COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 03.09.1997
COM(97) 369 final

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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

(presented by the Commission)

Explanatory Memorandum

1. BACKGROUND

With the introduction of the first legislation dealing with pharmaceuticals, twin principles of protection of public health and free movement of products were enshrined. Directive 65/65/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products requires that medicinal products must have a marketing authorisation prior to being placed on the market in the European Community. Further, the criteria upon which access to the marketplace is determined - quality, safety and efficacy - have been clearly set out. Demonstration, particularly of the latter two generally rely on clinical trials in human subjects.

The standards for the conduct of clinical trials have been developed progressively, both within the European Community and internationally. These standards were codified in the European Union guideline on Good Clinical Practice (GCP) in 1990 and are followed in clinical research by the pharmaceutical industry. With the globalisation of the pharmaceutical industry, the international harmonisation of the standards of were also undertaken - in the forum of the International Conference on Harmonisation.

Since January 1997, the internationally harmonised GCP is now incorporated into clinical practice within the Community by virtue of their inclusion in 'The rules governing medicinal products in the European Union' published by the Commission in accordance with the annex to Directive 75/318/EEC on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products as amended. Because such guidelines are not binding, a supportive legislative framework is required. This is to be achieved using two approaches: firstly, by this proposal for a Council Directive reinforcing existing practice and harmonising procedures for the commencement of clinical trials; secondly, with a delegation of power to the Commission to adopt a Directive containing the detailed principles and guidelines on GCP.

2. SUBSIDIARITY AND PROPORTIONALITY

All Member States have either legislative and/or administrative provisions relating to the commencement of a clinical trial. However, the requirements are not the same and given that current approaches to the demonstration of clinical safety and efficacy (for example, placebo controlled double blind trials) frequently involve thousands of subjects, the practice has developed of applying the same trial protocol in multiple investigational sites. These 'multi-centre' clinical trials, when conducted in the European Union, would frequently take place in more than one Member State. Thus, currently, the conduct of the same trial must comply with different national provisions resulting in delays of up to nine months in the initiation of a clinical trial with consequential delays for patients..

Therefore this legislative proposition is designed to build on the existing experience of the Member States , ensuring the same level of patient protection and scientific standards, but with a rationalisation of the documentary and administrative procedures involved in multi-centre clinical trials. Additionally, the proposal includes a series of definitions which have been internationally agreed and which codify the terms used in the Member States, on the basis of which clinical trial data generated in the European Union is internationally mobile.

It is important to note that this proposal, based on article 100a, is in fact a rationalisation of legislation since overall the administrative and bureaucratic requirements will be reduced in line with a 'risk-based' approach, thus allowing new medicines to be made available to patients in a timely manner. It is also intended to simplify the regulatory burden for small and medium companies e.g. start up biotechnology companies, for whom the current complexity of national requirements makes it almost impossible to conduct trials in more than one Member State.

3. PROTECTION OF THE TRIAL SUBJECT

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 draft Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine (The Convention on Human Rights and Biomedicine).

In practice, this means that the clinical trial has been considered by an Ethics Committee and by the competent authority of the Member State. Further, the investigator is responsible for the personal safety and well-being of subjects in a clinical trial. In the laws of the Member States, the protection of the trial subject is provided for both through adoption of international conventions and additional legislative provisions. In accordance with the principle of subsidiarity and given that the protection afforded by the different Member States appears sufficient and does not jeopardise the internal market, harmonisation is not proposed. However, some fundamental principles which are currently applied in all Member States are recalled in the proposal.

For the protection of subjects in a clinical trial, it is important that complete information is provided and that, as necessary, additional information may be requested. The subjects participation in the clinical trial is confidential and, as the data relating to the study may be available to third parties such as monitors and regulatory bodies, it should remain anonymous. All data should be secured against unauthorised access and confidentiality should be observed at all times. This directive is without prejudice to Directive 95/46/EEC on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

Prior to enrolment in a clinical trial, the trial subject should receive easy to understand information on the nature of the trial (Patient information) and be afforded the opportunity to ask and receive answers to questions. Consent to participate is then confirmed by the 'Informed consent' record.

Legal texts in themselves provide only a framework within which to work. Ethics cannot be grafted onto a trial - it must be built in from the outset. Ultimately an ethical attitude must pervade the approach to clinical investigation, its establishment and follow through.

4. ETHICS COMMITTEES

The Treaty on European Union recognise the need to respect the history, culture and traditions of the peoples of the Union. In Europe there is a diversity of cultural traditions. Equally there is diversity in religious beliefs. This combination has led to differing expectations and practices, both legal and ethical. Nonetheless, the solidarity of the peoples of the Union creates a firm basis for the construction of the future Europe.

