



**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**

  
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This draft revision of the existing detailed guidance aims at:

- Incorporating changes of the legislative framework (*inter alia*, paediatrics, advanced therapies); and
- Clarification and further harmonising the requirements of format and content of the request for authorisation, substantial amendment, and declaration of end of the clinical trial.

**The draft revised document is submitted for public consultation.** Contributions are invited from all stakeholders related to clinical trials. Stakeholders who are not established within the European Union are equally invited to comment.

**Contributions should be sent by e-mail to [entr-pharmaceuticals@ec.europa.eu](mailto:entr-pharmaceuticals@ec.europa.eu) on 8 September 2009 at the latest.**

Contributions will be made publicly available on the ‘Pharmaceuticals’ website of the Commission once the consultation period is over. If you do not wish your contribution to be made public please indicate this clearly and specifically in the submitted documentation. In this case, only an indication of the contributor will be disclosed.

All contributions will be carefully analysed by the Commission. The future version of the detailed guidance is going to build on this consultation.

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## 1. INTRODUCTION

### 1.1. Legal Basis

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**”) aims at harmonising the rules in the Community on request for authorisation of clinical trials, notification of amendments and declaration of the end of clinical trials.<sup>2</sup>

In this respect, Directive 2001/20/EC is exhaustive, i.e. the harmonisation is not based on minimum requirements, and Member States are not allowed to “add on” the Community rules.

In order to concretise further these rules, Article 9(8) of Directive 2001/20/EC 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.”*

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

<sup>2</sup> Cf. Whereas 10 of Directive 2001/20/EC: “*Clinical trials are a complex operation, generally lasting one or more years, usually involving numerous participants and several trial sites, often in different Member States. Member States' current practices diverge considerably on the rules on commencement and conduct of the clinical trials and the requirements for carrying them out vary widely. This therefore results in delays and complications detrimental to effective conduct of such trials in the Community. It is therefore necessary to simplify and harmonise the administrative provisions governing such trials by establishing a clear, transparent procedure and creating conditions conducive to effective coordination of such clinical trials in the Community by the authorities concerned.*”

The purpose of this document is to provide the necessary guideline to concretise the requirements in EU Member States and contracting States of the European Economic Area<sup>3</sup> for:

- Authorisation of a clinical trial on a medicinal product for human use;
- Notifications of substantial proposed amendments; and
- Declaration of the end of the clinical trial.

Member States and persons requesting authorisation of a clinical trial, substantially amending a protocol of a clinical trial, and declaring the end of a clinical trials shall consider this guidance when applying Directive 2001/20/EC and its implementing acts and guidance.

## 1.2. Scope

The scope of this guideline is the scope of Directive 2001/20/EC. Directive 2001/20/EC applies to all interventional clinical trials involving medicinal products 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>4</sup> (hereinafter “**Directive 2001/83/EC**”). This includes interventional clinical trials involving:

- Advanced therapy medicinal products 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<sup>5</sup> (hereinafter “**Regulation 1394/2007**”);
- Medicinal products derived from human blood or human plasma as defined in Article 1(10) of Directive 2001/83/EC;
- Immunological medicinal products as defined in Article 1(4) of Directive 2001/83/EC;
- Herbal medicinal products as defined in Article 1(3) of Directive 2001/83/EC;
- Radiopharmaceuticals as defined in Article 1(6) of Directive 2001/83/EC; and
- Homeopathic medicinal products as defined in Article 1(5) of Directive 2001/83/EC;

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<sup>3</sup> For the purpose of this document, reference to EU/EU Member States/Member State shall include EEA/EEA contracting State(s) unless indicated otherwise.

<sup>4</sup> OJ L 311, 28.11.2001, p. 67, as amended.

<sup>5</sup> OJ L 324, 10.12.2007, p. 121.

Directive 2001/20/EC also applies to medicinal products for paediatric population.

In particular, 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>6 7 8</sup>
- Cosmetic products as defined in Community legislation;<sup>9</sup>
- Food as defined in Community legislation.<sup>10</sup>

To draw the “borderline” between these sectoral legislations, the established criteria as set out in the jurisprudence of the European Court of Justice and the applicable guidelines apply.

### 1.3. Definitions

The definitions as contained in Directive 2001/20/EC, its implementing acts and applicable guidance apply. With regard to implementing guidelines, in particular the following guidance documents provide valuable additional clarification on legal terms:

- The *Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials* (on the term investigational medicinal products, “**IMPs**”);<sup>11</sup>
- Annex 13 to the guidelines on good manufacturing practices ‘Manufacture of investigational medicinal products’;<sup>12</sup>
- The *Commission Guidelines on Pharmacovigilance for Medicinal Products for Human Use*<sup>13</sup> (on the term non-interventional trial); and

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<sup>6</sup> Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (OJ L 169 , 12.7.1993, p. 1), as amended.

<sup>7</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), as amended.

<sup>8</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), as amended.

<sup>9</sup> Council Directive 76/768 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), as amended.

<sup>10</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, 1.02.2002), as amended.

<sup>11</sup> [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm)

<sup>12</sup> [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm)

- The *Questions and Answers Document on the Clinical Trials Directive*.<sup>14</sup>

## 2. REQUEST FOR A CLINICAL TRIAL AUTHORISATION

### 2.1. Procedural aspects

#### 2.1.1. Legal basis

Article 9(1), 2<sup>nd</sup> sub-paragraph 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>15</sup>

#### 2.1.2. Applicable delays for authorisation, tacit authorisation

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 possibly and may not exceed 60 days, subject to exceptions set out in this Article.

The validation of the request for authorisation thus forms part of the delay of 60 days. Day 0 is the day of submission of the request. If the request is valid, on day 60 at the latest the consideration of the request has to be finalised.

As regards national competent authorities, as a general rule, the absence of raising any grounds for non-acceptance is a tacit authorisation.<sup>16</sup> However, Article 9(5) and (6) of Directive 2001/20/EC set out important exceptions to this general rule.

#### 2.1.3. Scope of authorisation

The authorisation of a clinical trial by the national competent authority is valid for a clinical trial conducted in that Member State.

