COMMISSION DIRECTIVE 2005/28/EC

of 8 April 2005

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

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to 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 [1], and in particular Article 1(3), Article 13(1) and Article 15(5) thereof,

Whereas:

(1) Directive 2001/20/EC requires the adoption of principles of good clinical practice and detailed guidelines in line with those principles, minimum requirements for authorisation of the manufacture or importation of investigational medicinal products, and detailed guidelines on the documentation relating to clinical trials to verify their compliance with Directive 2001/20/EC.

(2) The principles and guidelines for good clinical practice should be such as to ensure that the conduct of clinical trials on investigational medicinal products, as defined in Article 2(d) of Directive 2001/20/EC, is founded in the protection of human rights and the dignity of the human being.

(3) Manufacturing requirements to be applied to investigational medicinal products are provided for by Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use [2]. Title IV 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 [3] contains the provisions applied for the authorisation for the manufacture of medicinal products as part of the requirements needed for the application for a marketing authorisation. Article 3(3) of that Directive establishes that these requirements are not applicable for medicinal products intended for research and development trials. It is therefore necessary to lay down minimal requirements regarding applications for and management of authorisations to manufacture or import investigational medicinal products, as well as for the granting and the content of the authorisations, in order to guarantee the quality of the investigational medicinal product used in the clinical trial.

(4) With regard to the protection of trial subjects and to ensure that unnecessary clinical trials will not be conducted, it is important to define principles and detailed guidelines of good clinical practice whilst allowing the results of the trials to be documented for use in a later phase.

(5) To ensure that all experts and individuals involved in the design, initiation, conduct and recording of clinical trials apply the same standards of good clinical practice, principles and detailed guidelines of good clinical practice have to be defined.

(6) Provisions for the functioning of the Ethics Committees should be established in each Member State on the basis of common detailed guidelines, in order to ensure the protection of the trial subject while at the same time allowing a harmonised application in the different Member States of the procedures to be used by Ethics Committees.

(7) To secure the compliance of clinical trials with the provisions on good clinical practice, it is necessary that inspectors ensure the practical effectiveness of such provisions. It is essential therefore to provide detailed guidelines on the minimum standards for the qualification of inspectors, in particular as regards their education and training. For the same reason, detailed guidelines on inspection procedures, in particular on the cooperation of the various agencies, and the follow-up to the inspections, should be laid down.

(8) The International Conference on Harmonisation (ICH) reached a consensus in 1995 to provide a harmonised approach for Good Clinical Practice. The consensus paper should be taken into account as agreed upon by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency, hereinafter 'the Agency', and published by the Agency.

[1] OJ L 121, 1.5.2001, p. 34.
[2] OJ L 262, 14.10.2003, p. 22.
[3] OJ L 311, 28.11.2003, p. 67. Directive as last amended by Directive 2004/27/EC (OJ L 136, 30.4.2004, p. 34).

(9) It is necessary that sponsors, investigators and other participants take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use, as agreed upon by the CHMP and published by the Agency, as well as the other pharmaceutical Community guidelines published by the Commission in the different volumes of The rules governing medicinal products in the European Community.

(10) In conducting clinical trials on investigational medicinal products for human use, the safety and the protection of the rights of trial subjects should be ensured. The detailed rules adopted by Member States pursuant to Article 3(1) of Directive 2001/20/EC, to protect from abuse individuals who are incapable of giving their informed consent should also cover individuals temporarily incapable of giving their informed consent, as in emergency situations.

