The definitions of Directive 2001/20/EEC 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.

4 Format and content of applications and notifications

4.1 Request for a clinical trial authorisation

The applicant must submit a valid request for authorisation to the competent authority. The list in attachment 1 indicates the core information and Member State specific information to be submitted as part of a valid application. 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 a copy of the opinion of the ethics committee in the MS concerned as soon as it is available. When an ethics committee responsible for giving a single opinion in a MS gives an unfavourable opinion the sponsor should inform the CA of the MS where he has applied for authorisation of the trial and provide them with a copy of the unfavourable opinion. 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. If an application is not valid the CA will inform the applicant and give the reasons.

The sponsor should make applications to fulfill the requirements of other Directives 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[1] and/or Directive 2001/18/EC[2] 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 the application.

[1] Directive 90/219/EC as amended by Directive 98/81/EC on the contained use of genetically modified organisms (GMOs)
[2] 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.

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[3]. 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. However 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 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 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.

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 with the inclusion of amendments, 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);
- 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

3 Detailed guidance on the European clinical trials database (EudraCT Database)

from what is normally expected according to the subject's medical condition.

4.1.5 Investigators Brochure

The content, format and procedures for updating the Investigator's Brochure (IB) should comply with 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.

If the IMP is marketed in any MS and its pharmacology is widely understood by medical practitioners, the sponsor can provide a simplified IMP dossier (see table 1) and an extensive investigators brochure may not be necessary.

4.1.6 Investigational Medicinal Product Dossier (IMPD)

The IMPD should give information on 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).

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 Full IMPD

This section indicates the type of scientific information that is required for a full IMPD and how it should be presented. The sponsor should submit a full 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.

A full 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 Evaluation 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. They should provide the information under the headings in Attachment 2 where it is available. 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 for IMPs and the guidance on application of the principles set out in Annex 13 (revised July 2003) to the Community Guide to GMP.

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 full 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 full IMPD are outlined in the relevant Community guidelines. In particular, applicants are referred to the Community guideline[4] (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 where appropriate. The sponsor should justify any deviations from these principles and provide a statement of the GLP status of studies.

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)[5]. These and other relevant guidelines are available from the EMEA website www.emea.eu.int.

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

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

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 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 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. This may require a letter of authorisation to cross-refer to the data submitted by another applicant. 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)
☐ With a change to the drug substance manufacture or manufacturer	S+P+A	SmPC[6]	SmPC
☐ 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 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[7]:			
☐ no new data available since CTA	No	No	No
☐ new data available since CTA	New Data	New Data	New Data
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 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. 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 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

[6] Where the change to drug substance manufacture produces a new potentially toxic substance such as a new impurity or degradation product or introduces a new material in the production of a biological product, additional non-clinical information may be required.
[7] This may require a letter of authorisation to cross-refer to the data submitted by another applicant.

situations, it is acceptable that the trade names of IMPs to be used are not identified, for instance:

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 an MA in the MS concerned. To notify this, they should complete Section D1b of the application form and in Section D2 they should provide the name routinely used to describe the product in the protocol under 'Product Name' and the name of the active substance.

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 D1b and in Section D2 they should provide the name routinely used to describe the regimen in the protocol under 'Product Name' and the name of each active substance.

c) In other trials the sponsor may wish to study the effect of a number of treatments on a specific illness without specifying the IMPs to be used. To achieve this he should identify the treatment using its ATC Code (level 3-5) in the protocol and complete Section D1b and D2 of the application form.

4.2 Notification of amendments

4.2.1 Scope

Article 10 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 forthwith.

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 i.e. those that are not 'substantial' as indicated by the criteria in 4.2.3. However, they should be recorded and be available on request for inspection at the trial site and/or the sponsors premises as appropriate.

4.2.3 Substantial amendments

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 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. Not all amendments to those aspects of a trial need to be notified, only those that meet the criteria of "substantial" above. Also the list is not exhaustive; a substantial amendment might occur in some other aspect of a trial.

