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Detailed guidance for the request for authorisation 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

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1 Legal Basis

Article 9.8 of the Directive 2001/20/EC[1] requires the Commission, in consultation with Member States, to draw up and publish detailed guidance on:

(a) the format and contents of the request to conduct a clinical trial on a medicinal product for human use as well as the documentation to be submitted to support that request on the quality and manufacture of the investigational medicinal product, any toxicological and pharmacological tests, the protocol and clinical information on the investigational medicinal product including the investigator's brochure;
(b) the presentation and content of notifications of substantial proposed amendments to the protocol;
(c) the declaration of the end of the clinical trial.

The Directive 2001/20/EC, the Directive, should be read in conjunction with this detailed guidance, Commission Directive 2005/28/EC[2] and other Commission Directives and detailed guidance on the Directive as well as the Member States implementing legislation.

2 Scope

This detailed guidance is intended to provide advice on the application format and contents of a request to the competent authority (CA) in any EU Member State for:

- Authorisation of a clinical trial on a medicinal product for human use;
- Notifications of substantial proposed amendments; and
- Declaration of the end of the clinical trial.

Directive 2001/20/EC applies to all investigational medicinal products, including the following types of product:

- Chemical entities;
- Biotechnology products;
- Cell therapy products;
- Gene therapy products;
- Plasma derived products;
- Other extractive products;
- Immunological medicinal products (such as: vaccines, allergens, immune sera);

[1] OJ L 121, 1.5.2001 p.24

[2] OJ L 91, 9.4.2005, p.13

- Herbal medicinal products;
- Radiopharmaceutical products; and
- Homeopathic products.

This detailed guidance should be followed unless it is otherwise justified in an application to the CA of the Member State in which the trial will take place**.**

3 Definitions

The definitions of Directive 2001/20/EC are applicable. An authorisation of a clinical trial by the competent authority of a Member State will be a Clinical Trial Authorisation (CTA) and will only be valid for a clinical trial conducted in that Member State. This authorisation does not imply approval of the development programme of the tested IMP.

Article 2(d) of the Directive defines an "investigational medicinal product" as:

"A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form."

Some clinical trial protocols require the use of non-investigational medicinal products (NIMPs) such as support or escape medication for preventive, diagnostic or therapeutic reasons and/or needed to ensure that adequate medical care is provided for the subject. They may also be used in accordance with the protocol to induce a physiological response. These products do not fall within the definition of investigational medicinal products in the Directive and may be supplied by the sponsor. The sponsor should provide details of these NIMPs and their proposed use in the trial protocol and ensure that they are of the necessary quality for human use after seeking advice and/or involvement of a Qualified Person where appropriate.

4 Format and content of applications and notifications

4.1 Request for a clinical trial authorisation

According to Article 9(2) of the Directive the applicant must submit a valid request for authorisation to the competent authority. When relevant, the sponsor should check the language requirements with the concerned competent authority before preparing the application. If the applicant is not the sponsor, they should enclose a letter from the sponsor authorising the applicant to act on their behalf[3]. The list in attachment 1 indicates the general information and Member State specific information to be submitted as part of a valid

[3] Article 7 of Directive 2005/28/EC

application. If an application is not valid the CA will inform the applicant and give the reasons. The sponsor should provide the CA with a list of competent authorities to which they have already made the same application with details of their decisions and those of the concerned ethics committees as an attachment to the covering letter.

The sponsor should provide the concerned CA with a copy of the concerned ethics committee opinion, whether he has submitted the application in parallel or in sequence, as soon as it is available unless the ethics committee informs him that they have copied their opinion to the concerned MS CA.

Unexpected events or additional information may require the sponsor to withdraw a request for authorisation before the CA has reached its decision about authorisation. The sponsor or his legal representative should inform the concerned MS CA(s) as soon as he becomes aware that he intends to withdraw the application. The initial contact should be by telephone, fax or e-mail and include the EudraCT number and other trial identification and be followed as soon as possible by a formal letter of withdrawal providing a brief description of the reasons.

If the sponsor wishes to resubmit the application, he must identify the application as a resubmission in the covering letter and by using a resubmission letter. This is the initial Eudract number with a letter after the number sequence: A for 1st resubmission, B for second resubmission, etc…..

The sponsor should make applications to fulfil other requirements that relate to clinical trials with IMPs where applicable. For example if the IMP is a genetically modified micro-organism (GMO) it may be necessary to obtain permission for its contained use or deliberate release in accordance with Directives 90/219/EC[4] and/or Directive 2001/18/EC[5] from the relevant competent authority in the MS concerned.

4.1.1 Covering Letter

The applicant should submit and sign a covering letter with the application. Its heading should contain the EudraCT number and the sponsor protocol number with a title of the trial. The text should draw attention to any special issues related to the application such as special trial populations, first administration of a new active substance to humans, unusual investigational medicinal products (IMPs), unusual trial designs etc. and indicate where the relevant information is in

[4] Directive 90/219/EC as amended by Directive 98/81/EC on the contained use of genetically modified organisms (GMOs)

[5] Directive 2001/18/EC of the European Parliament and of the council of 12 march 2001 on the deliberate release into the Environment of genetically modified organisms and repealing Council Directive 90/220/EEC 31 May 2001.

the application. The covering letter should draw attention to particular IMP's: GMO's, radiopharmaceuticals etc.

In addition, it should draw attention to any scientific advice related to the trial or IMP given by the EMEA or concerned MS or the competent authority of any other country and indicate where in the application an assessor can find a copy of the advice.

4.1.2 Allocation of the EudraCT number

Before submitting an application to the CA, the sponsor should obtain a unique EudraCT number from the EudraCT database by the procedure described in the detailed guidance on the European clinical trials database[6]. This number will identify the protocol for a trial whether conducted at a single site or at multiple sites in one or more member states. To obtain the EudraCT number automatically from the database the applicant will need to provide a few items of information. They will need to complete all the relevant parts of the form before submitting an application to the CA.

4.1.3 Application form

The application form can be accessed via the internet by the procedure described in Commission detailed guidance on the EudraCT database. Annex 1 of this guidance note shows the information required to complete the form. The application form should uniquely identify the clinical trial and the organisations and key individuals responsible for the conduct of the trial. Some of the information in the form, such as contact person and name of the investigator will be relevant in one Member State only. The applicant should print the completed form, sign and date it, and send it as part of the application to the CA of each Member State where he intends to conduct the trial. The applicant's signature will confirm that the sponsor is satisfied that, a) the information provided is complete, b) the attached documents contain an accurate account of the information available, c) in their opinion it is reasonable for the proposed clinical trial to be undertaken, and d) any information provided to both the CA and the ethics committee concerned is based on the same data. The sponsor should save the core data set or the full application form data set, according to national requirements as an XML file using the utilities feature linked to the form on its webpage and send a copy of this XML file, on a disk, with the application.