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<sup>13</sup> Volume 9A of The Rules Governing Medicinal Products in the European Union (Sept. 2008), Part 1, Point 7.1. (p. 90).

<sup>14</sup> [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm)

<sup>15</sup> Cf. also Whereas 11: “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. [...]”

<sup>16</sup> The term “authorisation” shall be used throughout this document.

This authorisation does not imply approval of the development programme of the tested IMP.

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

##### 2.1.4.1. Application is not valid

If an application is not valid the national competent authority will inform the applicant and give the reasons.

##### 2.1.4.2. Amendments during the authorisation phase

Following the submission of a request for authorisation, the sponsor may want to submit changes to the documentation. This may happen either:

- Following notification of grounds for non-acceptance by the national competent authority of the Member State concerned: In this case Article 9(3) of Directive 2001/20/EC applies; or
- At the initiative of the sponsor, for example following the opinion of the Ethics Committee or in view of new relevant safety information: In this case, the timeframe set out in Article 9(4) of Directive 2001/20/EC re-starts, i.e. the amended request for authorisation shall be considered as rapidly as possible and may not exceed 60 days.

##### 2.1.4.3. Withdrawals

Unexpected events or additional information may require the sponsor to withdraw a request for authorisation before the national competent authority has reached its decision about authorisation. The sponsor or his legal representative 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 telephone and, for reasons of traceability, by fax or e-mail and include the EudraCT number and other trial identification. It should be followed as soon as possible by a formal letter of withdrawal providing a brief description of the reasons.

If the sponsor wishes to resubmit the application, he must identify the application as a resubmission in the covering letter and use a resubmission letter. The initial EudraCT number should be used with a letter after the number sequence: A for 1<sup>st</sup> resubmission, B for second resubmission, etc.



### 2.1.5. *Interface with other authorisation requirements*

The sponsor 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 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>17</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>18</sup> from the relevant competent authority in the Member State concerned.

### 2.1.6. *Other issues*

For submission of requests for authorisation, the applicant should check the language requirements with the national competent authority of the Member State concerned before preparing the application.

## 2.2. **Covering Letter**

The applicant should submit and sign a covering letter with the application. Its heading should contain the EudraCT number and the sponsor protocol number with a title of the trial.

In the covering letter, the applicant should draw attention to peculiarities of the trial, and in particular particularities related to:

- (a) the trial population;
- (b) trial designs (such as whether the clinical trial includes the conducting of sub studies); and
- (c) IMPs and non-IMPs, such as GMOs, radiopharmaceuticals, narcotics and psychotropics.

Moreover, the covering letter should highlight if the trial involves a first administration of a new active substance to humans.

The applicant should indicate where the relevant information is contained in the application dossier.

In addition, the applicant should draw attention to any scientific advice related to the trial or IMP given by the European Medicines Agency (“**EMA**”) or the national competent authority of the Member State concerned or any other country and indicate where the copy of the advice is contained in the application.

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<sup>17</sup> OJ L 117, 8.5.1990, p. 1, as amended.

<sup>18</sup> OJ L 106, 17.4.2001, p. 1, as amended.

If the clinical trial is part of a Paediatrics Investigation Plan (“**PIP**”) as referred to in 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>19</sup>, this should be indicated in the cover letter together with the decision number of the EMEA.

The applicant shall set out precisely in the cover letter where the reference information is contained as regards the assessment whether an adverse reaction is a suspected unexpected serious adverse reaction (“**SUSAR**”) as defined in Directive 2001/20/EC and implementing Community guidelines.

### **2.3. Allocation of the EudraCT number**

Before submitting an application to the national competent authority, the sponsor should obtain a unique EudraCT number from the EudraCT database by the procedure described in the *Detailed guidance on the European clinical trials database*.<sup>20</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. The applicant will then need to complete all the relevant parts of the application form before submitting an application to the national competent authority.

### **2.4. Application form**

The application form is accessible via the internet by the procedure described in the *Detailed guidance on the European clinical trials database*.<sup>21</sup> The application form should uniquely identify the clinical trial and the organisations and key individuals responsible for the conduct of the trial.

Information on sub-studies should be provided in the relevant section of the application form.

Some of the information in the form, such as contact person and name of the investigator will be relevant in one Member State only. The applicant should print the completed form, sign and date it, and send it as part of the application to the national competent authority of the Member State concerned. The applicant's signature will confirm that the sponsor is satisfied that,

- (a) The information provided is complete;
- (b) The attached documents contain an accurate account of the information available;
- (c) In the sponsor's opinion it is reasonable for the proposed clinical trial to be undertaken;

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<sup>19</sup> OJ, L 378, 27.11.2006, p. 1.

<sup>20</sup> EudraLex, Volume 10; [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm)

<sup>21</sup> EudraLex, Volume 10; [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm)

- (d) Any information provided to both the national competent authority and the Ethics Committee is based on the same data;
- (e) SUSARs will be reported in accordance with the applicable guidelines; and
- (f) The result-related information of the clinical trial will be submitted in accordance with the Commission Communications 2009/C28/01 and 2008/C168/02 for paediatric clinical trials and non-paediatric clinical trials respectively after the end of the clinical trial.<sup>22</sup>

The applicant should save the full application form data set as an XML file using the utilities feature linked to the form on its webpage and submit a copy of this XML file, on a disk, with the application.

More information about the EudraCT application form is available here:

- Detailed guidance on the European clinical trials database;<sup>23</sup>
- EudraCT User Manual;<sup>24</sup>
- EudraCT Frequently Asked Questions.<sup>25</sup>

Moreover, EMEA is operating a help-desk for questions related to EudraCT.<sup>26</sup>

Certain information contained in the application form is going to be made public, following its entry into EudraCT by the national competent authority of the Member State concerned. This publication is done via rendering certain data fields contained in EudraCT public in accordance with the applicable guidelines published by the Commission.<sup>27</sup>

## 2.5. Protocol

According to Article 2(h), 1<sup>st</sup> period, of Directive 2001/20/EC, the protocol is “*a document that describes the objective(s), design, methodology, statistical considerations and organisations of a trial.*”

The content and format of the protocol should comply with Section 6 of the *Community guideline on Good Clinical Practice* (CPMP/ICH/135/95).<sup>28</sup> The

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<sup>22</sup> EudraLex, Volume 10; [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm)

<sup>23</sup> [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm)

<sup>24</sup> <http://eudract.emea.europa.eu/document.html>

<sup>25</sup> <http://eudract.emea.europa.eu/document.html>

<sup>26</sup> EudraCT Helpdesk, email: [eudract@emea.europa.eu](mailto:eudract@emea.europa.eu); Tel. (44-20) 75 23 75 23; Fax (44-20) 74 18 86 69.

