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Information and Notices

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(Continued overleaf)

EN

(1) Text with EEA relevance

I

(Information)

COMMISSION

Ecu (1)

7 October 1997

(97/C 306/01)

Currency amount for one unit:

Belgian and Luxembourg franc	40,5277	Finnish markka	5,88483
Danish krone	7,47642	Swedish krona	8,45067
German mark	1,96367	Pound sterling	0,691484
Greek drachma	310,068	United States dollar	1,12242
Spanish peseta	165,882	Canadian dollar	1,54097
French franc	6,60127	Japanese yen	136,778
Irish pound	0,766783	Swiss franc	1,61785
Italian lira	1931,44	Norwegian krone	7,89003
Dutch guilder	2,21183	Icelandic krona	79,7477
Austrian schilling	13,8192	Australian dollar	1,54987
Portuguese escudo	200,273	New Zealand dollar	1,75652
		South African rand	5,23439

The Commission has installed a telex with an automatic answering device which gives the conversion rates in a number of currencies. This service is available every day from 3.30 p.m. until 1 p.m. the following day.

Users of the service should do as follows:

— call telex number Brussels 23789,

— give their own telex code,

— type the code 'cccc' which puts the automatic system into operation resulting in the transmission of the conversion rates of the ecu,

— the transmission should not be interrupted until the end of the message, which is marked by the code 'ffff'.

Note: The Commission also has an automatic fax answering service (No 296 10 97/296 60 11) providing daily data concerning calculation of the conversion rates applicable for the purposes of the common agricultural policy.

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(1) Council Regulation (EEC) No 3180/78 of 18 December 1978 (OJ L 379, 30. 12. 1978, p. 1), as last amended by Regulation (EEC) No 1971/89 (OJ L 189, 4. 7. 1989, p. 1).

Council Decision 80/1184/EEC of 18 December 1980 (Convention of Lomé) (OJ L 349, 23. 12. 1980, p. 34).

Commission Decision No 3334/80/ECSC of 19 December 1980 (OJ L 349, 23. 12. 1980, p. 27).

Financial Regulation of 16 December 1980 concerning the general budget of the European Communities (OJ L 345, 20. 12. 1980, p. 23).

Council Regulation (EEC) No 3308/80 of 16 December 1980 (OJ L 345, 20. 12. 1980, p. 1).

Decision of the Council of Governors of the European Investment Bank of 13 May 1981 (OJ L 311, 30. 10. 1981, p. 1).

Information procedure — technical regulations

(97/C 306/02)

(Text with EEA relevance)

— Directive 83/189/EEC of 28 March 1983 laying down a procedure for the provision of information in the field of technical standards and regulations
(OJ L 109, 26. 4. 1983, p. 8).

— Directive 88/182/EEC of 22 March 1988 amending Directive 83/189/EEC
(OJ L 81, 26. 3. 1988, p. 75).

— Directive 94/10/EC of the European Parliament and the Council of 23 March 1994 materially amending for the second time Directive 83/189/EEC
(OJ L 100, 19. 4. 1994, p. 30).

Notifications of draft national technical regulations received by the Commission.

Reference (1)	Title	End of three-month standstill period (2)
97/376/DK	Act 361 of 2 June 1997 amending the Act on the registration tax for motor vehicles, etc. (change in the deduction for safety cushioning, index-regulating, etc.)	24. 10. 1997
97/476/B	Ministerial Decree establishing the conditions for the protected area	19. 8. 1997
97/477/F	Order on the elimination of amalgam waste from dental surgeries	5. 11. 1997
97/478/NL	Decree implementing Article 1 (4) of the 1982 Pesticides Act (Article 1)	6. 11. 1997
97/479/NL	Draft implementing Decree 1989/2 on quality standards (trading ban on dahlia seed)	7. 11. 1997
97/480/NL	Decree regulating the dumping of liquids into the soil (Dumping Decree on soil protection)	6. 11. 1997
97/484/NL	Decree designating protected indigenous animal and plant species (Decree relating to protected indigenous animal and plant species)	7. 11. 1997
97/485/NL	Weights and measures Regulation on weights	10. 11. 1997

(1) Year — registration number — Member State of origin.
(2) Period during which the draft may not be adopted.
(3) No standstill period since the Commission accepts the grounds of urgent adoption invoked by the notifying Member State.
(4) No standstill period since the measure concerns technical specifications or other requirements linked to fiscal or financial measures, pursuant to the third indent of the second paragraph of Article 1 (9) of Directive 93/189/EEC.
(5) Information procedure closed.