An applicant may request an electronic (XML) copy of the application form data that the concerned CA of the Member State enters into the EudraCT database (see C.1.5.1 of the application form). If requested it will be sent electronically as an XML file to up to five e-mail addresses (specified by the applicant in section C.1.5.1). If the applicant requires the

[6] Detailed guidance on the European clinical trials database (EudraCT Database)

transmission to be password protected he will need to set up a Eudralink account (see www.eudract.emea.eu.int for details). If he does not require a password protected transmission the XML file will be transmitted by less secure links. To change the instructions to the CA for this feedback the applicant should submit a Notification of Amendment (Annex 2) with the new information in Section I, and a revised application form XML file containing the new email addresses (and/or with those no longer required omitted). These requests will only have effect prospectively from the time the XML in question is entered into the database by the Competent Authority concerned.

4.1.4 Protocol

The content and format of the protocol should comply with the guidance in the Community guideline on Good Clinical Practice (CPMP/ICH/135/95). The version submitted should include all currently authorised amendments and a definition of the end of the trial. It should be identified by the title, a sponsor's code number specific for all versions of it, a number and date of version that will be updated when it is amended, and by any short title or name assigned to it, and be signed by the sponsor and principal investigator (or co-ordinating investigator for multicentre trials).

Among other things, it should include:

- The evaluation of the anticipated benefits and risks as required in Article 3(2)(a) of the Directive;
- A justification for including subjects who are incapable of giving informed consent or other special populations; and
- A description of the plan for the provision of any additional care of the subjects once their participation in the trial has ended, where it differs from what is normally expected according to the subject's medical condition.

A protocol may include a sub-study to be conducted at all trial sites or only at specific sites. The covering letter should draw attention to any sub-studies and information should be provided in Section F.2 of the application form and all other applicable sections and supporting documents.

4.1.5 Investigator's Brochure

The content, format and procedures for updating the Investigator's Brochure (IB) should comply with Article 8 of Directive 2005/28/EC and the Community guideline on Good Clinical Practice (CPMP/ICH/135/95). It should be prepared from all available information and evidence that supports the rationale for the proposed clinical trial and the safe use of the investigational medicinal product (IMP) in the trial and be presented in the format of summaries.

The approved Summary of Product Characteristics (SmPC) will replace the IB if the IMP is authorised in any MS, and it is used according to the terms of the marketing authorisation. But

when the conditions of use in the CT differ from those authorised, the SmPC should be complemented with a summary of relevant non-clinical and clinical data that support the use of the IMP in the clinical trial. When the IMP is identified in the protocol only by its active substance, the sponsor should elect one SPC as equivalent to the IB for all medicinal products that contain that active substance and are used at any clinical trial site.

For an international trial where the medicinal product to be used in each member state is the one authorised at a national level and the SmPC varies among member states, the sponsor should chose one SmPC to replace the IB for the whole CT.

The current IB or equivalent document (e.g. SPC for marketed products) will be the reference document for the assessment of the expectedness of any adverse reaction that might occur during the clinical trial.

4.1.6 Investigational Medicinal Product (IMP) Related Data

The information and data required to support the quality of the IMP should be provided in the following documents:

- Investigator's brochure (see 4.1.5);
- Investigational Medicinal Product Dossier (IMPD) (see 4.1.6.1);
- Simplified IMPD for known products (see table 1) (see 4.1.6.2);
- Summary of Product Characteristics (SmPC) (for products with a marketing authorisation in the Community) (see 4.1.6.2.2);
- Examples of the label in the national language;
- A copy of the manufacturing authorisation referred to in Article 13(1) of the Directive stating the scope of the authorisation, if the IMP is manufactured in the EU and does not have a marketing authorisation in the EU;
- If the IMP is not manufactured in the EU and does not have a marketing authorisation in the EU,
  - Certification of the Qualified Person (QP) that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality;
  - Certification of the GMP status of any active biological substance;
  - Copy of the importer's manufacturing authorisation as referred to in Article13(1) of the Directive;

And where applicable:

- Certificate of analysis in exceptional cases where impurities are not justified by the specification or when unexpected impurities (not covered by the specification) are detected;
- Viral safety studies and data; and

- TSE Certificate.

The IMPD should give information to justify the quality of any IMP to be used in the clinical trial, including reference products and placebos. It should also provide data from non-clinical studies and the previous clinical use of the IMP or justify in the application why information is not provided. Some Member States may require other information (see attachment 1, Member State Specific Information).

The applicant may either provide a stand alone IMPD or cross-refer to the IB for the pre-clinical and clinical parts of the IMPD. In the latter case, the summaries of pre-clinical information and clinical information should include data, preferably in tables, providing sufficient detail to allow assessors to reach a decision about the potential toxicity of the IMP and the safety of its use in the proposed trial. If there is some special aspect of the pre-clinical data or clinical data that requires a detailed expert explanation or discussion beyond what would usually be included in the IB, the sponsor should submit the pre-clinical and clinical information as part of the IMP dossier.

4.1.6.1 Investigational Medicinal Product Dossier (IMPD)

This section indicates the type of scientific information that is required for an IMPD and how it should be presented. The sponsor should submit an IMPD when they have not previously submitted any information about that chemical or biological product to the competent authority concerned and cannot cross-refer to information submitted by another sponsor. For instance, when the sponsor does not have a marketing authorisation for the IMP in any MS of the Community and the CA concerned has not granted them a CTA previously and they cannot cross-refer to the relevant information in another sponsor's application for the same product.

An IMPD should include summaries of information related to the quality, manufacture and control of the IMP, data from non-clinical studies and from its clinical use. It is preferable to present data in tabular form accompanied by the briefest narrative highlighting the main salient points. The dossier should not generally be a large document, however for trials with certain types of IMP exceptions can be agreed with the Member State(s) concerned.

Sponsors should preface the IMPD with a detailed table of contents and a glossary of terms. Where possible data should be provided under the headings and arranged in the order given in The Rules Governing Medicinal Products in the European Union Volume 2, Notice to Applicants Volume 2B Presentation and Content of the Dossier, Common Technical Document which can be accessed at the Commission website

www.pharmacos.eudra.org. The headings are not mandatory nor are they an exhaustive list. The major headings are listed in attachments 2, 3 and 4 for ease of reference. If there is no appropriate heading a new section may be added.

However, it is recognised that it will be inappropriate or impossible to provide information under all headings for all products. The dossier required will depend on many factors including the nature of the medicinal product, the stage of development, the population to be treated, the nature and severity of the disease and the nature and duration of exposure to the investigational medicinal product. Where it is necessary to omit data for reasons that are not obvious, scientific justification should be provided.

It is impossible to formulate detailed guidance to cover all situations. Sponsors are advised to use this detailed guidance as a starting point in their preparation of data packages for submission. In addition, the relevant Community guideline or European Commission decision should be followed for specific types of investigational medicinal product, clinical trial, or patient group. This type of information is available at the European Medicines Agency (EMEA) website www.emea.eu.int.

4.1.6.1.1 Quality data

The sponsor should submit summaries of chemical, pharmaceutical and biological data on any IMP.

