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VOLUME 10 - GUIDANCE DOCUMENTS APPLYING TO CLINICAL TRIALS**

**QUESTIONS & ANSWERS  
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**DRAFT – SUBMITTED FOR DISCUSSION TO THE AD-HOC GROUP FOR THE  
DEVELOPMENT OF IMPLEMENTING GUIDELINES FOR THE “CLINICAL TRIALS  
DIRECTIVE” 2001/20/EC**

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**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: What is a “clinical trial”?

1. **Answer:** A “clinical trial” is defined in Article 2 of Directive 2001/20/EC.<sup>1</sup> 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: 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 use<sup>2</sup> 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).

### 1.3. Question: Is the definition of 'medicinal product' relevant for the scope of the Directive 2001/20/EC?

4. **Answer:** Yes.

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<sup>1</sup> OJ L 121, 1.5.2001, p. 34.

<sup>2</sup> OJ L 311, 28.11.2001, p. 67, as amended.

5. When assessing whether a study is a clinical trial as defined in Directive 2001/20/EC, the first question is always whether the object of the study is a medicinal product (see also the algorithm in Annex).
6. 'Medicinal product' is defined in Article 1(2) of Directive 2001/83/EC. Art. 1(2) of the Medicinal Products Directive defines "medicinal product" as follows: "(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or (b) Any substance or combination of substances which may be used in or 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."
7. A substance is thus a medicinal product either by virtue of its "presentation" or its "function". A substance constitutes a medicinal product if it falls within either of these two categories.
8. To establish the 'borderline' between a medicinal product and other products, the established criteria, as further explained in detailed Commission guidance apply. Such Commission guidance exists in particular for the borderline
  - Medicinal product – cosmetic product;<sup>3</sup> and
  - Medicinal product – medical device<sup>4</sup>.
9. With regard to a medicinal product by "virtue of function", in some cases it may not be 100% certain whether the product which is object of the study exerts a pharmacological, immunological or metabolic action. In this respect reference is made to Section 1.2. of the Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial ('detailed guidance CT-1').<sup>5</sup>

**1.4. A study might involve the administration of a medicinal product, while the object of the investigation is not the administered medicinal product, but exclusively the physiology of the body. Are these studies 'clinical trials' as defined in Directive 2001/20/EC?**

10. **Answer:** No.
11. There may be studies which have as the only object to investigate the physiology of the body. In these studies, a medicinal product is administered only in order to obtain a physiological response in order to study the physiology of the body, i.e. without the medicinal product itself being the object of the investigation. Rather, the medicinal product is administered to provoke a pharmacological response which is needed to study the physiology of the body.

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<sup>3</sup> [http://ec.europa.eu/enterprise/sectors/cosmetics/files/doc/guidance\\_doc\\_cosm-medicinal\\_en.pdf](http://ec.europa.eu/enterprise/sectors/cosmetics/files/doc/guidance_doc_cosm-medicinal_en.pdf)

<sup>4</sup> [http://ec.europa.eu/enterprise/sectors/medical-devices/files/meddev/2\\_1\\_3\\_rev\\_3-12\\_2009\\_en.pdf](http://ec.europa.eu/enterprise/sectors/medical-devices/files/meddev/2_1_3_rev_3-12_2009_en.pdf)

<sup>5</sup> OJ C 82, 30.3.2010, p. 1.

12. Examples are a study of the physiology of the retina where a pupil dilator may be used in order to enable the study of the physiology of the retina. Another example is the use of a vasodilator to study how the endothelial function is affected by disease (or other factors not including medicinal products), the use of diagnostic agents to study the effect of disease (or other factors not including medicinal products) or the use of a challenge agent to study the effect of disease (or other factors not including medicinal products). This issue is also relevant for radiopharmaceuticals used as diagnostic agents (see below).
13. These studies are not 'clinical trials' as defined in Article 2(a) of Directive 2001/20/EC. Consequently, the medicinal product administered is not an investigational medicinal product as defined in Article 2(d) of Directive 2001/20/EC.
14. These studies are not regulated at EU-level. It is up to Member States to decide whether and how they to regulate these studies.
15. However, care has to be taken as to whether the object of an investigation is being 'switched', in the course of a study, from the physiology of the body to the pharmacological effect triggered by the medicinal product. In this case, a study may 'turn into' a clinical trial which falls within the scope of Directive 2001/20/EC, provided it is not non-interventional.

