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*(Information)*INFORMATION FROM EUROPEAN UNION INSTITUTIONS, BODIES, OFFICES  
AND AGENCIES

## EUROPEAN COMMISSION

**Communication from the Commission — 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 (CT-1)**

(2010/C 82/01)

## 1. INTRODUCTION

## 1.1. Legal basis

1. This detailed guidance is based on Article 9(8) of Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 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 <sup>(1)</sup> (hereinafter Directive 2001/20/EC), which establishes that:

'In consultation with Member States, the Commission shall draw up and publish detailed guidance on:

(a) the format and contents of the request referred to in paragraph 2 (i.e. submission of a valid request for authorisation to the competent authority of the Member State in which the sponsor plans to conduct the clinical trial) as well as the documentation to be submitted to support that request, on the quality and manufacture of the investigational medicinal product, any toxicological and pharmacological tests, the protocol and clinical information on the investigational medicinal product including the investigator's brochure;

(b) the presentation and content of the proposed amendment referred to in point (a) of Article 10 on substantial amendments made to the protocol;

(c) the declaration of the end of the clinical trial.'

2. This guidance does address aspects related to Ethics Committees only insofar as the provisions contained in Directive 2001/20/EC are identical with regard to both the national competent authority and the Ethics Committee. This means that the following sections in this guidance also apply to Ethics Committees:

— Procedural aspects of notification of 'substantial amendments' (Sections 3.1 to 3.3, and 3.5 to 3.8); and

— Declaration of the end of the trial (Section 4).

Regarding the other aspects, reference is made to the separate Commission guidance based on Article 8 of Directive 2001/20/EC.

3. According to Article 3(1) of Directive 2001/20/EC, all national requirements as regards clinical trials have to be consistent with the procedures and timescales set out in Directive 2001/20/EC, such as the procedures and timescales for authorisation of a clinical trial, notification of a substantial amendment, and declaration of the end of the clinical trial. This document provides guidance on these aspects.

4. EU Member States, contracting States of the European Economic Area (EEA) <sup>(2)</sup> and persons who request authorisation of a clinical trial (applicants), notify substantial amendments, and declare the end of a clinical trial in the EU should consider this guidance when applying Directive 2001/20/EC.

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

<sup>(2)</sup> For the purposes of this document, references to the EU, EU Member States or Member States should be understood to include the EEA or EEA contracting States, unless indicated otherwise.

### 1.2. Scope

5. This guidance addresses the requests for authorisation, amendments, and declaration of the end of clinical trials within the scope of Directive 2001/20/CE. Directive 2001/20/EC applies to all clinical trials as defined in Article 2(a) of this Directive. As regards the term 'medicinal products', this refers to medicinal products for human use as defined in Article 1(2) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use<sup>(1)</sup> (hereinafter Directive 2001/83/EC). This includes medicinal products where the pharmacological, immunological, or metabolic action of the product is still uncertain and being explored.

6. This includes also medicinal products which are specifically addressed in the EU law on pharmaceuticals, such as advanced therapy medicinal products<sup>(2)</sup> or medicinal products derived from human blood or human plasma as defined in Article 1(10) of Directive 2001/83/EC.

7. Directive 2001/20/EC also applies to interventional clinical trials with medicinal products for the paediatric population and interventional clinical trials with medicinal products manufactured or reconstituted in a (hospital) pharmacy and intended to be supplied directly to the clinical trials participants.

8. The exclusions contained in Article 3 of Directive 2001/83/EC are not relevant as regards the scope of Directive 2001/20/EC and of this guidance.

9. Directive 2001/20/EC does not apply to:

- medical devices, active implantable medical devices, and *in vitro* diagnostic medical devices as defined in Community legislation<sup>(3)</sup>,<sup>(4)</sup>,<sup>(5)</sup>,

- cosmetic products as defined in Community legislation<sup>(6)</sup>,

- food as defined in Community legislation<sup>(7)</sup>.

10. To draw the 'borderline' between these sectoral legislations (e.g. medicinal products/food, medicinal products/cosmetic products, medicinal products/medical devices), the established criteria as set out in the case law of the European Court of Justice apply and reference is made to the relevant guidelines<sup>(8)</sup>.

### 1.3. Definitions

11. The definitions contained in Directive 2001/20/EC, its implementing acts and relevant guidance documents in the current version apply also for this guidance. With regard to implementing guidelines, the following guidance documents in particular provide valuable additional definitions:

- Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials (on the term 'investigational medicinal products')<sup>(9)</sup>,

- Annex 13 to the Guidelines on good manufacturing practice — Manufacture of investigational medicinal products<sup>(10)</sup>,

- Commission Guidelines on Pharmacovigilance for Medicinal Products for Human Use (on the term 'non-interventional trial')<sup>(11)</sup>, and

- Questions and Answers Document on the Clinical Trials Directive<sup>(12)</sup>.

<sup>(1)</sup> OJ L 311, 28.11.2001, p. 67.

<sup>(2)</sup> As defined in Article 2(1)(a) of 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 (OJ L 324, 10.12.2007, p. 121) (hereinafter Regulation (EC) No 1394/2007).

<sup>(3)</sup> Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (OJ L 169, 12.7.1993, p. 1).

<sup>(4)</sup> Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices (OJ L 189, 20.7.1990, p. 17).

<sup>(5)</sup> Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices (OJ L 331, 7.12.1998, p. 1).

<sup>(6)</sup> Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products (OJ L 262, 27.9.1976, p. 169).

<sup>(7)</sup> Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety (OJ L 31, 1.2.2002, p. 1), as amended.

<sup>(8)</sup> cf., for example, [http://ec.europa.eu/enterprise/sectors/cosmetics/cosmetic-products/borderline-products/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/cosmetics/cosmetic-products/borderline-products/index_en.htm)

<sup>(9)</sup> [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)

<sup>(10)</sup> [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)

<sup>(11)</sup> Volume 9A of *The Rules Governing Medicinal Products in the European Union* (Sept. 2008), Part 1, Point 7.1. (p. 90).

<sup>(12)</sup> [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)

12. For the purposes of this guidance, 'Member State concerned' means the Member State where the clinical trial is intended to be performed. For a given clinical trial there may be several Member States concerned (multinational clinical trials). 'ICH country' means a third country which is party to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, i.e. Japan and the US.

## 2. REQUEST FOR A CLINICAL TRIAL AUTHORISATION

### 2.1. Procedural aspects

#### 2.1.1. Legal basis

13. Article 9(1), second subparagraph, and (2) of Directive 2001/20/EC reads as follows:

'The sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion and inasmuch as the competent authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance. ...

Before commencing any clinical trial, the sponsor shall be required to submit a valid request for authorisation to the competent authority of the Member State in which the sponsor plans to conduct the clinical trial<sup>(1)</sup>.

<sup>(1)</sup> cf. also recital 11 of Directive 2001/20/EC: "As a rule, authorisation should be implicit, i.e. if there has been a vote in favour by the Ethics Committee and the competent authority has not objected within a given period, it should be possible to begin the clinical trials."

#### 2.1.2. Request for authorisation, applicable timelines, tacit authorisation

14. The applicant submits a request for authorisation of a clinical trial to the national competent authority of the Member State concerned.

