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The rules governing medicinal products in the European Union

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NOTICE TO APPLICANTS

Questions & Answers

Clinical Trial Documents

April 2006

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General Notes

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well being of trial subjects are protected, and that the clinical trial data are credible.

Requirements for the conduct of clinical trials in the EU including GCP and GMP and inspections of these, are provided for in the Clinical Trial Directive ([Directive 2001/20/EC](#)).

Clinical trials included in any marketing authorisation application in the EU are required to be conducted in accordance with GCP ([Directive 2001/83/EC](#) Annex I).

Europe has adopted the [ICH-GCP](#) in July 1996 and this is published in EudraLex [Volume 3](#). ICH has developed unified standards for the EU, US and Japan. Further information on ICH can be found on DG Enterprise and Industry [ICH](#) site.

Additional information on GCP can be found on the websites of international organisations such as the Council for International Organizations of Medical Science ([CIOMS](#)) and World Medical Association has developed the Declaration of Helsinki ([WMA](#)).

In case of Regulatory or Administrative questions concerning EU related procedures, please send an E-mail to birka.lehmann@cec.eu.int

Questions in relation to legislation

Question 1: Will trials ongoing at the time of implementation need to be entered on to the EudraCT database or receive a EudraCT number. Will there be any transitional arrangements for trials started before the implementation date?

Answer:

Only trials commencing as of 1 May 2004, with at least one site in one Member State (MS) where the transposition of the *Article 11* of Directive 2001/20/EC is finalised have to be entered in the EudraCT database, and receive a EudraCT number.

Where a trial has commenced in one Member State prior to 1 May 2004, but application is made in another Member State post 1 May 2004, a EudraCT number should be obtained on the occasion of the application made post 1 May 2004 and the electronic data form set submitted with the application to the new Member States concerned. The competent authority(ies) in the Member State(s) where the application(s) was (were) made prior to 1 May 2004, should be informed by the sponsor as soon as possible of the EudraCT number. In MS where transposition is not finalised, the entry on to the EudraCT database and the application for an EudraCT number is not mandatory, but only recommended.

Question 2: Provisions of the Directive 2001/20/EC will not be implemented in some Member States on the 1st of May 2004. How will the studies conducted after the 1st of May 2004 in such Member States be taken into account during the assessment of a marketing authorisation dossier?

Answer: Annex I of Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use provides in the “Introduction and general principles”, paragraph 8, that “*all clinical trials conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. If they are to be taken into account during the assessment of an application for marketing authorisation, clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on the basis of principles of good clinical practice and ethical principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki.*”

In the context of a late implementation of provisions of the Directive in a Member state, a clinical trial conducted in that Member State will be taken into account during the assessment of a marketing application if it is designed, implemented and reported in accordance with:

- the local regulations;
- principles of good clinical practice and ethical principles which are at least equivalent to those laid down in the community guideline Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

Questions in relation to the sponsor/investigator and the legal representative (article 2 and article 19 of Directive 2001/20/EC)

Question 3: The definition and responsibilities of sponsor are given in Article 2 of Directive 2001/20/EC

(e) 'sponsor': an individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial;

How should this definition be interpreted?

Answer:

As defined in the Directive the sponsor can be an individual, a company, an institution or an organisation. The sponsor does not need to be located in an EU Member State but has to have a legal representative in the EU. The investigator and the sponsor may be the same person.

The sponsor may delegate any or all of his trial-related tasks/duties and functions to an individual, company, institution or organisation. In cases where there are tasks and functions delegated to other persons/parties, there must be still an overall sponsor for the trial. Any trial-related duties and functions that are delegated to a third party should be specified in writing.

The sponsor might delegate his tasks and duties e.g.

- for compiling the documents for the application to the Ethics Committee and/or Competent Authorities including
 - obtaining details of the manufacturing and import authorisation;
- for the monitoring of the trial including all responsibilities for the pharmacovigilance reporting system according to Articles 16 and 17 of Directive 2001/20/EC.

However, in such cases the sponsor remains ultimately responsible for ensuring that the conduct of the trials and the final data generated by those trials comply with the requirements of Directive 2001/20/EC as well as of Directive 2001/83/EC in the case of a marketing authorisation application.

Allocation of trial-related responsibilities

Prior to initiating a trial, the sponsor should define, establish and allocate all trial-related duties and functions.

A number of parties may agree, in writing, to form an organisation according to Article 2 of Directive 2001/20/EC and to distribute the sponsors tasks/duties and functions between different 'person(s) and/or 'organisation(s)'. This is done in such a way that the collective agreement fulfils all the required roles and responsibilities of the sponsor.

The organisation will be identified by its name and by the EudraCT number (YYYY-NNNNNN-CC and a group name) for the purpose of the trial and on the related documents.