(11) Non-commercial clinical trials conducted by researchers without the participation of the pharmaceutical industry may be of great benefit to the patients concerned. Directive 2001/20/EC recognises the specificity of these non-commercial clinical trials. In particular, when trials are conducted with authorised medicinal products and on patients with the same characteristics as those covered by the authorised indication, requirements already fulfilled by these authorised medicinal products, as far as manufacturing or importation are concerned, should be taken into consideration. However, it could also be necessary, due to the specific conditions under which non-commercial trials are conducted, that Member States foresee specific modalities to be applied to these trials not only when conducted with authorised medicinal products and on patients with the same characteristics, in order to comply with the principles imposed by this Directive, in particular as far as the manufacturing or import requirements for authorisation and the documentation to be submitted and archived for the trial master file are concerned. The conditions under which the non-commercial research is conducted by public researchers and the places where this research takes place, make the application of certain of the details of good clinical practice unnecessary or guaranteed by other means. Member States will ensure in these cases, when providing for specific modalities, that the objectives of the protection of the rights of patients who participate in the trial, as well as, in general, the correct application of the good clinical practice principles, are achieved. The Commission will prepare a draft with guidance in this respect.

(12) The measures provided for in this Directive are in accordance with the opinion of the Standing Committee on Medicinal Products for Human Use,

HAS ADOPTED THIS DIRECTIVE:

CHAPTER 1

SUBJECT-MATTER

Article 1

1. This Directive lays down the following provisions to be applied to investigational medicinal products for human use:

(a) the principles of good clinical practice and detailed guidelines in line with those principles, as referred to in Article 1(3) of Directive 2001/20/EC, for the design, conduct and reporting of clinical trials on human subjects involving such products;

(b) the requirements for authorisation of the manufacture or importation of such products, as provided for in Article 13(1) of Directive 2001/20/EC;

(c) the detailed guidelines, provided for in Article 15(5) of Directive 2001/20/EC, on the documentation relating to clinical trials, archiving, qualifications of inspectors and inspection procedures.

2. When applying the principles, detailed guidelines and requirements referred to in paragraph 1, Member States shall take into account the technical implementing modalities provided for in the detailed guidance published by the Commission in The Rules governing medicinal products in the European Union.

3. When applying the principles, detailed guidelines and requirements referred to in paragraph 1 to non-commercial clinical trials conducted by researchers without the participation of the pharmaceutical industry, Member States may introduce specific modalities in order to take into account the specificity of these trials as far as Chapters 3 and 4 are concerned.

4. Member States may take into account the special position of trials whose planning does not require particular manufacturing or packaging processes, carried out with medicinal products with marketing authorisations within the meaning of Directive 2001/83/EC, manufactured or imported in accordance with the same Directive and conducted on patients with the same characteristics as those covered by the indication specified in the marketing authorisation.

Labelling of investigational medicinal products intended for trials of that nature may be subject to simplified provisions laid down in the good manufacturing practice guidelines on investigational medicinal products.

Member States shall inform the Commission as well as the other Member States of any specific modalities implemented in accordance with this paragraph. These modalities will be published by the Commission.

CHAPTER 2

GOOD CLINICAL PRACTICE FOR THE DESIGN, CONDUCT, RECORDING AND REPORTING OF CLINICAL TRIALS

SECTION 1

GOOD CLINICAL PRACTICE

Article 2

1. The rights, safety and well being of the trial subjects shall prevail over the interests of science and society.

2. Each individual involved in conducting a trial shall be qualified by education, training, and experience to perform his tasks.

3. Clinical trials shall be scientifically sound and guided by ethical principles in all their aspects.

4. The necessary procedures to secure the quality of every aspect of the trials shall be complied with.

Article 3

The available non-clinical and clinical information on an investigational medicinal product shall be adequate to support the proposed clinical trial.

Clinical trials shall be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996).

Article 4

The protocol referred to in point (h) of Article 2 of Directive 2001/20/EC shall provide for the definition of inclusion and exclusion of subjects participating in a clinical trial, monitoring and publication policy.

The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.

Article 5

All clinical trial information shall be recorded, handled, and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected.

SECTION 2

THE ETHICS COMMITTEE

Article 6

1. Each Ethics Committee established under Article 6(1) of Directive 2001/20/EC shall adopt the relevant rules of procedure necessary to implement the requirements set out in that Directive and, in particular, in Articles 6 and 7 thereof.

2. The Ethics Committees shall, in every case, retain the essential documents relating to a clinical trial, as referred to in Article 15(5) of Directive 2001/20/EC, for at least three years after completion of that trial. They shall retain the documents for a longer period, where so required under other applicable requirements.

3. Communication of information between the Ethics Committees and the competent authorities of the Member States shall be ensured through appropriate and efficient systems.

SECTION 3

THE SPONSORS

Article 7

1. A sponsor may delegate any or all of his trial-related functions to an individual, a company, an institution or an organisation.

However, in such cases, the sponsor shall remain responsible for ensuring that the conduct of the trials and the final data generated by those trials comply with Directive 2001/20/EC as well as this Directive.

2. The investigator and the sponsor may be the same person.

SECTION 4

INVESTIGATOR'S BROCHURE

Article 8

1. The information in the investigator's brochure, referred to in Article 2(g) of Directive 2001/20/EC, shall be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician or potential investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial.

The first subparagraph shall apply also to any update of the investigator's brochure.

2. If the investigational medicinal product has a marketing authorisation, the Summary of Product Characteristics may be used instead of the investigator's brochure.

3. The investigator's brochure shall be validated and updated by the sponsor at least once a year.

CHAPTER 3

MANUFACTURING OR IMPORT AUTHORISATION

Article 9

1. Authorisation, as provided for in Article 13(1) of Directive 2001/20/EC, shall be required for both total and partial manufacture of investigational medicinal products, and for the various processes of dividing up, packaging or presentation. Such authorisation shall be required even if the products manufactured are intended for export.

Authorisation shall also be required for imports from third countries into a Member State.

2. Authorisation, as provided for in Article 13(1) of Directive 2001/20/EC, shall not be required for reconstitution prior to use or packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member States to carry out such processes and if the investigational medicinal products are intended to be used exclusively in those institutions.

Article 10

1. In order to obtain the authorisation the applicant must meet at least the following requirements:

(a) specify in his application the types of medicinal products and pharmaceutical forms to be manufactured or imported;

(b) specify in his application the relevant manufacture or import operations;

(c) specify in his application, where relevant as in the case of viral or non-conventional agents' inactivation, the manufacturing process;

(d) specify in his application the place where the products are to be manufactured or have at his disposal, for their manufacture or importation, suitable and sufficient premises, technical equipment and control facilities complying with the requirements of Directive 2003/94/EC as regards the manufacture, control and storage of the products;

(e) have permanently and continuously at his disposal the services of at least one qualified person as referred to in Article 13(2) of Directive 2001/20/EC.

For the purposes of point (a) of the first subparagraph, 'types of medicinal products' include blood products, immunological products, cell therapy products, gene therapy products, biotechnology products, human or animal extracted products, herbal products, homeopathic products, radiopharmaceutical products and products containing chemical active ingredients.

2. The applicant shall provide with his application documentary evidence that he complies with paragraph 1.

Article 11

1. The competent authority shall issue the authorisation only after verifying the accuracy of the particulars provided by the applicant pursuant to Article 10 by the means of an inquiry carried out by its agents.

2. Member States shall take all appropriate measures to ensure that the procedure for granting an authorisation is completed within 90 days of the day on which the competent authority receives a valid application.

3. The competent authority of the Member State may require from the applicant further information concerning the particulars supplied pursuant to Article 10(1), including in particular information concerning the qualified person at the disposal of the applicant in accordance with point (e) of Article 10(1).

Where the competent authority concerned exercises that right, the application of the time-limits laid down in paragraph 2 shall be suspended until the additional data required have been supplied.

Article 12

1. In order to ensure that the requirements laid down in Article 10 are complied with, authorisation may be made conditional on the carrying out of certain obligations imposed either when authorisation is granted or at a later date.

2. An authorisation shall apply only to the premises specified in the application and to the types of medicinal products and pharmaceutical forms specified in that application pursuant to point (a) of Article 10(1).

Article 13

The holder of the authorisation shall at least comply with the following requirements:

(a) to have at his disposal the services of staff that comply with the legal requirements existing in the Member State concerned both as regards manufacture and controls;

(b) to dispose of the investigational/authorised medicinal products only in accordance with the legislation of the Member State concerned;

(c) to give prior notice to the competent authority of any changes he may wish to make to any of the particulars supplied pursuant Article 10(1) and, in particular, to inform the competent authority immediately if the qualified person referred to in Article 13(2) of Directive 2001/20/EC is replaced unexpectedly;

(d) to allow agents of the competent authority of the Member State concerned access to his premises at any time;

(e) to enable the qualified person referred to in Article 13(2) of Directive 2001/20/EC to carry out his duties, for example by placing at his disposal all the necessary facilities;

(f) to comply with the principles and guidelines for good manufacturing practice for medicinal products as laid down by Community law.

Detailed guidelines in line with the principles referred to in point (f) of the first paragraph will be published by the Commission and revised where necessary to take account of technical and scientific progress.

Article 14

If the holder of the authorisation requests a change in any of the particulars referred to in points (a) to (e) of Article 10(1), the time taken for the procedure relating to the request shall not exceed 30 days. In exceptional cases, this period of time may be extended to 90 days.

Article 15

The competent authority shall suspend or revoke the authorisation, as a whole or in part, if the holder of the authorisation fails at any time to comply with the relevant requirements.

CHAPTER 4

THE TRIAL MASTER FILE AND ARCHIVING

Article 16

The documentation referred to Article 15(5) of Directive 2001/20/EC as the trial master file shall consist of essential documents, which enable both the conduct of a clinical trial and the quality of the data produced to be evaluated. Those documents shall show whether the investigator and the sponsor have complied with the principles and guidelines of good clinical practice and with the applicable requirements and, in particular, with Annex I to Directive 2001/83/EC.

The trial master file shall provide the basis for the audit by the sponsor's independent auditor and for the inspection by the competent authority.

The content of the essential documents shall be in accordance with the specificities of each phase of the clinical trial.

The Commission shall publish additional guidance in order to specify the content of these documents.

Article 17

The sponsor and the investigator shall retain the essential documents relating to a clinical trial for at least five years after its completion.

They shall retain the documents for a longer period, where so required by other applicable requirements or by an agreement between the sponsor and the investigator.

Essential documents shall be archived in a way that ensures that they are readily available, upon request, to the competent authorities.

The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

Article 18

Any transfer of ownership of the data or of documents shall be documented. The new owner shall assume responsibility for data retention and archiving in accordance with Article 17.

Article 19

The sponsor shall appoint individuals within its organisation who are responsible for archives.

Access to archives shall be restricted to the named individuals responsible for the archives.

Article 20

The media used to store essential documents shall be such that those documents remain complete and legible throughout the required period of retention and can be made available to the competent authorities upon request.

Any alteration to records shall be traceable.

CHAPTER 5

INSPECTORS

Article 21

1. The inspectors, appointed by the Member States pursuant to Article 15(1) of Directive 2001/20/EC, shall be made aware of and maintain confidentiality whenever they gain access to confidential information as a result of good clinical practice inspections in accordance with applicable Community requirements, national laws or international agreements.

2. Member States shall ensure that inspectors have completed education at university level, or have equivalent experience, in medicine, pharmacy, pharmacology, toxicology or other relevant fields.

3. Member States shall ensure that inspectors receive appropriate training, that their training needs are assessed regularly and that appropriate action is taken to maintain and improve their skills.

Member States shall also ensure that the inspectors have knowledge of the principles and processes that apply to the development of medicinal products and clinical research. Inspectors shall also have knowledge of applicable Community and national legislation and guidelines applicable to the conduct of clinical trials and the granting of marketing authorisations.

The inspectors shall be familiar with the procedures and systems for recording clinical data, and with the organisation and regulation of the healthcare system in the relevant Member States and, where appropriate, in third countries.

4. Member States shall maintain up-to-date records of the qualifications, training and experience of each inspector.

5. Each inspector shall be provided with a document setting out standard operating procedures and giving details of the duties, responsibilities and ongoing training requirements. Those procedures shall be maintained up to date.

6. Inspectors shall be provided with suitable means of identification.

7. Each inspector shall sign a statement declaring any financial or other links to the parties to be inspected. That statement shall be taken into consideration when inspectors are to be assigned to a specific inspection.

Article 22

In order to ensure the presence of skills necessary for specific inspections, Member State may appoint teams of inspectors and experts with appropriate qualifications and experience to fulfil collectively the requirements necessary for conducting the inspection.

CHAPTER 6

INSPECTION PROCEDURES

Article 23

1. Good clinical practice inspections may take place on any of the following occasions:

(a) before, during or after the conduct of clinical trials;

(b) as part of the verification of applications for marketing authorisation;

(c) as a follow-up to the granting of authorisation.

2. In accordance with Article 15(1) and (2) of Directive 2001/20/EC, inspections may be requested and coordinated by the European Medicines Agency within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council [1], especially in connection with clinical trials relating to applications through the procedure established by this Regulation.

3. Inspections shall be conducted in accordance with the inspection guidance documents developed to support the mutual recognition of inspection findings within the Community.

4. Improvement and harmonisation of inspection guidance shall be achieved by the Member States, in collaboration with the Commission and the Agency, through joint inspections, agreed processes and procedures and sharing of experience and training.

Article 24

Member States shall make publicly available within their territories the documents relating to the adoption of good clinical practice principles.

They shall establish the legal and administrative framework within which their good clinical practice inspections operate, with definition of the powers of inspectors for entry into clinical trial sites and access to data. In so doing they shall ensure that, on request and where appropriate, inspectors of the competent authority of the other Member States also have access to the clinical trial sites and data.

[1] OJ L 136, 30.4.2004, p. 1.

Article 25

Member States shall provide for sufficient resources and shall in particular appoint an adequate number of inspectors to ensure effective verification of compliance with good clinical practice.

Article 26

Member States shall establish the relevant procedures for verification of good clinical practice compliance.

The procedures shall include the modalities for examining both the study management procedures and the conditions under which clinical trials are planned, performed, monitored and recorded, as well as follow-up measures.

Article 27

Member States shall establish the relevant procedures for the following:

(a) appointing experts for accompanying inspectors in case of need;

(b) requesting inspections/assistance from other Member States, in line with Article 15(1) of Directive 2001/20/EC and for cooperating in inspections in another Member State;

(c) arranging inspections in third countries.

Article 28

Member States shall maintain records of national and, if applicable, international inspections including the good clinical practice compliance status, and of their follow-up.

Article 29

1. In order to harmonise the conduct of inspections by the competent authorities of the different Member States, guidance documents containing the common provisions on the conduct of those inspections shall be published by the Commission after consultation with the Member States.

2. Member States shall ensure that national inspection procedures are in compliance with the guidance documents referred in paragraph 1.

3. The guidance documents referred to in paragraph 1 may be updated regularly according to scientific and technical development.

Article 30

1. Member States shall lay down all necessary rules to ensure that confidentiality is respected by inspectors and other experts. With regard to personal data, the requirements of Directive 95/46/EC of the European Parliament and of the Council [1] shall be respected.

2. Inspection reports shall be made available by the Member States only to the recipients referred to in Article 15(2) of Directive 2001/20/EC, in accordance with national regulations of the Member States and subject to any arrangements concluded between the Community and third countries.

CHAPTER 7

FINAL PROVISIONS

Article 31

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 29 January 2006 at the latest. They shall forthwith communicate to the Commission the text of those provisions and a correlation table between those provisions and this Directive.

When Member States adopt these provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

2. Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

Article 32

This Directive shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

Article 33

This Directive is addressed to the Member States.

Done at Brussels, 8 April 2005.

For the Commission
Günter VERHEUGEN
Vice-President

[1] OJ L 281, 23.11.1995, p. 31.