Applicants should refer to the relevant Community guidelines on the requirements for the quality documentation for IMPs intended for marketing in the EU (Draft, CHMP/QWP/185401/2004) where applicable. The Directive requires sponsors to supply IMPs for a clinical trial whose manufacture complies with the principles of Good Manufacturing Practice (GMP) set out in Directive 2003/94/EC and the guidance on application of the principles set out in Annex 13 (revised July 2003) to the Community Guide to GMP[7].

To document this requirement the applicant should provide the following:

- A copy of the manufacturing authorisation referred to in Article 13(1) of the Directive and Article 11 of Directive 2005/28/EC stating the scope of the authorisation, if the IMP is manufactured in the EU and does not have a marketing authorisation in the EU;
- If the IMP is not manufactured in the EU and does not have a marketing authorisation in the EU,

[7] Annex 13 to Volume 4 of the Rules Governing Medicinal Products in the European Union.

- Certification of the Qualified Person (QP) that the manufacturing site works in compliance with GMP at least equivalent to EU GMP;
- Certification of the GMP status of any active biological substance;
- Copy of the importer's authorisation as referred to in Article13(1) of the Directive;

In exceptional cases, where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected, the certificate of analysis for test product should be attached. Where applicable, the TSE Certificate and viral safety data should be provided.

4.1.6.1.2 Non-clinical pharmacology and toxicology data

The sponsor should also provide summaries of non-clinical pharmacology and toxicology data for any IMP to be used in the clinical trial or justify why they have not. They should also provide a reference list of studies conducted and appropriate literature references. Full data from the studies and copies of the references should be made available on request. Wherever appropriate it is preferable to present data in tabular form accompanied by the briefest narrative highlighting the main salient points. The summaries of the studies conducted should allow an assessment of the adequacy of the study and whether the study has been conducted according to an acceptable protocol. Sponsors should as far as possible provide the non-clinical information in the IMPD under the headings in attachment 3. The headings are not mandatory nor are they an exhaustive list.

This section should provide a critical analysis of the available data, including justification for deviations and omissions from the detailed guidance and an assessment of the safety of the product in the context of the proposed clinical trial rather than a mere factual summary of the studies conducted.

The studies needed as a basis for the non-clinical section of the IMPD are outlined in the relevant Community guidelines. In particular, applicants are referred to the Community guideline[8] (CPMP/ICH/286/95). These and other relevant guidelines are available from the EMEA website www.emea.eu.int.

All studies should be conducted according to currently acceptable state-of-the-art protocols. In addition, they should meet the requirements of Good Laboratory Practice guidelines where appropriate. The sponsor should justify any deviations from these guidelines and provide a statement of the GLP status of all studies.

[8] Community guideline 'Note for guidance on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals'(CPMP/ICH/286/95)

The test material used in the toxicity studies should be representative of that proposed for clinical trial use in terms of qualitative and quantitative impurity profiles. The preparation of the test material should be subject to appropriate controls to ensure this and thus support the validity of the study.

4.1.6.1.3 Previous clinical trial and human experience data

This section should provide summaries of all available data from previous clinical trials and human experience with the proposed IMP(s) in this section. They should as far as possible provide the information under the headings in attachment 4. The headings are not mandatory nor are they an exhaustive list.

All studies should have been conducted in accordance with the principles of Good Clinical Practice (GCP). This should be confirmed by the sponsor in a statement of the GCP status of all studies and where this is not the case, he should provide an explanation or justification if available.

There are no specific requirements for data from clinical studies that must be provided before a clinical trial authorisation can be granted. However applicants should take account of the general guidance on clinical trials in the development of a medicinal product in the Community guideline (CPMP/ICH/291/95)[9]. These and other relevant guidelines are available from the EMEA website www.emea.eu.int.

4.1.6.1.4 Overall risk and benefit assessment

This section should provide a brief integrated summary that critically analyses the non-clinical and clinical data in relation to the potential risks and benefits of the proposed trial. The text should identify any studies that were terminated prematurely and discuss the reason(s). Any evaluation of foreseeable risks and anticipated benefits for studies on minors or incapacitated adults should take account of the provisions set out in Article 3 to 5 of the Directive.

The aim of the non-clinical pharmacology and toxicity testing is to indicate the principal hazards of a new medicinal product. The sponsor should use the relevant pharmacology, toxicology and kinetic results as the basis of extrapolation to indicate possible risks in humans. As a guide to what may occur in humans, the sponsor should integrate all the available data, analyse the pharmacological and toxic actions of the IMP and use the results to suggest possible mechanisms and the exposure required to produce them. Where appropriate, they should discuss safety margins in terms of relative systemic exposure to the investigational medicinal product, preferably based on AUC and Cmax data, rather than in terms of applied

[9] 'Note for guidance on general considerations for clinical trials (CPMP/ICH/291/95)'

dose. They should also discuss the clinical relevance of any findings in the non-clinical and clinical studies along with any recommendations for further monitoring of effects and safety in the clinical trials.

4.1.6.2 Simplified IMPD

4.1.6.2.1 When to use a simplified IMPD

A simplified IMPD may be submitted if information related to the IMP has been assessed previously as part of a marketing authorisation (MA) in any MS of the Community or as part of a clinical trial application to the CA concerned. Information on a placebo may also be provided as a simplified IMPD. The text should include a discussion of the potential risks and benefits of the proposed trial (see section 4.1.6.1.4). Guidance on the types of previous assessment and the associated categories of information required is provided in Table 1. Where appropriate, sponsors are allowed to cross-refer to the IMPD submitted by another applicant and held by the competent authority. This may require a letter from the other applicant to authorise the competent authority to cross-refer to their data. The sponsor should have relevant information about this IMP that can be included in the investigator's brochure. In addition, an appropriate and adapted content of the IMP dossier may be allowed occasionally by the competent authority, provided that it is justified and agreed before the application is submitted.

Table 1. Reduced information requirements for IMPs known to the concerned competent authority

Types of Previous Assessment	Quality Data	Non-clinical Data	Clinical Data
The IMP has a MA in any EU Member State and is used in the trial:			
Within the conditions of the SmPC	SmPC	SmPC	SmPC
Outside the conditions of the SmPC	SmPC	Yes (if appropriate)	Yes (if appropriate)
After it has been blinded	P+A	SmPC	SmPC
Another pharmaceutical form or strength of the IMP has a MA in any EU Member State and:			
the IMP is supplied by the MAH	P+A	Yes	Yes
The IMP has no MA in any EU Member State but drug substance is part of a product with a marketing authorisation in a MS and:			
is supplied from the same manufacturer	P+A	Yes	Yes
is supplied from another manufacturer	S+P+A	Yes	Yes
The IMP has a previous CTA in the Member State(s) concerned[10]:			
no new data available since CTA	No	No	No
new data available since CTA	New Data	New Data	New Data

[10] The sponsor should provide a letter of authorisation to cross-refer to the data submitted by another applicant.

