

3. Notification
on the clinical trial of medicinal products for human use.

**A joint publication of the Federal Institute for Drugs and Medical Devices and
the Paul Ehrlich Institute**

for the request to the competent authority for the authorisation of a clinical trial according to § 40 para. 1 sentence 2 of the German Medicines Act (*Arzneimittelgesetz, AMG*), as well as § 7 of the statutory regulation according to § 42 para. 3 of the AMG (GCP-V) for the notification of subsequent amendments during the conduct of the clinical trials according to § 10, as well as for the notification of the end of the clinical trial according to § 13 paragraph 8 and 9 of this statutory regulation.

August 10, 2006

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Explanations on the guidelines in Addendum 4 "*Common technical document headings for clinical data*" of "*Detailed guidance for 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*"

(Guideline ENTR/CT 1)

I. Introduction

This notification describes in form and content the requirements for the documentation to be submitted with the request for the authorisation by the competent authority of a clinical trial of medicinal products for human use according to **§ 42 para. 2 German Medicines Act (AMG)**, as well as **§ 7 para. 1, 2, 4, 5, 6 and 7 of the GCP-V**, as well as the requirements according to **§ 10 para. 1 and 3** (subsequent amendments) and according to **§ 13 para. 8** (notification of the end of the clinical trial) and **9** (summary of the final report) of the GCP-V. **Directive 2001/20/EG** and its implementation in national law serve to harmonise the regulatory requirements for clinical trials of medicinal products for human use in the European Union member states. The rights, safety and well-being of all participants in clinical trials should thus be ensured. The observance of internationally recognised quality requirements for the planning, conduct and documentation of clinical trials should guarantee the credibility of the results. Bureaucratic hindrances between the member states should be overcome, and the conduct of clinical trials should be accelerated, especially in event of multinational or multicentric trials.

Short processing periods in the authorisation process help enable clinical trials to commence without delay. This can only be put into practice when the requests for authorisation are structured as uniformly as possible and the statements and documents for the investigational medicinal products are presented in such a way that the benefit and risk of their use can be evaluated. This notification should help the applicant to prepare an authorisation request and explain legal requirement of the AMG and the GCP-V.

The provisions of the AMG on the clinical trial of medicinal products for humans apply to all investigational medicinal products and include the following groups of medicinal products:

- a) pharmaceuticals with chemically-defined active substances;
- b) biotechnologically produced pharmaceuticals;
- c) somatic or xenogenic cell therapeutics;
- d) pharmaceuticals for gene therapy;
- e) immunological pharmaceuticals such as vaccines, allergens, immune sera;
- f) blood preparations;
- g) herbal medicinal products;
- h) radiopharmaceutical products;
- i) homeopathic and anthroposophic pharmaceuticals

The extent of the documents to be submitted for the authorisation of a clinical trial depends on the type of investigational medicinal products, the status of their development and their conditions of implementation in the clinical trial applied for.

The requirements are generally based on the guidelines from the *Note for guidance on general considerations for clinical trials (CPMP/ICH291/95)* and the relevant guidelines¹ on special queries. Deviations from these recommendations may be necessary in specific cases for medical, methodical or ethical reasons; although these are to be explained and substantiated.

¹ http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm

An evaluation according to **§ 42 para. 2 AMG** is to be conducted on the basis of these documents, particularly of the safety of the affected persons² in comparison with the intended study population, the criteria for inclusion and exclusion, the concomitant medications to be expected or excluded, as well as planned supervision measures.

II. Index of the documentation to be submitted by the sponsor with the request for authorisation

The following documents and information are to be submitted with the request for authorisation to the competent authority in electronic and written form:

1. An accompanying letter in German signed by the sponsor³ or his representative or proxy with the corresponding power of attorney in German or English specifying
 - a) the name or company and the address of the sponsor and, if present, his representative located in the European Union or other contracting state of the Treaty on the European Economic Area,
 - b) the EudraCT number of the clinical trial,
 - c) the trial protocol code of the sponsor,
 - d) the title of the clinical trial,
 - e) indications of particularities of the clinical trial and references to the sources of the applicable information in the documents presented (for example first-time administration of the active substance to humans, administration to a special population of test subjects or patients, etc.),
 - f) a confirmation that the documents submitted in paper form are identical to those submitted in electronic form;
2. the completed application form in written and electronic form⁴;
3. the copy of the confirmation for the EudraCT number assigned by the European Databank;
4. the trial protocol⁵ signed by the sponsor or his representative and, in the event of monocentric trials, signed by the principal investigator or investigator, or, in the event of multicentric trials with multiple trial sites, signed by the coordinating investigator, specifying the EudraCT number, complete title and, if applicable, the short title of the clinical trial, the sponsor's trial protocol code, the version and date of authorisation on the cover page;
5. a plan for the further treatment and medical supervision of the affected persons after the end of the clinical trial according to **§ 7 para. 2 no. 13 GCP-V**;
6. justification corresponding to the trial goal for the gender distribution of the group of affected persons according to **§ 7 para. 2 no. 12 GCP-V**;

² Definition according to **§ 3 para. 2a GCP-V**

³ according to **§ 4 para. 24 AMG**

⁴ Annex 1 of the **ENTR/CT 1** guideline

⁵ Trial protocol according to **Note for guidance on good clinical practice, No. 6: Clinical trial protocol and protocol amendments (CPMP/ICH/135/95)**