The Commission draws attention to the judgment given on 30 April 1996 in the 'CIA Security' case (C-194/94), in which the Court of Justice ruled that Articles 8 and 9 of Directive 83/189/EEC are to be interpreted as meaning that individuals may rely on them before the national court which must decline to apply a national technical regulation which has not been notified in accordance with the Directive.

This judgment confirms the Commission's communication of 1 October 1986 (OJ C 245, 1. 10. 1986, p. 4).

Accordingly, breach of the obligation to notify renders the technical regulations concerned inapplicable, so that they are unenforceable against individuals.

Information on these notifications can be obtained from the national administrations, a list of which was published in *Official Journal of the European Communities* C 324 of 30 October 1996.

Non-opposition to a notified concentration

(Case No IV/M.976 — Banco Santander/San Paolo/Finconsumo)

(97/C 306/03)

(Text with EEA relevance)

On 15 September 1997, the Commission decided not to oppose the above notified concentration and to declare it compatible with the common market. This decision is based on Article 6 (1) (b) of Council Regulation (EEC) No 4064/89. The full text of the decision is available only in English and will be made public after it is cleared of any business secrets it may contain. It will be available:

— as a paper version through the sales offices of the Office for Official Publications of the European Communities (see list on the last page),

— in electronic form in the 'CEN' version of the Celex database, under document number 397M0976. Celex is the computerized documentation system of European Community law; for more information concerning subscriptions please contact:

EUR-OP,
Information, Marketing and Public Relations (OP/4B),
2, rue Mercier,
L-2985 Luxembourg,
tel: (352) 29 29 424 55, fax: (352) 29 29 427 63.

Initiation of proceedings

(Case No IV/M.950 — Hoffmann-LaRoche/Boehringer Mannheim)

(97/C 306/04)

(Text with EEA relevance)

On 2 October 1997, the Commission decided to initiate proceedings in the above-mentioned case after finding that the notified concentration raises serious doubts as to its compatibility with the common market. The initiation of proceedings opens a second phase investigation with regard to the notified concentration. The decision is based on Article 6 (1) (c) of Council Regulation (EEC) No 4064/89.

The Commission invites interested third parties to submit their observations on the proposed concentration.

In order to be fully taken into account in the procedure, observations should reach the Commission not later than 15 days following the date of this publication. Observations can be sent by fax ((32-2) 296 43 01/296 72 44) or by post, under reference IV/M.950 — Hoffmann-LaRoche/Boehringer Mannheim, to:

European Commission,
Directorate-General for Competition (DG IV),
Directorate B — Merger Task Force,
Avenue de Cortenberg/Kortenberglaan 150,
B-1040 Brussels.

Prior notification of a concentration

(Case No IV/M.1001 — Preussag/Hapag-Lloyd)

(Case No IV/M.1019 — Preussag/TUI)

(97/C 306/05)

(Text with EEA relevance)

1. On 30 September 1997, the Commission received notification of two proposed concentrations pursuant to Article 4 of Council Regulation (EEC) No 4064/89 [1], (a) by which the undertaking Preussag AG (D) acquires within the meaning of Article (1) (b) of the Regulation control of the whole of the undertaking Hapag-Lloyd AG (D) by way of purchase of securities; (b) the undertaking Preussag AG acquires within the meaning of Article 3 (1) (b) of the Regulation control of the undertaking Touristik Union International GmbH & Co. KG (TUI) by way of a contract concerning the execution of the voting rights which the undertaking Westdeutsche Landesbank Girozentrale (WestLB) has in the undertaking TCT Touristik Beteiligungs GmbH & Co. KG as far as this companies' interest of 30 % in TUI is concerned.

2. The business activities of the undertakings concerned are:

— Preussag AG: production of steel and hardcoal, energy and raw materials, trade and logistic, mechanical engineering and shipbuilding, building equipment, transports,

— Hapag-Lloyd: container shipping, tourist charter flights, transport and logistic, travel agencies. Holding of a 30 % interest in the TUI,

— TUI: tour operator.