Ethical principles therefore reflect the culture, tradition and expectation of peoples. Ethics also reflect the views of their time, and perforce must be adjusted in time. Thus the expression of detailed ethical requirements in legislative texts has not been the practice in the Member States. Rather the standards and principles to be followed are enshrined in legal form.

This experience has been followed in this proposal. Thus, the principles of consultation, opinions in writing and the necessity of on-going submission of information to the independent ethics committee are set out. Generally, each centre where a clinical trial is conducted sets up an independent ethics committee the membership of which consists of doctors other than those involved in the trial, nurses and/or other healthcare professionals as well as non medical people such as lawyers, administrator, and lay people. This committee acts to screen the clinical trial in order to ensure the protection of the rights, safety and well-being of human subjects involved in the trial. By virtue of this independent review, public assurance of that protection is also attained.

Thus the following principles have been elaborated:

- For the same clinical trial, all Ethics Committees must be supplied with the same information;

- The opinion of the Ethics committee of the site where the trial actually takes place must be obtained, particularly as it is this committee that will be most familiar with the facilities and qualifications of the investigator.

However, the administrative procedures including the scientific documentation to be made available in order to obtain an ethical committee opinion do lend themselves to rationalisation, at the high standard necessary for the protection of trial subjects.

For multi-centre multi Member State clinical trials, up to 50 or 60 sites might be involved. The co-ordination of ethical opinions from all of these sites can impose difficulties and delays. In a number of Member States, procedures have already been set up whereby either a national ethics committee, or a co-ordination of regional committees or the ethics committee of the principal investigator takes the lead in giving an opinion for the trial. Thereafter, the ethics committees of each site either accepts or rejects the trial for that site.

This approach has been followed in the proposal - each Member State would establish its own procedure for achieving a 'lead' opinion for a multi-centre multi-Member State clinical trial. Thus instead of say 50 or 60 separate opinions, there would be an opinion per Member State, with an acceptance or rejection of the trial by the Ethics Committee of the investigational site.

5. INNOVATIVE ENVIRONMENT

The pharmaceutical industry in Europe is highly innovatory and contributes to public health by virtue of bringing forth new medicines for disease conditions for which treatment is currently insufficient or not available. The innovative nature of the industry relies on research, particularly clinical research. Equally, the conduct of research in Europe contributes to the knowledge base of the performance in practice of the medicinal product in the European patient, and permits clinical investigators to work intimately with evolving science. Therefore it is important that clinical research should not be inhibited by unnecessary administrative duplication.

In most Member States there is a requirement to either notify or receive approval from the competent authority before commencing a clinical trial in the territory of that Member State. In addition to protecting the trial subject, the current experience with systems of notification/approval has proven effective and therefore provides the basis for this part of the proposal. Thus, a sponsor would notify the competent authority of the clinical trial, the competent authority would have the opportunity to react but if there was no reaction, the trial would be deemed to be approved. This approval would be valid for the duration of the trial.

Major pharmaceutical innovations rely, for the demonstration of safety and efficacy on multi-centre clinical trials. Recent publications have illustrated that a base of 2000 to 3000 human subjects would not be exceptional in the development of a new active substance. As such clinical trials are conducted in universities, hospitals or clinics, none of which would individually be capable of recruiting the required number of subjects, up to 50 or 60 centres would be involved in a single trial. In the European Union these centres are spread across more than one Member State. Initially the possibility for a single procedure for the commencement of trans-national clinical trials had been considered. this would have provided the possibility whereby, at the request of the sponsor, a single application could have been submitted to the recently established European Agency for the Evaluation of Medicinal Products. However, concerns were raised that the experiences of Good Clinical Practices and the extent of co-operation between Member States in this area were thus far insufficient to provide a basis for a Community procedure at this time. The Commission regrets that it therefore was not possible to propose such a Community dimension in this proposal, but would wish to revisit this aspect when some experience has been gained.

It is important that on-going information on clinical trials be available to all competent authorities. Thus selected elements of the initial application, as well as amendments to the trial along with the summary notification of the end of the trial, whether this is due to an early interruption of the trial or in line with the anticipated duration, would be registered in a database, accessible only to competent authorities. Equally, the information to be submitted to Member States prior to commencement of a clinical trial is to be harmonised, both in content and format, thus ensuring that all Member States receive the same information. Included as part of this information is the necessary toxicological and pharmacological tests in animals performed as a pre-determination of risk for human health.