**1.5. Question: How does the issue set out in Question 1.4. apply to PET studies?**

16. **Answer:** A radiopharmaceutical used as diagnostic agent in a PET study is a medicinal product.
17. If the object of the study is the diagnostic potential of the diagnostic agent, the study is a clinical trial and the diagnostic agent is the IMP.
18. Studies may have as object a medicinal product 'A' (radiopharmaceutical or other) while, in addition, a diagnostic agent 'B' is used to study the effect of the medicinal product A. In this case, the study is a clinical trial. In this study, the medicinal product A is an investigational medicinal product as defined in Article 2(d) of Directive 2001/20/EC. However, the medicinal product 'B' is *not* an investigational medicinal product as defined in Article 2(d) of Directive 2001/20/EC.
19. If the object of the study is only a physiological characteristic where the PET is merely used to study that characteristic, ie there is no medicinal product being object of the study, the study is not a clinical trial. These studies are not regulated at EU-level. It is up to Member States to decide whether and how they to regulate these studies.

**1.6. Question: A study might involve a medical device – what does this mean in terms of EU regulation of clinical trials?**

20. **Answer:** In terms of EU-regulation for clinical trials, a medical device can play a role in different contexts:

21. a) The object of the study is **one integral product** which is a 'combination' of a medical device and a medicinal product:<sup>6</sup> In these cases, firstly the regulatory status of this product (either medicinal product or medical device) needs to be determined in accordance with the definitions in the applicable legislation.<sup>7</sup> In deciding whether the product falls under the definition 'medicinal product' or 'medical device', particular account shall be taken of the principal mode of action. Further information is set out in Commission guidance.<sup>8</sup> If this assessment reveals that the product which is object of the study is a medicinal product, the regulatory framework of Directive 2001/20/EC applies. If this assessment reveals, however, that the product which is object of the study is a medical device, Directive 2001/20/EC does not apply. For example, in the case of a prefilled syringe, this product would usually be a medicinal product (with an integral 'delivery product')<sup>9</sup>. An interventional study would be a clinical trial and thus fall within the regulatory framework of Directive 2001/20/EC.
22. b) The object of the study is **a medicinal product - however, during the clinical trial medical devices are used** (this is frequently the case in practice; sometimes the medical devices are supplied by the sponsor) without these being object of a study: In these cases, Directive 2001/20/EC applies. The medical devices not being object of the study have to comply with the EU-rules for the placing on the market and putting into service of medical devices.
23. c) The object of the study is **two separate products**: one is a medicinal product and one is a medical device. These two separate products may administered/used on subjects in the same group ('arm'), or in different 'arms' (for example, a study might compare a warming medical device applied on the skin with a warming medicinal product applied topically). In these cases Directive 2001/20/EC applies to the aspect of the study having as object the medicinal product. Regarding the medical device being object of the study, Directive 2001/20/EC does not apply, but the EU-rules applicable to medical devices. Member States, while taking into account that two different sets of legislations apply, may have arrangements in place which lead to a single authorising decision for this type of studies.

**1.7. Question: Is a study addressing the time of surgery a clinical trial, if patients receive otherwise standard treatment with medicines?**

24. **Answer:** This is a case by case decision and it depends from whether the object of the study is one of those listed in Article 2(a) of Directive 2001/20/EC. If this is not

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<sup>6</sup> This includes also 'combined advanced therapy medicinal products' as defined in Article 2(1)(d) of the Regulation (EC) 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products.

<sup>7</sup> Regarding medicinal products: See Question 1.3. Regarding medical devices: Directive 93/42/EEC regarding medical devices, Directive 98/79/EC regarding in vitro diagnostic medical devices, or Directive 90/385/EEC regarding active implantable medical devices (texts are accessible here: [http://ec.europa.eu/enterprise/sectors/medical-devices/regulatory-framework/index\\_en.htm#h2-%0A-----legislation%0A-----](http://ec.europa.eu/enterprise/sectors/medical-devices/regulatory-framework/index_en.htm#h2-%0A-----legislation%0A-----) ).