The IMP is a placebo	P+A	No	No

(S: Drug substance data; P : Drug product data; A : appendices of the IMPD; SmPC: summary of product characteristics)

4.1.6.2.2 IMPD for Marketed products

The sponsor may submit the current version of the SmPC as the IMPD if an IMP has a marketing authorisation in any Member State in the EU and is being used in the same form, for the same indications and with a dosing regimen covered by the SmPC. The SmPC must be understandable by the concerned competent authority (translation may be necessary). It will also be sufficient for studies of dosing regimens not covered by the SmPC when the sponsor can show that the information in the SmPC justifies the safety of the proposed new regimen. Otherwise they should submit additional non-clinical data and/or clinical data to support the safety of its use in the new indication, new patient population and/or the new dosing regimen as appropriate. If the applicant is the marketing authorisation holder and he has submitted an application to vary the SmPC, which has not yet been authorised, the nature of the variation and the reason for it should be explained in the covering letter.

There are situations where the IMP to be used in the CT has a MA in the MS concerned but the protocol allows that any brand of the IMP with an MA in that MS may be administered to the trial subjects. In those situations, providing that the IMP is not modified e.g. overencapsulated, it is acceptable that IMPs to be used are only identified by the active substance name or ATC code as follows:

a) A sponsor may wish to conduct a trial with an active substance that is available in the Community in a number of medicines with MAs and different trade names. In which case, the protocol may define the treatment in terms of the active substance only and not specify the trade name of each product. This is to allow investigators to administer any brand name of these products that contains the active substance in the required pharmaceutical form with a MA in the MS concerned. To notify this, they should complete section D.2.2.1 of the application form and in section D.3.1 they should provide the name routinely used to describe the product in the protocol under ‘Product Name’ and the name of the active substance in D.3.8 or D.3.9.

   When the IMP is defined in the protocol in terms of its active substance, the sponsor should elect one medicine with a MA in the Community and submit its SmPC as equivalent to the IMPD for all medicinal products that contain that active substance used at any of the clinical trial sites.

b) In some trials the sponsor may wish to allow investigators in the same multicentre trial to administer different regimens of IMPs, e.g. groups of anticancer drugs, according to local clinical practice at each investigator site in the MS. They should define the acceptable treatment regimens in the protocol and notify this in the application form by completing Section D.2.2.2 and in Section D.3.1 they should provide the name routinely used to describe the regimen in the protocol under 'Product Name' and the name of each active substance in D.3.8 or D.3.9.

c) In other trials the sponsor may wish to study the effect of a number of medical treatments on a specific illness without specifying the IMPs to be used except that they have a MA in the MS concerned. To achieve this he should identify the treatment using its ATC Code (level 3-5) in the protocol and complete Section D.2.2.3 and D.3.3 of the application form.

When the IMP is defined in the protocol in terms of its ATC code, the sponsor could replace the IMPD by one representative SmPC for each active substance pertaining to that ATC group. Alternatively, he could provide a collated document containing information equivalent to that in the representative SmPCs for each active substance that could be used as an IMP in the clinical trial.

4.1.7. Non-investigational medicinal products (NIMPs) used in the trial

There are situations where the protocol may require the use of NIMPs (see also Section 3). For instance NIMPs may be used as background treatments, 'escape' or rescue medication or for diagnostic purposes or to induce a physiological response (i.e. challenge agents) (See guidance on "What is an IMP?). They should be described in the protocol.

It is strongly recommended that NIMPs with MA in the MS concerned are used for these purposes when possible. When this is not possible, the next choice should be NIMPs with MA in another MS. A SmPC for each NIMP with a MA should be submitted with the CTA application dossier.

Where NIMPs without a MA in the EU are used, or used outside the conditions of a MA, a NIMP dossier may be requested by the competent authority according to national requirements.

4.2 Notification of amendments

4.2.1 Scope

Article 10(a) of the Directive allows amendments to be made to the conduct of a clinical trial after its commencement. It does not require notification of non-substantial amendments; only amendments that are substantial must be notified to the CA and ethics committee concerned (see Section 4.2.3). In

addition when a sponsor and/or investigator must take urgent safety measures to protect the trial subjects from immediate hazard Article 10(b) allows them to do so before notifying the CA, but they must notify them as soon as possible.

4.2.2 Non-substantial amendments

The sponsor does not have to notify non-substantial amendments to the documentation provided to the competent authority or the ethics committee, (that is those that do not meet the criteria of substantial set out in 4.2.3.1). However, they should be recorded and if appropriate included in the next update of the IB and be available on request for inspection at the trial site and/or the sponsors premises as appropriate.

4.2.3 Substantial amendments

4.2.3.1 What is a substantial amendment?

Substantial amendments to the conduct of the clinical trial may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial.

Amendments to the trial are regarded as "substantial" where they are likely to have a significant impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any IMP used in the trial.

In all cases, an amendment is only to be regarded as "substantial" when one or more of the above criteria are met. Attachment 5 provides headings of aspects of a trial to which a sponsor might need to make a substantial amendment. The list is not exhaustive; a substantial amendment might occur in some other aspect of a trial. Not all amendments to those aspects of a trial need to be notified, only those that meet the criteria of "substantial" above.

4.2.3.2 Protocol

When the sponsor intends to make a substantial amendment to the protocol that would make a significant impact on the criteria in 4.2.3.1 he should notify the concerned CA and relevant ethics committee. For instance reducing the number of clinic visits might impact on the safety or physical or mental integrity of the subjects. Introducing a new monitoring procedure or a change in the principal investigator might significantly affect the conduct or management of the trial respectively. The use of a new measurement for the primary endpoint could alter the scientific value of the trial. Altering the procedure for reconstitution and administration of an IMP could affect the safe use of an IMP in the trial. These types of changes would be considered substantial amendments.

4.2.3.3 Initial scientific documents supporting the Clinical Trial Authorisation (CTA)

The sponsor should notify a substantial amendment to the scientific documents submitted to support the request for a CTA when certain new information becomes available: for instance, data from additional studies of pharmacology, toxicology or clinical use of an IMP used in the trial which might alter the initial risk to benefit evaluation of the supporting documents in relation to the criteria in section 4.2.3.1; or any change to the IB that alters the product safety profile in such a way that the pharmacovigilance reporting will be altered.

4.2.3.4 Initial CTA application form

Some information key to the criteria of a substantial amendment in Section 4.2.3.1 may be documented only in the CTA application form – for instance a change to the legal representative of the sponsor in the Community, the revocation, suspension or substantial relevant amendment of the MA of the IMP or transfer of sponsor responsibilities to a new individual or organisation. Changes to this type of key information in the form should be notified as a substantial amendment.

4.2.4 Procedure for notification

Substantial amendments to the information supporting the initial authorisation of the trial or to the protocol should be reported using the Amendment Notification Form at Annex 2[11]. The sponsor should first assess on a case-by-case basis whether or not an amendment is substantial using criteria from 4.2.3.1 above.

Where a substantial amendment affects more than one clinical trial for a particular investigational medicinal product, the sponsor may make a single notification to the competent authority concerned, provided that the covering letter and notification includes a list of all affected clinical trials with their EudraCT numbers and respective amendment code numbers.

The applicant should also submit a covering letter and sign it. Its heading should contain the EudraCT number and the sponsor protocol number with the title of the trial and an amendment code number. The text should draw attention to any special issues related to the amendment and indicate where the relevant information or text is in the original application. The covering letter should identify any information not in the Notification of Amendment that might impact on the risk to trial participants.

