COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 26.04.1999
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97/0197 (COD)

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

(presented by the Commission pursuant to Article 189 a (2)
of the EC-Treaty)

EXPLANATORY MEMORANDUM

A. Principles

1. In September 1997 the Commission submitted the 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 [COM(97)369; 97/0197 (COD)] for adoption by the co-decision procedure laid down in Article 189b of the Treaty establishing the European Community.

The Economic and Social Committee was consulted for its opinion and, at its plenary session on 28 January 1998, adopted a series of amendments, on which the Commission has given its opinion. On 17 November 1998 the European Parliament adopted a series of amendments on first reading. On this occasion the Commission gave its position on each amendment and indicated which it was going to include and which it could not accept.

In the light of the foregoing, the Commission has drafted this amended proposal.

2. The Commission has made two types of amendment.

First, additions have been made to numerous points in the original proposal which seemed too elliptic or could have been open to diverging interpretations when the time came for national legislation to implement them. This explains the importance of the rewording of the original text. However, these are only clarifications or practical details and make no difference to the substance of the rules, which have just been reworded or presented in different form.

Second, in response to the Economic and Social Committee's opinion and the first reading by the European Parliament, it was felt that new provisions should be added to bring the proposal closer into line with the Community legislation already in force on medicinal products and ensure more efficient implementation of the Directive. These new provisions are not only compatible with the subsidiarity principle but should ensure stronger application thereof.

B. Explanation of the principal amendments

1. Informed consent

To guarantee stronger protection of clinical trial subjects and in response to European Parliament amendments 6, 8 and 10, new provisions on informed consent have been added. First, a practical definition has been added in Article 2 followed, in Article 3(2), by procedures for giving or revoking such consent, particularly in the case of minors or of incapacitated adults.

The amended text also lays down clearer conditions for clinical trial subjects who so wish to have access to an independent contact able to supply them with further information. To this end, Article 3(4) clearly places responsibility for organising the corresponding arrangements on the sponsor, ending, at the same time, the legitimate concerns about confidentiality.

2. Ethics committee

– To underline that this committee is the ethical authority and that it is essential to obtain its favourable opinion first and to avoid confusion about the unique function which it alone is empowered to exercise, Article 4(4) defines the role of the ethics committee in greater detail compared with the role of the competent authorities in the Member States which exercise the exclusive prerogatives of the public authorities on authorisation (Article 7(4)), control (Article 10(1) and (2) and Article 13), information (Article 9) and, where appropriate, penalties (Article 10(3)).

– The amended proposal gives the ethics committee a stronger role, no longer limited almost exclusively to the phase preceding commencement of the clinical trial, as was the case in the original proposal. In this connection, in line with Parliament's amendments 21, 22 and 27, the content of the information to be submitted to the ethics committee has been widened substantially to cover the entire clinical trial, from before commencement to completion. This includes: pharmacovigilance data, with the concepts of events and reactions now covered by two separate Articles (14 and 15); measures taken by the competent authorities during the clinical trial in the event of shortcomings on the part of the sponsor or investigator (Article 10(1) and (2)); knowledge of the result of inspections to verify compliance with good clinical practice during conduct of the clinical trial (Article 13(2)).

– The procedures for referring to the committee for its opinion have been clarified by creating a stronger link between Article 4(4) and (5) and Article 7(1) and (2), the effect of which is to draw a clear distinction between the different phases before commencement of a clinical trial. It has also been made clear that the ethics committee must be reconsulted if the sponsor makes substantial amendments to the protocol being followed which could impair subjects' safety and, therefore, call into question the original favourable opinion (new Article 8(1)). This is the reason for splitting the original Article 7 and adding a new Article 8 covering activities well after the start of the clinical trial.

– Finally, Article 5(2) clearly defines the role and relative positions of the ethics committee or committees for the different sites involved in the same clinical trial on the one hand and the ethics committee chosen to issue the single opinion on a particular clinical trial at Member State level on the other.

3. Exchanges of information

Since around 60% of the multi-centre clinical trials today involve several Member States, it is imperative to exchange information between the Member States involved, both on commencement of the clinical trials and on progress with them. For example, information on the results of the clinical trials is primordial for mutual recognition of national marketing authorisations for medicinal products. Strict application of the subsidiarity principle combined with geographical centralisation of these data in a specialised base with all the requisite protection would greatly facilitate such mutual recognition.

To this end, the amended proposal reinforces the original text by adding provisions on the practical arrangements for such centralisation at Community level (new Article 9(1)) and clearly defining the role played by the Commission in organising and

coordinating such exchanges of information (Article 9(4)) vis-à-vis the competent authorities and the sponsor of the clinical trial.

4. Compatibility with existing Community legislation

It was found that the original Commission proposal was not fully compatible with the principles and objectives of the current centralised marketing authorisation procedures for medicinal products, as set out in the Commission communication on the subject[1].

In this context, the European Agency for the Evaluation of Medicinal Products is responsible for evaluating all medicinal products derived from biotechnological processes (Part A of the Annex to Council Regulation (EEC) No 2309/93). It is therefore essential for the Agency to know of the existence and content of the clinical trials on such products, as it will have to analyse the relevant clinical data when evaluating the products with a view to granting them a Community marketing authorisation. Consequently, Article 7(3) of the amended proposal makes it mandatory to send the Agency a copy of the notification of commencement of a clinical trial so that it can assess the content thereof in preparation for subsequent evaluation of the product should it fall under Part A of the Annex to Regulation (EEC) No 2309/93. If the product falls under Part B of the same Annex, the sponsor has the option of deciding whether or not to notify the Agency.

5. Procedure for commencement of a clinical trial

Based on Parliament's amendments 15 and 18, the biggest change made to the original proposal concerns the procedure for commencement of clinical trials. The new procedure deliberately opts for simplification, which should equal speed and efficiency, by putting the accent on the "notification procedure". For the sponsor this entails informing the competent authorities of any plans to proceed with a clinical trial, by means of a "notification". The content and safeguards for monitoring this notification procedure are laid down in detail in Article 7(1) and (2).

In practice, the notification is equivalent to tacit authorisation which the competent authorities have full powers to revoke before it takes effect, exercising their power to raise grounds for non-acceptance as laid down in Article 7(2). The notification procedure also draws a clear distinction between the prerogatives of the ethics committee and the powers of the competent authorities in the Member States, as mentioned in the first paragraph of Section B.2. In any event, only the competent authorities may issue written authorisation for a clinical trial, where such authorisation is mandatory.

In the case of clinical trials on medicinal products covered by Part A of the Annex to Regulation (EEC) No 2309/93, the amended proposal specifies that this notification of the clinical trial must be accompanied by a written authorisation granted by the competent authorities of the Member States concerned within the time limits set in the amended proposal (Article 7(4)).

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[1] OJ C 229, 22.7.1998, p. 4.

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Original text	Amended 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	Proposal for a **EUROPEAN PARLIAMENT AND COUNCIL DIRECTIVE .../../EC** 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,	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 Treaty establishing the European Community, and in particular Article 100a thereof,
Having regard to the proposal from the Commission,	Having regard to the proposal from the Commission[5],
Having regard to the opinion of the Economic and Social Committee,	Having regard to the opinion of the Economic and Social Committee[6],
Acting in accordance with the procedure laid down in Article 189b of the Treaty,	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	(1) (Unchanged)

[1] OJ No L 22, 9.2.1965, p. 369/65.

[2] OJ No L 147, 9.6.1975, p. 1.

[3] OJ No L 281, 23.11.1995, p. 31

[4] OJ No L 147, 9.6.1975, p. 13.

[5] OJ No C 306, 8.10.1997, p. 9.

[6] OJ No C 95, 30.3.1998, p. 1.

uniform rules on the compilation of dossiers including their presentation;	
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;	(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;
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;	(4) (Unchanged)
	(5) Whereas for medicinal products falling within the scope of Part A of the Annex to Council Regulation (EEC) No 2309/93[7], 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

[7] OJ No L 214, 24.8.1993, p.1.

[8] OJ No L 193, 17.7.1991, p.30.

	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;
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;	(6) (Unchanged)
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/EEC 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[3];	(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)
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 co-	(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 co-

operation 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',	operation between the Commission and the Member States within a 'Standing Committee on Medicinal Products for Human Use',
HAVE ADOPTED THIS DIRECTIVE:	HAVE ADOPTED THIS DIRECTIVE:
CHAPTER I **Scope and definitions**	**Scope**
Article 1	*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.	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 (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.	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. 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.	3. (Unchanged)
4. All clinical trials, including bioavailability and bioequivalence studies, shall be	4. (Unchanged)

designed, conducted and reported in accordance with the standard of good clinical practice.	
	Definitions
Article 2	*Article 2*
For the purposes of this Directive the following definitions shall apply:	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.	*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.
Adverse Reaction: All noxious and unintended responses to an investigational medicinal product related to any dose.	*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.
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.	*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.
Ethics Committee: An independent body constituted of healthcare professionals and non-	*4. – Investigational medicinal product:* A pharmaceutical form of an active substance or

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.	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.
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.	*5. – Sponsor*: An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.
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.	*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.
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.
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.	*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.
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.	*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.
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. *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.	*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. *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.
CHAPTER II **Protection of trial subjects** *Article 3*	**Protection of clinical trial subjects** *Article 3*
1. This Directive is without prejudice to the measures laid down in Member States concerning the protection of trial subjects.	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 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.	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. 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.	3. (Unchanged)
4. The trial subject shall be provided with a contact point, independent of the investigating team, where further information may be obtained.	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	**Ethics committee opinion**

	Article 4	*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.	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.
	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.	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.
2.	The opinion of an ethics committee shall be delivered before a clinical trial commences.	(see paragraph 2)
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	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

written opinion of the ethics committee shall be given to the applicant, in writing, within 30 days of receipt of a valid application.	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.
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.	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	*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.	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.
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	(Unchanged)

information that is given to trial subjects.	
CHAPTER III	
Commencement of a clinical trial	**Commencement of a clinical trial**
Article 7	*Article 7*
	The Member States shall take the measures necessary to ensure that the procedure described hereinafter is followed for commencement of a clinical trial.
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.	
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.	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.
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.	(see new Article 8, paragraph 1)

	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.	(see new Article 8, paragraph 2)
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.	(see new Article 8, paragraph 3)
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.	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 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 paragraph 4 of Article 7. On the basis of the details referred to in paragraph 3 of Article 4 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. In the case of clinical trials subject to the prior written authorisation referred to in paragraph 4 of Article 7, 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*	**Exchange of information** *Article 9 (ex 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.	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 paragraph 1 of Article 7, any amendments made to the notification, as provided for in paragraph 2 of Article 7, any amendments made to the protocol, as provided for in paragraph 1 of Article 8, the favourable opinion of the ethics committee and the declaration of termination of the clinical trial.
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.	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 paragraph 1 of Article 7 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 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.	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.
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.
	Infringements

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 paragraph 1 of Article 7 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[4].	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[8] laying down the principles of good manufacturing practice for medicinal products and of the related texts.

2. Chapters IV and V of Directive 75/319/EEC shall apply to investigational 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. 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.	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 Articles 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 11	*Article 12 (ex 11)*
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 of Directive 75/319/EEC.	(Unchanged)
CHAPTER V	
Compliance	**Compliance with good clinical practice**
Article 12	*Article 13 (ex 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.	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 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. 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.
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 co-ordination of such inspections shall be undertaken by the European Agency for the Evaluation of Medicinal Products.	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. 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.	4. (Unchanged)
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.	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
CHAPTER VI **Clinical safety reporting** *Article 13*	**Notification of adverse events** *Article 14 (ex 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.	1. (Unchanged)
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.	2. (Unchanged)
3. For reported deaths, the investigator shall supply the sponsor and the ethics committee with any additional requested information.	3. (Unchanged)
	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))*
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	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.

	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.	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.
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.	(see new Article 14, paragraph 4)
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.	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.
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.	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.
		Article 16 (ex 13(8))
8.	The Commission, in consultation with the European Agency for the Evaluation of Medicinal Products, Member States, and interested parties, shall draw up guidance	(Unchanged)

on the collection, verification and presentation of adverse event/reaction reports.	
CHAPTER VII	
General provisions	**General provisions**
Article 14	*Article 17 (ex 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.	
Article 15	*Article 18 (ex 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 16	*Article 19 (ex 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)
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	*Article 20 (ex 17)*
This Directive is addressed to the Member States.	(Unchanged)

Done at XXXX, *For the European Parliament* *For the Council* *The President* *The President*	Done at Brussels, *For the European Parliament* *For the Council* *The President* *The President*

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