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[8]. The sponsor should first assess on a case-by-case basis whether or not an amendment is substantial using criteria from 4.2.3 above and the list of headings in attachment 5. Where a substantial amendment affects more than one protocol 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 protocols with their EudraCT numbers.

The sponsor or his legal representative in the Community 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 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 committee, the sponsor should make 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 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 should be sufficient to

[8] This procedure should also be followed to report substantial amendments to the relevant ethics committee. See detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use.

submit the amendment notification form (Annex 2) indicating in the first page that it is "for information".

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 F. 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;
- description of the amendment and reason.

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

- summaries of data, if applicable;
- an updated overall risk benefit assessment, where applicable;
- 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 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 if 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 if 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 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 within 15 days using the form at annex 3. They may not recommence the trial in that MS until 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

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 declaration of end of trial form at Annex 3.

4.2.10 Infringements

Where the CA has objective grounds for considering 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

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 end of the trial within 90 days of the end of the clinical trial. Whenever a trial is terminated early the sponsor must notify the competent authority(ies) concerned within 15 days and clearly explain the reasons.

If the sponsor decides not to commence the trial initially or not to recommence the trial after halting it, they should notify the competent authority(ies) concerned using the form at Annex 3. They do not have to expedite the notification but should submit a letter that should identify the protocol, its sponsor's protocol code number and EudraCT number and provide a brief explanation of the reasons for not starting the trial or for ending it.

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).

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 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

INFORMATION REQUIRED	AT	BE	DK	FI	FR	DE	EL	IT	IE	LU	NL	PT	ES	SE	UK
CORE INFORMATION															
Receipt of confirmation of EUDRACT number	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Covering letter	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Application form	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Protocol with all current amendments	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Investigator's brochure	Yes	Yes A	Yes	Yes A	Yes	Yes	Yes A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes A
Investigational Medicinal Product Dossier (IMPD)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes A	Yes	Yes
Simplified IMPD for known products. See table 1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes A	Yes	Yes
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	Yes	Yes
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	Yes	Yes	Yes	Yes	Yes
Copy of ethics committee opinion in the MS concerned when available	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes B	Yes	Yes
ADDITIONAL INFORMATION FOR SPECIAL SITUATIONS															
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
MS SPECIFIC INFORMATION															
Subject related															
Informed consent form	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Subject information leaflet	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No
Arrangements for recruitment of subjects	Yes	No	No	Yes	No	No	No	No	No	No	Yes	No	No	No	No
Protocol related									A						
Summary of the protocol in the national language	No	B	No	No	Yes	No		Yes	Yes	A	Yes	No	Yes	No	Yes
Outline of all active trials with the same IMP	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Peer review of trial when available	Yes	No	No	No	Yes	Yes	Yes	No	No	Yes	Yes	No	No	No	No
Ethical assessment made by the principal/coordinating investigator	No	No	Yes	No	No	No		No	No	No	Yes	No	No	No	No

INFORMATION REQUIRED	AT	BE	DK	FI	FR	DE	EL	IT	IE	LU	NL	PT	ES	SE	UK
IMP related															
If IMP manufactured in E.U. :															
– 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	Yes	Yes
If IMP not manufactured in E.U. :															
Declaration of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes A
– Copy of the importer authorization as referred to in Art. 13.1. of the Directive	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes		Yes	Yes	Yes
Certificate of analysis for test product in exceptional cases :															
– Where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	Yes	C	Yes	Yes	Yes	Yes		Yes	Yes	B	Yes		Yes	Yes	Yes
Viral safety studies	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Examples of the label in the national language	No	C	No	No	No	Yes		Yes	Yes	B	Yes	Yes	Yes	Yes	Yes
Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	C	Yes	Yes	Yes	No		Yes	Yes	B	Yes	Yes	Yes	Yes	Yes
TSE Certificate when applicable	Yes	Yes	Yes	Yes	Yes A	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Declaration of GMP status of active biological substance	Yes	Yes	Yes	Yes	No	Yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Facilities & staff related															
Facilities for the trial	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No
CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	No	No	Yes	No	No	Yes	No	Yes	Yes	Yes	No	No	No	No
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	No	No	No	No
Information about supporting staff	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No
Finance related															
Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	No	No	No	Yes	No	Yes	No	No	B	Yes	Yes	No	No	No
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
Compensations to investigators	Yes	No	No	No	Yes	No	Yes	Yes	No	No	Yes	Yes	No	No	No
Compensations to subjects	Yes	No	No	No	No	No	Yes	Yes	No	No	Yes	Yes	No	No	No
Agreement between the sponsor and the trial site	No	No	No	No	No	No	No	Yes	No	No	Yes	Yes B	No	No	No