15. In accordance with Article 9(4) of Directive 2001/20/EC, consideration of a valid request for authorisation by the national competent authority shall be carried out as rapidly as possible and may not exceed 60 calendar days.

16. Validation of the request for authorisation is included in the period of 60 calendar days. Day 0 is the day of receipt of the request. If the request is valid, and by day 60 no ground for non-acceptance has been raised, the clinical trial is authorised by the national competent authority of the Member State concerned (tacit authorisation<sup>(1)</sup>).

<sup>(1)</sup> The term 'authorisation' will be used throughout this document.

17. However, Article 9(4), (5) and (6) of Directive 2001/20/EC sets out important exceptions to the rules on timelines and tacit authorisation as regards certain medicinal products, including medicinal products the active ingredient of which is a biological product of human or animal origin, or contains biological components of human or animal origin, or the manufacturing of which requires such components. Exceptions also apply to medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms.

#### 2.1.3. Scope of authorisation

18. The authorisation of a clinical trial by the national competent authority is valid for a clinical trial conducted in that Member State. This authorisation is not to be considered as scientific advice on the development programme of the investigational medicinal product (IMP) tested.

#### 2.1.4. Follow-up to request for authorisation

##### 2.1.4.1. Application is not valid

19. If an application is not valid, the national competent authority should inform the applicant of this within the first 10 calendar days of the period referred to in Section 2.1.2. The reasons should be given.

##### 2.1.4.2. Changes to the submitted to documentation during the evaluation phase

20. Following the submission of a request for authorisation, the submitted documentation may change. This may happen either:

— following information by the national competent authority that the application is not valid (see Section 2.1.4.1). In this case, the time limit set out in Article 9(4) of Directive 2001/20/EC starts again when a valid request has been received;

— at the initiative of the applicant. In practice, the applicant may have an interest in changing submitted documentation. This may happen as a consequence of grounds for non-acceptance by the national competent authority of another Member State or a third country concerned if the applicant wants to ensure that the documentation submitted in all Member States/third countries concerned is identical. In this case, the time limit set out in Article 9(4) of Directive 2001/20/EC starts again; or

— following notification of grounds for non-acceptance by the competent authority of the Member State concerned: in this case Article 9(3) of Directive 2001/20/EC applies.

### 2.1.4.3. Withdrawals

21. Unexpected events or additional information may require the applicant to withdraw a request for authorisation before the national competent authority has reached its decision on authorisation. The applicant should inform the national competent authority of the Member State concerned as soon as he becomes aware that he intends to withdraw the application. The initial contact should be by fax or e-mail and include the EudraCT number and other trial identification. Where the initial contact is by telephone, this should be followed up, for reasons of traceability, by fax or e-mail. The initial contact should be followed as soon as possible by a formal letter of withdrawal providing a brief description of the reasons.

22. If the applicant wishes to resubmit the application, he must identify the application as a resubmission in the cover letter (resubmission letter) and in the dedicated field of the clinical trial application form. The initial EudraCT number is used with a letter after the number sequence: A for first resubmission, B for second resubmission, and so on.

### 2.1.5. Interface with other authorisation requirements

23. The applicant should make applications to fulfil other requirements that relate to clinical trials with IMPs where applicable. For example, if the IMP is a genetically modified organism (GMO) it may be necessary to obtain permission from the relevant competent authority in the Member State concerned for its contained use or deliberate release in accordance with Council Directive 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms<sup>(1)</sup> or 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<sup>(2)</sup>.

### 2.1.6. Other issues

24. The application dossier should be submitted as electronic version only, i.e. via telematics system (if nationally available), e-mail, or a posted CD-ROM. If documentation is sent by paper, it should be limited to the signed cover letter only.

25. The Commission encourages national competent authorities to accept the English language in their communication with applicants and for documentation which is not destined for the public or the clinical trial participant, such as scientific documentation.

<sup>(1)</sup> OJ L 117, 8.5.1990, p. 1.

<sup>(2)</sup> OJ L 106, 17.4.2001, p. 1.

## 2.2. Allocation of EudraCT number

26. Before submitting an application to the national competent authority, the applicant should obtain a unique EudraCT number from the EudraCT Community Clinical Trial System<sup>(3)</sup> by the procedure described in the current version of the Detailed guidance on the European clinical trials database<sup>(4)</sup>. This number identifies 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<sup>(5)</sup>.

## 2.3. Cover letter

27. The applicant should submit a signed cover letter with the application. Its subject line should contain the EudraCT number and the invariable sponsor protocol number (if available) with the title of the trial.

28. In the cover letter, the applicant should draw attention to peculiarities of the trial.

29. However, in the cover letter it is not necessary to reproduce information which is already contained in the clinical trial application form, with the following exceptions:

- specific features of the trial population, such as clinical trial participants not able to give informed consent or minors;
- whether the trial involves the first administration of a new active substance to humans;
- whether there is scientific advice related to the trial or IMP given by the European Medicines Agency (the Agency) or the national competent authority of a Member State or third country; and
- whether the trial is part or is intended to be part of a Paediatric Investigation Plan (PIP) as referred to in Title II, Chapter 3 of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use<sup>(6)</sup>. If the Agency has already issued a Decision on the PIP, the cover letter should contain the link to the Decision of the Agency on its website (see also Section 2.9).

<sup>(3)</sup> <https://eudract.ema.europa.eu/>

<sup>(4)</sup> EudraLex, Volume 10; [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)

<sup>(5)</sup> Note that paediatric clinical trials included in an agreed PIP and performed in a third country have to be entered into EudraCT as well (cf. point 2.2.1. of Commission Communication 2009/C28/01).

<sup>(6)</sup> OJ L 378, 27.11.2006, p. 1.

30. In the cover letter, the applicant should highlight whether the IMP or NIMP is a narcotic and psychotropic.
31. The applicant should indicate where the relevant information is contained in the application dossier.
32. The applicant should set out precisely in the cover letter where in the application dossier the reference safety information is contained for assessing whether an adverse reaction is a suspected unexpected serious adverse reaction (SUSAR).
33. In the case of a resubmission letter (see Section 2.1.4.3), the applicant should highlight the changes as compared to the previous submission.

#### 2.4. Clinical trial application form

34. For clinical trials falling within the scope of the Directive 2001/20/EC, there is a unique, EU-wide clinical trial application form provided for and published in Volume 10 of EudraLex — The Rules Governing Medicinal Products in the European Union <sup>(1)</sup>.
35. Some of the information in the form, such as information related to the applicant and the name of the investigators, will be relevant in one Member State only.
36. The applicant's signature will confirm that the sponsor is satisfied that:
- the information provided is complete,
  - the attached documents contain an accurate account of the information available,
  - the clinical trial will be conducted in accordance with the protocol, and
  - the clinical trial will be conducted, and SUSARs and result-related information will be reported, in accordance with the applicable legislation.
37. If the form is submitted in paper form (cf. Section 2.1.6), the applicant should save the full clinical trial application form data set as an XML file using the utilities feature and submit an electronic copy of this XML file on a CD-ROM.