<sup>27</sup> Eudralex, Volume 10, Chapter V ([http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm) )

<sup>28</sup> [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm)

version submitted should include all currently authorised amendments and a definition of the end of the trial. It should be identified by the title, a sponsor's code number specific for all versions of it, a number and date of version that will be updated when it is amended, and by any short title or name assigned to it, and be signed by the sponsor and principal investigator (or co-ordinating investigator for multicentre trials).

It should include also:

- The evaluation of the anticipated benefits and risks as required in Article 3(2)(a) of Directive 2001/20/EC;
- 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;
- A justification for including subjects who are incapable of giving informed consent or other special populations;
- A clear and unambiguous definition of the end of the trial in question; and
- A description of the plan for the provision of any additional care of the subjects once their participation in the trial has ended, where it differs from what is normally expected according to the subject's medical condition.

A protocol should clearly address sub-studies conducted at all trial sites or only at specific sites.

With regard to first-in-human clinical trials, the safety of participants can be enhanced by identification and planned mitigation of factors associated with risk. A protocol for first-in-human clinical trials involving medicinal products should describe the strategies to

- identify risks, taking into account all available preclinical data and identified risk factors; and
- mitigate risks, including precautionary measures such as training of investigator and personnel, and emergency measures.

In designing and preparing the study the Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products<sup>29</sup> should be followed. It provides guidance on the following key aspects of the protocol that should be designed to mitigate risk factors:

- choice of subjects;
- route and rate of administration;
- estimation of the first dose in human;

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<sup>29</sup> EMEA/CHMP/SWP/28367/07 (see <http://www.emea.europa.eu/pdfs/human/swp/2836707enfin.pdf>).

- precautions to apply between doses within a cohort;
- precautions to apply between cohorts;
- dose escalation scheme;
- stopping rules and decision making;
- monitoring and communication of adverse events/reactions; and
- investigator site facilities and personnel.

In general, the higher the potential risk associated with an IMP and its pharmacological target, the greater the precautionary measures that should be exercised in the design of the first-in-human study.

## 2.6. Investigator’s Brochure

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.*”

A request for authorisation has to be accompanied with an IB. 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, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures.

The content, format and procedures for updating the IB has to comply with Article 8(1) of the *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>30</sup> (hereinafter referred to as 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 format of summaries.

The approved Summary of Product Characteristics (“**SmPC**”) may replace 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. If the conditions of use in the clinical trial differ from those authorised, the SmPC should be complemented with a summary of relevant non-clinical and clinical data that support the use of the IMP in the clinical trial. When 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.

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<sup>30</sup> OJ L91, 9.4.2005, p. 13.

For an international trial where the medicinal product to be used in each Member State is the one authorised at a national level and the SmPC varies among Member States, the sponsor should choose one SmPC to replace the IB for the whole clinical trial.

The current IB or equivalent document (e.g. SmPC for marketed products) will be the reference document for the assessment of the expectedness of any adverse reaction that might occur during the clinical trial.

## 2.7. Investigational Medicinal Product Dossier

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.”

The IMP Dossier (“**IMPD**”) gives information to justify the quality of any IMP (i.e. including reference product and placebo) to be used in the clinical trial. It should also provide data from non-clinical studies and the previous clinical use of the IMP or justify in the application why information is not provided.

The IMPD should be prefaced with a detailed table of contents and a glossary of terms.

The IMPD should include summaries of information related to the quality, manufacture and control of the IMP, data from non-clinical studies and from its clinical use. It is preferable to present data in tabular form accompanied by the briefest narrative highlighting the main salient points. The dossier should not generally be a large document, however for trials with certain types of IMPs exceptions can be agreed with the Member State concerned.

Generally speaking, where possible data should be provided under the headings and arranged in the order given in the *Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials*.<sup>31</sup> The main headings are reproduced in attachments 1-3.

If there is no appropriate heading a new section may be added.

Where it is necessary to omit data for reasons that are not obvious, scientific justification should be provided. It is recognised that it will be inappropriate or impossible to provide information under all headings for all products. The dossier required will depend on many factors including the nature of the medicinal product, the stage of development, the population to be treated, the

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<sup>31</sup> CHMP/QWP/185401/2004 final  
([http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm))

nature and severity of the disease and the nature and duration of exposure to the IMP. It is impossible to formulate detailed guidance to cover all situations. Applicants are advised to use the abovementioned guideline as a starting point in their preparation of data packages for submission. In addition, the specific guidance for various types of IMPs, clinical trial, or patient groups should be followed. This specific information is available in Volume 3 of *EudraLex - The rules governing medicinal products in the European Union*.<sup>32</sup>

If the IMP is reconstituted in the sense of Article 9(2) of Directive 2005/28/EC, this process shall be defined in the IMPD.

With regard to some specific points, the following shall be highlighted:

#### 2.7.1. *Quality data*

Where applicable, the Guideline on virus safety evaluation of biotechnological investigational medicinal products<sup>33</sup> should be followed.

To document compliance with the principles of Good Manufacturing Practice (“GMP”) set out in Directive 2003/94/EC and the implementing detailed guideline for IMPs,<sup>34</sup> the following information shall be provided:

- If the IMP does not have a marketing authorisation in the EU, but is manufactured in the EU, a copy of the manufacturing authorisation as referred to in Article 13(1) of Directive 2001/20/EC stating the scope of the manufacturing authorisation;
- If the IMP does not have a marketing authorisation and is not manufactured in the EU,
  - a copy of the importation authorisation as referred to in Article 13(1) of Directive 2001/20/EC;
  - certification by the qualified person that the manufacturing complies with good manufacturing practices (“GMP”) at least equivalent to the GMP in the Community;
  - certification of the CMP compliance of the manufacturing of any active biological substance.