INFORMATION REQUIRED BY NEW MEMBER STATES' COMPETENT AUTHORITIES

INFORMATION REQUIRED	CY	CZ	EE	HU	LV	LT	MT	PL	SK	SI		NO	IS
CORE INFORMATION													
Receipt of confirmation of EUDRACT number		Yes	Yes		No	Yes						Yes	
Covering letter		Yes		Yes	Yes	Yes						Yes	
Application form		Yes	Yes	Yes	Yes	Yes						Yes	
Protocol with all current amendments		Yes	Yes	Yes	Yes	Yes						Yes	
Investigator's brochure		Yes	Yes	Yes	Yes	Yes						Yes	
Investigational Medicinal Product Dossier (IMPD)		Yes	Yes	Yes	No	Yes						Yes	
Simplified IMPD for known products. See table 1		Yes	Yes	Yes	No	Yes						Yes	
Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community)		Yes	Yes	Yes	Yes	Yes						Yes	
List of Competent Authorities to which the application has been submitted and details of decisions		Yes	Yes	Yes	Yes A	Yes						Yes	
Copy of ethics committee opinion in the MS concerned when available		Yes	Yes	No	Yes	Yes						Yes	
ADDITIONAL INFORMATION FOR SPECIAL SITUATIONS													
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	
Copy of authorisation for contained use release of genetically modified organisms (when applicable and available)		No		?								No	
MS SPECIFIC INFORMATION													
Subject related													
Informed consent form		Yes	Yes	Yes	Yes	Yes						Yes	
Subject information leaflet		Yes	Yes	Yes	Yes	Yes						Yes	
Arrangements for recruitment of subjects		Yes	No	Yes	No	Yes						No	
Protocol related													
Summary of the protocol in the national language		Yes	No	No	No	Yes						No	
Outline of all active trials with the same IMP		Yes	Yes	Yes	No	Yes						Yes	
Peer review of trial when available		No	No	Yes	No	Yes						No	
Ethical assessment made by the principal/coordinating investigator		No	No	No	No	No						Yes A	

INFORMATION REQUIRED	CY	CZ	EE	HU	LV	LT	MT	PL	SK	SI		NO	IS
IMP related													
If IMP manufactured in E.U. :													
☐ 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	
If IMP not manufactured in E.U. :													
☐ Declaration of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP		Yes	Yes	Yes	Yes	Yes						Yes	
☐ Copy of the importer authorization as referred to in Art. 13.1. of the Directive			Yes	Yes	Yes	Yes						Yes	
Certificate of analysis for test product in exceptional cases :													
☐ Where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected		Yes	Yes	Yes A	Yes B	Yes						Yes	
Viral safety studies		Yes	Yes	Yes	Yes C	Yes						Yes	
Examples of the label in the national language		No	Yes	Yes	Yes	Yes A						Yes	
Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals		Yes	Yes	Yes	Yes C	Yes						No B	
TSE Certificate when applicable		Yes	Yes	Yes	Yes	Yes						Yes	
Declaration of GMP status of active biological substance		Yes	Yes	Yes	No	Yes						Yes	
Facilities & staff related			No										
Facilities for the trial		No		Yes	Yes	No						No	
CV of the coordinating investigator in the MS concerned (for multicentre trials)		No		Yes	No	No						C	
CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)		No		Yes	Yes	Yes						C	
Information about supporting staff		No		No	Yes	No						No	
INFORMATION REQUIRED													
Finance related			No										
Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial		No		Yes	Yes	Yes						Yes	
Any insurance or indemnity to cover the liability of the sponsor or investigator		No	Yes	Yes	Yes	Yes						Yes	
Compensations to investigators		No		Yes	No	No						No	
Compensations to subjects		No		Yes	No	No						No	
Agreement between the sponsor and the trial site		No		Yes	No	Yes						No	

MEMBER STATES ADDITIONAL EXPLANATION

The letters (e.g. A.B.C.) preceding information below refer to letters under the MS column in the table above and provide additional explanation about the information to be provided. The asterisks (*) refer to asterisks in the table above and provide comments from MS for discussion.

Belgium:

A. With the waiver laid down by the provisions of this guideline;
B. If available;
C. On request.

Finland:

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

France:

A. If not in the IMPD

Greece:

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

Hungary:

A. Certificate of analysis for test product required in every case.

Ireland:

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

Latvia:

A. On request. In all cases the list of the countries where application has been submitted;
B. In all cases certificate of analysis for the test product should be submitted;
C. On request.

Lithuania:

A. For authorised products in Lithuania, for others according to the Directive 2001/20/EC "in at least the official language on the outer packaging of investigational medicinal products or where there is no outer packaging, on the immediate packaging".

Luxembourg:

A. If availble ;
B. On request.

Norway:

A. The application form specific to the ethics committee in Norway should be sent to NoMA
B. A copy of the authorisation is not required by NoMA, but the authorisation needs to be obtained from another authority.
C. To be determined

Portugal :

A. List of investigators;
B. With letter declaring conflicts of interest.

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.

UK

A. On request

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

3.2.S DRUG SUBSTANCE

3.2.S.1 General Information:
3.2.S.1.1 Nomenclature
3.2.S.1.2 Structure
3.2.S.1.3 General Properties

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

3.2.S.3 Characterisation
3.2.S.3.1 Elucidation of Structure and Other Characteristics
3.2.S.3.2 Impurities

3.2.S.4 Control of Drug Substance:
3.2.S.4.1 Specification
3.2.S.4.2 Analytical Procedures
3.2.S.4.3 Validation of Analytical Procedures
3.2.S.4.4 Batch Analyses
3.2.S.4.5 Justification of specification

3.2.S.5 Reference Standards or Materials

3.2.S.6 Container Closure System:

3.2.S.7 Stability

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Medicinal Product:

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

3.2.P.2.2 Drug Product
3.2.P.2.2.1 Formulation Development
3.2.P.2.2.2 Overages
3.2.P.2.2.3 Physicochemical and Biological Properties

3.2.P.2.3 Manufacturing Process Development

ATTACHMENT 2 (CONTD)

3.2.S.6 Container Closure System

3.2.P.2.5 Microbiological Attributes
3.2.P.2.6 Compatibility

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

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

3.2.P.5 Control of drug product
3.2.P.5.1 Specification(s)
3.2.P.5.2 Analytical Procedures
3.2.P.5.3 Validation of Analytical Procedures
3.2.P.5.4 Batch Analyses
3.2.P.5.5 Characterisation of Impurities
3.2.P.5.6 Justification of Specification(s)

3.2.P.6 Reference Standards or Materials:

3.2.P.7 Container Closure System:

3.2.P.8 Stability

3.2.A APPENDICES
3.2.A.1 Facilities and Equipment:
3.2.A.2 Adventitious Agents Safety Evaluation:
3.2.A.3 Novel Excipients