7. confirmation according to **§ 7 para. 2 no. 15 of the GCP-V** that the persons affected shall be informed of the dissemination of their pseudonymous data in the scope of the documentation and notification obligations according to **§ 12** and **§ 13 GCP-V** to the recipient named therein, with the explanation that affected persons not consenting to the dissemination of information cannot be included in the clinical trial;
8. names and addresses of the facilities which, as trial sites or trial laboratories, are involved in the clinical trial, as well as those of the principal investigators and the coordinating investigator of the clinical trial.
(Explanatory note added to this translation: the principal investigator is the responsible investigator for one trial site where several subinvestigators may be involved, the coordinating investigator⁶ is responsible for the clinical trial.)
9. The investigator's brochure in accordance with the *Note for Guidance on Good Clinical Practice, CPMP/ICH/135/95, Nr. 7: Investigator's Brochure (IB)* specifying the version and date of authorisation on the cover page;
10. statement of the professions of those investigators who are not physicians, the scientific requirements of their respective professions and experience in patient care prerequisite of the pursuit of his profession, as well as demonstration that the respective profession is qualified to carry out research on humans, and demonstration of the particular circumstances of the clinical trial justifying the member of the respective profession to act as an investigator according to **§ 7 para. 2 Nr. 6 of the GCP-V**;
11. the Investigational Medicinal Product Dossier (IMPD) with the following content:
 - a) documents on quality and manufacturing;
 - b) documents on pharmacological / toxicological trials;
 - c) draft of the intended designation of the investigational medicinal product corresponding to **§ 5 GCP-V**;
 - d) the manufacturing license of all manufacturers with headquarters in the EU or the European Economic Area in copy;
 - e) if applicable, the license for importation to the EU in copy;
 - for importers with headquarters in Germany according to **§ 72 AMG**,
 - for importers with headquarters in another member state of the EU according to Article 13 para. 1 of the **Directive 2001/20/EG**

in addition to the importation license, a GMP compliance certificate signed by the competent representative of the importer is to be submitted

 - f) documents on the results of hitherto conducted clinical trials, as well as further published clinical findings
 - g) summary of the benefit-risk assessment

⁶ German: Leiter der klinischen Prüfung

For the standardisation of the IMPD at the EU level, the documents can be submitted to the IMPD separately according to **GCP-V § 7 para. 4 no. 1 letters c), d), and e)**. If the statements required according to **§ 7 para. 4 no. 1 letters b), f) and g)** GCP-V are already documented in the Investigator's Brochure, the corresponding sections of this document may be referenced in the IMPD. Required supplements resulting from the current level of knowledge are to be specified to the IMPD in an addendum. A record of the amendments carried out is to be attached with the submission of an amended version of the IMPD. If the investigational medicinal product is a placebo, the content of the IMPD is limited to the documents on quality and manufacture according to **§ 7 para. 4 no. 1 letters a) and c) of the GCP-V**.

The investigator's information is to be validated and updated by the sponsor at least once per year. Renewed submission is only necessary in the event of substantial amendments according to **§ 10 para. 1 of the GCP-V** (see below, **section VII**).

Investigational medicinal products containing active substances that are generally known and are used in connection with a clinical trial to produce specific reactions (**§ 3 para. 3 of the GCP-V**), and are employed under the conditions stated in **Annex 13 Revision 1 Note**⁷ do not require a complete IMPD, as long as the substances they contain are not of biological origin. By means of the material on scientific findings submitted, the sponsor should substantiate that the application of the substance in the scope of the production of specific reactions is known and, with respect to the planned application in the clinical trial, harmless. In this case, only the certification of release by a competent person⁸ is to be submitted.

For investigational medicinal products already approved in a member state of the European Community, the Summary of Product Characteristics (SmPC, see **Appendix II / 1**) may be submitted in place of the dossier in accordance with the conditions specified in **§ 7 para. 5 of the GCP-V**. In this case, the submission of the investigator's information is also omitted according to **No. 9**;

12. proof of insurance according to **§ 42 para. 2 no. 3 AMG** in connection with **§ 40 para. 1 sentence 3 no. 8 and para. 3 AMG**, if the investigational medicinal product is a xenogenic cell therapeutic;
13. the documents according to **§ 7 para. 4 no. 3 of the GCP-V** for investigational medicinal products containing genetically modified organisms⁹;
14. the name and address of the competent ethics committee according to **§ 42 para. 1 sentence 1 and 2 of the AMG** and the name and address of the competent authorities of the other European Union member states and other contracting states of the Treaty on the European Economic Area in which the clinical trial is to be implemented;
15. if applicable, substantiated statements of negative evaluations of the competent ethics committees of other European Union member states or other contracting states of the

⁷ **Annex 13 Revision 1, July 2003 (F2/BL D2003): Page 1, note**

⁸ see Article 13 para. 2 of the Directive **2001/20/EG**

⁹ For investigational medicinal products consisting of or containing a genetically modified organism or combination of genetically modified organisms, an exposition and assessment of the health risks to the environment and persons not concerned, as well as an exposition of the precautions scheduled, and, according to Addendum III of this directive, further information which is specified there in greater detail, are to be submitted to the competent authority according to § 7 (4) 3 of the GCP of August 9, 2004 according to Addendum II of Directive 2001/18/EG of the European Parliament and European Council on the intentional release of genetically modified organisms in the environment.