In exceptional cases, where impurities are not justified by the specification or when unexpected impurities (not covered by

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<sup>32</sup> [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol3\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol3_en.htm)

<sup>33</sup> Doc. Ref. EMEA/CHMP/BWP/398498/2005  
(<http://www.emea.europa.eu/pdfs/human/bwp/39849805enfin.pdf>)

<sup>34</sup> Annex 13 to Volume 4 of *EudraLex - the Rules Governing Medicinal Products in the European Union*  
([http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm))

specification) are detected, the certificate of analysis for test product should be attached. Where applicable, the TSE Certificate and viral safety data should be provided.

### 2.7.2. *Non-clinical pharmacology and toxicology data*

The sponsor should also provide summaries of non-clinical pharmacology and toxicology data for any IMP included in the clinical trial or justify why he does not provide them. 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 the briefest narrative highlighting the main salient points. The summaries of the studies conducted should allow an assessment of the adequacy of the study and whether the study has been conducted according to an acceptable protocol.

This section should provide a critical analysis of the available data, including justification for deviations and omissions from the detailed guidance and an assessment of the safety of the product in the context of the proposed clinical trial rather than a mere factual summary of the studies conducted.

The studies needed as a basis for the non-clinical section of the IMPD are outlined in the relevant Community guidelines. In particular, applicants are referred to the specific Community guidelines contained in Volume 3 of Eudralex<sup>35</sup>, and in particular the guideline *Non-clinical safety studies for the conduct of human clinical trials* (CPMP/ICH/286/95).

All studies should be conducted according to currently acceptable state-of-the-art protocols. In addition, they should meet the requirements of Good Laboratory Practice (“GLP”) guidelines where appropriate. The sponsor should justify any deviations from these guidelines and provide a statement of the GLP status of all studies.

The test material used in the toxicity studies should be representative of that proposed for clinical trial use in terms of qualitative and quantitative impurity profiles. The preparation of the test material should be subject to appropriate controls to ensure this and thus support the validity of the study.

### 2.7.3. *Previous clinical trial and human experience data*

This section should provide summaries of all available data from previous clinical trials and human experience with the proposed IMPs.

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<sup>35</sup> [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol3\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol3_en.htm)



All studies should have been conducted in accordance with the principles of GCP. To this end, the applicant shall submit the following:

- a statement of the GCP status of the clinical trials referred to;
- in case the clinical trials referred to **has** been performed in third countries, a reference to the entry of this clinical **trial** in a public register, if available. In case a clinical trial is not published in a register, this should be explained and justified.

There are no specific requirements for data from clinical studies that must be provided before a clinical trial authorisation can be granted. However applicants should take account of the general guidance in the Community guideline *General considerations for clinical trials* (CPMP/ICH/291/95).<sup>36</sup>

#### 2.7.4. *Overall risk and benefit assessment*

This section should provide a brief integrated summary that critically analyses the non-clinical and clinical data in relation to the potential risks and benefits of the proposed trial. The text should identify any studies that were terminated prematurely and discuss the reasons. Any evaluation of foreseeable risks and anticipated benefits for studies on minors or incapacitated adults should take account of provisions set out in Article 3 to 5 of Directive 2001/20/EC.

The aim of the non-clinical pharmacology and toxicity testing is to indicate the principal hazards of a new medicinal product. The sponsor should use the relevant results in terms of pharmacology, toxicology and kinetics as the basis of extrapolation to indicate possible risks in humans.

As a guide to what may occur in humans, the sponsor should integrate all the available data, analyse the pharmacological and toxic actions of the IMP and use the results to suggest possible mechanisms and the exposure required to produce them. Where appropriate, the sponsor should discuss safety margins in terms of relative systemic exposure to the IMP, preferably based on AUC and Cmax data, 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.

## 2.8. **Simplified IMPD**

The sponsor has the possibility to submit a simplified IMPD if the information can be made available by referring to other submissions. This is the case if:

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<sup>36</sup> <http://www.emea.europa.eu/htms/human/ich/ichefficacy.htm>

- the information related to the IMP is contained in the IB;
- the information related to the IMP is contained in another clinical trial application to the national competent authority of the Member State concerned and has been assessed previously; or
- the information related to the IMP is contained in the SmPC and has been assessed previously as part of a marketing authorisation in any Member State or in an ICH country.

Information on a placebo may also be provided as a simplified IMPD.

#### 2.8.1. *Possibility to cross-refer to the IB*

The applicant may either provide a stand alone IMPD or cross-refer to the IB for the pre-clinical and clinical parts of the IMPD. In the latter case, the summaries of pre-clinical information and clinical information should include data, preferably in tables, providing sufficient detail to allow assessors to reach a decision about the potential toxicity of the IMP and the safety of its use in the proposed trial. If there is some special aspect of the pre-clinical data or clinical data that requires a detailed expert explanation or discussion beyond what would usually be included in the IB, the sponsor should submit the pre-clinical and clinical information as part of the IMPD.

#### 2.8.2. *Possibility to refer to an IMPD as submitted previously*

The IMPD may have been submitted by another applicant and held by the national competent authority of the Member State concerned. In these cases sponsors are allowed to cross-refer to other documentation in the dossier or previously submitted by the sponsor or another applicant. This may require a letter from the other applicant to authorise the national competent authority to cross-refer to their data.

#### 2.8.3. *Possibility to refer to the Possibility to refer to the SmPC*

The sponsor may submit the current version of the SmPC as the IMPD if an IMP has a marketing authorisation in any Member State or in an ICH country and is being used in the same form, for the same indications and with a dosing regimen covered by the SmPC. The SmPC must be understandable by the national competent authority of the Member State concerned (translation may be necessary). The SmPC will also be sufficient for studies of dosing regimens not covered by the SmPC when the sponsor can show that the information in the SmPC justifies the safety of the proposed new regimen. Otherwise the sponsor should submit additional non-clinical data or clinical data to support the safety of its use in the new indication, new patient population or the new dosing regimen as appropriate. If the applicant is the marketing authorisation holder and ~~he has~~ submitted an application to vary the SmPC, which has not yet been authorised, the nature of the variation and the reason for it should be explained in the covering letter.

