



EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels, 16 December 2008
ENTR/F/2/SF D(2008) 41047

**THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN UNION
VOLUME 10 - GUIDANCE DOCUMENTS APPLYING TO CLINICAL TRIALS**

QUESTIONS & ANSWERS

VERSION 2.0 (DECEMBER 2008)

Document history:	
Date of adoption of draft by the ad-hoc group for the development of implementing guidelines for the “Clinical Trials Directive” 2001/20/EC:	
Date of publication by the Commission:	16 December 2008
Date of entry into force:	N/A
Supersedes:	Version 1.0 of April 2006
Changes compared to superseded version 1.0:	Deleted Q&A: # 2
	New Q&As: ## 12, 13
	Revised Q&As: ## 1, 6; Annex

Keywords: Clinical trials, Directive 2001/20/EC, Directive 2005/28/EC, Questions and answers

Important notice: The views expressed in this questions and answers document are not legally binding. Ultimately, only the European Court of Justice can give an authoritative interpretation of Community law.

All updates to this questions and answers document are presented and discussed in the “*Ad hoc* group for the development of implementing guidelines for the ‘Clinical Trials Directive’ 2001/20/EC”. This group is chaired by the Commission and is composed of representatives of all EU Member States and EEA contracting parties.

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1. THE SCOPE OF CLINICAL TRIALS REGULATION IN THE EU

1.1. Question 1: What is a “clinical trial”?

1. **Answer:** A “clinical trial” is defined in Article 2 of Directive 2001/20/EC.¹ The decision tree in Annex 1 can be used to identify whether a trial is a clinical trial in the sense of that Directive.

1.2. Question 2: The provisions of the Directive 2001/20/EC will not be implemented in some Member States on the 1st of May. 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?

2. **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 use² 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.”*
3. 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).

¹ OJ L 121, 1.5.2001, p. 34.

² OJ L 311, 28.11.2001, p. 67, as amended.

2. SPONSOR/LEGAL REPRESENTATIVE; INVESTIGATOR

2.1. Question 3: How is “sponsor” defined?

4. **Answer:** “Sponsor” is defined in Article 2(e) of Directive 2001/20/EC: “an individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial.”
5. Thus, 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.³ The investigator and the sponsor may be the same person.⁴

2.2. Question 4: Can the sponsor delegate tasks or responsibilities?

6. **Answer:** The sponsor may delegate any or all of his trial-related tasks/duties and functions to an individual, company, institution or organisation.⁵ The sponsor might delegate e.g.
 - the compiling the documents for the application to the Ethics Committee and/or Competent Authorities including obtaining details of the manufacturing and import authorisation;
 - the monitoring of the trial including all responsibilities for the pharmacovigilance reporting system according to Articles 16 and 17 of Directive 2001/20/EC.
7. In cases where there are tasks and functions delegated to other persons/parties, there must be still an overall sponsor for the trial. 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.⁶
8. Prior to initiating a trial, the sponsor should define, establish and allocate all trial-related duties and functions. Any trial-related duties and functions that are delegated to a third party should be specified in writing.
9. 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.

³ Article 19 of Directive 2001/20/EC.

⁴ Article 7(2) of Directive 2005/28/EC.

⁵ Article 7(1) of Directive 2005/28/EC.

⁶ Article 7(1) of Directive 2005/28/EC.

10. 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.

2.3. Question 5: What are the responsibilities of the legal representative of a non EEA-sponsor in view of Article 19 of Directive 2001/20/EC?

11. **Answer:** If the sponsor is not established in the Community a legal representative of the sponsor has to be established in the Community.⁷ The legal representative shall have the position of the sponsor with regard to civil and criminal liability in the Community.
12. Only one legal representative can act on behalf of one sponsor in one clinical trial.
13. 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 the EU.
14. 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.
15. 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.
16. The applicant for the application to the competent authority and the Ethics Committee might be different from the legal representative.

3. CLINICAL TRIALS APPLICATION PROCEDURE, ETHICS COMMITTEES

3.1. Question 6: 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?

17. **Answer:** Section 4 of the “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 to be valid if all required documents are complete. If that is the case the applicant will be informed and the review period starts*”. According to Article 6(5) of Directive 2001/20/EC, the Ethics Committee opinion must be provided (for most trials) within 60 days of receipt of a valid Ethics Committee application.
18. 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.

⁷ Article 19 of Directive 2001/20/EC.

3.2. Question 7: After the receipt of the opinion of the Ethics Committee, is the applicant allowed to appeal against the opinion?

19. **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.

3.3. Question 8: 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?

20. **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.

3.4. Question 9: Change of site or principal investigator

21. It is common that all sites 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?**
22. **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.
23. 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.

3.5. Question 10: What is the requirement to be an expert (in paediatrics) in Ethics Committee?

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

4. “INFORMED CONSENT” AND OTHER SUBSTANTIAL REQUIREMENTS FOR CONDUCTING CLINICAL TRIALS

4.1. Question 11: What is meant by ‘compensation for participation’ in a trial (Article 4(d) of Directive 2001/20/EC)?

25. **Answer:** This is addressed in the “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” under item 21 in the example of a module 2 for the application form to the Ethics Committees: “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.”

