the modification should be considered as substantial. In such cases, the applicant/promoter of the clinical trial can always ask the opinion of the R&D department of the Federal Agency for Medicinal Products and Health Products via the general e-mail address: ct.rd@fagg-afmps.be.