38. More information about the clinical trial application form, and how to fill it in, is available in the current version of these documents:
- Detailed guidance on the European clinical trials database <sup>(2)</sup>,
  - EudraCT User Manual <sup>(3)</sup>, and
  - EudraCT Frequently Asked Questions <sup>(4)</sup>.
39. In addition, the Agency operates a help desk to support applicants who have questions related to EudraCT <sup>(5)</sup>.
40. Certain information contained in the clinical trial application form will be made public, following its entry into EudraCT by the national competent authority of the Member State concerned. This is done by rendering certain data fields contained in EudraCT public in accordance with the applicable guidelines published by the Commission <sup>(6)</sup>.

#### 2.5. Protocol

41. According to Article 2(h), first sentence, of Directive 2001/20/EC, the protocol is 'a document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial.'
42. The protocol should be identified by the title, the sponsor's protocol code number specific for all versions of it (if available), a date and number of version that will be updated when it is amended, and a short title or name assigned to it.
43. For the content and format of the protocol, reference is made to Section 6 of the Community guideline on Good Clinical Practice (CPMP/ICH/135/95) <sup>(7)</sup>. In particular, the protocol should include:
- a clear and unambiguous definition of the end of the trial in question. In most cases this 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; and

<sup>(1)</sup> [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)

<sup>(2)</sup> [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)

<sup>(3)</sup> <http://eudract.ema.europa.eu/document.html>

<sup>(4)</sup> <http://eudract.ema.europa.eu/document.html>

<sup>(5)</sup> EudraCT Helpdesk, e-mail: [eudract@ema.europa.eu](mailto:eudract@ema.europa.eu); Tel. +44 2075237523; Fax +44 2074188669.

<sup>(6)</sup> EudraLex, Volume 10, Chapter V ([http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)).

<sup>(7)</sup> [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)

- a description of the plan for the provision of any additional care for the trial participants once their participation in the trial has ended, where it differs from what is normally expected according to the medical condition of the clinical trial participant.
44. The protocol should clearly address sub-studies conducted at all trial sites or only at specific sites.
45. The protocol should also contain the relevant information for the assessment of the clinical trial by the Ethics Committee. To this end, the protocol should include the following information:
- a discussion of the relevance of the clinical trial and its design to allow assessment in view of Article 6(3)(a) of Directive 2001/20/EC,
  - an evaluation of the anticipated benefits and risks as required in Article 3(2)(a) of Directive 2001/20/EC (cf. Article 6(3)(b) of Directive 2001/20/EC),
  - a justification for including participants who are incapable of giving informed consent or other special populations, such as minors (cf. Article 6(3)(g) of Directive 2001/20/EC), and
  - a detailed description of the recruitment and informed consent procedure, especially when participants are incapable of giving informed consent (cf. Article 6(3)(k) of Directive 2001/20/EC).
46. More details are provided in the separate Commission guidance based on Article 8 of Directive 2001/20/EC.
47. A sponsor may wish to conduct a clinical trial with an active substance that is available in the European Union with different trade names in a number of medicines with marketing authorisations in the Member State concerned. This may be the case, for example, in order to address local clinical practice at each clinical trial site in the Member State concerned. In this case the protocol may define the treatment in terms of the active substance or Anatomical Therapeutic Chemical (ATC) code (level 3-5) only and not specify the trade name of each product.
48. With regard to notification of adverse events, the protocol
- may identify serious adverse events which do not require immediate reporting by the investigator (cf. Article 16(1) of Directive 2001/20/EC), and
  - shall identify adverse events or laboratory anomalies critical to safety evaluations to be reported to the sponsor (cf. Article 16(2) of Directive 2001/20/EC).
49. In certain cases, issues of unblinding of IMPs might need to be addressed in the protocol. For details, reference is made to the guidelines on adverse reaction reporting published in Volume 10 of EudraLex — The Rules Governing Medicinal Products in the European Union <sup>(1)</sup>.
50. Regarding first-in-human clinical trials, additional guidance is provided in the Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products <sup>(2)</sup>.
51. The protocol should be accompanied by a synopsis of the protocol.
52. The protocol should be signed by the sponsor and:
- the overall coordinating investigator for a multi-centre (incl. multinational) trial, or
  - the principal investigator in a single-site trial.
- ## 2.6. Investigator's brochure
53. According to Article 2(g) of Directive 2001/20/EC, the investigator's brochure (IB) is 'a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in human subjects.'
54. A request for trial authorisation has to be accompanied by an IB or a document used in place of the IB (see below). Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures.

<sup>(1)</sup> [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)

<sup>(2)</sup> EMEA/CHMP/SWP/28367/07 (see <http://www.ema.europa.eu/pdfs/human/swp/2836707enfin.pdf>).

55. The content, format and procedures for updating the IB have to comply with Article 8(1) of Commission Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products <sup>(1)</sup> (hereinafter Directive 2005/28/EC) and 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 IMP in the trial and be presented in the form of summaries.

56. The approved summary of product characteristics (SmPC) may be used in place of the IB if the IMP is authorised in any Member State or ICH country and is used according to the terms of the marketing authorisation. Regarding ICH countries, the document equivalent to the SmPC is used. If the conditions of use in the clinical trial differ from those authorised, the SmPC should be supplemented with a summary of relevant non-clinical and clinical data that support the use of the IMP in the clinical trial. Where the IMP is identified in the protocol only by its active substance, the sponsor should elect one SmPC as equivalent to the IB for all medicinal products that contain that active substance and are used at any clinical trial site.

57. For a multinational trial where the medicinal product to be used in each Member State is the one authorised at national level and the SmPC varies among Member States, the sponsor should choose one SmPC to replace the IB for the whole clinical trial. This SmPC should be the one best suited to ensure patient safety.

58. The IB as last amended and approved by the national competent authority or equivalent document (e.g. SmPC for marketed products) serves as the reference safety information for the assessment of the expectedness of any adverse reaction that might occur during the clinical trial.

## 2.7. IMP dossier

59. Article 2(d) of Directive 2001/20/EC defines an IMP as follows:

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

60. The IMP dossier (IMPD) gives information related to the quality of any IMP (i.e. including reference product and

placebo), manufacture and control of the IMP, and data from non-clinical studies and from its clinical use. However, in many cases where the IMP has a marketing authorisation, an IMPD is not required. Reference is made to Section 2.7.1 (regarding compliance with Good Manufacturing Practice, GMP) and Section 2.7.3 (regarding data).

### 2.7.1. GMP compliance

61. As regards GMP compliance, in the following cases no documentation needs to be submitted:

- the IMP has a marketing authorisation in the EU or in an ICH country, is not modified, and is manufactured in the EU, or
- the IMP is not manufactured in the EU, but has a marketing authorisation in the EU, and is not modified.

62. If the IMP does not have a marketing authorisation in the EU or an ICH country and is not manufactured in the EU, the following documentation should be submitted:

- a copy of the importation authorisation as referred to in Article 13(1) of Directive 2001/20/EC, and
- a certification by the qualified person (QP) in the EU that the manufacturing complies with GMP at least equivalent to the GMP in the EU. Regarding this certification, there are specific arrangements provided for in the Mutual Recognition Agreements between the EU and third countries <sup>(2)</sup>.