The potential for risk to the environment which may be associated with investigational medicinal products containing or consisting of genetically modified organisms needs to be subjected to an environmental risk assessment similar to that provided for by Directive 90/220/EEC on the deliberate release into the environment of genetically modified organisms. The Report[1] on the review of Directive 90/220/EEC is favourable to the 'verticalisation' of part B as this would allow for more efficient and sector-adapted approaches. Also, it seems likely in the future that the pharmaceutical sector would be a sector where this would be particularly relevant. Thus once appropriate experience has been gained, this Directive would be reconsidered with a view to verticalising the assessment of part B of Directive 90/220/EEC.

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[1] COM(96) 630 final

Currently, trials undertaken in other Member States are not required to be notified, thus there is a gap in the information available to competent authorities - this is particularly the case for multi-centre trials. Given the importance of this information, including for the marketing authorisation assessment process, the need to exchange information on clinical trials becomes evident. Therefore the establishment of a database repository capable of providing access to the above-mentioned data elements and accessible to all competent authorities is provided for.

In the pharmaceutical sector, an electronic network linking the competent authorities of the Member States, the European Agency for the Evaluation of Medicinal Products and the Commission is being established under the name EudraNet. Within this the exchange of summary information on clinical trials can readily be achieved and the possibility for electronic transmission of information by sponsors could also be explored. Further, this exchange would benefit the equivalence of the evaluation process conducted in the Member States such that there can be mutual confidence and trust in the conduct of clinical trials.

6. GOOD MANUFACTURING PRACTICE

In Directive 65/65/EEC, article 2, and in Article 34 of Directive 75/319/EEC an exemption from chapters II to V of the Directive 65/65/EEC is provided for 'medicinal products intended for research and development trials'. Thus such medicinal products do not require a marketing authorisation, and their manufacture has not been subjected to a manufacturing authorisation, nor do the labelling provisions apply. Nonetheless, all Member States agreed, at the time that the Commission Directive 91/356/EEC was adopted that the principles of Good Manufacturing Practice should be complied with in the manufacture of medicinal products intended for use in clinical trials. Many Member States have introduced this requirement in their national legislation.

In order to avoid differing requirements which are particularly problematic in the case of multi-centre multi-Member State clinical trials, the proposal applies the principles of Good Manufacturing Practice to investigational medicinal products, including a manufacturing authorisation from the competent authority.

Equally the provisions for labelling need to be codified so as to ensure that investigational medicinal products can move across national boundaries. The Commission's working party of Inspectors had already considered these issues, and had prepared a guideline (III/3004/91 of 22.12.92) which recommended minimum information for inclusion in the label. To support the application of GMP, the annex to the Guide for Good Manufacturing Practice is being revised to include an updating of the guideline III/3004/91 and will be available shortly.

Because of the (sometimes) small quantities required for a clinical trial, many investigational medicinal products are manufactured in laboratories or even hospital pharmacies. The progressive application of the training requirements of the 'qualified person' as set out in article 23 of Directive 75/319/EEC would avoid disruption of the current supplies of such products and therefore a special derogation is provided for.

7. VERIFICATION OF COMPLIANCE

The concept of GCP serves to emphasise the need for and importance of a clear paper trail of the clinical trial, from its inception to its completion and analysis. Implicit in the requirement that clinical trials meet the standard of GCP is the need for audit of the study. Audit may be carried out by an independent internal unit of the sponsor or by external contractors. An audit certificate should result.

Inspection by the relevant competent authority is an officially conducted audit. Thus the adherence to the standard can be assured. Some Member States have legislative provisions empowering inspection of clinical trial sites and/or sponsors and/or individual patient files. The absence of a Community mechanism of mutual recognition of inspections done by the Member States may cause difficulties in the acceptability of studies carried out in other Member States.

The international acceptability of clinical trials conducted in the Community, particularly by authorities outside the European Community, requires a legislative underpinning of the compliance of clinical trials with the standard of GCP.

Further, in order to achieve optimum protection of health, the resources allocated to pharmaceutical research should not be squandered on obsolete or repetitive tests whether within the Community or in third countries. Therefore, the international harmonisation of technical requirements for the development of medicinal products should continue to be pursued. International fora, including the International Conference on Harmonisation, allow for the scientific establishment of standards which can prevent duplication.

Thus the proposal provides for verification of compliance with GCP on behalf of the Community by inspectors appointed by Member States. The possibility for inspection of trials done outside the Community, the results of which are submitted as part of the marketing authorisation application is also provided for as is a requirement on those subject to inspection to allow inspection.

The need to share knowledge and experience, and to build a system for inspection is evident. The establishment of common criteria for conducting inspection in order to ensure mutual recognition between Member States, the inspection procedures for multi-centre multi-national studies, the qualification of inspectors and the elaboration of inspection reports are practical aspects which would be elaborated in guidelines. As it would not be practicable or an effective use of resources to inspect every trial, inspection of quality systems would be developed. Equally, the inspection report indicating the level of compliance with GCP following inspection would need to be set out.

8. PHARMACOVIGILANCE

It is clear that the same standards of monitoring the safety in use of medicinal products should be used for investigational medicinal products. Thus the provisions for pharmacovigilance are extended to include investigational medicinal products.

In the exercise on codification of the Community legislation relating to medicinal products for human use, the procedures for reporting pharmacovigilance are being rationalised. The updated procedures for reporting have thus been incorporated in this proposal.

9. INTERNATIONAL HARMONISATION

A process of technical harmonisation of technical requirements for pharmaceutical has been on-going for the last number of years. This is called International Conference on Harmonisation (ICH). Within ICH, a Good Clinical Practice guideline has been elaborated on the basis of the European guideline of 1990.

In order to maintain international consistency, the definitions of ICH as well as procedures where relevant have been retained in the proposal. The only exceptions are in the terminology for medicinal products (in USA the word 'drug' is frequently used) and in the definition of Independent Ethics Committee where the description of the membership reflects European expressions rather than international ones i.e. *"healthcare* ~~medical/scientific~~ professionals and non-medical/~~(non-scientific)~~ members".

The need to establish international harmonisation of inspection and assurance of compliance with GCP, with the possibility of mutual recognition of inspections, is also recognised and needs to be addressed.

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of .....

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 Directive 65/65/EEC[2] 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 Directive 75/318/EEC [3] lays down 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, 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,

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[2] OJ No L22, 9.2.65, p. 1

[3] OJ No L147, 9.6.75, p.1

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;

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;

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;

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;

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[4].

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 unacceptable level of risk;

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';

HAVE ADOPTED THIS DIRECTIVE:

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[4] OJ No L281, 23.11.95, p.31

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.

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.

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.

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.

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 investigator 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.

   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.

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.

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 personal data, in particular regarding the information that is given to trial subjects.

CHAPTER III

Commencement of a clinical trial

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.

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.

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 on one occasion only the application 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.

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.

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.

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.

Article 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.

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

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

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

CHAPTER IV

Manufacture, import and labelling of investigational medicinal products

Article 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[5].

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

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[5] OJ No L147, 9.6.75, p.13

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

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.

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.

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.

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 at 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.

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 7 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 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 twelve 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 occurring within their territory to an investigational medicinal product 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.

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.

CHAPTER VII

General provisions

Article 14

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

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

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.

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.

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.

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.

Article 17

This Directive is addressed to the Member States.

Done at XXXX,

For the European Parliament
The President

For the Council
The President

FINANCIAL STATEMENT

1 TITLE OF OPERATION:

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

2 BUDGET HEADING INVOLVED:

B-5 3000

3 LEGAL BASIS:

Article 100a of the Treaty establishing the European Community.

4 DESCRIPTION OF OPERATION

4.1 General objective:

To contribute to achieving the objectives laid down by the Treaty:

- ensuring a high-level of human health protection particularly for human subjects in clinical trials for new medicinal products;
- harmonisation of the Member States' requirements in order to avoid duplication of effort and waste of resource.

4.2 Period covered and arrangements for renewal:

After the adoption of the Directive, the Commission would have a delegation of power to introduce a Commission Directive on Good Clinical Practice (technical standards). This could be foreseen for 1999.

5 CLASSIFICATION OF EXPENDITURE OR REVENUE

5.1 Compulsory/Non-compulsory expenditure

Some expert working parties (see 7.1) - non-compulsory expenditure

5.2 Differentiated/Non-differentiated appropriations

Differentiated appropriation (B5-3000)

5.3 Type of revenue involved:

There are no receipts following this action.

6 TYPE OF EXPENDITURE OR REVENUE

Technical work directly linked to the preparation of the Commission Directive through the Regulatory Committee procedure (A).

Technical work in the development of guidelines - working parties of experts from Member States (B).

7 FINANCIAL IMPACT

7.1 Method of calculating total cost of operation (relation between individual and total costs):

The expected cost could be estimated on the basis of number of meetings:

(a) Preparation of the proposal: -

- expert working parties (2 meetings in 1997, and in 1998);
- consultation of the Pharmaceutical Committee (during a regular meeting).