5. ADVERSE REACTION REPORTING

5.1. Question 12: Ninety Day report for Early Phase Trials

26. **Sometimes, even late in the development process, Phase I, short term metabolism or pharmacokinetic studies are conducted. Once the development progresses to Phase II, should the sponsor notify the annual safety report and no longer provide the short term safety report for each trial as described above or does he need to provide a short term safety report for every Phase I study?**

27. **Answer:** Chapter 5.2.2. of the “Detailed Guidance on the Collection, Verification and Presentation of Adverse Reaction Reports Arising From Clinical Trials on Medicinal Products for Human Use”⁸ reads: “In case of a first-in-man trial and subsequent short term metabolism or pharmacokinetic studies the safety report should be notified within 90 days of the end of trial together with the notification of the end of the trial according to Article 10(c) of Directive 2001/20/EC”.

28. However, the intent of the guidance is that the 90 day report is intended for early phase development. Once development has progressed to Phase II and III, and the annual safety reports have started, there is no ongoing requirement to submit 90 day safety reports for each and every phase I trial conducted in parallel with the Phase II or III trials.

5.2. Question 13: SUSAR Reporting

29. **With reference to Article 17(1)(a) of Directive 2001/20/EC, what are the timelines for sponsors regarding the reporting of initial and follow-up information about suspected unexpected serious adverse reactions that are fatal or life threatening?**

30. **How should this be handled from a practical point of view as regards electronic reporting in accordance with ICH E2B(R2)?**

⁸ http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/21_susar_rev2_2006_04_11.pdf

31. **Answer:** For fatal and life threatening SUSARs the sponsor should report at least the minimum information⁹ as soon as possible¹⁰ and in any case no later than seven days after being made aware of the case.

- If the initial report is incomplete, e.g., if the sponsor has not provided all the information/assessment within seven days, the sponsor should submit a completed report based on the initial information within an additional eight days. In this instance, the receipt date should not be changed with regard to the initial report. As regards the electronic reporting of Individual Case Safety Reports (ICSRs) this means that the date specified in the ICH E2B(R2) field A.1.6 'Receive date' should equal the date specified in the ICH E2B(R2) field A.1.7 'Receipt date'.
- If significant¹¹ new information on an already reported case is received by the sponsor, the clock starts again at day zero¹² i.e. at the date of receipt of new information (field A.1.7). This information should be reported as a follow-up report within 15 days. As regards the electronic reporting of Individual Case

⁹ Minimum information (ICH E2BR(2) guideline): The minimum information for the transmission of a report should include at least the EudraCT number, one identifiable patient (section B.1), one identifiable reporter (section A.2), one reaction/event (section B.2), and one suspect drug (section B.4). Because it is often difficult to obtain all the information, any one of several data elements is considered sufficient to define an identifiable patient (e.g., initials, age, sex) or an identifiable reporter (e.g., initials, address, qualification). It is also recognized that the patient and the reporter can be the same individual and still fulfil the minimum reporting criteria. In addition, to properly process the report, the following administrative information should be provided: the sender's (case) safety report unique identifier (A.1.0.1), the date of receipt of the most recent information (A.1.7), the worldwide unique case identification number (A.1.10) and the sender identifier (A.3.1.2).

¹⁰ Article 17(1)(a) Directive 2001/20/EC.

¹¹ Significant new information relates to any new or updated information on the case that impacts on the medical interpretation of the case e.g. change in the causality assessment. Therefore, the identification of significant new information requiring expedited reporting always requires medical judgement. Situations where the seriousness and/or expectedness criteria and/or the causality assessment related to an individual case are downgraded (e.g. follow up information leads to a change of the expectedness from serious unexpected to serious expected or causality assessment is changed from related to non-related) should also be considered as significant change and thus reported on an expedited basis. In addition, the sponsor should also report follow-up information on an expedited basis, where new administrative information is available, that could impact on the case management e.g. new case identifiers have become known to the sponsor, which may have been used in previous transmissions (ICH E2B(M) field A.1.11 'Other case identifiers in previous transmissions'); this information may be specifically relevant for the receiver to manage potential duplicates. Another example refers to ICH E2B(M) field A.1.8 'Additional available documents held by sender', whereby new documents that have become available to the sponsor may be relevant for the medical assessment of the case. In contrast, non-significant information, which does not impact on the medical evaluation of the case, does not require expedited reporting. This may refer for example to minor changes of dates (e.g. the day of the birth date) or corrections of typos in the previous case version. Naturally, medical judgment should be applied, as a change to the birth date may constitute a significant change (e.g. with implications on the age information of the patient).

¹² The clock for expedited reporting starts (day 0) as soon as the minimum information has been brought to the attention of the sponsor or an organisation having a contractual arrangement with the sponsor for this clinical trial. The same applies if significant new information on the case is received by the sponsor, i.e. the reporting time clock begins again for the submission of the follow-up report from the day the sponsor receives relevant follow-up information.

Safety Reports (ICSRs) this means that the date specified in the ICH E2B(R2) field A.1.6'Receive date' should be equal the date when the initial report was received and in the ICH E2B(R2) field A.1.7'Receipt date' the date should be indicated when significant new information on the case was received by the Sponsor.

ANNEX: DECISION TREE TO ESTABLISH A WHETHER A TRIAL IS A “CLINICAL TRIAL”

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.</p> <p>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; • A food product^{iv} (including dietary supplements) not presented as a medicine; • A cosmetic product^v • 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^{vi} 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^{vii}?</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>
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ⁱ Cf. Article 1(2) of Directive 2001/83/EC, as amended.

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} 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.

^v 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.

^{vi} 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.

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