63. In all other cases, to document compliance with GMP as set out in Directive 2003/94/EC and the implementing detailed guideline for IMPs <sup>(3)</sup>, the applicant should submit a copy of the manufacturing/importing authorisation as referred to in Article 13(1) of Directive 2001/20/EC stating the scope of the manufacturing/importation authorisation.

### 2.7.2. Data related to the IMP

#### 2.7.2.1. Introductory remarks

64. Regarding data, the IMPD can be replaced by other documentation which may be submitted alone or with a simplified IMPD. The details for this ‘simplified IMPD’ are set out in Section 2.7.3.

<sup>(2)</sup> More information is available here: <http://www.ema.europa.eu/Inspections/docs/000204en.pdf>

<sup>(3)</sup> Annex 13 to Volume 4 of EudraLex — The Rules Governing Medicinal Products in the European Union ([http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)).

<sup>(1)</sup> OJ L 91, 9.4.2005, p. 13.

65. The IMPD should be prefaced with a detailed table of contents and a glossary of terms.
66. The information in the IMPD should be concise. The IMPD should not be unnecessarily voluminous. It is preferable to present data in tabular form accompanied by brief narrative highlighting the main salient points.
67. Regarding various specific types of IMPs, guidance is also given by the Agency, and made available in Volume 3 of EudraLex — The Rules Governing Medicinal Products in the European Union <sup>(1)</sup>.

#### 2.7.2.2. Quality data

68. Quality data should be submitted in a logical structure, such as the headings of the current version of the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials <sup>(2)</sup>. This document also contains guidance for quality of placebos.
69. As regards biotechnological IMPs, reference is made to the Guideline on virus safety evaluation of biotechnological investigational medicinal products, as amended <sup>(3)</sup>.
70. In exceptional cases, where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected, the certificate of analysis for test products should be attached. Applicants should assess the need to submit a TSE Certificate.

#### 2.7.2.3. Non-clinical pharmacology and toxicology data

71. The applicant should also provide summaries of non-clinical pharmacology and toxicology data for any IMP used in the clinical trial. He 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 a brief 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.

72. Non-clinical pharmacology and toxicology data should be submitted in a logical structure, such as the headings of the current version of Module 4 of the Common Technical Document <sup>(4)</sup>, or of the eCTD format.
73. Reference is made to the specific Community guidelines contained in Volume 3 of EudraLex <sup>(5)</sup>, and especially the Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals, as amended (CPMP/ICH/286/95).
74. This section should provide a critical analysis of the data, including justification for omissions of data, 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.
75. The protocols should meet the requirements of Good Laboratory Practice (GLP) guidelines where appropriate. The applicant should provide a statement of the GLP status of all studies.
76. 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 the controls necessary to ensure this and thus support the validity of the study.

#### 2.7.2.4. Previous clinical trial and human experience data

77. Clinical trial and human experience data should be submitted in a logical structure, such as the headings of the current version of Module 5 of the Common Technical Document <sup>(6)</sup>, or of the eCTD format.
78. This section should provide summaries of all available data from previous clinical trials and human experience with the proposed IMPs.
79. All studies should have been conducted in accordance with the principles of Good Clinical Practice (GCP). To this end, the applicant should submit the following:
- a statement of the GCP compliance of the clinical trials referred to,

<sup>(1)</sup> [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)

<sup>(2)</sup> CHMP/QWP/185401/2004 final ([http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)).

<sup>(3)</sup> Ref. EMEA/CHMP/BWP/398498/2005 (<http://www.ema.europa.eu/pdfs/human/bwp/39849805enfin.pdf>).

<sup>(4)</sup> [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-2/b/update\\_200805/ctd\\_05-2008\\_en.pdf](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf)

<sup>(5)</sup> [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-3/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-3/index_en.htm)

<sup>(6)</sup> [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-2/b/update\\_200805/ctd\\_05-2008\\_en.pdf](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf)

- where a clinical trial referred to has been performed in third countries, a reference to the entry of this clinical trial in a public register, if available. Where a clinical trial is not published in a register, this should be explained and justified.
80. There are no specific requirements for data from clinical studies that must be provided before a clinical trial authorisation can be granted. Rather, this is to be assessed on a case-by-case basis. In this respect, guidance is provided in the guideline General considerations for clinical trials (CPMP/ICH/291/95) <sup>(1)</sup>.
- 2.7.2.5. Overall risk and benefit assessment**
81. 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 unless this information is already provided in the protocol. In the latter case, the applicant should cross-refer to the relevant section in the protocol. The text should identify any studies that were terminated prematurely and discuss the reasons. Any evaluation of foreseeable risks and anticipated benefits for studies on minors or incapacitated adults should take account of the provisions set out in Articles 3 to 5 of Directive 2001/20/EC.
82. Where appropriate, the sponsor should discuss safety margins in terms of relative systemic exposure to the IMP, preferably based on area under the curve (AUC) data, or peak concentration ( $C_{max}$ ) data, whichever is considered more relevant, rather than in terms of applied dose. The sponsor 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.

### 2.7.3. Simplified IMPD by referring to other documentation

83. The applicant has the possibility to refer to other documentation which may be submitted alone or with a simplified IMPD to contain the information as set out in Table 1.

#### 2.7.3.1. Possibility to refer to the IB

84. The applicant may either provide a stand-alone IMPD or cross-refer to the IB for the preclinical 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 preclinical data or clinical data that requires a detailed expert explanation or discussion beyond what would usually be included in the IB, the applicant should submit the preclinical and clinical information as part of the IMPD.

#### 2.7.3.2. Possibility to refer to the SmPC or to the assessment of the IMPD in another clinical trials application

85. The applicant may submit the current version of the SmPC (or, as regards ICH countries, the documentation equivalent to the SmPC) as the IMPD if an IMP has a marketing authorisation in any Member State or in an ICH country. The exact requirements are detailed in Table 1.
86. Moreover, the IMPD may have been submitted previously by the same applicant or by another applicant and held by the national competent authority of the Member State concerned. In these cases applicants are allowed to cross-refer to the previous submission. If the submission was made by another applicant, a letter from that applicant should be submitted authorising the national competent authority to cross-refer to that data. The exact requirements are detailed in Table 1.

87.

Table 1

Content of simplified IMPD

Types of previous assessment	Quality data	Non-clinical data	Clinical data
The IMP has an MA in any EU Member State or ICH country and is used in the trial:			
— within the conditions of the SmPC	SmPC		
— outside the conditions of the SmPC	SmPC	If appropriate	If appropriate
— after modification (e.g. blinding)	P+A	SmPC	SmPC

<sup>(1)</sup> <http://www.ema.europa.eu/htms/human/ich/ichefficacy.htm>

Types of previous assessment	Quality data	Non-clinical data	Clinical data
Another pharmaceutical form or strength of the IMP has an MA in any EU Member State or ICH country and the IMP is supplied by the MA holder	SmPC+P+A	Yes	Yes
The IMP has no MA in any EU Member State or ICH country but the active substance is part of a medicinal product with an MA in an EU Member State and			
— is supplied by the same manufacturer	SmPC+P+A	Yes	Yes
— is supplied by another manufacturer	SmPC+S+P+A	Yes	Yes
The IMP was subject to a previous CTA and authorised in the Member State concerned <sup>(1)</sup> and has not been modified and			
— no new data is available since last amendment to the CTA	Reference to previous submission		
— new data is available since last amendment to the CTA	New data	New data	New data
— is used under different conditions	If appropriate	If appropriate	If appropriate

(S: Data relating to the active substance; P: Data relating to the IMP; A: Appendices to the current version of the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials <sup>(2)</sup>.)