<sup>8</sup> [http://ec.europa.eu/enterprise/sectors/medical-devices/documents/guidelines/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/medical-devices/documents/guidelines/index_en.htm), in particular [http://ec.europa.eu/enterprise/sectors/medical-devices/files/meddev/2\\_1\\_3\\_rev\\_3-12\\_2009\\_en.pdf](http://ec.europa.eu/enterprise/sectors/medical-devices/files/meddev/2_1_3_rev_3-12_2009_en.pdf)

<sup>9</sup> See point B.2.1 of MEDDEV 2.1/3 rev 3.



the case, the study is not a clinical trial. The sponsor has the responsibility to provide clear information on the object of the study.

**1.8. Question: Does the Clinical Trial Directive 2001/20/EC apply to clinical trials with IMPs which fall under the 'hospital exemption' for advanced therapy medicinal products?**

25. **Answer:** Yes.

26. The 'hospital exemption' for advanced therapy medicinal products, which is contained in Article 3(7) of the Directive 2001/83/EC<sup>10</sup> is irrelevant for the scope of the 'Clinical Trials Directive' 2001/20/EC (see also section 1.2, para. 8, of the detailed guidance CT-1<sup>11</sup>). The Directive 2001/20/EC applies to any clinical trial with advanced therapy investigational medicinal products.

**1.9. Question: Is an authorised medicinal product used as comparator in a clinical trial an investigational medicinal product?**

27. **Answer:** Yes.

28. According to Article 2(d) of Directive 2001/20/EC, an investigational medicinal product (“IMP”) is “*a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial [...]*”.

29. Comparators are medicinal products used as a reference in a clinical trial vis-à-vis the substance being tested.

30. The definition of IMP in Article 2(d) of Directive 2001/20/EC clarifies further that it “includes” “[...] *products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form*”. This is intended to clarify what the definition entails. It does not mean that a non-modified medicinal product with a marketing authorisation is not an IMP.

31. The purpose for the inclusion of comparators into the definition of IMP is that they play a fully equivalent, symmetric, role as counterparts to the “tested products”, and this from the inception of the protocol to the interpretation of the study results. The comparator is an IMP and the conditions (circuit, traceability and accountability methods) under which the comparator is used are to be strictly the same as those of the “tested product”.

32. Regarding IMPs there are a number of regulatory requirements. Note, however, that the regulatory framework is adapted to situations where the IMP is used in the authorised form and for the authorised indication. This holds in particular for

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<sup>10</sup> As amended by Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.

<sup>11</sup> OJ C82, 30.3.2010, p. 1.

- the information requirements for request for authorisation to be submitted to the national competent authority of the Member State concerned;<sup>12</sup> and
- the requirements for the labelling of IMP a set out in Article 14 of Directive 2001/20/EC and Annex 13 to the guidelines on good manufacturing practices – Manufacture of investigational medicinal products.<sup>13</sup>

#### 1.10. Question: What can be considered a “non-interventional trial”?

33. **Answer:** According to Article 1(1), 2<sup>nd</sup> period of Directive 2001/20/EC, non-interventional clinical trials are excluded from the scope of this Directive.
34. “Non-interventional trial” is defined in Article 2(c) of Directive 2001/20/EC as follows: *“a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data”*.
35. Thus, a trial is non-interventional if the following requirements are cumulatively fulfilled:
- The medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;
  - The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and
  - No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.
36. The purpose for excluding these trials from the scope of the Directive 2001/20/EC is that these trials are typically of a lower risk than interventional clinical trials. Moreover, this restriction shall ensure that medical activities which are normal clinical practice and as such part of the general medical surveillance of a patient are excluded from the scope of the Directive 2001/20/EC.

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<sup>12</sup> Cf. Point 4.1.6.2. of the Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (Revision 2 of October 2005).