In the case of substantial amendments that affect information submitted to both the competent authority and the ethics

[11] This procedure should also be followed to report substantial amendments to the relevant ethics committee. See detailed guidance CT-06-EN

committee, the sponsor should make arrangements to submit the notifications in parallel.

For substantial amendments to information that only the CA assesses (e.g. quality data in most of the MS), the sponsor should not only submit the amendment to the CA but also make arrangements to inform the ethics committee that they have made the application. Similarly, the sponsor should inform the CA of any substantial amendment to information for which only the ethics committee is responsible (e.g. facilities for the trial). To provide this information it will be sufficient to submit the notification of amendment form (Annex 2) once the decision on the amendment has taken place, indicating in Section A.4 that it is "for information only", and attaching a copy of the decision.

When a sponsor proposes to change the co-ordinating investigator, the principal investigator at a trial site or add a new site for a clinical trial he should notify the CA and the relevant ethics committee. He can meet this obligation by submitting a Notification of Amendment (Annex 2) and completing section H of the form. The investigator at the new site should not enter participants into the trial until the ethics committee has given a favourable opinion and according to MS regulation the CA has indicated it has no grounds for non-acceptance in response to the notification.

Applicants should be aware that these procedures set out to provide for rapid and efficient processing of substantial amendments, and in that context, unsatisfactory documentation is likely to lead to a refusal of the amendment. Refusals do not prejudice the applicant's right to resubmission.

4.2.5 Format and content of notification

The notification of a substantial amendment should include the following information:

a) Covering letter, including reason for qualification as a substantial amendment.

b) Application form (Annex 2) that contains:

- Identification of CT (title, EudraCT number, sponsor's protocol code number);
- Identification of applicant;
- Identification of the amendment (sponsor's amendment number and date). One amendment could refer to several changes in the protocol or scientific supporting documents;
- A description of the amendment and the reason for it.

c) An extract of the modified documents showing previous and new wording, where applicable

d) The new version of modified documents where the changes are so widespread and/or substantial that they justify a new version, identified with updated number of version and date.

e) Supporting information including, where applicable:
- Summaries of data;
- An updated overall risk benefit assessment;
- Possible consequences for subjects already included in the trial;
- Possible consequences for the evaluation of the results.

f) Where applicable, if a substantial amendment changes the core data or the full application form data set (according to national requirements) in the XML file accompanying the initial application for the trial, the sponsor should submit a revised copy of the XML file with the Notification of Amendment, incorporating amended data. The application for substantial amendment should identify the fields to be changed, by attaching a print out of the revised form showing the amended fields highlighted.

4.2.6 Implementation

The sponsor may implement a substantial amendment when the ethics committee opinion is favourable and the CA has raised no grounds for non-acceptance. For amendments submitted to either the ethics committee alone or the CA alone, the sponsor may implement the amendment when the ethics committee opinion is favourable or the CA has raised no grounds for non-acceptance respectively.

4.2.7 Time for response

Article 10(a) of the Directive requires an ethics committee to give an opinion on a proposed substantial amendment within 35 days. It does not set out a period within which the competent authority must respond to such a notification. However, as guidance, the amendment may be implemented after 35 days from the receipt of a valid notification of an amendment if the CA has not raised grounds for non-acceptance. However, if the CA consults a group or committee in accordance with Article 9(4) of the Directive, the time for response could be extended. In this case the CA should notify the sponsor of the duration of the extension.

4.2.8 Urgent Amendments

Article 10(b) requires a sponsor and investigator to take appropriate urgent safety measures to protect subjects against any immediate hazard where new events relating to the conduct of the trial or the development of the IMP are likely to affect the safety of the subjects. These safety measures such as temporarily halting of the trial may be taken without prior authorisation from the competent authority. The sponsor must inform the competent authority and the ethics committee

concerned of the new events, the measures taken and their plan for further action as soon as possible. This should be by telephone in the first place followed by a written report. When the sponsor halts a clinical trial (stops recruitment of new subjects and/or interrupts the treatment of subjects already included in the trial), they should notify the CA and ethics committee concerned as soon as possible and not later than 15 days as a substantial amendment (see 4.2.3). They may not recommence the trial in that MS until they have notified a substantial amendment to restart the trial and the ethics committee has given a favourable opinion and the CA has not raised grounds for non-acceptance of the recommencement.

4.2.9 Suspension of a trial by the Competent Authority

According to Article 12 of the Directive the CA may suspend or prohibit a clinical trial in the member state concerned where it has objective grounds for considering that the conditions in the authorisation are not being met or has doubts about the safety or scientific validity of the clinical trial. Before they reach their decision, they must inform the sponsor, except where there is imminent risk, and ask the sponsor and/or the investigator for their opinion. The sponsor should immediately investigate the grounds for suspension or prohibition and provide a report within one week addressing the issues raised and any exceptional circumstances that might have led to those conditions not being met. When the CA suspends a trial, they must inform the other competent authorities, the ethics committee concerned, the EMEA and the Commission. If the trial is terminated following a suspension, the sponsor should notify the CA using the procedure in 4.3.2.

4.2.10 Infringements

Where the CA has objective grounds for considering that the sponsor or investigator or any other person involved in the conduct of the trial no longer meets the obligations laid down, the CA may set a course of action that a sponsor must take to remedy any infringement of those obligations. The course of action should have a timetable for its implementation and a date when the sponsor should report back to the CA on the progress and completion of its implementation. The CA must inform the other competent authorities, the ethics committee concerned and the Commission of this course of action.

In these circumstances the sponsor should immediately implement the course of action set by the CA and report to the CA and the ethics committee concerned on the progress and completion of its implementation in accordance with the timetable set.

4.3 Declaration of the end of a clinical trial

4.3.1 Legal Basis and Scope

Article 10 (c) of Directive 2001/20/EC requires the sponsor of a clinical trial to notify the competent authority of the Member State concerned that the clinical trial has ended.

4.3.2 Procedure for declaring the end of the trial

4.3.2.1 When is the end of the trial?

The definition of the end of the trial should be provided in the protocol and any change to this definition for whatever reason should be notified as a substantial amendment. In most cases it will be the date of the last visit of the last patient undergoing the trial. Any exceptions to this should be justified in the protocol.

The sponsor should make an end of trial declaration using the form at Annex 3 when:

- the trial ends in the territory of the Member State(s) concerned;
- the complete trial has ended in all participating centres in all countries within and outside the Community.

The sponsor must notify the concerned MS CA(s) of the end of the trial in their territory within 90 days of the end of the clinical trial using the form at Annex 3. In addition when the trial is completed in all countries concerned by the trial, the sponsor should notify the Member State(s) concerned within 90 days using the form at Annex 3. The Member State(s) competent authority(ies) will be responsible for entering this information into the EudraCT database.

4.3.2.2 Premature end of a trial

According to Article 10(c) of the Directive whenever a trial is terminated early (premature end) the sponsor must notify the CA concerned immediately and at least within 15 days from when the trial is halted and clearly explain the reasons. The sponsor should notify this as a Declaration of End of Trial using the form at Annex 3 including trials suspended by the CA.