<sup>(1)</sup> The sponsor should provide a letter of authorisation to cross-refer to the data submitted by another applicant.

<sup>(2)</sup> CHMP/QWP/185401/2004 final ([http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)).

88. If the applicant is the MA holder and he has submitted an application to vary the SmPC, which has not yet been authorised, and which is relevant for the assessment of the IMPD in terms of patient safety, the nature of the variation and the reason for it should be explained.

pertaining to that ATC group. Alternatively, he may provide a collated document containing information equivalent to that in the representative SmPCs for each active substance that could be used as an IMP in the clinical trial.

89. If the IMP is defined in the protocol in terms of active substance or ATC code (see above, Section 2.5), the applicant may replace the IMPD by one representative SmPC for each active substance/active substance

#### 2.7.4. IMPD in cases of placebo

90. If the IMP is a placebo, the information requirements can be reduced in line with the requirements set out in Table 2.

91.

Table 2

#### IMPD in cases of placebo

IMPD in for placebo	Quality data	Non-clinical data	Clinical data
The IMP is a placebo	P+A	No	No
The IMP is a placebo and the placebo has the same composition as the tested IMP, is manufactured by the same manufacturer, and is not sterile	No	No	No

IMPD in for placebo	Quality data	Non-clinical data	Clinical data
The IMP is a placebo and has been submitted in a previous CTA in the Member State concerned	No	No	No

(S: Data relating to the active substance; P: Data relating to the IMP; A: Appendices to the current version of the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials <sup>(1)</sup>.)

<sup>(1)</sup> CHMP/QWP/185401/2004 final ([http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)).

## 2.8. Non-investigational medicinal products used in the trial

92. Medicinal products used in the context of a clinical trial and not falling within the definition of an IMP are non-investigational medicinal products (NIMPs). The 'borderline' between IMPs and NIMPs is described in the Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials <sup>(1)</sup>.
93. It is strongly recommended that NIMPs with marketing authorisation in the Member State concerned are used. When this is not possible, the next choice should be NIMPs with marketing authorisation in another Member State. When this is not possible, the next choice should be NIMPs with marketing authorisation in an ICH country or a third country having a mutual recognition agreement with the EU (MRA country) <sup>(2)</sup>. When this is not possible, the next choice should be NIMPs with a marketing authorisation in another third country. Otherwise, a NIMP with no marketing authorisation may be used.
94. For the requirements of the NIMP dossier, reference is made to the applicable guideline published in EudraLex — The Rules Governing Medicinal Products in the European Union, Volume 10 <sup>(3)</sup>.

## 2.9. Other documents to be submitted, Overview

95. The following additional documents should be contained in the application dossier submitted to the national competent authority of the Member State concerned:
1. A copy of the opinion of the Ethics Committee of the Member State concerned, whether the application has been submitted in parallel or in sequence, as soon as it is available, unless the Ethics Committee informs the applicant that it has copied its opinion to the national competent authority of the Member State concerned. A submission of this document subsequently to the submission of a request for authorisation is not to be considered as a change of the documentation as referred to in Section 2.1.4.2.
  2. If available, a copy of the summary of scientific advice from any Member State or the Agency with regard to the clinical trial. A submission of this document

subsequently to the submission of a request for authorisation is not to be considered as a change of the documentation as referred to in Section 2.1.4.2.

3. If the clinical trial is part of an agreed PIP, a copy of the Agency's Decision on the agreement on the PIP, and the opinion of the Paediatric Committee, unless these documents are fully accessible via the internet. In the latter case, the link to this documentation in the cover letter is sufficient (see Section 2.3). A submission of this document subsequently to the submission of a request for authorisation is not to be considered as a change of the documentation as referred to in Section 2.1.4.2.
  4. The content of the labelling of the IMP.
  5. In case of fees, proof of payment.
96. Table 3 contains the final overview of the documentation to be submitted.

Table 3

### List of documentation to be provided to the national competent authority of the Member State concerned in accordance with this detailed guidance

- 
- Cover letter with the contents set out in Section 2.3,
  - Clinical trial application form,
  - Protocol with the contents set out in Section 2.5,
  - IB, or document replacing the IB, as set out in Section 2.6,
  - IMPD/simplified IMPD, as set out in Sections 2.7 and 2.7.3,
  - NIMP dossier as set out in Section 2.8,
  - The additional pieces of documentation as set out in Section 2.9.
- 

## 2.10. Additional national requirements for documents

97. The national requirements for the content of the clinical trial application dossier can be more comprehensive than the list of documentation set out in Section 2.9 in the following two cases:

<sup>(1)</sup> cf. [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)

<sup>(2)</sup> These third countries are Australia, Canada, Japan, New Zealand and Switzerland.

<sup>(3)</sup> cf. [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)

2.10.1. *Documents relating to information relevant for Ethics Committees but exceptionally considered by national competent authorities in accordance with Article 6(4) of Directive 2001/20/EC*

98. Documents relating to information which is, according to Article 6(2) of the Directive 2001/20/EC, only assessed by the Ethics Committee should not be submitted to the national competent authority of the Member State concerned.

99. However, if a Member State has decided, in accordance with Article 6(4) of Directive 2001/20/EC, that its national competent authority is responsible for considering:

- the provisions for indemnity or compensation,
- insurance or indemnity to cover the liability of the investigator/sponsor,
- compensation and rewards of investigators and clinical trial participants, or
- the agreement between the sponsor and the clinical trial sites.

The relevant documentation should be submitted to the national competent authority of this Member State.

100. Member States who decide to extend the scope of assessment of the national competent authority are under an obligation to notify the Commission, the other Member States, and the Agency of this. Those Member States are listed on the 'clinical trials website' of the European Commission <sup>(1)</sup>.

2.10.2. *Documents relating to information on a more comprehensive protection of the clinical trial participant in accordance with Article 3(1) of Directive 2001/20/EC*

101. Some Member States may have national provisions on the protection of clinical trial subjects in place which are more comprehensive than the provisions of the Directive 2001/20/EC (cf. Article 3(1) of Directive 2001/20/EC).

102. In order for the national competent authority to assess compliance with these national provisions (hereinafter referred to as 'underlying national provisions'), Member States may require additional information in the clinical trial application dossier.

103. However, Member States may only request this additional information if the underlying national provision is compliant with Directive 2001/20/EC. This requires in particular, that the underlying national provision:

- is clearly aimed at a more comprehensive protection of the clinical trial subject than the provisions of Directive 2001/20/EC,
- is appropriate and proportionate in view of the aim pursued,
- is consistent with the procedures set out in Directive 2001/20/EC, and
- is consistent with the timescales set out in Directive 2001/20/EC.