<sup>13</sup> [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm)

**1.11. Question: Can a study which is started after exposure of a medicinal product has finished be considered as a clinical trial as defined in Directive 2001/20/EC?**

37. **Answer:** Reference is made to the algorithm in Annex. The definition of clinical trials is independent of whether the study is started and conducted after the administration of the medicinal product.
38. For this kind of study, it is particularly relevant to consider whether it falls within the definition of non-interventional trial. In particular, it has to be assessed whether the intervention is an additional diagnostic or monitoring procedure. In this respect, reference is made to column 'E' of the algorithm in Annex, as well as question 1.5.
39. If the study fulfils the criteria of a clinical trial, and is not a non-interventional trial, Directive 2001/20/EC applies.
40. Obviously, as in these cases the administration of the medicinal product has already been completed when the study starts, certain rules relating to the IMP (e.g. on labelling) would not be applicable.
41. When designing this kind of study it is a particular challenge to ensure that its result as credible, as the medicinal product had not been administered in the context of a clinical trial and thus it had not necessarily been administered in accordance with good clinical practice. This holds in particular for the exposure to the previous treatment.

**2. SPONSOR/LEGAL REPRESENTATIVE; INVESTIGATOR**

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

42. **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.”
43. 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 or the EEA, which includes Iceland, Norway, and Liechtenstein.<sup>14</sup> The investigator and the sponsor may be the same person.<sup>15</sup>

**2.2. Question: Is the person financing a clinical trial always considered as “sponsor” in the sense of Article 2(e) of Directive 2001/20/EC?**

44. **Answer:** A sponsor is defined in Article 2(e) of Directive 2001/20/EC as “an individual, company, institution or organisation which takes responsibility of the initiation, management and/or financing of a clinical trial”.
45. Every clinical trial has to have a sponsor.

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<sup>14</sup> Article 19 of Directive 2001/20/EC.

<sup>15</sup> Article 7(2) of Directive 2005/28/EC.

46. However, it follows from Article 2(e) of Directive 2001/20/EC that the sponsor is not necessarily the person financing a clinical trial. While that person *may* be the sponsor, the sponsor may also be the person which presents himself as the person taking the responsibility for the initiation or the management of the trial.

### **2.3. Question: Can the sponsor delegate tasks/functions?**

47. **Answer:** The sponsor may delegate any or all of his trial-related tasks/functions to an individual, company, institution or organisation.<sup>16</sup> 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 reporting according to Articles 16 and 17 of Directive 2001/20/EC.

48. In cases where there are tasks/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.<sup>17</sup>

49. Prior to initiating a trial, the sponsor should define, establish and allocate all trial-related tasks/functions. Any trial-related tasks/functions that are delegated to a third party should be specified in writing.

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

51. 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.

### **2.4. Question: Does the Directive 2001/20/EC establish that the sponsor or his legal representative according to Article 19(2) are liable under civil and criminal law?**

52. **Answer:** No.

53. Directive 2001/20/EC, in referring to the "responsibility for the initiation, management and/or financing of a clinical trial" (Article 2(e) of Directive 2001/20/EC) refers to the responsibility for compliance with the Directive.

54. Responsibility in terms of civil law (i.e. liability, for example compensation for damages occurred to a patient), or criminal law (i.e. punishment, for example

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<sup>16</sup> Article 7(1) of Directive 2005/28/EC.

<sup>17</sup> Article 7(1) of Directive 2005/28/EC.

criminal sanction of a bodily injury caused by negligence), is not governed by Directive 2001/20/EC, cf. Article 19(1) of Directive 2001/20/EC. In this respect, the applicable laws of the Member States apply.

55. This also holds for cases where the sponsor has a legal representative in an EU Member State or EEA State, Article 19(1) of Directive 2001/20/EC. While the existence of a legal representative within the EU/EEA might be supportive to ensure effective sanctioning under national civil or criminal law, the rules for civil and criminal liability remain governed by the national laws of the Member States.

**2.5. Question: Can a sponsor established in a third country open a subsidiary or branch in a Member State in order to comply with the requirement of Directive 2001/20/EC that the sponsor or a legal representative of the sponsor must be established in the EU?**

56. **Answer:** Yes.

57. Article 19 of Directive 2001/20/EC requires that the sponsor or a legal representative of the sponsor is established in the EU.

58. This does not exclude the possibility that this establishment is a branch or subsidiary of a legal person having its principal seat outside the EU. This establishment could be the sponsor or act as legal representative of the sponsor established outside the EU.

**2.6. Question: What are the requirements for the legal representative of a non EEA-sponsor in view of Article 19 of Directive 2001/20/EC?**

59. **Answer:** If the sponsor is not established in the Community a legal representative of the sponsor has to be established in the Community.<sup>18</sup>

60. Only one legal representative can act on behalf of one sponsor in one clinical trial.

61. 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.

62. 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.

63. 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: The detailed guidance CT-1 refers, in its section 2.9., sub-section 4, to the content of the labelling of the IMP. Does this mean a mock-up?**

64. **Answer:** No.

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<sup>18</sup> Article 19 of Directive 2001/20/EC.

65. Only the text that is labelled on the IMP should be included in the application dossier.

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

66. 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: 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?**

67. 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. Questions: 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?**

68. Answer: This requires an amendment to the clinical trial dossier. For the question whether this amendment is “substantial”, and, in the affirmative, what body has to assess this substantial amendment, reference is made to the relevant guidelines.

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

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

#### **4. SAFETY REPORTING**

**4.1. Question: Can the National Competent Authority or the Ethics Committee oblige the sponsor to report all suspected *expected* serious adverse reactions (in addition to the suspected *unexpected* serious adverse reactions, as per Article 17(1)(a)(b) of Directive 2001/20/EC)?**

70. Answer: Yes. The authorisation/favourable opinion may be made conditional upon such requirement. However, suspected *expected* serious adverse reactions are not SUSARS and shall not be reported as such.

**4.2. Question: How long is the annual safety report to be submitted to the national competent authority and the Ethics Committee of a Member State?**

71. Answer: This is addressed in the 'Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on

medicinal products for human use (CT-3).<sup>19</sup> According to the detailed guidance CT-3 the annual safety report (Development Safety Update Report) should be submitted to the national competent authority and to the Ethics Committee of the Member State where the treatment of subjects is still ongoing.<sup>20</sup>

72. It should be considered that the 'treatment of subjects' in a given Member State is ongoing in that Member State until the last visit of the last subject in that Member State. If the 'end of the trial' is defined differently in the protocol, this 'end of the trial' should be considered for the territory of each respective Member State concerned.

## 5. MANUFACTURING AND IMPORTATION OF IMPs

- 5.1. Question: A clinical trial with an IMP which is an officinal formula falls within the scope of the Clinical Trials Directive.<sup>21</sup> What does this mean for the requirements as regards manufacturing authorisation?**

73. **Answer:** Article 13 of the Clinical Trials Directive applies, ie the manufacturing of the investigational medicinal product is subject to the holding of an authorisation. However, in accordance with Article 9(2) of Directive 2005/28/EC, an authorisation is not required for reconstitution or packaging under certain conditions. Annex 13 to the EU Guidelines for Good Manufacturing Practice contains more information concerning the term "reconstitution".<sup>22</sup>

## 6. "INFORMED CONSENT" AND OTHER SUBSTANTIAL REQUIREMENTS FOR CONDUCTING CLINICAL TRIALS

- 6.1. Question: What is meant by 'compensation for participation' in a trial (Article 4(d) of Directive 2001/20/EC)?**

74. **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."

- 6.2. Question: When can the obligatory insurance coverage stop?**

75. **Answer:** According to Article 3(2)(f) of Directive 2001/20/EC, a clinical trial may be undertaken only, if provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor.

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<sup>19</sup> OJ C172, 11.6.2011, p. 1.

<sup>20</sup> §126 of the detailed guidance CT-3.

<sup>21</sup> See §8 of the detailed guidance CT-1.

<sup>22</sup> ENTR/F/2/AM/an D(2010) 3374, p. 3 ([http://ec.europa.eu/health/files/eudralex/vol-4/2009\\_06\\_annex13.pdf](http://ec.europa.eu/health/files/eudralex/vol-4/2009_06_annex13.pdf))

76. There are no specific Community provisions on when this insurance coverage can stop.
77. However, the purpose of Article 3(2)(f) of Directive 2001/20/EC is to ensure that a clinical trial subject can obtain compensation for damages caused by the clinical trial - independently of the financial capacity of the investigator/sponsor. In view of this purpose of the provision, and in the absence of specific Community rules, the insurance should provide coverage for the period in which such damages can arise and lawfully be claimed by the clinical trials subject.
78. As a Community Directive by definition is binding to the result to be achieved while leaving open to EU Member States the choice of form and methods, it is up to the Member State to establish specific rules, if any. If no such rules are established at Member States level, it is up to the sponsor to assess, on the basis of the principle set out above and the clinical trial in question (in particular in view of the risk it implies for the clinical trials subject), the necessary period of coverage.
79. Note, that, in accordance with Article 6(3)(i) of Directive 2001/20/EC, aspects of insurance or indemnity to cover the liability of the investigator and sponsor are considered by the Ethics Committee or, in accordance with Article 6(4) of Directive 2001/20/EC, by the national competent authority of the Member State concerned.

## 7. END OF TRIAL

### 7.1. Question: How is “end of trial” defined?

80. **Answer:** The regulation of clinical trials refers repeatedly to end of trial. This is done in several contexts (see below). Therefore, and in view of these different constellations, there is no general definition of “end of trial”. Rather, the content of the notion has to be considered in view of the context to assess its meaning. For example:
81. Declaration of end of the trial: Article 10(c) of Directive 2001/20/EC refers to the end of the trial and fixes a deadline for notification to the national competent authority and the ethics committee of the Member State concerned. The purpose of this declaration is to inform the national competent authority and the Ethics Committee that in principle no further regulatory surveillance of the trial is required. As this may depend of the clinical trial in question, the applicant for a clinical trial should include in the protocol submitted to the national competent authority of the Member State concerned, a definition of the end of the trial as applicable for the clinical trial in question.<sup>23</sup> In this context, the end of trial is usually the date of the last visit of the last clinical trial subject.<sup>24</sup>
82. Submission of result-related information on paediatric trials to the EMEA: In this respect, reference is made to the “completion” of the trial. A trial is considered as

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<sup>23</sup> Cf. Point 4.1.4. and point 4.3.1. of the Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (Revision 2 of October 2005).

<sup>24</sup> Ibidem.



completed when the last visit of the last patient has occurred, as foreseen in the latest version of the protocol.<sup>25</sup>

**7.2. What is the reporting deadline for early termination for reasons not based on grounds of safety, but on other grounds?**

83. **Answer:** This is addressed in section 4.2.2. of the detailed guidance CT-1.

84. This section states that '*an earlier end of the clinical trials which is not based on grounds of safety, but on other grounds, such as faster recruitment than anticipated, is not considered as 'early termination'*'.

85. There may be cases where a trial is ended earlier for reasons of lack of efficacy.

86. If the lack of efficacy impacts on the assessment of the acceptable risk to the safety of the subject, this is to be understood as a safety issue.

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<sup>25</sup> Cf. point 2.2.2. of the Guideline 2009/C28/01 on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMA), in accordance with Article 41 of Regulation (EC) No 1901/2006 (February 2009).

**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
<b>A CLINICAL TRIAL OF A MEDICINAL PRODUCT?</b>				<b>A NON-INTERVENTIONAL CLINICAL TRIAL?</b>
Is it a medicinal product (MP)? <sup>i</sup>	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 &amp; 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 substance<sup>ii</sup> 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"> <li>• Human whole blood<sup>iii</sup>;</li> <li>• Human blood cells;</li> <li>• Human plasma;</li> <li>• A food product<sup>iv</sup> (including dietary supplements) not presented as a medicine;</li> <li>• A cosmetic product<sup>v</sup></li> <li>• A medical device</li> </ul>	<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 pharmacokinetics, e.g., absorption, distribution, metabolism or excretion?</p>	<p>D.1. To ascertain or verify/compare the efficacy<sup>vi</sup> 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<sup>vii</sup>?</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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<sup>i</sup> Cf. Article 1(2) of Directive 2001/83/EC, as amended.

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

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

<sup>iv</sup> 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.

<sup>v</sup> 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.

<sup>vi</sup> 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.

<sup>vii</sup> Assignment of patients to a treatment group by randomisation planned by a clinical trial protocol cannot be considered as current practice.