(b) Action following adoption of the proposal: -

- Regulatory Committee for adoption of the Commission Directive (1 meeting in 1999);
- expert working groups (on average, 2 meetings per annum)

7.2 Itemised breakdown of cost

Commitment appropriations ECU million (at current prices)

Break-down	1997	1998	1999	2000	2001	2002	Total
a	50,000	50,000					100,000
b			75,000	50,000	50,000	50,000	225,000
Total	50,000	50,000	75,000	50,000	50,000	50,000	325,000

7.3 Operational expenditure for studies, experts etc. included in Part B of the budget

Publication of guidelines supporting the operation and implementation of the directive which would be included in the 'Rules governing medicinal products in the European Union' as part of volume 3. Therefore there is no additional cost (already covered by the annual budget for publications).

7.4 Schedule of commitment and payment appropriations

ECU million

	1997	1998	1999	2000	2001	2002 and subs. yrs	Total
Commitment appropriations	50,000	50,000	75,000	50,000	50,000	50,000	325,000
Payment appropriations							
1997	50,000						50,000
1998		50,000					50,000
1999			75,000				75,000
2000				50,000			50,000
2001					50,000		50,000
2002 and subs. yrs						50,000	50,000
Total							325,000

8 FRAUD PREVENTION MEASURES

The normal measures for control of expenditure, used for meetings, will apply.

9 ELEMENTS OF COST-EFFECTIVENESS ANALYSIS

9.1 Specific and quantified objectives; target population

Delays in the initiation of multi centre clinical trials have been identified by the pharmaceutical industry as well as bodies such as the European Organisation for Research and Treatment of Cancer (EORTC). A memorandum regarding these delays and the disadvantages of collaborative clinical research in Europe as compared to the U.S. have pointed to delays of up to six months in the initiation of research.

The Industrial Research and Development Advisory Committee of the European Commission (IRDAC) has proposed that future legislation for the initial testing of new medicinal products should be standardised throughout the EC - the establishment of a fast-acting procedure for approving and facilitating the initiation of clinical trials would make clinicalresearch more efficient n Europe (a rough guide to cost of clinical research is 2.5 million ECU per month).

The proposal also includes measures to improve both of these problems and aims at contributing towards ensuring a high level of health protection for human subjects in clinical trials.

9.2 Grounds for the operation

This proposal is designed to harmonise the legislative provisions relating to the conduct of clinical trials for medicinal products for human use. It incorporates internationally established standards and principles of protection for the human subject, streamlines the administrative procedures for initiating a clinical trial, harmonises the reporting procedures for on-going safety monitoring and introduces surveillance measures through inspection.

The technical harmonisation required to achieve the Single market for pharmaceuticals was completed in 1992. As part of this process, clinical trials which have been conducted in accordance with Community rules do not require to be repeated within the Community.

For the protection of European citizens who participate in clinical trials, the principles of Good Clinical Practices which find their origin in the Declaration of Helsinki are a fundamental requirement. The EC guidelines on Good Clinical Practice (GCP), adopted by the Committee for Proprietary Medicinal Products in July '90, was acclaimed internationally as setting out, in a clear and concise manner, the standard for GCP. This was further evidenced by the GCP of the World Health Organisation which was largely based on the Community text. In addition, the European guideline provided the framework for a tripartite GCP guideline between the EC, the USA and Japan within the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH).

Recent reports and correspondence have highlighted real difficulties in the area of clinical development of new medicinal products particularly delays in the initiation of multi centre clinical trials (ethics committee opinion and competent authority acceptance); manufacture and labelling of investigational medicinal products; demonstration of compliance to GCP. These delays can cost industry up to six months delay (at an average of 1 million ECU per month).

9.3 Monitoring and evaluation of the operation

Evaluation will be by means of tracking implementation of Community legislation in Member States and monitoring the rate of development of new medicinal products.

10 ADMINISTRATIVE EXPENDITURE (SECTION III, PART A OF THE BUDGET)

Actual mobilization of the necessary administrative resources will depend on the Commission's annual decision on the allocation of resources, taking into account the number of staff and additional amounts authorized by the budgetary authority.

10.1 Effect on the number of posts

Type of post		Staff to be assigned to managing the operation		Source		Duration
		Permanent posts	Temporary posts	Existing resources in the DG or department concerned	Additional resources	
Officials or temporary staff	A B C	0.25		Yes		on-going
Other resources						
Total						

If additional resources are required, indicate the pace at which they will have to be made available.

10.2 Overall financial impact of additional human resources

No additional staff are required.

10.3 Increase in other administrative expenditure as a result of the operation

ECU

Budget heading	Amounts	Method of calculation
B5-3000	Marginal	Publication already exists, additional pages only
Total		

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