104. The Commission is going to ensure compliance of underlying national provisions with these requirements.

### 3. NOTIFICATION OF AMENDMENTS AND RELATED MEASURES

#### 3.1. Legal basis and scope

105. Article 10(a) of Directive 2001/20/EC reads as follows:

'After the commencement of the clinical trial, the sponsor may make amendments to the protocol. If those amendments are substantial and are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, the sponsor shall notify the competent authorities of the Member State or Member States concerned of the reasons for, and content of, these amendments and shall inform the ethics committee or committees concerned in accordance with Articles 6 (Ethics Committee) and 9 (Commencement of clinical trial).'

106. In view of the identical legal consequences of an amendment that is 'substantial and likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial' and an amendment that is 'otherwise significant', the term 'substantial amendment' used in this guidance refers to both types of amendments.

<sup>(1)</sup> [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/clinical-trials/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/clinical-trials/index_en.htm)

107. Notification/submission of information<sup>(1)</sup> is only obligatory if the amendment is a substantial amendment. Directive 2001/20/EC does not require notification, nor immediate submission of information of non-substantial amendments. Neither national competent authorities of the Member State concerned, nor its Ethics Committee can oblige the sponsor to submit non-substantial amendments. In this regard, the rules for non-substantial amendments (cf. Section 3.6) apply.

### 3.2. The notion of 'amendment'

108. The following changes do not count as an 'amendment' as referred to in Article 10(a) of Directive 2001/20/EC:

- a change to the documentation submitted to the national competent authority during the ongoing assessment of the request for authorisation by the national competent authority (for these aspects see Section 2.1.4.2), and
- a change to the documentation submitted to the Ethics Committee during the ongoing assessment of the request for authorisation by the Ethics Committee.

109. Article 10(a) of Directive 2001/20/EC refers only to amendments to the approved protocol. This is to be understood as encompassing all documentation submitted in the context of the approved protocol.

110. The annual safety report (ASR) in accordance with Article 17(2) of Directive 2001/20/EC is not per se an amendment and thus does not have to be notified as a substantial amendment to the national competent authority of the Member State concerned. However, the sponsor has to verify whether the data presented in the ASR requires a change to the documentation submitted with the request for authorisation of a clinical trial. If this amendment is substantial, the rules for notification of substantial amendments apply to these changes.

111. A change of the contact person or in the contact details of the contact person (e.g. a change of e-mail or postal address) is not considered as an amendment, if the sponsor and legal representative remain identical. However, the sponsor should ensure that the national competent authority of the Member State concerned is aware of this change as soon as possible, in order to allow the national competent authority to exercise its supervisory function.

### 3.3. The notion of 'substantial'

112. 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 clinical trial participants, or
- the scientific value of the trial.

113. In all cases, an amendment is only to be regarded as 'substantial' when one or both of the above criteria are met.

114. It is up to the sponsor to assess whether an amendment is to be regarded as 'substantial'. This assessment is to be made on a case-by-case basis in view of the above criteria. While the responsibility for this assessment lies with the sponsor, in cases where the sponsor consults the national competent authority advice should be given without delay and free of charge.

115. In applying these criteria, however, care has to be taken to avoid over-reporting. In particular, not every change to the clinical trial application form is by default to be considered as a 'substantial' amendment.

116. The annual update of the IB in accordance with Article 8 of Directive 2005/28/EC is not per se a substantial amendment. However, the sponsor has to verify whether the update relates to changes which are to be considered as substantial. In that case, the rules for notification of substantial amendments apply to the change.

117. The sponsor should assess also whether the combination of substantial amendments lead to changes of the clinical trial to an extent that it has to be considered as a completely new clinical trial, which would then be subject to a new authorisation procedure.

### 3.4. Examples

118. In view of these criteria the following examples should serve as guidance for the case-by-case decision of the sponsor. These examples relate only to the aspects assessed by the national competent authority of the Member State concerned. For aspects considered by the Ethics Committee, reference is made to the Commission guidance based on Article 8 of Directive 2001/20/EC.

#### 3.4.1. Amendments as regards the clinical trials protocol

119. With regard to the protocol, the following is a non-exhaustive list of amendments that are typically 'substantial':

- (a) change of main objective of the clinical trial;

<sup>(1)</sup> Directive 2001/20/EC distinguishes between notification of the national competent authority and information of the Ethics Committee. For the purposes of this guidance, both submissions will be referred to as 'notification'.

- (b) change of primary or secondary endpoint which is likely to have a significant impact on the safety or scientific value of the clinical trial;
- (c) use of a new measurement for the primary endpoint;
- (d) new toxicological or pharmacological data or new interpretation of toxicological or pharmacological data which is likely to impact on the risk/benefit assessment;
- (e) a change in the definition of the end of the trial, even if the trial has in practice already ended;
- (f) addition of a trial arm or placebo group;
- (g) change of inclusion or exclusion criteria, such as changes to age range, if these changes are likely to have a significant impact on the safety or scientific value of the clinical trial;
- (h) reducing the number of monitoring visits;
- (i) change of a diagnostic or medical monitoring procedure which is likely to have a significant impact on the safety or scientific value of the clinical trial;
- (j) withdrawal of an independent data monitoring board;
- (k) change of IMPs;
- (l) change of dosing of IMPs;
- (m) change of mode of administration of IMPs;
- (n) a change of study design which is likely to have a significant impact on primary or major secondary statistical analysis or the risk/benefit assessment.
120. With regard to the protocol, the following is a non-exhaustive list of amendments that are typically not 'substantial':
- (a) changes to the identification of the trial (e.g. change of title, etc.);
- (b) the addition/deletion of exploratory/tertiary endpoints;
- (c) a minor increase in the duration of the trial (< 10 % of the overall time of the trial);
- (d) an increase in duration of > 10 % of the overall time of the trial, provided that:
- the exposure to treatment with the IMP is not extended,
  - the definition of the end of the trial is unchanged, and
  - monitoring arrangements are unchanged;
- (e) a change in the number of clinical trial participants per trial site, if the total number of participants in the Member State concerned is identical or the increase/decrease is insignificant in view of the absolute number of participants;
- (f) a change in the number of clinical trial participants in the Member State concerned, if the total number of participants is identical or the increase/decrease is insignificant in view of the absolute number of participants;
- (g) a change in the documentation used by the research team for recording study data (e.g. case report form or data collection form);
- (h) additional safety monitoring which is not part of an urgent safety measure but is taken on a precautionary basis;
- (i) minor clarifications to the protocol;
- (j) correction of typographical errors.
- 3.4.2. *Amendments as regards the IMPD*
121. With regard to changes in the IMPD, guidance is contained in Chapter 8 of the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials <sup>(1)</sup>.
- 3.4.3. *Amendments as regards the IB*
122. With regard to the IB, the following is a non-exhaustive list of amendments that are typically 'substantial':
- (1) CHMP/QWP/185401/2004 final ([http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)).