There are situations where the IMP to be used in the Clinical Trial has a marketing authorisation in the Member State concerned but the protocol allows that any brand of the IMP with an marketing authorisation in that Member State may be administered to the trial subjects. In those situations, provided that the IMP is not modified e.g. overencapsulated, it is acceptable that IMPs to be used are only identified by the active substance name or ATC code as follows:

2.8.3.1. A sponsor may wish to conduct a clinical trial with an active substance that is available in the Community in a number of medicines with marketing authorisations and different trade names. In this case the protocol may define the treatment in terms of the active substance only and not specify the trade name of each product. This is to allow investigators to administer any brand name of these products that contains the active substance in the required pharmaceutical form with a marketing authorisation in the Member State concerned.

When the IMP is defined in the protocol in terms of its active substance, the sponsor should elect one medicine with a marketing authorization in the Community and submit its SmPC as equivalent to the IMPD for all medicinal products that contain that active substance used at any of the clinical trial sites.

2.8.3.2. In some trials the sponsor may wish to allow investigators in the same multicentre trial to administer different regimens of IMPs with marketing authorisation in the Member States concerned, e.g. groups of anticancer drugs, according to local clinical practice at each investigator site in the Member State.

2.8.3.3. In other trials the sponsor may wish to study the effect of a number of medical treatments on a specific illness without specifying the IMPs to be used except that they have a marketing authorisation in the Member State concerned. To achieve this he should identify the treatment using its Anatomic Therapeutic Chemical (“ATC”) code (level 3-5) in the protocol. When the IMP is defined in the protocol in terms of its ATC code, the sponsor may replace the IMPD by one representative SmPC for each active substance pertaining to that ATC group. Alternatively, he could 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.

#### 2.8.4. *Placebo*

If the IMP is a placebo, the information requirements can be reduced in line with the requirements set out in Table 1.

## 2.8.5. Overview

**Table 1: Reduced information requirements for IMPs known to the national competent authority of the Member State concerned**

Types of Previous Assessment	Quality Data	Non-clinical Data	Clinical Data
The IMP has a MA in any EU Member State or ICH country and is used in the trial without any modification of the IMP: Within the conditions of the SmPC Outside the conditions of the SmPC After it has been blinded	SmPC SmPC P+A	SmPC Yes (if appropriate) SmPC	SmPC Yes (if appropriate) SmPC
Another pharmaceutical form or strength of the IMP has a MA in any EU Member State and the IMP is supplied by the MAH	SmPC+P+A	Yes	Yes
The IMP has no MA in any EU Member State but drug substance is part of a medicinal product with a marketing authorisation in a MS and: is supplied from the same manufacturer is supplied from another manufacturer	SmPC+P+A SmPC+S+P+A	Yes Yes	Yes Yes
The IMP has a previous CTA in the Member State concerned <sup>37</sup> and has not been modified no new data available since CTA new data available since CTA different conditions of use	No New Data If appropriate	No New Data If appropriate	No New Data If appropriate
The IMP is a placebo	P+A	No	No
The IMP is a placebo and the placebo has the same composition, is manufactured by the same manufacturer and is not sterile	No	No	No
The IMP is a placebo and has a previous CTA in the Member State concerned	No	No	No

(S: Drug substance data; P: Drug product data; A: appendices of the IMPD)

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

Medicinal products used in the context of a clinical trial and not falling within the definition of 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>38</sup>

It is strongly recommended that NIMPs with marketing authorisation in the Member State concerned are used for these purposes when possible. When this is not possible, the next choice should be NIMPs with marketing authorisation in another Member State. A SmPC for each NIMP with a marketing authorisation should be submitted with the clinical trials application dossier.

<sup>37</sup> The sponsor should provide a letter of authorisation to cross-refer to the data submitted by another applicant.

<sup>38</sup> Cf. [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm)

Where NIMPs without a marketing authorisation in the EU are used, or used outside the conditions of a marketing authorisation, a NIMP dossier may be requested by the competent authority of the Member State concerned on a case-by-case basis if this is necessary in order to fully assess the safety of the clinical trial.

## **2.10. Other documents to be submitted**

The following additional documents should be submitted as attachment to the covering letter:

- If the applicant is not the sponsor, a letter from the sponsor authorising the applicant to act on their behalf;<sup>39</sup>
- A list of national competent authorities to which the sponsor has already made the same application with details of their decisions;
- 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 sponsor that it has copied its opinion to the national competent authority of the Member State concerned;
- If available, a copy of the summary of scientific advice from any Member State or the EMEA or peer reviews with regard to the clinical trial;
- If applicable and available, the Paediatric Investigation Plan (“**PIP**”) summary report, the opinion of the Paediatric Committee and the decision of the EMEA.

## **3. NOTIFICATION OF AMENDMENTS**

### **3.1. Legal basis and scope**

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’].”*

Notification/submission for information<sup>40</sup> is only obligatory if the amendment is substantial or otherwise significant. Directive 2001/20/EC does not require notification of non-substantial amendments.

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<sup>39</sup> Cf. Article 7 of Directive 2005/28/EC.

### 3.2. The notion of “amendment”

Substantial amendments as referred to in Article 10(a) of Directive 2001/20/EC are only those which are introduced after approval of the clinical trial by the national competent authority or the Ethics Committee respectively.

This means that the following is not an “amendment”:

- 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 example following the opinion of the Ethics Committee (see above, point 2.1.4.); and
- A change to the documentation submitted to the Ethics Committee during the ongoing assessment of the request for authorisation by the Ethics Committee, for example following the opinion of the national competent authority.

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

The Annual Safety Report (“**ASR**”) in accordance with Article 17(2) of Directive 2001/20/EC is *not* an amendment. However, the sponsor has to verify whether the data presented in the ASR requires an amendment and whether this is to be considered as substantial. In that case, the rules for notification of substantial amendments apply to them.

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 them.

Changes of the contact details of the sponsor (e.g. a change of email or postal address) are not considered as amendment, if the sponsor remains identical. This information should be transmitted to the national competent authority of the Member State concerned as soon as possible.

### 3.3. The notion of “substantial”

Amendments to the trial are regarded as “substantial” and “otherwise significant”<sup>41</sup> where they are likely to have a significant impact on:

- the safety or physical or mental integrity of the subjects;

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<sup>40</sup> Directive 2001/20/EC distinguishes between *notification* of the national competent authority and *information* of the Ethics committee. For the purpose of this guideline, both submissions shall be referred to as “notification”.

<sup>41</sup> In view of the wide notion of „substantial“, the substantial bearing of the further qualification of „otherwise significant“ is of very minor relevance.

- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any IMP used in the trial.

In all cases, an amendment is only to be regarded as “substantial” when one or more of the above criteria are met.


The decision whether an amendment is “substantial” is to be taken on a case-by-case basis in view of the criteria above.

In applying these criteria, however, care has to be taken to avoid over-reporting.

In view of these criteria the following examples shall serve as guidance for the case-by-case decision of the sponsor.

### 3.3.1. *Amendments as regards the clinical trials protocol*

With regard to the protocol, the following is a non-exhaustive list of amendments which are typically “substantial”:

- Reducing the number of clinic visits (this might significantly impact on the safety or physical or mental integrity of the subjects);
- Introducing a new monitoring procedure or a change in the principal investigator (this might significantly affect the conduct or management of the trial respectively);
- The use of a new measurement for the primary endpoint (this could significantly alter the scientific value of the trial);
- Change to the definition of end of trial (this could significantly impact on the scientific value of the clinical trial);
- Change in principal or co-ordinating investigator (this could significantly impact on the conduct or management of the trial);
- Addition of clinical trial sites. 

With regard to the protocol, the following is a non-exhaustive list of amendments which are typically *not* “substantial”:

- Minor changes in the recruitment procedure;
- Change of the number of trial subjects per trial site as long as the total number of trial subjects is the same;
- Correction of typographical errors;
- Change in the documentation used by the research team for recording study data (e.g. in the case report form);

- The adding/deleting of exploratory/tertiary endpoints;
- Limited lengthening of the trial time.

### 3.3.2. *Amendments as regards the Investigational Medicinal Products Dossier*

With regard to IMP Dossier, the following is a non-exhaustive list of amendments that are typically “substantial”:

- Altering the procedure for reconstitution and administration of an IMP (this could significantly affect the safe use of an IMP in the trial);
- Data from additional studies of pharmacology, toxicology or clinical use of an IMP used in the trial which might alter the initial risk to benefit evaluation of the supporting documents;

With regard to IMP Dossier, the following is a non-exhaustive list of amendments that are typically *not* “substantial”:

- Minor changes in the labelling of the investigational product;

### 3.3.3. *Amendments as regards other initial scientific documents supporting the Request for authorisation of the clinical trial*

With regard to initial scientific documents, the following is a non-exhaustive list of amendments that are typically “substantial”:

- The transfer of sponsor responsibilities to a new individual or organisation;
- The revocation or suspension of the marketing authorisation of the IMP;
- Any change to the IB that alters the product safety profile and safety monitoring arrangements.

With regard to other initial scientific documents, the following is an example for an amendment which is typically *not* “substantial”:

- Changes of internal organization of the sponsor or of the person to which certain tasks have been delegated.

In addition, concerning changes to the IMPD, reference is made to Chapter 8 of the *Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials*.<sup>42</sup>

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<sup>42</sup> CHMP/QWP/185401/2004 final  
[http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm)



### 3.4. Procedure for notification – Who should be notified?

The substantial amendments may relate to information relevant for assessment by national competent authorities, Ethics Committees, or both.

For substantial amendments to information that is assessed only by the national competent authority (e.g. quality data of the IMP), the sponsor should only notify the amendment to the national competent authority.

For substantial amendments to information that is assessed only by the Ethics Committee (e.g. facilities of the trial), the sponsor should only notify the amendment to the Ethics Committee.

It is recommended that the respective other body is informed about the substantial amendment. To provide this information it will be sufficient to submit the Substantial Amendment Form once the decision on the substantial amendment has taken place, indicating in Section A.4 that it is “for information only”, and attaching a copy of the decision.

In the case of substantial amendments that affect information that is assessed by both the national competent authority and the Ethics Committee, the sponsor should submit the notifications in parallel.

### 3.5. Format and content of notification

Substantial amendments to the information supporting the initial authorisation of the trial or to the protocol should be reported using the Amendment Notification Form as published in volume 10 of *Eudralex – the Rules Governing Medicinal Products in the European Union*.<sup>43</sup>

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 of the Member State concerned. The covering letter and the notification should contain a list of all affected clinical trials with their EudraCT numbers and respective amendment code numbers.

The notification of a substantial amendment should include the following:

- (a) A signed covering letter, including
  - In its heading the EudraCT number and the sponsor protocol number with the title of the trial and the sponsor’s amendment code number;
  - Identification of applicant;

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<sup>43</sup> [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm)

- Identification of the amendment (sponsor's substantial amendment code number<sup>44</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;
- Identification of any information not contained in the Amendment Notification Form which might impact on the risk to trial participants;
- Where applicable, the list of all affected clinical trials with EudraCT numbers and respective amendment code numbers (see above).

(b) Amendment Notification Form as published in Volume 10 of *Eudralex – the Rules Governing Medicinal Products in the European Union*.<sup>45 46</sup>

(c) A description of the amendment:

- An extract of the modified documents showing previous and new wording in track-change version, as well as the extract only showing the new wording.
- Notwithstanding the previous point, if the changes are so widespread and/or far-reaching that they justify an entire new version of the document, a new version of the entire document, identified with updated number of version and date. In this case, an additional table should list the amendments to the documents;

(d) Discussion and justification of the relevance of the amendments as substantial in view of their potential implications on the safety or ethical soundness of the clinical trial. Where practicable, this should be laboured into the documentation provided under (c);

(e) Supporting information including, where applicable:

- Summaries of data;
- An updated overall risk benefit assessment;

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<sup>44</sup> The code number identifies the amendment and refers to all the submitted documents. The sponsor decides which code to be used. Section E1 of the amendment form should be completed with version and date of the new amendment to which this form relates.

<sup>45</sup> [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm)

<sup>46</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.

- Possible consequences for subjects already included in the trial;
  - Possible consequences for the evaluation of the results.
- (f) If a substantial amendment implies changes to entries of the EudraCT application form, the sponsor should submit a revised copy of the XML file incorporating amended data. The notification of a substantial amendment should identify the fields to be changed, by attaching a print out of the revised form showing the amended fields highlighted.

### **3.6. Time for response, implementation**

Article 10(a), 2<sup>nd</sup> and 3<sup>rd</sup> sub-paragraph 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.”*

Thus, the Ethics Committee has to give an opinion on a proposed substantial amendment within 35 days. With regard to the national competent authority, no deadline is set in Directive 2001/20/EC. As guidance, and in view of the approval time for requests for authorisation, the national competent authority should respond within 35 days from the receipt of the valid notification of an amendment. This response time may be extended if such an 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 these cases, the national competent authority should notify the sponsor of the duration of the extension and its reasons. If the national competent authority states, prior to expiry of the 35 days deadline, that it raises no grounds for non-acceptance, the sponsor does not have to await the expiry of the 35 days deadline.

For amendments submitted to either the Ethics Committee alone or the national competent authority alone, the sponsor may implement the amendment when the Ethics Committee opinion is favourable or the national competent authority has raised no grounds for non-acceptance respectively.

Applicants should be aware that these procedures shall ensure a rapid and efficient processing of substantial amendments. Against this background, unsatisfactory documentation is likely to lead to a refusal of the substantial amendment. Refusals do not prejudice the applicant’s right to resubmission.

### 3.7. *Ex post* notification of urgent safety measures

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

*“[W]ithout 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.”*

Examples for urgent safety measures are as follows:

- there is a need to change immediately the Contract Research Organisation (“CRO”) during the conduct of a study or transfer of certain responsibilities towards a different CRO because of hazard risk;
- a trial is halted following the recommendations of a Data Safety Monitoring Board on the grounds of patient safety or a lack of efficacy;
- there is a need to add a test to be performed on new patients since an unexpected characteristic of the compound has been observed and needs to be followed-up in newly recruited patients ;

Moreover, a temporary halt of the trial (see below, 3.8.) may, depending on the reasons, be considered as urgent safety measure.

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. This should be done by telephone and, for reasons of traceability, also by e-mail or fax in the first place followed by a written report.

Note, that the *ex post* notification of urgent safety measures is independent of the obligation to

- notify substantial amendments (cf. above);
- notify early termination of the trial within 15 days in accordance with Article 10(c) of Directive 2001/20/EC (cf. 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.

### 3.8. Temporary halt of a trial

A temporary halt of a trial is a stop of the trial with the intention to resume it.

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 done immediately and at the least, in accordance with the deadline set out in Article 10(c) 2<sup>nd</sup> period of Directive 2001/20/EC, within 15 days from when the trial is temporarily halted.

The reasons and scope, e.g. stopping recruitment and/or interrupting treatment of subjects already included, should be clearly explained.

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

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) 2<sup>nd</sup> period of Directive 2001/20/EC (cf. below, point 4.2.).

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

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.”*

If the trial is terminated following a suspension, the rules on end of trials notification apply (cf. below, Section 4.).

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

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.”*

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.

The sponsor should immediately implement the “course of action” set by the national competent authority and report to the national competent authority of the Member State concerned on the progress and completion of its implementation in accordance with the timetable set.

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”.

### **3.11. Non-substantial amendments**

The sponsor does not have to notify the national competent authority or the Ethics Committee of non-substantial amendments to the documentation provided. However, non-substantial amendments should be recorded and if appropriate included in the next update of the relevant document and be available on request for inspection at the trial site and/or the sponsor premises as appropriate.

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

### **4.1. Legal Basis and Scope**

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.”*

“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 and any change to this definition for whatever reason should be notified as a substantial amendment. In most cases it will be the date of the last visit of the last patient undergoing the trial. Any exceptions to this should be justified in the protocol.

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

The sponsor should make an end of trial declaration using the form published in Volume 10 of *Eudralex – the Rules Governing Medicinal Products in the European Union*<sup>47</sup> when:

- the trial ends in the territory of the Member State concerned;

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<sup>47</sup> [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm)

- the complete trial has ended in all participating centres in all countries within and outside the Community.

#### 4.2.1. *Standard deadline*

The sponsor must notify the national competent authority of the Member State concerned within 90 days of the end of the clinical trial that the trial has ended. The end of the clinical trial is defined in the protocol (see above).

In addition, when the trial is completed in all participating centres, i.e. in the Member States concerned and in third countries, the sponsor should notify the Member States concerned within 90 days.

The notified Member State is responsible for entering this information into the EudraCT database.

#### 4.2.2. *Shortened deadline for early termination/premature end*

In the case of an early termination, sponsor must notify the end of the trial to the national competent authority of the Member State concerned immediately and at least within 15 days from when the trial is halted and clearly explain the reasons.

“Premature end” is considered as “early termination”.

### **4.3. Clinical trial summary report**

The clinical trial summary report is part of the end of trials notification. However, the clinical trial summary report can be submitted subsequently to the end of trials notification. With regard to the modalities of the submission of the clinical trial summary report, its format and content and its accessibility for the public, reference is made to the applicable guidelines and in particular Commission Communications 2009/C28/01 and 2008/C168/02.<sup>48</sup>

### **4.4. Follow-up**

If a new event occurs after the termination of the trial that is likely to change the risk/benefit analysis of the trial and could still have an impact on the trial participants, the sponsor should notify the national competent authority and Ethics Committee of the Member State concerned and provide a proposed course of action.

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<sup>48</sup> [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10\\_en.htm](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm)

**ATTACHMENT 1: COMMON TECHNICAL DOCUMENT - HEADINGS FOR IMP QUALITY DATA**

- 2.1.S DRUG SUBSTANCE
- 2.1.S.1 General Information:
  - 2.1.S.1.1 Nomenclature
  - 2.1.S.1.2 Structure
  - 2.1.S.1.3 General Properties
- 2.1.S.2 Manufacture:
  - 2.1.S.2.1 Manufacturer(s)
  - 2.1.S.2.2 Description of Manufacturing Process and Process Controls
  - 2.1.S.2.3 Control of Materials
  - 2.1.S.2.4 Controls of Critical Steps and Intermediates
  - 2.1.S.2.5 Process Validation and/or Evaluation
  - 2.1.S.2.6 Manufacturing Process Development
- 2.1.S.3 Characterisation:
  - 2.1.S.3.1 Elucidation of Structure and Other Characteristics
  - 2.1.S.3.2 Impurities
- 2.1.S.4 Control of Drug Substance:
  - 2.1.S.4.1 Specification
  - 2.1.S.4.2 Analytical Procedures
  - 2.1.S.4.3 Validation of Analytical Procedures
  - 2.1.S.4.4 Batch Analyses
  - 2.1.S.4.5 Justification of specification
- 2.1.S.5 Reference Standards or Materials
- 2.1.S.6 Container Closure System:



2.1.S.7	Stability
2.1.P	MEDICINAL PRODUCT
2.1.P.1	Description and Composition of the Medicinal Product:
2.1.P.2	Pharmaceutical Development:
2.1.P.2.1	Components of the Medicinal Product
2.1.P.2.1.1	Drug Substance
2.1.P.2.1.2	Excipients
2.1.P.2.2	Medicinal Product
2.1.P.2.2.1	Formulation Development
2.1.P.2.2.2	Overages
2.1.P.2.2.3	Physicochemical and Biological Properties
2.1.P.2.3	Manufacturing Process Development
2.1.P.2.4	Container Closure System
2.1.P.2.5	Microbiological Attributes
.P.2.6	Compatibility
2.1.P.3	Manufacture:
2.1.P.3.1	Manufacturer(s)
2.1.P.3.2	Batch Formula
2.1.P.3.3	Description of Manufacturing Process and Process Controls
2.1.P.3.4	Controls of Critical Steps and Intermediates
2.1.P.3.5	Process Validation and/or Evaluation
2.1.P.4	Control of Excipients:
2.1.P.4.1	Specifications:
2.1.P.4.2	Analytical Procedures
2.1.P.4.3	Validation of Analytical Procedures

- 2.1.P.4.4 Justification of Specifications
- 2.1.P.4.5 Excipients of Human or Animal Origin
- 2.1.P.4.6 Novel Excipients
  
- 2.1.P.5 Control of Medicinal Product:
  - 2.1.P.5.1 Specification(s)
  - 2.1.P.5.2 Analytical Procedures
  - 2.1.P.5.3 Validation of Analytical Procedures
  - 2.1.P.5.4 Batch Analyses
  - 2.1.P.5.5 Characterisation of Impurities
  - 2.1.P.5.6 Justification of Specification(s)
  
- 2.1.P.6 Reference Standards or Materials:
  
- 2.1.P.7 Container Closure System:
  
- 2.1.P.8 Stability:
  
- 2.1.A APPENDICES
  - 2.1.A.1 Facilities and Equipment:
  - 2.1.A.2 Adventitious Agents Safety Evaluation:
  - 2.1.A.3 Novel Excipients:
  - 2.1.A.4 Solvents for Reconstitution and Diluents:

**ATTACHMENT 2: COMMON TECHNICAL DOCUMENT - HEADINGS FOR NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY DATA**

- 2.2.1 Pharmacodynamics:
  - 2.2.1.1 Brief summary
  - 2.2.1.2 Primary Pharmacodynamics
  - 2.2.1.3 Secondary Pharmacodynamics
  - 2.2.1.4 Safety Pharmacology
  - 2.2.1.5 Pharmacodynamic interactions
  - 2.2.1.6 Discussion and conclusion
- 2.2.2 Pharmacokinetics
  - 2.2.2.1 Brief Summary
    - 2.2.2.2.1 Methods of analysis
    - 2.2.2.3 Absorption
    - 2.2.2.4 Distribution
    - 2.2.2.5 Metabolism
    - 2.2.2.6 Excretion
    - 2.2.2.7 Pharmacokinetic Drug Interactions
    - 2.2.2.8 Other Pharmacokinetic Studies
    - 2.2.2.9 Discussion and conclusions including evaluation of toxicokinetics
- 2.2.3 Toxicology:
  - 2.2.3.1 Brief Summary
  - 2.2.3.2 Single Dose Toxicity
  - 2.2.3.3 Repeat-Dose Toxicity\*
  - 2.2.3.4 Genotoxicity:
    - 2.2.3.4.1. In vitro
    - 2.2.3.4.2. In vivo \*
  - 2.2.3.5. Carcinogenicity \*
  - 2.2.3.6. Reproductive and Developmental Toxicity \*
  - 2.2.3.7. Local Tolerance
  - 2.2.3.8. Other Toxicity Studies

2.2.3.9. Discussion and Conclusions.

\* These sections should be supported by toxicokinetic evaluations

**ATTACHMENT 3: COMMON TECHNICAL DOCUMENT - HEADINGS FOR CLINICAL TRIAL AND PREVIOUS HUMAN EXPERIENCE DATA**

- 2.3.1. Clinical pharmacology
  - 2.3.1.1. Brief summary
  - 2.3.1.2. Mechanism of primary action
  - 2.3.1.3. Secondary pharmacological effects
  - 2.3.1.4. Pharmacodynamic interactions
  
- 2.3.2. Clinical pharmacokinetics
  - 2.3.2.1. Brief summary
  - 2.3.2.2. Absorption
  - 2.3.2.3. Distribution
  - 2.3.2.4. Elimination
  - 2.3.2.5. Pharmacokinetics of active metabolites
  - 2.3.2.6. Plasma concentration-effect relationship
  - 2.3.2.7. Dose and time-dependencies
  - 2.3.2.8. Special patient populations
  - 2.3.2.9. Interactions
  
- 2.3.3. Human exposure
  - 2.3.3.1. Brief summary
  - 2.3.3.2. Overview of Safety and Efficacy
  - 2.3.3.3. Healthy subject studies
  - 2.3.3.4. Patient studies
  - 2.3.3.5. Previous human experience
- 2.3.4. Benefits and risks assessment