3. On preliminary examination, the Commission finds that the notified concentration could fall within the scope of Regulation (EEC) No 4064/89. However, the final decision on this point is reserved.

4. The Commission invites interested third parties to submit their possible observations on the proposed operation.

Observations must reach the Commission not later than 10 days following the date of this publication. Observations can be sent by fax ((32-2) 296 43 01 or 296 72 44) or by post, under reference IV/M.1001 — Preussag/Hapag-Lloyd, IV/M.1019 — Preussag/TUI, to:

European Commission,
Directorate-General for Competition (DG IV),
Directorate B — Merger Task Force,
Avenue de Cortenberg/Kortenberglaan 150,
B-1040 Brussels.

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[1] OJ L 395, 30. 12. 1989; corrigendum: OJ L 257, 21. 9. 1990, p. 13.

STATE AID

C 10/94 (ex NN 104/93)

Greece

(97/C 306/06)

(Text with EEA relevance)

(Articles 92 to 94 of the Treaty establishing the European Community)

Communication from the Commission, pursuant to Article 93 (2) of the EC Treaty to the other Member States and interested parties concerning aid which the Greek Government plans to grant to Hellenic shipyard plc

In the letter reproduced below, the Commission notified the Greek Government of its decision to terminate the procedure initiated on 16 February 1994 [1] and extended on 8 January 1997 [2].

'Article 10 of Council Directive 90/684/EEC [3] provides, in its second paragraph, that "during 1991, operating aid for shipbuilding, ship conversion and ship repair not related to new contracts may be considered compatible with the common market if granted for the financial restructuring of yards in connection with a systematic and specific restructuring programme linked to the disposal by sale of the yards."

On 23 December 1992 [4], on the basis of the undertakings given by the Greek Government that its public yards would be privatized by 31 March 1993, the Commission accepted that the write off of the debts of the four yards affected by Article 10 — in the amounts notified to it — was compatible with the said provisions.

The Greek Government having failed to respect the March 1993 deadline, on 16 February 1994 [5], the Commission decided to initiate proceedings pursuant to Article 93 (2) of the EC Treaty in respect of the operating aid given by Greece to the two yards that at that time were still under State ownership, i.e. the Hellenic and the Neorion shipyards.

After the Neorion yard was privatized, on 26 July 1995 [6], the Commission decided to close the procedure under Article 93 (2), of the EC Treaty, with a positive decision for the aid to the Neorion yard and a negative decision concerning the aid to the Hellenic yard.

However, at the request of the Greek Government, claiming that the sale of the yard was imminent, the Commission decided to suspend notification of that decision. In its September 1995 meetings the Commission twice put off execution of the July 1995 decision.

49 % of the shares in the yard were sold on 18 September 1995 to a co-operative of the yard's workers. Greece thus made use of the opportunity to keep a majority holding in one of the yards, justified by defence reasons as provided for in Article 10 (3).

On 31 October 1995 [7], the Commission took a new decision by which it approved the aid to the Neorion yard and revoked the final negative decision for Hellenic Shipyards. As regards this yard, it requested that a business plan proving the viability and profitability of the yard be submitted not later than 11 January 1996.

The plan was notified as requested. The conditions set in Article 10 of the Directive and in the October 1995 Commission Decision for approval of the aid were met. However, as regards the level of debts to be cleared, these had increased considerably due to interests and penalties on the initial Dr 44 billion approved by the Commission in 1992. The new debts are part of the liabilities of the yard. The Commission considered that aid to cover new debts constituted new aid.

On 8 January 1997 [8] based on this assessment, the Commission decided to extend the existing procedure that covered the initial aid amount of Dr 44 billion to the Hellenic shipyard to the total amount of aid for clearance of debts at the moment of privatization. No comments from third parties were received in the context of this extension of procedure.

[1] OJ C 138, 20. 5. 1994.
[2] OJ C 80, 13. 3. 1997, p. 8.
[3] OJ L 380, 31. 12. 1990.
[4] OJ C 88, 30. 3. 1993.
[5] OJ C 138, 20. 5. 1994.
[6] PV(95) 1258, 26. 7. 1995, SEC(95) 1322/2, 24. 7. 1995.
[7] OJ C 68, 6. 3. 1996.
[8] OJ C 80, 13. 3. 1997, p. 8.