- (a) new toxicological or pharmacological data or new interpretation of toxicological or pharmacological data of relevance for the investigator;
- (b) changes to the reference safety information for the annual safety report.
- 3.4.4. *Amendments as regards other initial documents supporting the request for authorisation of the clinical trial*
123. With regard to other initial documents, the following is a non-exhaustive list of amendments that are typically 'substantial':
- (a) a change of sponsor or the sponsor's legal representative;
- (b) the revocation or suspension of the IMP's marketing authorisation.
124. With regard to other initial documents, the following is a list of amendments that are typically *not* 'substantial':
- (a) any change of persons other than the sponsor or his legal representative, for example applicant, clinical research associates (CRAs) who monitor the clinical trial for the investigator, and clinical research organisations (CROs) (note that the responsibility vis-à-vis the national competent authority for the clinical trial is always with the sponsor or his legal representative);
- (b) any change in the contact details of persons referred to in the documentation (see, however, Section 3.2 as regards contact details of the contact person);
- (c) changes to the internal organisation of the sponsor or of the persons to whom certain tasks have been delegated;
- (d) changes in the logistical arrangements for storing/transporting samples;
- (e) change of technical equipment;
- (f) addition or deletion per se of another Member State or third country concerned.
126. For substantial amendments to information that is assessed only by the national competent authority of the Member State concerned, the sponsor should only notify the amendment to the national competent authority.
127. For substantial amendments to information that is assessed, according to Directive 2001/20/EC, only by the Ethics Committee of the Member State concerned, the sponsor should only notify the amendment to the Ethics Committee. This is in particular of relevance for the information relating to:
- the clinical trial site (Article 6(3)(f) of Directive 2001/20/EC),
  - the written information to be given to the clinical trial participant in order to obtain informed consent (Article 6(3)(g) of Directive 2001/20/EC), and
  - the investigator (Article 6(3)(d) of Directive 2001/20/EC).
128. These aspects are addressed in the separate Commission guidance based on Article 8 of Directive 2001/20/EC.
129. In the case of substantial amendments that affect information assessed by both the national competent authority and the Ethics Committee of the Member State concerned, the sponsor should submit the notifications in parallel.
130. There is no need to notify 'for information only' substantial amendments to one body (national competent authority or Ethics Committee), if this information is assessed by the respective other body.
131. In practice, it is necessary that the national competent authority and the Ethics Committee in the Member State concerned communicate with each other in order to ensure the exchange of expertise or information. This may be in particular relevant, for example, for:
- assessing scientific information requiring specific expertise,
  - ensuring effective inspections of clinical trials sites, and
  - updating relevant information in EudraCT.

### 3.5. Who should be notified?

125. Substantial amendments may relate to information relevant for assessment by the national competent authority, the Ethics Committee, or both.

### 3.6. Non-substantial amendments

132. The sponsor does not have to notify non-substantial amendments to the national competent authority or the Ethics Committee. However, non-substantial amendments should be recorded and contained in the documentation when it is subsequently submitted, for example in the subsequent notification of a substantial amendment. This is of particular relevance for the Clinical Trial Application Form: This form should be updated in its entirety at the occasion of a substantial amendment. Documentation of non-substantial amendments should also be available on request for inspection at the trial site or the sponsor premises as appropriate.

### 3.7. Format and content of notification

133. The notification of a substantial amendment should include the following:

(a) a signed cover letter, including:

- in its subject line the EudraCT number and the sponsor protocol number (if available) with the title of the trial and the sponsor's amendment code number allowing unique identification of the substantial amendment. Care should be taken to use the code number consistently;
- identification of the applicant;
- identification of the amendment (sponsor's substantial amendment code number<sup>(1)</sup> and date). One amendment could refer to several changes in the protocol or scientific supporting documents;
- a highlighted indication of any special issues related to the amendment and indication where the relevant information or text is in the original application dossier;
- identification of any information not contained in the Amendment Notification Form that might impact on the risk to trial participants;
- where applicable, a list of all affected clinical trials with EudraCT numbers and respective amendment code numbers (see above);

(b) the Amendment Notification Form, as amended, which is published in Volume 10 of EudraLex —

<sup>(1)</sup> The code number identifies the amendment and refers to all the documents submitted. The sponsor decides which code to be used. Section E1 of the amendment form should be completed with the date and version of the new amendment to which this form relates.

The Rules Governing Medicinal Products in the European Union<sup>(2)</sup>. Only this Amendment Notification Form should be used;

(c) a description of the amendment:

- an extract from the amended documents showing previous and new wording in track changes, as well as the extract only showing the new wording;
- notwithstanding the previous point, if the changes are so widespread or far-reaching that they justify an entire new version of the document, a new version of the entire document. In this case, an additional table should list the amendments to the documents. In this list, identical changes can be grouped.

The new version should be identified with the date and an updated version number.

(d) supporting information including, where applicable:

- summaries of data,
- an updated overall risk/benefit assessment,
- possible consequences for subjects already included in the trial,
- possible consequences for the evaluation of the results;

(e) if a substantial amendment involves changes to entries on the clinical trial application form, a revised copy of the XML file incorporating amended data. If the form is not submitted via a telematics system, the fields affected by the substantial amendment should be highlighted in the revised form<sup>(3)</sup>.

134. Where a substantial amendment affects more than one clinical trial of the same sponsor and the same IMP, the sponsor may make a single notification to the national competent authority/Ethics Committee of the Member State concerned. The cover letter and the notification should contain a list of all clinical trials affected with their EudraCT numbers and respective amendment code numbers. If the substantial amendment involves changes to several clinical trial application forms, all forms should be updated (see Section 3.7).

<sup>(2)</sup> [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)

<sup>(3)</sup> Section A4 of the CTA form should contain the version and date of the protocol originally authorised and this should not be changed when the protocol is later amended. Section B4 of the amendment form should contain the version and date of the currently authorised protocol. Note that Section H of the CTA form does not need to be changed, as it concerns the status of the CTA application to the Ethics Committee at the time of the CTA submission to the CA.

### 3.8. Time for response, implementation

135. Article 10(a), second and third subparagraph, of Directive 2001/20/EC reads as follows:

‘On the basis of the details referred to in Article 6(3) and in accordance with Article 7, the Ethics Committee shall give an opinion within a maximum of 35 days of the date of receipt of the proposed amendment in good and due form. If this opinion is unfavourable, the sponsor may not implement the amendment to the protocol.

If the opinion of the Ethics Committee is favourable and the competent authorities of the Member States have raised no grounds for non-acceptance of the ... substantial amendments, the sponsor shall proceed to conduct the clinical trial following the amended protocol. Should this not be the case, the sponsor shall either take account of the grounds for non-acceptance and adapt the proposed amendment to the protocol accordingly or withdraw the proposed amendment.’

136. Accordingly, the Ethics Committee has to give within 35 calendar days an opinion on a valid submission of a proposed substantial amendment. If a submission is not considered as valid by the Ethics Committee, the Ethics Committee should inform the applicant of this within the first 10 calendar days of this 35-day period. The reasons should be given.
137. With regard to the national competent authority, no deadline is set in Directive 2001/20/EC., and in view of the approval time for requests for authorisation, the national competent authority are invited to respond within 35 calendar days of receipt of the valid notification of an amendment. Validation of the submission is included in this period. If a submission is not valid (for example, the dossier does not contain the documentation required according to this guidance), the national competent authority are invited to inform the applicant of this within the first 10 calendar days of this 35-day period. The reasons should be given. This response time may be extended if such extension is justified in view of the nature of the substantial amendment, for example if the national competent authority has to consult an expert group or committee. In such cases, the national competent authority should notify the sponsor of the duration of the extension and its reasons. If the national competent authority states that it raises no grounds for non-acceptance, the sponsor can implement the changes, even if fewer than 35 days have elapsed since the filing of the substantial amendment.