Implications on non-commercial clinical trials support received

Support from industry by providing medicinal products free or at reduced costs or by providing financial or material or scientific support should not be taken to imply that industry is participating in the trials for the purpose of the Commission Directive on Good Clinical Practice and should not disqualify the trial from being regarded as a non-commercial trial.

Question 3 a: The definition and responsibilities of the legal representative of a non EEA-sponsor according to Article 19¹

If the sponsor is not established in the Community a legal representative of the sponsor must to be established in the Community. The legal representative shall have the position of the sponsor with regard to civil and criminal liability in the Community.

It is required to have one legal representative located in the EU for a non-EU sponsored trial taking place in EU.

Only one legal representative can act on behalf of one sponsor in one clinical trial. If the sponsor is the same for several different trials, it is not required to have **one** legal representative located in the EU for **all non-EU** sponsored trials taking place in EU.

It is acceptable to use an established company as a legal representative. It is also acceptable to have one central legal representative in EU for all trials.

It is not acceptable to divorce responsibilities for liability for trial conduct. In the absence of the sponsor in the EU, the legal representative should be responsible for the civil and criminal liability of the sponsor in accordance to Article 19 of Directive 2001/83/EC.

¹ Article 19(1) This Directive is without prejudice to the civil and criminal liability of the sponsor or investigator. To this end, the sponsor or the legal representative of the sponsor must be established in the Community.

The applicant for the application to the competent authority and the Ethics Committee might be different from the legal representative.

Questions in relation to the application

Question 4: Validation of application for Ethics Committee opinion

Section 6.1.1 of the detailed guidance ‘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’ states that “*the application to the Ethics Committee is considered valid if it fulfils the requirements listed. If that is the case, the applicant will be informed and the review period starts*”. According to the Directive, Ethics Committee opinion must be provided (for most trials) within 60 days of receipt of a valid Ethics Committee application. Will the 60 day approval period commence when a valid application is submitted or when the Ethics Committee notifies the Sponsor that the application is valid? Is there a danger that Ethics Committees will delay the notification of validity to gain time?

Answer:

Validation is an administrative check that all required documents are available, with dates and signatures where required, so that the Ethics Committee can start to evaluate the dossier and can give an opinion. The 60 day approval period commences when Ethics Committee has informed the sponsor that it has reached the conclusion that the application is valid.

Question 4a: Ethics Committee opinion and appeal

After the receipt of the opinion of the Ethics Committee is the applicant allowed to appeal against the opinion?

Answer:

As the opinion taken by the Ethics Committees has a legal implication, according to national legislation in place in Member States, appeal procedures should be possible.

Question 5: Multi-centre/multi-national trial

Where an application for a clinical trial is submitted in more than one Member State, has a company or non-commercial research organisation to await positive opinions from all Member States Ethics Committees and authorisations/ statements of no grounds for non-acceptance from competent authorities, , before commencing the trial in any of the Member States?

Answer:

No, the sponsor/investigator can commence a clinical trial in the Member State concerned if the positive opinion of the Ethics Committee in that Member State and the authorisation/statement of no grounds for non-acceptance of the competent authority in question, have been given.

Question 5a: Change of site or principal investigator

It is common that all sites that have been invited to participate in a clinical trial did not have time to reach a decision on whether to participate or not before the application is submitted to the Competent Authorities and Ethics Committees. What should the sponsor do when additional sites want to participate after the trial has started or when there is a change of the principal investigator in an ongoing trial? If a site does not start the trial, but was listed on the application form when the trial got authorisation, what should the sponsor do?

Answer:

When a sponsor proposes to add a new site for a clinical trial, this should be notified to the Competent Authority as well as to the relevant Ethics Committee. The Ethics Committee will have to give a positive opinion on the participation of the new site and the new principal investigator. The sponsor's obligation can be met by submitting a Notification of Amendment Form and completing section D and F of the application form.

The same procedure can be used to notify a change of the co-ordinating or a principal investigator. Both changes are considered as substantial amendments.

Question 6: What is meant by 'compensation for participation' in a trial (Article 4 d)?

Answer: This subject is addressed in the guidance to Ethics Committees under item 21 in Section 7.2 in the example of a module 2 for the application form to the Ethics Committees. Item 21 reads: "Amount and procedure for remuneration or compensation of subjects" and the following explanation is given: "description of amount paid during the participation in the trial and for what, i.e. travel costs, loss of earning and discomfort etc."

Question 7: What is the requirement to be an expert (in paediatrics) in Ethics Committee?

Answer: The requirement for membership in an Ethics Committee is to be defined in national regulations.

Question 8: Article 2 of Directive 2001/20/EC defines the clinical trials. Further guidance is requested.

The following algorithm/decision tree can be used to answer the question "Is it a clinical trial of a medicinal product?"

IS IT A CLINICAL TRIAL OF A MEDICINAL PRODUCT?

This algorithm and its endnotes will help you answer that question. Please start in column A and follow the instructions. Additional information is provided in the notes at the end of the table. If you have doubts about the answer to any of the questions contact the clinical trials unit of your competent authority.

A	B	C	D	E
A CLINICAL TRIAL OF A MEDICINAL PRODUCT?				A NON-INTERVENTIONAL CLINICAL TRIAL?
Is it a medicinal product (MP)? ⁱ	Is it not a medicinal product?	What effects of the medicine are you looking for?	Why are you looking for those effects?	How are you looking for those effects?
<p>If you answer no to <u>all</u> the questions in column A, the activity is not a clinical trial on a MP.</p> <p>If you answer yes to <u>any</u> of the questions below go to column B.</p>	<p>If you answer yes to the question below in column B the activity is not a clinical trial on a MP.</p> <p>If you answer no to this question below go to column C.</p>	<p>If you answer no to <u>all</u> the questions in column C the activity is not a clinical trial under the scope of Directive 2001/20/EC.</p> <p>If you answer yes to <u>any</u> of the questions below go to column D.</p>	<p>If you answer no to <u>all</u> the questions in column D the activity is not a clinical trial under the scope of Directive 2001/20/EC.</p> <p>If you answer yes to <u>any</u> of the questions below go to column E.</p>	<p>If you answer yes to <u>all</u> these questions the activity is a non-interventional trial which is outside the scope of Directive 2001/20/EC. If your answers in columns A,B,C & D brought you to column E and you answer no to <u>any</u> of these questions the activity is a clinical trial within the scope of the Directive.</p>
<p>A.1 Is it a substanceⁱⁱ or combination of substances presented as having properties for treating or preventing disease in human beings ?</p> <p>A.2 Does the substance function as a medicine? i.e. can it be administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis or is otherwise administered for a medicinal purpose?</p> <p>A.3 Is it an active substance in a pharmaceutical form?</p>	<p>B.1 Are you <u>only</u> administering any of the following substances?</p> <ul style="list-style-type: none"> • Human whole bloodⁱⁱⁱ; • Human blood cells; • Human plasma; • Tissues except a somatic cell therapy medicinal product^{iv}; • A food product^v (including dietary supplements) not presented as a medicine; • A cosmetic product^{vi} • A medical device 	<p>C.1 To discover or verify/compare its clinical effects?</p> <p>C.2 To discover or verify/compare its pharmacological effects, e.g. pharmacodynamics?</p> <p>C.3 To identify or verify/compare its adverse reactions?</p> <p>C.4 To study or verify/compare its absorption, distribution, metabolism or excretion?</p>	<p>D.1 To ascertain or verify/compare the efficacy^{vii} of the medicine?</p> <p>D.2 To ascertain or verify/compare the safety of the medicine?</p>	<p>E.1 Is this a study of one or more medicinal products, which have a marketing authorisation in the Member State concerned?</p> <p>E.2 Are the products prescribed in the usual manner in accordance with the terms of that authorisation?</p> <p>E.3 Does the assignment of any patient involved in the study to a particular therapeutic strategy fall within current practice and is not decided in advance by a clinical trial protocol^{viii}?</p> <p>E.4 Is the decision to prescribe a particular medicinal product clearly separated from the decision to include the patient in the study?</p> <p>E.5 Will no diagnostic or monitoring procedures be applied to the patients included in the study, other than those which are applied in the course of current practice?</p> <p>E.6 Will epidemiological methods be used for the analysis of the data arising from the study?</p>

ⁱ Article 1.2 of Directive 2001/83/EC is replaced by Article 1.1 of Directive 2004/27/EC which provides the definition of "medicinal product" which applies for the purposes of Directive 2001/20/EC.

ⁱⁱ Substance is any matter irrespective of origin e.g. human, animal, vegetable or chemical that is being administered to a human being.

ⁱⁱⁱ This does not include derivatives of human whole blood, human blood cells and human plasma that involve a manufacturing process.

^{iv} Somatic cell therapy medicinal products use somatic living cells of human (or animal) origin, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventative effect (in humans) through metabolic, pharmacological and immunological means.

^v Any ingested product which is not a medicine is regarded as a food. A food is unlikely to be classified as a medicine unless it contains one or more ingredients generally regarded as medicinal and indicative of a medicinal purpose.

^{vi} The Cosmetic Directive 76/768/EC, as amended harmonises the requirements for cosmetics in the European Community. A "cosmetic product" means any substance or preparation intended for placing in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and mucous membranes of the oral cavity with the view exclusively or principally to cleaning them, perfuming them or protecting them in order to keep them in good condition, change their appearance or correct body odours.

^{vii} Efficacy is the concept of demonstrating scientifically whether and to what extent a medicine is capable of diagnosing, preventing or treating a disease and derives from EU pharmaceutical legislation.

^{viii} Assignment of patients to a treatment group by randomisation planned by a clinical trial protocol cannot be considered as current practice.