4.3.2.3 Temporary halt of a trial

When a sponsor halts the trial temporarily, he should notify the concerned CAs and ethics committees immediately and at least within 15 days from when the trial is temporarily halted. This should be as a substantial amendment using the form at Annex 2 as described in section 4.2.3 and clearly explain the reasons and scope e.g. stopping recruitment and/or interrupting treatment of subjects already included. To restart the trial he should make the request as a substantial amendment using the form at Annex 2 and providing evidence that it is safe to restart the trial. If the sponsor decides not to recommence a

temporarily halted trial he should notify the competent authority(ies) concerned within 15 days of his decision, using the form at Annex 3 and provide a brief explanation of the reasons for ending the trial.

4.3.2.4 Clinical trial report

The sponsor should also provide a summary of the clinical trial report within one year of the end of the trial to the competent authority of the Member State(s) concerned as required by the regulatory requirement(s) and to comply with the Community guideline on Good Clinical Practice (CPMP/ICH/135/95). The format of this summary should comply as much as possible with annex 1 of the Community guideline on the Structure and Content of Clinical Study Reports (CPMP/ICH/137/95).

4.3.2.5 Follow up

If a new event occurs after the termination of the trial that is likely to change the risk/benefit analysis of the trial and could still have an impact on the trial participants, the sponsor should notify the competent authority and ethics committee concerned and provide a proposed course of action.

4.3.3 Format and content

The declaration of the end of the trial should be notified using the form at Annex 3.

The following information should be provided:

- Name and address of the sponsor or his legal representative in the Member State;
- Title of the trial;
- EudraCT number;
- Sponsor's protocol code number;
- Date of end of trial in the Member State concerned;
- Date of end of complete trial in all participating centres in all countries when available.

When the trial is terminated early, the end of clinical trial report should also provide the following information:

- Justification of the premature ending or of the temporary halt of the trial;
- Number of patients still receiving treatment at time of study termination;
- Proposed management of patients receiving treatment at time of halt or study termination;
- Consequences for the evaluation of results.

Attachment 1: Information required by MS for applications to a competent authority. Some of this information may be provided in the application form.

INFORMATION REQUIRED BY MEMBER STATES' COMPETENT AUTHORITIES

	MS SPECIFIC INFORMATION	AT	BE	DK	FI	FR	DE	GR	IT	IE	LU	NL	PT	ES	SE	UK
1	**General**															
1.1	Receipt of confirmation of EudraCT number	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.2	Covering letter	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.3	Application form	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.4	List of Competent Authorities within the Community to which the application has been submitted and details of decisions	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	A	Yes	Yes	Yes	Yes
1.5	Copy of ethics committee opinion in the MS concerned when available	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	A	Yes	B	Yes	Yes
1.6	Copy/summary of any scientific advice	Yes	Yes	Yes	No	Yes	No	No	No	No	No	Yes	No		Yes	Yes
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
1.8	Will accept application to CA in English	Yes	Yes	Yes	Yes	A	No	No	No	Yes	No	Yes	A		Yes	Yes
2	**Subject related**															
2.1	Informed consent form	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
2.2	Subject information leaflet	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No
2.3	Arrangements for recruitment of subjects	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No
3	**Protocol related**									A						
3.1	Protocol with all current amendments	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3.2	Summary of the protocol in the national language	No	B	No	No	Yes	No		Yes	Yes	A	Yes	No	Yes	No	No
3.3	Peer review of trial when available, not compulsory	Yes	No	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No
3.4	Ethical assessment made by the principal/coordinating investigator	No	No	Yes	No	No	No		No	No	No	Yes	No	No	No	No

INFORMATION REQUIRED BY NEW MEMBER STATES' COMPETENT AUTHORITIES

	MS SPECIFIC INFORMATION	AT	BE	DK	FI	FR	DE	GR	IT	IE	LU	NL	PT	ES	SE	UK
4	**IMP related**															
4.1	Investigator's brochure	Yes	Yes	Yes	A	Yes	Yes	A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	A	Yes	Yes
4.3	Simplified IMPD for known products. See table 1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	A	Yes	Yes
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.5	Outline of all active trials with the same IMP	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.6	If IMP manufactured in E.U. and if no marketing authorisation in EU:															
4.6.1	– Copy of the manufacturing authorization referred to in Art. 13(1) of the Directive stating the scope of this authorization	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.7	If IMP not manufactured in E.U. and if no marketing authorisation in EU::															
4.7.1	Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.7.2	Certification of GMP status of active biological substance	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.7.3	– Copy of the importer's manufacturing authorization as referred to in Art. 13(1) of the Directive	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.8	Certificate of analysis for test product in exceptional cases :															
4.8.1	– Where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	Yes	C	Yes	Yes	Yes	Yes	No	Yes	Yes	B	Yes	Yes	Yes	Yes	Yes
4.9	Viral safety studies when applicable.	Yes	Yes	Yes	Yes	B	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	B	Yes	Yes	Yes	Yes	Yes
4.11	TSE Certificate when applicable	Yes	Yes	Yes	Yes	B	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.12	Examples of the label in the national language	No	Yes	No	No	No	Yes	No	Yes	Yes	B	Yes	Yes	Yes	Yes	Yes

INFORMATION REQUIRED BY NEW MEMBER STATES' COMPETENT AUTHORITIES

	MS SPECIFIC INFORMATION	AT	BE	DK	FI	FR	DE	GR	IT	IE	LU	NL	PT	ES	SE	UK
5	**Facilities & staff related**															
5.1	Facilities for the trial	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	No	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	No	No	No
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	No	No	No	No	No	Yes	No	Yes	No	Yes	Yes	No	No	No
5.4	Information about supporting staff	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No
6	**Finance related**															
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	No	No	No	No	No	Yes	No	No	B	Yes	Yes	No	No	No
6.2	Any insurance or indemnity to cover the liability of the sponsor or investigator	Yes	No	No	No	Yes	No	Yes	No	No	B	Yes	Yes	No	No	No
6.3	Compensations to investigators	Yes	No	No	No	C	No	Yes	Yes	No	No	Yes	Yes	No	No	No
6.4	Compensations to subjects	Yes	No	No	No	No	No	Yes	Yes	No	No	Yes	Yes	No	No	No
6.5	Agreement between the sponsor and the trial site	No	No	No	No	No	No	No	Yes	No	No	B	B	No	No	No
6.6	Agreement between the investigators and the trial sites	No	No	No	No	No	No	No	No	No	No	B	No	No	No	No
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	Yes	No	No	No	No	No	No	No	No	No	B	No	No	No	No

INFORMATION REQUIRED BY NEW MEMBER STATES' COMPETENT AUTHORITIES

	MS SPECIFIC INFORMATION	CY	CZ	EE	HU	LV	LT	MT	PL	SK	SI	NO	IS
1	**General**												
1.1	Receipt of confirmation of EUDRACT number	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
1.2	Covering letter	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.3	Application form	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.4	List of Competent Authorities to which the application has been submitted and details of decisions	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.5	Copy of ethics committee opinion in the MS concerned when available	Yes	Yes	Yes	No	Yes	Yes	A	No	Yes	Yes	Yes	Yes
1.6	Copy/summary of any scientific advice												Yes
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
1.8	Will accept application to CA in English	Yes	Yes	Yes	A	A	A	B	No	A	A	No	Yes
2	**Subject related**												
2.1	Informed consent form	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.2	Subject information leaflet	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	Yes	No	Yes	No	No	No	Yes	Yes	No	No	No
3	**Protocol related**												
3.1	Protocol with all current amendments	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3.2	Summary of the protocol in the national language	Yes	Yes	No	Yes	No	Yes	C	No	Yes	Yes	No	No
3.3	Peer review of trial when available	Yes	No	No	Yes	No	Yes	No	No	Yes	No	No	No
3.4	Ethical assessment made by the principal/coordinating investigator	Yes	No	No	No	No	No	No	No	No	No	Yes	No

INFORMATION REQUIRED BY NEW MEMBER STATES' COMPETENT AUTHORITIES

	MS SPECIFIC INFORMATION	CY	CZ	EE	HU	LV	LT	MT	PL	SK	SI	NO	IS
	MS SPECIFIC INFORMATION												
4	**IMP related**												
4.1	Investigator's brochure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
4.3	Simplified IMPD for known products. See table 1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.5	Outline of all active trials with the same IMP	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
4.6	If IMP manufactured in E.U. and if no marketing authorisation in EU:												
4.6.1.1	Copy of the manufacturer authorization referred to in Art. 13(1) of the Directive stating the scope of this authorization	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.7	If IMP not manufactured in E.U. and no marketing authorisation in EU :												
4.7.1	Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.7.2	Certification of GMP status of active biological substance	Yes	Yes	Yes	Yes	B	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.7.3	Copy of the importer's manufacturing authorization as referred to in Art. 13(1) of the Directive	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.8	Certificate of analysis for test product in exceptional cases :												
4.8.1.1	Where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	Yes	Yes	Yes	B	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.9	Viral safety studies when applicable	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	A	Yes
4.11	TSE Certificate when applicable	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.12	Examples of the label in the national language	Yes	No	Yes	Yes	Yes	Yes	D	Yes	Yes	Yes	Yes	Yes

INFORMATION REQUIRED BY NEW MEMBER STATES' COMPETENT AUTHORITIES

	MS SPECIFIC INFORMATION	CY	CZ	EE	HU	LV	LT	MT	PL	SK	SI	NO	IS
5	**Facilities & staff related**												
5.1	Facilities for the trial	Yes	No	No	Yes	Yes	No	Yes	No	Yes	No	Yes	No
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5.4	Information about supporting staff	No	No	No	No	Yes	No	Yes	No	No	No	No	No
6	**Finance related**												
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	No	No	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the sponsor or investigator	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No
6.3	Compensations to investigators	No	No	No	Yes	No	No	Yes	Yes	No	No	No	No
6.4	Compensations to subjects	No	No	No	Yes	No	No	No	Yes	No	No	No	No
6.5	Agreement between the sponsor and the trial site	No	No	No	Yes	No	Yes	Yes	Yes	Yes	No	No	No
6.6	Agreement between the investigators and the trial sites	No	No	Yes	No	No	No	No	No	No	No	No	No
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	No	No	No	No	No	No	No	No	No	No	No	No

MEMBER STATES ADDITIONAL EXPLANATION

The letters (e.g. A.B.C.) below refer to letters in the relevant MS column in the table above and provide additional explanation about the information to be provided.

Belgium:

A. not applicable
B. If available;
C. On request

Finland:

A. IB is only necessary when the product has no MA .

France:

A. Except informed consent form, subject information leaflet and summary of the protocol which must be in French.
B. When applicable and if not in the IMPD.
C. This information will not be provided to Afssaps but to another body of the CA.

Greece:

A. I.B. is only necessary when the product has no MA;
B. CV from the principal investigator.

Hungary:

A. Application form: format in English accepted; Application form: answers in English accepted; and Application form: answers in local language accepted
B. Certificate of analysis for test product required in every case.

Ireland:

A. Full listing of names/addresses of members of Ethics Committee;

Latvia:

A. Application form: format in English accepted; Application form: answers in English accepted; and Application form: answers in local language accepted.
B. On request

Lithuania:

A. Should also be submitted in the Lithuanian language.

Luxembourg:

A. If available ;
B. On request.

Malta

A. Application form: format in English accepted; Application form: answers in English accepted; and Application form: answers in local language NOT accepted
B. Health Ethics Committee of Malta
C. Summary of protocol should be in one of the official languages e.g. Maltese and/or English.
D. Examples of the label should be in one of the official languages e.g. Maltese and/or English.

Additional Maltese requirements may be found in the 'Guidance notes on Good Clinical Practice'. These will be accessible on http://www.health.gov.mt/mru/.

Netherlands:

A: Advisable, but not obligatory
B: Should be available on request

Norway:

A. A copy of the authorisation is not required by NoMA, but the authorisation needs to be obtained from another authority.

Portugal :

A. Except covering letter, which should be in the official language, Portuguese.
B. List of investigators;

Slovak Republic

A. Accepts the application form in English but it must be submitted in Slovak at the same time. The covering letter and written information have to be in Slovak.

Slovenia:

A. Covering letter, summary of protocol, informed consent form and subject information leaflet must be in Slovene language

Spain:

A. Investigational medicinal products requiring a full IMPD will require the qualification as "Producto en investigacvión Clínica" (PEI) basically on the basis of the IMPD document;
B. The notification of ethics committee favourable opinion and agreement of the management board of the site would be necessary before the authorisation takes place.

Common Technical Document
Information is provided on web-site: http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm
Notice to Applicants Volume 2B

Attachment 2: Common Technical Document Headings for:
Investigational Medicinal Product Quality Data

2.1.S DRUG SUBSTANCE
2.1.S.1 General Information:
2.1.S.1.1 Nomenclature
2.1.S.1.2 Structure
2.1.S.1.3 General Properties

2.1.S.2 Manufacture:
2.1.S.2.1 Manufacturer(s)
2.1.S.2.2 Description of Manufacturing Process and Process Controls
2.1.S.2.3 Control of Materials
2.1.S.2.4 Controls of Critical Steps and Intermediates
2.1.S.2.5 Process Validation and/or Evaluation
2.1.S.2.6 Manufacturing Process Development

2.1.S.3 Characterisation:
2.1.S.3.1 Elucidation of Structure and Other Characteristics
2.1.S.3.2 Impurities
2.1.S.4 Control of Drug Substance:
2.1.S.4.1 Specification
2.1.S.4.2 Analytical Procedures
2.1.S.4.3 Validation of Analytical Procedures
2.1.S.4.4 Batch Analyses
2.1.S.4.5 Justification of specification

2.1.S.5 Reference Standards or Materials

2.1.S.6 Container Closure System:

2.1.S.7 Stability

2.1.P MEDICINAL PRODUCT
2.1.P.1 Description and Composition of the Medicinal Product:

2.1.P.2 Pharmaceutical Development:
2.1.P.2.1 Components of the Medicinal Product
2.1.P.2.1.1 Drug Substance
2.1.P.2.1.2 Excipients

2.1.P.2.2 Medicinal Product
2.1.P.2.2.1 Formulation Development
2.1.P.2.2.2 Overages
2.1.P.2.2.3 Physicochemical and Biological Properties

2.1.P.2.3 Manufacturing Process Development

ATTACHMENT 2 (CONTD)

2.1.P.2.4 Container Closure System

2.1.P.2.5 Microbiological Attributes
.P.2.6 Compatibility

2.1.P.3 Manufacture:
2.1.P.3.1 Manufacturer(s)
2.1.P.3.2 Batch Formula
2.1.P.3.3 Description of Manufacturing Process and Process Controls
2.1.P.3.4 Controls of Critical Steps and Intermediates
2.1.P.3.5 Process Validation and/or Evaluation

2.1.P.4 Control of Excipients:
2.1.P.4.1 Specifications:
2.1.P.4.2 Analytical Procedures
2.1.P.4.3 Validation of Analytical Procedures
2.1.P.4.4 Justification of Specifications
2.1.P.4.5 Excipients of Human or Animal Origin
2.1.P.4.6 Novel Excipients

2.1.P.5 Control of Medicinal Product:
2.1.P.5.1 Specification(s)
2.1.P.5.2 Analytical Procedures
2.1.P.5.3 Validation of Analytical Procedures
2.1.P.5.4 Batch Analyses
2.1.P.5.5 Characterisation of Impurities
2.1.P.5.6 Justification of Specification(s)

2.1.P.6 Reference Standards or Materials:

2.1.P.7 Container Closure System:

2.1.P.8 Stability:

2.1.A APPENDICES
2.1.A.1 Facilities and Equipment:
2.1.A.2 Adventitious Agents Safety Evaluation:
2.1.A.3 Novel Excipients:
2.1.A.4 Solvents for Reconstitution and Diluents:

Attachment 3: Common Technical Document Headings for:
Investigational Medicinal Product Quality Data
Headings for Non-clinical pharmacology and toxicology data

2.2.1 Pharmacodynamics:
2.2.1.1 Brief summary
2.2.1.2 Primary Pharmacodynamics
2.2.1.3 Secondary Pharmacodynamics
2.2.1.4 Safety Pharmacology
2.2.1.5 Pharmacodynamic interactions
2.2.1.6 Discussion and conclusion

2.2.2 Pharmacokinetics
2.2.2.1 Brief Summary
2.2.2.2.1 Methods of analysis

2.2.2.3 Absorption
2.2.2.4 Distribution
2.2.2.5 Metabolism
2.2.2.6 Excretion
2.2.2.7 Pharmacokinetic Drug Interactions
2.2.2.8 Other Pharmacokinetic Studies
2.2.2.9 Discussion and conclusions including evaluation of toxicokinetics

2.2.3 Toxicology:
2.2.3.1 Brief Summary
2.2.3.2 Single Dose Toxicity
2.2.3.3 Repeat-Dose Toxicity*
2.2.3.4 Genotoxicity:
2.2.3.4.1. In vitro
2.2.3.4.2. In vivo *
2.2.3.5. Carcinogenicity *
2.2.3.6. Reproductive and Developmental Toxicity *
2.2.3.7. Local Tolerance
2.2.3.8. Other Toxicity Studies
2.2.3.9. Discussion and Conclusions.

* These sections should be supported by toxicokinetic evaluations

Attachment 4: Common Technical Document Headings for:
Investigational Medicinal Product Quality Data
Headings for Clinical trial and previous human experience data

2.3.1. Clinical pharmacology
2.3.1.1. Brief summary
2.3.1.2. Mechanism of primary action
2.3.1.3. Secondary pharmacological effects
2.3.1.4. Pharmacodynamic interactions

2.3.2. Clinical pharmacokinetics
2.3.2.1. Brief summary
2.3.2.2. Absorption
2.3.2.3. Distribution
2.3.2.4. Elimination
2.3.2.5. Pharmacokinetics of active metabolites
2.3.2.6. Plasma concentration-effect relationship
2.3.2.7. Dose and time-dependencies
2.3.2.8. Special patient populations
2.3.2.9. Interactions

2.3.3. Human exposure
2.3.3.1. Brief summary
2.3.3.2. Overview of Safety and Efficacy
2.3.3.3. Healthy subject studies
2.3.3.4. Patient studies
2.3.3.5. Previous human experience
2.3.4. Benefits and risks assessment

4. Appendices

Attachment 5: Headings for aspects of a trial that might involve a substantial amendment.

In all cases, an amendment is only to be regarded as "substantial" where they are likely to have a significant impact on:

- The safety or physical or mental integrity of the patients;
- The scientific values of the trial;
- The conduct or management of the trial;
- The quality or safety of any IMP used in the trial.

The headings below are examples of aspects of a trial where amendments may need to be made, of which only some need to be notified as substantial. There may be other aspects of the trial where amendments meet the criteria for substantial in section 4.2.3.1.

Amendments related to the protocol

Purpose of trial
Design of trial
Informed consent
Recruitment procedure
Measures of efficacy
Schedule of samples
Addition or deletion of tests or measures
Number of participants
Age range of participants
Inclusion criteria
Exclusion criteria
Safety monitoring
Duration of exposure to the investigational medicinal product(s)
Change of posology of the investigational medicinal product(s)
Change of comparator
Statistical analysis

Amendments related to the trial arrangements

Change of the principal investigator or addition of new ones
Change of the co-ordinating investigator
Change of the trial site or addition of new sites (See section 4.2.4 on how to notify changes)
Change of the sponsor or legal representative
Change of the CRO assigned significant tasks
Change of the definition of the end of the trial

Amendments related to the IMP

Changes to investigational medicinal product quality data concerning:
Change of name or code of IMPs
Immediate packaging material

Manufacturer(s) of active substance
Manufacturing process of the active substance
Specifications of active substance
Manufacture of the medicinal product
Specification of the medicinal product
Specification of excipients where these may affect product performance
Shelf-life including after first opening and reconstitution
Major change to the formulation
Storage conditions
Test procedures of active substance
Test procedures of the medicinal product
Test procedures of non-pharmacopoeial excipients

Changes to non-clinical pharmacology and toxicology data where this is relevant to the ongoing trials (i.e. altered risk:benefit assessment).

For example concerning:

Results of new pharmacology tests
New interpretation of existing pharmacology tests
Result of new toxicity tests
New interpretation of existing toxicity tests
Results of new interaction studies

Changes to clinical trial and human experience data where this is relevant to the ongoing trials (i.e. altered risk:benefit assessment.

For example concerning:

Safety related to a clinical trial or human experience with the investigational medicinal product
Results of new clinical pharmacology tests
New interpretation of existing clinical pharmacology tests
Results of new clinical trials
New interpretation of existing clinical trial data
New data from human experience with the investigational medicinal product
New interpretation of existing data from human experience with the investigational medicinal product