138. For amendments submitted to either the Ethics Committee alone or to the national competent authority alone, the sponsor may implement the amendment when the Ethics Committee opinion is favourable or the competent national authority has raised no grounds for non-acceptance.
139. Up until then, the trial can continue on the basis of the original documentation, unless the rules for urgent safety measures apply.
140. Applicants should be aware that these procedures are intended to ensure rapid and efficient processing of substantial amendments. Against this background, unsatisfactory documentation is likely to lead to non-acceptance of the substantial amendment. Non-acceptance does not prejudice the applicant’s right to resubmission.
141. Upon approval, it is the sponsor’s responsibility to ensure communication of the changes to the investigators.

### 3.9. Notification of urgent safety measures

142. Article 10(b) of Directive 2001/20/EC reads as follows:

‘Without prejudice to point (a), in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where the new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. The sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the Ethics Committee is notified at the same time.’

143. Examples of urgent safety measures are if, for reasons of safety of the clinical trial participants, a trial is temporarily halted (see Section 3.10) or additional monitoring measures are set up.
144. Urgent safety measures may be taken without prior notification to the national competent authority. However, the sponsor must inform *ex post* the national competent authority and the Ethics Committee of the Member State concerned of the new events, the measures taken and the plan for further action as soon as possible. Where the initial contact is by telephone, this should be followed up, for reasons of traceability, by fax or e-mail. It should be followed by a written report.
145. The *ex post* notification of urgent safety measures is independent of the obligation to:

- notify substantial amendments (see above),
- notify early termination of the trial within 15 days in accordance with Article 10(c) of Directive 2001/20/EC (see below, Section 4.2.2), and
- notify adverse events and serious adverse reactions in accordance with Articles 16 and 17 of Directive 2001/20/EC.

### 3.10. Temporary halt of a trial

146. A temporary halt of a trial is a stoppage of the trial which is not envisaged in the approved protocol and where there is an intention to resume it.

147. A temporary halt can be:

- a substantial amendment, or
- part of an urgent safety measure as referred to in Article 10(b) of Directive 2001/20/EC. In this case, the notification of the temporary halt of a trial should be made immediately and, at the latest, in accordance with the deadline set out in Article 10(c), second sentence, of Directive 2001/20/EC, within 15 days from when the trial is temporarily halted.

148. The reasons and scope, e.g. stopping recruitment or interrupting treatment of subjects already included, should be clearly explained in the notification (in case of substantial amendment, see Section 3.7) or in the *ex post* information (in case of urgent safety measures, see Section 3.9).

149. The restart of the trial should be treated as a substantial amendment providing evidence that it is safe to restart the trial.

150. If the sponsor decides not to recommence a temporarily halted trial he should notify the national competent authority of the Member States concerned within 15 days of his decision in accordance with Article 10(c), second sentence, of Directive 2001/20/EC (see Section 4.2).

### 3.11. Suspension/prohibition of a clinical trial by the national competent authority in case of doubts about safety or scientific validity

151. Article 12(1) of Directive 2001/20/EC reads as follows:

‘Where a Member State has objective grounds for considering that the conditions in the request for

authorisation referred to in Article 9(2) are no longer met or has information raising doubts about the safety or scientific validity of the clinical trial, it may suspend or prohibit the clinical trial and shall notify the sponsor thereof.

Before the Member State reaches its decision it shall, except where there is imminent risk, ask the sponsor and/or the investigator for their opinion, to be delivered within one week.

In this case, the competent authority concerned shall forthwith inform the other competent authorities, the Ethics Committee concerned, the Agency and the Commission of its decision to suspend or prohibit the trial and of the reasons for the decision.’

152. If the trial is terminated following a suspension, the rules on end of trial notification apply (see below, Section 4.2).

### 3.12. Non-compliance with the applicable rules on clinical trials

153. Article 12(2) of Directive 2001/20/EC reads as follows:

‘Where a competent authority has objective grounds for considering that the sponsor or the investigator or any other person involved in the conduct of the trial no longer meets the obligations laid down, it shall forthwith inform him thereof, indicating the course of action which he must take to remedy this state of affairs. The competent authority concerned shall forthwith inform the Ethics Committee, the other competent authorities and the Commission of this course of action.’

154. The ‘course of action’ of the national competent authority should have a timetable for its implementation and a date when the sponsor should report back to the national competent authority on the progress and completion of its implementation.

155. The sponsor should ensure that the ‘course of action’ set by the national competent authority is immediately implemented and report to the national competent authority of the Member State concerned on the progress in and completion of its implementation in accordance with the timetable set.

156. The national competent authority must inform the other national competent authorities, the Ethics Committee of the Member State concerned and the Commission of the ‘course of action’.

#### 4. DECLARATION OF THE END OF A CLINICAL TRIAL

##### 4.1. Legal basis and scope

157. Article 10(c) of Directive 2001/20/EC reads as follows:

‘Within 90 days of the end of a clinical trial the sponsor shall notify the competent authorities of the Member State or Member States concerned and the Ethics Committee that the clinical trial has ended. If the trial has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.’

158. ‘End of the trial’ is not defined in Directive 2001/20/EC. The definition of the end of the trial should be provided in the protocol (for guidance, see Section 2.5). For changes to the definition see under Section 3.4.1.

##### 4.2. Procedure for declaring the end of the trial

###### 4.2.1. General rules

159. The sponsor has to make an end of trial declaration when the complete trial has ended in all Member States/third countries concerned. The end of the clinical trial is defined in the protocol (see Section 4.1).

160. This declaration has to be made to the national competent authority and the Ethics Committee of all Member States concerned within 90 days of the end of the clinical trial. To this end, the form published in Volume 10 of EudraLex — The Rules Governing Medicinal Products in the European Union <sup>(1)</sup> should be used.

161. The notified Member States are responsible for entering this information into the EudraCT database.

###### 4.2.2. Shortened deadline for early termination

162. An earlier end of the clinical trial which is not based on grounds of safety, but on other grounds, such as faster recruitment than anticipated, is not considered as ‘early termination’.

163. In the case of early termination, the sponsor must notify the end of the trial to the national competent authority and the Ethics Committee of the Member State concerned immediately and at the latest within 15 days after the trial is halted, clearly explain the reasons, and describe follow-up measures, if any, taken for safety reasons.

##### 4.3. Clinical trial summary report

164. The clinical trial summary report is part of the end of trial notification, albeit usually submitted only subsequently to the end of trial notification. The sponsor should provide this summary report within one year of the end of the complete trial for non-paediatric clinical trials. For paediatric clinical trials, the timelines are set out in the Commission Communication 2009/C28/01. Regarding the arrangements for submitting the clinical trial summary report, its format, content, and its accessibility for the public, reference is made to the Commission Communications 2009/C28/01 and 2008/C168/02 and their implementing technical guidance documents <sup>(2)</sup>.

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<sup>(1)</sup> [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)

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<sup>(2)</sup> [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm)