

II

(Preparatory Acts)

COMMISSION

Amended proposal for a European Parliament and Council Directive 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⁾

(1999/C 161/05)

(Text with EEA relevance)

COM(1999) 193 final — 97/0197(COD)

(Submitted by the Commission pursuant to Article 189a(2) of the EC-Treaty on 27 April 1999)

⁽¹⁾ OJ C 306, 8.10.1997, p. 9.

ORIGINAL TEXT

Proposal for a European Parliament and Council Directive on the approximation of provisions laid down by law, regulation or administrative action relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 100a thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the Economic and Social Committee,

Acting in accordance with the procedure laid down in Article 189b of the Treaty,

Whereas Council Directive 65/65/EEC ⁽¹⁾ requires that applications for authorisation to place a medicinal product on the market should be accompanied by a dossier containing particulars and documents relating to the results of tests and clinical trials carried out on the product; whereas Council Directive 75/318/EEC ⁽²⁾ lays down uniform rules on the compilation of dossiers including their presentation;

⁽¹⁾ OJ L 22, 9.2.1965, p. 1.

⁽²⁾ OJ L 147, 9.6.1975, p. 1.

AMENDED TEXT

Proposal for a European Parliament and Council Directive 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

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 100a thereof,

Having regard to the proposal from the Commission ⁽¹⁾,

Having regard to the opinion of the Economic and Social Committee ⁽²⁾,

Acting in accordance with the procedure laid down in Article 189b of the Treaty,

(1) (Unchanged)

⁽¹⁾ OJ C 306, 8.10.1997, p. 9.

⁽²⁾ OJ C 95, 30.3.1998, p. 1.

ORIGINAL TEXT

AMENDED TEXT

Whereas the accepted basis for the conduct of clinical trials in humans is founded in the current revision of the Declaration of Helsinki and the Council of Europe Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine; whereas the trial subject's protection is safeguarded through risk assessment based on toxicological experiments prior to any clinical trial, screening by ethics committees and Member States authorities and the protection of personal data;

Whereas, in order to achieve optimum protection of health, the resources allocated to pharmaceutical research must not be squandered on obsolete or repetitive tests whether within the Community or in third countries; whereas, the harmonisation of technical requirements for the development of medicinal products should therefore be pursued through the appropriate fora, including the International Conference on Harmonisation;

Whereas, for multi-centre clinical trials conducted in more than one Member State, with many investigational sites involved, a delay in the commencement of the trial may be caused by the multiplicity and diversity of procedures for obtaining opinions of ethics committees; whereas, for such trials, a single opinion for each Member State concerned reduces delays without jeopardising the well-being of the people participating in the trial with the possibility of rejecting it in specific sites if facilities are not appropriate;

(2) Whereas the accepted basis for the conduct of clinical trials in humans is founded in the current revision of the Declaration of Helsinki and the Council of Europe Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine; whereas the clinical trial subject's protection is safeguarded through risk assessment based on the results of toxicological experiments prior to any clinical trial, screening by ethics committees and Member States' competent authorities, and rules on the protection of personal data;

(3) Whereas it is incumbent on the Member States to lay down rules to safeguard protection of individuals who are incapable of giving their consent, such as minors and incapacitated adults; whereas such persons are incapable of giving their free consent to take part in a clinical trial; whereas, therefore, such consent must be given in writing by their parents or their guardian or their legal representative;

(4) (Unchanged)

(5) Whereas for medicinal products falling within the scope of Part A of the Annex to Council Regulation (EEC) No 2309/93⁽¹⁾, which include products intended for gene therapy or cell therapy, prior scientific evaluation by the European Agency for the Evaluation of Medicinal Products, assisted by the Committee for Proprietary Medicinal Products, is mandatory before the Commission grants marketing authorisation; whereas in the course of this evaluation the Committee may request full details of the results of the clinical trials on which the application for marketing authorisation is based and, consequently, on the manner in which these trials were conducted, and the same Committee may go so far as to request the applicant for marketing authorisation to conduct further clinical trials; whereas, therefore, provision must be made to allow the abovementioned Agency to have full information on the conduct of any clinical trial proposed for such medicinal products;

(6) (Unchanged)

⁽¹⁾ OJ L 214, 24.8.1993, p. 1.

ORIGINAL TEXT

AMENDED TEXT

Whereas information both on the commencement and on the termination of a clinical trial should be available to the Member States where the trial takes place, and relevant information on clinical trials should be exchanged between Member States;

(7) Whereas information on the content, commencement and termination of a clinical trial should be available to the Member States where the trial takes place and all the other Member States must have access to the same information which will be indispensable for them at the time of mutual recognition of the marketing authorisations for the corresponding medicinal product or products; whereas, therefore, a European database bringing together this confidential information should be set up;

(8) Whereas 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; whereas 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; whereas this therefore results in delays and complications detrimental to effective conduct of such trials in the Community; whereas it is therefore necessary to harmonise these practices in order to simplify and shorten them by establishing a clear, transparent procedure and creating conditions conducive to effective coordination of such clinical trials by the Community authorities concerned, thereby favouring completion of the internal market;

Whereas the standards of good manufacturing practice should be applied to investigational medicinal products; whereas special provisions for the labelling of investigational medicinal products should be set out;

(9) (Unchanged)

Whereas verification of compliance with the standards of good clinical practice and the need to subject data, information and documents to inspection in order to confirm that they have been properly generated, recorded and reported is essential in order to justify the involvement of human subjects in clinical trials; whereas the person participating in a trial should be made aware of and consent to the scrutiny of personal information during inspection by competent authorities and properly authorised persons, provided that such personal information is treated as strictly confidential and is not made publicly available;

(10) (Unchanged)

Whereas this Directive is without prejudice to Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data ⁽¹⁾;

(11) (Unchanged)

Whereas it is also necessary to make provisions for the monitoring of adverse reactions occurring in clinical trials using Community surveillance (pharmacovigilance) procedures in order to ensure the immediate cessation of any clinical trial in which there is an unacceptable level of risk;

(12) (Unchanged)

⁽¹⁾ OJ L 281, 23.11.1995, p. 31.

ORIGINAL TEXT

Whereas the conduct of clinical trials must regularly be adapted to scientific and technical progress in order to ensure optimum protection of the trial subject; whereas it is therefore necessary to introduce a rapid procedure for adapting to technical progress the requirements regarding the conduct of clinical trials, whilst ensuring close cooperation between the Commission and the Member States within a 'Committee for the Adaptation to Technical Progress of the Directives on the Removal of Technical Barriers to Trade in the Medicinal Products Sector',

HAVE ADOPTED THIS DIRECTIVE:

CHAPTER I

Scope and definitions*Article 1*

1. This Directive deals with clinical trials including multi-centre trials on human subjects involving medicinal products as defined in Article 1 of Directive 65/65/EEC but excludes non-interventional clinical trials.

2. Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki (1964), and that the clinical trial data are credible.

3. The principles and guidelines of good clinical practice shall be adopted in the form of a directive addressed to the Member States, in accordance with the procedure laid down in Article 2c of Council Directive 75/318/EEC. Detailed guidelines in line with those principles shall be published by the Commission and revised as necessary to take account of technical and scientific progress.

4. All clinical trials, including bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the standard of good clinical practice.

AMENDED TEXT

(13) Whereas the conduct of clinical trials must regularly be adapted to scientific and technical progress in order to ensure optimum protection of the trial subject; whereas it is therefore necessary to introduce a rapid procedure for adapting to technical progress the requirements regarding the conduct of clinical trials, whilst ensuring close cooperation between the Commission and the Member States within a 'Standing Committee on Medicinal Products for Human Use',

HAVE ADOPTED THIS DIRECTIVE:

Scope*Article 1*

1. The purpose of this Directive is to lay down provisions relating to the implementation of good clinical practice in the conduct of clinical trials, including multi-centre trials, on human subjects designed to develop medicinal products, as defined in Article 1 of Council Directive 65/65/EEC. This Directive shall not apply to non-interventional clinical trials.

2. Good clinical practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles set out in the amended 1964 Declaration of Helsinki, and that the results of the clinical trials are credible.

3. (Unchanged)

4. (Unchanged)

ORIGINAL TEXT

AMENDED TEXT

Article 2

For the purposes of this Directive the following definitions shall apply:

Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Adverse reaction: All noxious and unintended responses to an investigational medicinal product related to any dose.

Clinical trial: Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational medicinal product(s), and/or to identify any adverse reactions to an investigational medicinal product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.

This includes clinical trials done in either one site or multiple sites, whether in one Member State or more than one Member State, but excludes non-interventional trials.

Ethics committee: An independent body constituted of healthcare professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Definitions

Article 2

For the purposes of this Directive the following definitions shall apply:

1. *Clinical trial:* Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal products, and/or to identify any adverse reactions to one or more investigational medicinal products and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal products with the object of ascertaining their safety and/or efficacy.

This includes clinical trials performed either on a single site or on multiple sites in the course of these clinical trials.

2. *Multi-centre clinical trial:* A clinical trial conducted according to a single protocol but at more than one site, and therefore, by more than one investigator, in which the trial sites may be located in a single Member State, in a number of Member States and/or in Member States and third countries.
3. *Non-interventional clinical trial:* A clinical trial where the selection of subjects or the attribution of medicinal products or the examinations carried out or medical and biological follow-up of subjects fall within current medical practice.

4. *Investigational medicinal product:* 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.

ORIGINAL TEXT

Inspection: The act by a competent authority of conducting an official review of documents, facilities, records, arrangements for quality assurance, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments deemed appropriate by the competent authority.

Investigational medicinal product: A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when 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 an authorised use.

Investigator: A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Investigator's brochure: A compilation of the clinical and non-clinical data on the investigational medicinal product(s) which is relevant to the study of the investigational medicinal product(s) in human subjects.

Multi-centre trial: A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator. Trial sites may be located in a single Member State, in a number of Member States and/or in Member States and third countries.

Non-interventional trial: A clinical trial where the selection of subjects or the attribution of medicinal products or the examinations carried out or medical and biological follow-up of subjects falls within current medical practice.

AMENDED TEXT

5. *Sponsor:* An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

6. *Investigator:* A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

7. *Investigator's brochure:* A compilation of the clinical and non-clinical data on the investigational medicinal product or products which is relevant to the study of the product or products in human subjects.

8. *Protocol:* A document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial, the term 'protocol' referring to the protocol, successive versions of the protocol and protocol amendments.

9. *Subject:* An individual who takes part in a clinical trial, either as a recipient of the investigational medicinal product or as a control receiving a placebo or other medicinal product.

10. *Informed consent:* Decision to take part in a clinical trial, taken freely and given in writing after being duly informed of the full details, by any responsible adult trial subject or, where appropriate, by the parents, guardian or legal representative, on behalf of minors and incapacitated adults.

ORIGINAL TEXT

AMENDED TEXT

Protocol: A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The term protocol refers to protocol, successive versions of the protocol and protocol amendments.

Serious adverse event or serious adverse reaction: Any untoward medical occurrence that at any dose results in death, is life-threatening, requires (non-elective) inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Sponsor: An individual, company, institution or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Subject: An individual who participates in a clinical trial, either as a recipient of the investigational medicinal product or as a control.

Unexpected adverse reaction: An adverse reaction not mentioned in the investigator's brochure or in the summary of product characteristics, if any.

11. *Ethics committee:* An independent body constituted of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection by, among other things, expressing an opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and documents to inform trial subjects and obtain their informed consent.

12. *Inspection:* The act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect.

13. *Adverse event:* Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

14. *Adverse reaction:* All noxious and unintended responses to an investigational medicinal product related to any dose.

15. *Serious adverse event or serious adverse reaction:* Any untoward event or reaction that at any dose results in death, threatens the life of the subject, requires non-elective inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity or is a congenital anomaly or birth defect.

16. *Unexpected adverse reaction:* An adverse reaction not mentioned in the investigator's brochure or, in the case of medicinal products already authorised, in the summary of product characteristics.

ORIGINAL TEXT

AMENDED TEXT

CHAPTER II

Protection of trial subjects*Article 3*

1. This Directive is without prejudice to the measures laid down in Member States concerning the protection of trial subjects.

2. A clinical trial may only be undertaken if the risks to the subject are not disproportionate to the potential benefits of the medicinal research. The right of the subject to physical and mental integrity shall be respected, as well as the right to privacy.

3. The medical care given to, and medical decisions made on behalf of subjects shall be the responsibility of an appropriately qualified healthcare practitioner or, when appropriate, of a qualified dentist.

4. The trial subject shall be provided with a contact point, independent of the investigating team, where further information may be obtained.

Ethics Committee opinion*Article 4*

1. The function and responsibility of an ethics committee shall be to safeguard the rights, safety and well-being of all trial subjects.

Protection of clinical trial subjects*Article 3*

1. This Directive shall apply without prejudice to the national provisions on the protection of clinical trial subjects, if they are more comprehensive than the provisions of this Directive and consistent with the procedures and time-scales specified therein.

2. A clinical trial may be undertaken only if, in particular:

- (a) the risks to the subject are not disproportionate to the benefits expected for human health;
- (b) the rights of the subject to physical and mental integrity and to privacy are safeguarded;
- (c) the subject has given informed consent in the appropriate form;
- (d) the subject may withdraw from the clinical trial at any time, without any resulting detriment to the subject, by revoking the informed consent, as defined in Article 2.

3. (Unchanged)

4. On the responsibility of the sponsor, who shall adopt the consequent organisational arrangements, the clinical trial subject shall be provided with a contact point, independent of the investigator team, from which further information may be obtained on the procedure for the clinical trial, whenever it could affect the trial subject personally.

Ethics committee opinion*Article 4*

1. For the purposes of implementation of the clinical trials provided for by this Directive, the Member States shall take the measures necessary for establishment and operation of ethics committees, as defined in Article 2.

2. The ethics committee shall give its opinion on any subject requested before a clinical trial commences.

ORIGINAL TEXT

In preparing its opinion, the ethics committee shall consider, at least, the relevance of the trial and the trial design, the protocol, the suitability of the investigator, supporting staff, and available facilities; the adequacy and completeness of the written information to be given to the subjects, their relatives, guardians and, if necessary, legal representatives and by which consent is to be obtained; provision for compensation/treatment in the case of injury or death of a subject if attributable to a clinical trial, and any insurance or indemnity to cover the liability of the investigator and sponsor; the extent to which investigators and subjects may be rewarded or compensated for participation in the trial.

2. The opinion of an ethics committee shall be delivered before a clinical trial commences.

3. In order to apply for an opinion of an ethics committee, an application with documentation shall be submitted. The written opinion of the ethics committee shall be given to the applicant, in writing, within 30 days of receipt of a valid application.

4. Within that period, the ethics committee may send a single request for information supplementary to that already supplied. In this case the period shall be extended by a further 30 days.

Article 5

1. Member States shall establish a procedure by which a single ethics committee opinion can be achieved for that Member State. For multi-centre clinical trials conducted in more than one Member State, this procedure shall provide for the single opinion for that Member State.

AMENDED TEXT

3. In preparing its opinion, the ethics committee shall consider, in particular:

- (a) the relevance of the clinical trial and the trial design;
- (b) the protocol;
- (c) the suitability of the investigator and supporting staff;
- (d) the quality of the facilities;
- (e) the adequacy and completeness of the written information to be given to the subjects, their relatives, guardians and, if necessary, legal representatives and by which informed consent is to be obtained;
- (f) provision for compensation in the case of injury or death attributable to a clinical trial;
- (g) any insurance or indemnity to cover the liability of the investigator and sponsor;
- (h) the arrangements for rewarding or compensating investigators and subjects for participation in the trial.

(see paragraph 2)

4. In order to obtain the opinion of an ethics committee, the sponsor shall submit to the committee a request for an opinion with documentation giving the reasons for the proposed clinical trial. Within 30 days of official submission of the application for an opinion, the ethics committee shall give its reasoned opinion to the sponsor and the competent authority in the Member State concerned.

5. Within the period of examination of the application for an opinion, the ethics committee may send a single request for information supplementary to that already supplied by the sponsor. In this case the ethics committee shall have a further 30 days from receipt of the supplementary information to give its definitive opinion on the proposed clinical trial.

Article 5

1. For multi-centre clinical trials limited to a single Member State, Member States shall establish a procedure providing for adoption of a single ethics committee opinion for that Member State. In the case of multi-centre clinical trials involving more than one Member State simultaneously, a single ethics committee opinion shall be given for each Member State concerned by the clinical trial.

ORIGINAL TEXT

AMENDED TEXT

2. Member States may, in addition, provide for an opinion of the ethics committee for each site on the facilities and capabilities of that site in relation to the proposed clinical trial. Within 15 days of receipt of the opinion provided for in paragraph 1, the ethics committee for the site shall, by issuing an opinion, either accept or reject the conduct of the trial in that site.

2. In the case of multi-centre clinical trials the Member States may provide for the ethics committee for a particular centre amongst all the centres involved in the multi-centre clinical trial to give an opinion covering only the facilities and capabilities of that particular centre to conduct the trial. The ethics committee for this particular centre shall have a maximum of 15 days from the date of receipt of the opinion referred to in paragraph 1 to give its own duly reasoned opinion: if this opinion is negative, the clinical trial may not be conducted at this single centre, without prejudice to the situation in the other centres concerned or to the opinion referred to in paragraph 1.

*Article 6**Article 6*

The Commission, in consultation with the Member States and interested parties, shall draw up detailed guidance on the application format and documentation to be submitted in an application for an ethical committee opinion, and on the appropriate safeguards for the protection of information that is given to trial subjects.

(Unchanged)

CHAPTER III

Commencement of a clinical trial**Commencement of a clinical trial***Article 7**Article 7*

1. Before commencing a clinical trial, an application shall be submitted by the sponsor to the Member States where the trial will take place.

1. Before commencing any clinical trial, the sponsor shall be required to submit notification thereof to the competent authorities of the Member State or States where the sponsor plans to conduct the trial at the same time as submitting the request for an opinion referred to in paragraph 4 of Article 4.

2. Member States shall authorise sponsors to commence clinical trials once the ethics committee has issued a favourable opinion. Member States may however decide that certain clinical trials will be subject to paragraph 3.

2. The sponsor may not start a clinical trial until the ethics committee has issued a favourable opinion and unless the competent authorities of the Member State concerned have notified the sponsor of no grounds for non-acceptance within 30 days of receipt of the notification referred to in paragraph 1.

3. In the case of clinical trials not covered by the provisions of paragraph 2, Member States shall authorise a sponsor to commence clinical trials at the end of a period of 30 days after receipt of a valid application unless reasoned grounds for non-acceptance have been notified within this time period.

ORIGINAL TEXT

Within 30 days of receipt of the said grounds for non-acceptance, the sponsor may amend the application on one occasion only in order to take due account of the grounds set out in the notification. If the sponsor does not amend the application as provided for, the application is deemed to have been rejected.

4. Amendments to the protocol shall be notified to the Member States. These amendments shall be deemed to be accepted unless the competent authority notifies grounds for non-acceptance within 30 days.

In cases where grounds for non-acceptance are raised, the procedure in paragraph 3 shall be followed.

5. Notwithstanding paragraph 4, provisional urgent safety measures may be taken by the sponsor in order to eliminate an immediate hazard to trial subjects.

AMENDED TEXT

Should this not be the case, within 30 days of receipt of the grounds for non-acceptance from the competent authorities of the Member State concerned, the sponsor may amend, on one occasion only, the content of the notification referred to in paragraph 1 of this Article in order to take due account of the grounds given. If the sponsor fails to amend the notification accordingly, the notification shall be considered rejected and the clinical trial may not commence.

3. In the case of clinical trials on investigational medicinal products corresponding to the medicinal products corresponding to the characteristics defined in Part A of the Annex to Council Regulation (EEC) No 2309/93, particularly products intended for gene therapy and products intended for cell therapy, a copy of the notification referred to in paragraph 1 of this Article or of the amended notification provided for in paragraph 2 of this Article shall be sent to the European Agency for the Evaluation of Medicinal Products.

In the case of clinical trials on investigational medicinal products corresponding to the characteristics defined in Part B of the Annex to Council Regulation (EEC) No 2309/93, the sponsor shall have the option of sending the notification referred to in paragraph 1 of this Article or the amended notification provided for in paragraph 2 of this Article to the European Agency for the Evaluation of Medicinal Products.

4. However, prior written authorisation shall be required before commencing clinical trials on the medicinal products referred to in Part A of the Annex to Council Regulation (EEC) No 2309/93 and on all other medicinal products with special characteristics defined and approved in the form of a directive adopted by the procedure laid down in Article 2c of Council Directive 75/318/EEC.

This authorisation to commence shall be granted by the competent authorities of the Member States within 60 days of receipt of the notification referred to in paragraph 1 of this Article and after the ethics committee has given a favourable opinion, without prejudice to the procedure applicable in the event of the grounds for non-acceptance referred to in paragraph 2 of this Article.

The abovementioned authorisation to commence the clinical trial shall be sent to the sponsor. The ethics committee and the European Agency for the Evaluation of Medicinal Products shall be informed that this authorisation has been granted.

(see new Article 8 (1))

(see new Article 8, (2))

ORIGINAL TEXT

6. Within 90 days of the end of a clinical trial, the sponsor shall notify the Member States that the clinical trial is ended. This period shall be reduced to 15 days in the case of early termination of the trial.

7. The Commission shall, in consultation with the Member States, draw up detailed guidance on the format and contents for applications as well as the documentation to be submitted in relation to the quality and manufacture of the investigational medicinal product, any toxicological and pharmacological tests, protocol and clinical information on the investigational medicinal product including the investigator's brochure, in addition to the content of the notification of the end of the clinical trial.

AMENDED TEXT

(see new Article 8, (3))

5. In consultation with the Member States, the Commission shall draw up detailed guidance on the format and contents of the notification referred to in paragraph 1 of this Article as well as the documentation to be submitted to support this notification on the quality and manufacture of the investigational medicinal product, any toxicological and pharmacological tests, protocol and clinical information on the investigational medicinal product including the investigator's brochure, in addition to the declaration of the end of the clinical trial.

Conduct of a clinical trial*Article 8*

(new)

Amendments may be made to the conduct of a clinical trial following the procedure described hereinafter.

1. After commencement of the clinical trial, the sponsor may make substantial amendments to the protocol likely to have an impact on the safety of the trial subjects or to change the criteria for scientific evaluation, the criteria for inclusion or exclusion of trial subjects, the number of trial subjects, the duration of the treatment, the doses of the investigational medicinal products and the clinical and biological examinations carried out in the course of follow-up of the trial subjects. In this case 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 thereof and the European Agency for the Evaluation of Medicinal Products if the clinical trial in question meets the requirements of the first indent of Article 7(4).

On the basis of the details referred to in Article 4(3) and subject to the requirements of Article 5, the ethics committee shall give an opinion on the proposed amendment within 30 days of notification thereof. 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 abovementioned substantial amendments within 30 days of notification thereof, 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 these grounds and adapt the proposed amendment to the protocol accordingly or withdraw the proposed amendment.

ORIGINAL TEXT

AMENDED TEXT

In the case of clinical trials subject to the prior written authorisation referred to in Article 7(4), the sponsor may not proceed to conduct the clinical trial following the amended protocol unless the ethics committee has given a favourable opinion and the competent authorities of the Member States have given a new authorisation taking account of these amendments.

2. Without prejudice to paragraph 1, in the light of the circumstances, notably the occurrence of unexpected adverse reactions or events, the sponsor shall take appropriate urgent safety measures to protect the subjects in a clinical trial against any immediate hazard. The sponsor shall inform the competent authorities and the ethics committee of these measures.
3. 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.

Exchange of information*Article 8*

1. Extracts from the initial application, amendments as appropriate and the notification at the end of the clinical trial shall be entered by the Member States in whose territory the trial takes place into a database accessible only to Member States, the European Agency for the Evaluation of Medicinal Products and the Commission.

2. At the request of any Member State or the Commission, the competent authority to whom the trial was notified shall supply all appropriate information concerning that clinical trial.

3. In the case of multi-centre clinical trials conducted in more than one Member State where there are differences between the Member States, the Commission may request the Member States concerned to establish the reasons for the difference which shall be considered by all Member States.

Exchange of information*Article 9*

(ex 8)

1. The Member States in whose territory the clinical trial takes place shall enter in a European database, accessible only to the competent authorities of the Member States, the European Agency for the Evaluation of Medicinal Products and the Commission, extracts from the notification referred to in Article 7(1), any amendments made to the notification, as provided for in Article 7(2), any amendments made to the protocol, as provided for in Article 8(1), the favourable opinion of the ethics committee and the declaration of termination of the clinical trial.

2. At the request of any Member State, the European Agency for the Evaluation of Medicinal Products or the Commission, the competent authority to which the notification referred to in Article 7(1) was submitted shall supply all further information concerning the clinical trial in question other than the data already in the European database.

3. In the case of multi-centre clinical trials involving more than one Member State, where there are differences between the Member States with regard to the conditions for commencement or conduct of the clinical trial, the Commission may request the Member States concerned to establish the reasons for the differences, which shall be considered by all the Member States in consultations organised by the Commission with the assistance of the European Agency for the Evaluation of Medicinal Products.

ORIGINAL TEXT

AMENDED TEXT

4. The Commission, in consultation with the Member States, shall draw up detailed guidance on the relevant data to be included in this database as well as methods for the electronic communication of the data.

4. In consultation with the Member States, the Commission shall draw up detailed guidance on the relevant data to be included in this European database which it operates with the assistance of the European Agency for the Evaluation of Medicinal Products as well as the methods for electronic communication of the data. This detailed guidance drawn up shall keep the data strictly confidential.

*Article 9**Article 10*

(ex 9)

1. Where the conditions of the application cease to be met or in the event that new information raising doubts as to safety or science becomes available, the Member State may suspend or prohibit the trial. It shall forthwith inform the other Member States and the Commission thereof.

1. Where a Member State has objective grounds for considering that the conditions in the notification referred to in Article 7(1) are no longer met or has information raising doubts about the safety or science of the clinical trial, it may suspend or prohibit the clinical trial and shall notify the sponsor thereof.

The Member State shall inform the other Member States and the Commission of the decisions taken and the reasons for those decisions.

In this case, the Member State concerned shall forthwith inform the other Member States, the ethics committee concerned, the European Agency for the Evaluation of Medicinal Products and the Commission of its decision to suspend or prohibit the trial and the reasons for the decision.

2. Where a Member State is of the opinion that the sponsor or the investigator is no longer fulfilling his obligations as laid down, it shall forthwith inform the other Member States and the Commission, stating the reasons in detail and indicating the course of action.

2. Where a Member State has objective grounds for considering that the sponsor or the investigator is no longer meeting the obligations laid down, it shall forthwith inform them, indicating the course of action which it considers necessary to remedy this state of affairs. The Member State concerned shall forthwith inform the ethics committee, the other Member States and the Commission of this plan.

The Member State shall forthwith inform the Commission of the commencement of any infringement proceedings.

3. Where non-observance of the provisions governing the conduct of clinical trials prompts a Member State to initiate administrative or legal proceedings against the sponsor or investigator, it shall forthwith inform the other Member States, the Commission and, where appropriate, the European Agency for the Evaluation of Medicinal Products.

CHAPTER IV

Manufacture, import and labelling of investigational medicinal products**Manufacture and import of investigational medicinal products***Article 10**Article 11*

(ex 10)

1. Member States shall take all appropriate measures to ensure that the manufacture and import of investigational medicinal products is subject to the authorisation referred to in Article 16 of Council Directive 75/319/EEC⁽¹⁾.

1. Member States shall take all appropriate measures to ensure that the manufacture, whether in a Member State or in a third country, of investigational medicinal products used in a clinical trial conducted in the European Community meets the requirements of Commission Directive 91/356/EEC⁽¹⁾ laying down the principles of good manufacturing practice for medicinal products and of the related texts.

⁽¹⁾ OJ L 147, 9.6.1975, p. 13.

⁽¹⁾ OJ L 193, 17.7.1991, p. 30.

ORIGINAL TEXT

AMENDED TEXT

2. Chapters IV and V of Directive 75/319/EEC shall apply to investigational medicinal products.

3. A person engaging in the activities of the person referred to in Article 21 of Directive 75/319/EEC in a Member State as regards investigational medicinal products at the time when this Directive is brought into force in that State but without complying with the provisions of Article 23 and 24 of Directive 75/319/EEC shall be eligible to continue to engage in those activities for the purpose of manufacture of investigational medicinal products in the Member State concerned.

Article 11

1. For investigational medicinal products, the particulars to appear in, at least, the national language(s) on the outer packaging of investigational medicinal products or, where there is no outer packaging, on the immediate packaging shall be published by the Commission in the good manufacturing practice guideline on investigational medicinal products to be adopted in accordance with Article 19a Directive 75/319/EEC.

CHAPTER V

Compliance*Article 12*

1. Compliance with the provisions of good clinical practice shall be verified on behalf of the Community by inspection at relevant sites, including the trial site and manufacturing site, at any laboratory used in the trial and/or at the sponsor's premises, by inspectors appointed by Member States.

2. Following inspection, an inspection report shall be prepared which shall be made available, upon request, to the sponsor, any other Member State or the European Agency for the Evaluation of Medicinal Products.

2. The Member States shall authorise imports of investigational medicinal products from third countries and free movement thereof within the Community, provided the qualified person referred to in paragraph 3 can certify that quality control and batch approval have been carried out in accordance with paragraph 1.

3. Any person engaging in the activities of the qualified person referred to in Article 21 of Council Directive 75/319/EEC as regards investigational medicinal products at the time when this Directive is brought into force in the Member State where that person is but without complying with the conditions laid down in Article 23 and 24 of Council Directive 75/319/EEC shall be authorised to continue those activities to manufacture investigational medicinal products in the Member State concerned.

Labelling*Article 12*

(ex 11)

(Unchanged)

Compliance with good clinical practice*Article 13*

(ex 12)

1. To verify compliance with the provisions on good clinical practice, the Member States shall appoint inspectors to inspect the sites concerned with any clinical trial conducted, particularly the trial site or sites, the manufacturing site for the investigational medicinal product, any laboratory used for analyses in the clinical trial and/or the sponsor's premises if the analyses are carried out there.

The inspections shall be conducted by a Member State, which shall inform the European Agency for the Evaluation of Medicinal Products; they shall be carried out on behalf of the Community and the results shall be recognised by all the other Member States. These inspections shall be coordinated by the European Agency for the Evaluation of Medicinal Products.

2. Following inspection, an inspection report shall be prepared and sent to the sponsor. A copy of this report shall be sent to the European Agency for the Evaluation of Medicinal Products. Upon reasoned request, the investigator, the ethics committee, any other Member State and the Commission may consult this report.

ORIGINAL TEXT

3. Where there are differences between Member States as to whether the provisions of this Directive have been complied with, the Commission may request a new inspection. The coordination of such inspections shall be undertaken by the European Agency for the Evaluation of Medicinal Products.

4. Subject to any arrangements which may have been concluded between the Community and third countries, the Commission may, upon receipt of a reasoned request from a Member State or on its own initiative, require that the trial site and/or the sponsor's premises and/or the manufacturer established in a third country submit to an inspection. The inspection shall be undertaken by appropriately qualified inspectors from the Community.

5. The Commission, in consultation with the Member States, the European Agency for the Evaluation of Medicinal Products and interested parties, shall draw up detailed guidelines on the documentation, archiving, appropriate qualification of inspectors and inspection procedures for the demonstration of compliance with this Directive.

CHAPTER VI

Clinical safety reporting*Article 13*

1. The investigator shall report all serious adverse events immediately to the sponsor except for those serious adverse events that the protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the trial subjects.

2. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the ethics committee and the sponsor according to the reporting requirements and within the time periods specified in the protocol.

3. For reported deaths, the investigator shall supply the sponsor and the ethics committee with any additional requested information.

AMENDED TEXT

3. At the behest of the European Agency for the Evaluation of Medicinal Products, the Commission may request reinspection should verification of compliance with the provisions of this Directive reveal differences between Member States.

4. (Unchanged)

5. In consultation with the Member States, the European Agency for the Evaluation of Medicinal Products and interested parties, the Commission shall draw up detailed guidelines on the documentation relating to the clinical trial, which shall constitute the master file on the trial, archiving, qualifications of inspectors and inspection procedures to verify compliance by the clinical trial in question with this Directive and with the texts adopted to implement it

Notification of adverse events*Article 14*

(ex 13)

1. (Unchanged)

2. (Unchanged)

3. (Unchanged)

ORIGINAL TEXT

AMENDED TEXT

4. The sponsor shall ensure that all relevant information about fatal or life-threatening unexpected adverse reactions are recorded and reported as soon as possible to the Member State in whose territory the reaction occurred, but in any case no later than seven days after first knowledge by the sponsor that a case qualifies. All other serious adverse reactions that are not fatal or life-threatening shall be reported as soon as possible but no later than within 15 days. The sponsor shall also inform all investigators.

5. In addition, the sponsor shall maintain detailed records of all suspected adverse events which are reported to him by the investigator(s). These records shall be submitted to the Member States in whose territory the clinical trial is being conducted.

6. At least every 12 months during the clinical trial, the sponsor shall provide the Member States in whose territory the clinical trial is being conducted with a line listing of all suspected serious adverse reactions which have occurred in the whole study and a summary overview of the subjects' safety in the trial.

7. Each Member State shall ensure that all suspected serious unexpected adverse reactions to an investigational medicinal product occurring within their territory which are brought to their attention are recorded and reported immediately to the European Agency for the Evaluation of Medicinal Products, and in no case later than 15 days following the receipt of the information.

The European Agency for the Evaluation of Medicinal Products shall inform the competent authorities of the Member States.

4. The sponsor shall keep detailed records of all suspected adverse events which are reported to him by the investigator or investigators. These records shall be submitted to the Member States in whose territory the clinical trial is being conducted.

Notification of adverse reactions

Article 15

(ex 13(4), (6) and (7))

1. The sponsor shall ensure that all relevant information about unexpected serious adverse reactions which are fatal or life-threatening to a clinical trial subject are recorded and reported to the Member State in whose territory the reaction occurred as soon as possible, but no later than 7 days after the sponsor first knew of a case of this type.

All other unexpected serious adverse reactions that are not fatal or life-threatening to a subject shall be reported by the sponsor as soon as possible, within not more than 15 days, to the Member State in whose territory the reaction occurred and to the ethics committee.

The sponsor shall also inform all the other investigators of the unexpected serious adverse reactions to the medicinal product.

(see new Article 14(4))

2. Once a year throughout the clinical trial, the sponsor shall provide the Member States in whose territory the clinical trial is being conducted with a line listing of all suspected unexpected serious adverse reactions which have occurred over this period and a summary overview of the subjects' safety in the clinical trial.

3. Each Member State shall ensure that, no later than 15 days following occurrence within their territory, all suspected unexpected serious adverse reactions referred to in paragraph 2 are recorded and brought to its knowledge immediately and subsequently notified to the European Agency for the Evaluation of Medicinal Products, which shall forthwith inform the competent authorities of the other Member States.

ORIGINAL TEXT

AMENDED TEXT

8. The Commission, in consultation with the European Agency for the Evaluation of Medicinal Products, Member States and interested parties, shall draw up guidance on the collection, verification and presentation of adverse event/reaction reports.

(Unchanged)

Article 16
(ex 13(8))

CHAPTER VII

General provisions*Article 14*

This Directive is without prejudice to the general civil and criminal liability of the sponsor or the investigator.

(Unchanged)

Unless Member States have established precise conditions for exceptional circumstances, medicinal products used in clinical trials shall not be sold. Member States shall inform the Commission of such conditions.

General provisions

Article 17
(ex 14)

Article 15

Any amendment which may be necessary to update the provisions of this Directive to take account of scientific and technical progress shall be adopted in accordance with the provisions of Article 2c of Directive 75/318/EEC.

(Unchanged)

Article 18
(ex 15)

Article 16

Member States shall take all appropriate measures to comply with this Directive before 1 January 1999. They shall forthwith inform the Commission thereof.

Member States shall take all measures necessary to comply with this Directive before 1 . . . 2001. They shall forthwith inform the Commission thereof.

When Member States adopt these provisions, these shall contain a reference to this Directive or shall be accompanied by such reference at the time of their official publication. The procedure for such reference shall be adopted by Member States.

(Unchanged)

Article 19
(ex 16)

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

(Unchanged)

Article 17

This Directive is addressed to the Member States.

(Unchanged)

Article 20
(ex 17)