By letter dated 20 February 1997, Greece presented its comments and informed the Commission of the exact amount of debts to be written off, for which the Commission's approval is necessary. The current debts of the yard amount to Dr 112,6 billion. Out of this amount, Dr 11,765 billion concern current business of the yard and will remain in its accounts. Dr 46,355 billion correspond to credits for the building of military vessels, activity which is outside the scope of the EC Treaty. This leaves Dr 54,525 billion (Dr 10,525 billion higher than the amount initially approved), that constitutes aid and which the Greek Government cannot write off without the Commission's prior approval. The Commission could not give this approval on the basis of the provisions of the 7th Directive.

On 2 June 1997, Council Regulation (EC) No 1013/97 of 2 June 1997 on aid to certain shipyards under restructuring (*) was adopted. Article 1 (3) of this regulation provides that aid in the form of a waiver-of debts of "Hellenic shipyards", up to the amount of Dr 54,525 billion, corresponding to debts related to civil work of the yard as existing on 31 December 1991 and accrued by interest rates and penalties until 31 January 1996, may be regarded as compatible with the Treaty.

As requested by the Commission, a business plan was received on 11 January 1996. This plan was drawn up by an international, independent consultant and aims at restoring the financial and economic viability of the yard. In September 1996, management of the yard was awarded, through open bid procedure, to an independent private company with the special task of implementing that plan.

(*) OJ L 148, 6. 6. 1997, p. 1.

The business plan aims at restoring the competitiveness of the yard through increased productivity and modernization. The yard is expected to return to profitability in 1998. The main elements of the plan are a labour restructuring programme and an investment one. The number of employees is to be reduced from 2 966 to 2 000 and work is to be organized in a more flexible and rational way. Investments will be made to replace old and obsolete equipment with new updated technology. As a result, an increase in productivity is expected which will allow the yard to compete successfully with other yards both at national and at international level.

At present, the plan is being implemented according to schedule in the areas of labour organization and management. The investment programme has not yet started, due to the fact that the yard's liabilities reduce its credit-worthiness, thus hindering the yard from raising funds in the market for the necessary financing. Once it is executed, the ongoing restructuring should be completed and the yard should return to viability.

Finally, the Commission notes that Regulation 1013/97 was adopted by the Council with the condition that no further operating aid for restructuring purposes will be made available for the yards covered by the regulation. Accordingly, no such restructuring aid can be granted to this yard in future.

In light of the above, the Commission has decided to close the procedure pursuant to Article 93 (2) by authorizing the aid subject to the conditions described in this letter. Should the Commission consider that any of these conditions have not been complied with, it may require the suppression and/or recovery of the aid.'

Standing invitation to tender pursuant to Commission Regulation (EEC) No 570/88 of 16 February 1988 on the sale of butter at reduced prices and the granting of aid for butter and concentrated butter for use in the manufacture of pastry products, ice-cream and other foodstuffs

(97/C 306/07)

(See notice in Official Journal of the European Communities *No L 55 of 1 March 1988, page 31)*

Tender No: 215

Date of Commission Decision: 30 September 1997

(ECU/100 kg)

Formula			A/C—D		B	
Incorporation procedure			With tracers	Without tracers	With tracers	Without tracers
Minimum price	Butter ≥ 82 %	Unaltered	—	—	—	—
		Concentrated	—	—	—	—
Processing security		Unaltered	—		—	
		Concentrated	—		—	
Maximum aid amount	Butter ≥ 82 %		125	121	—	—
	Butter < 82 %		120	116	—	—
	Concentrated butter		154	150	154	150
	Cream		—	—	54	—
Processing security	Butter		138	—	138	—
	Concentrated butter		170	—	170	—
	Cream		—	—	60	—

Communication of Decisions under sundry tendering procedures in agriculture (milk and milk products)

(97/C 306/08)

(See notice in Official Journal of the European Communities *No L 360 of 21 December 1982, page 43)*

(ECU/100 kg)

Standing invitation to tender	Tender No	Date of Commission Decision	Maximum aid	End-use security
Commission Regulation (EEC) No 429/90 of 20 February 1990 on the granting by invitation to tender of an aid for concentrated butter intended for direct consumption in the Community (OJ No L 45, 21. 2. 1990, p. 8)	175	30. 9. 1997	179	197

Communication of Decisions under sundry tendering procedures in agriculture (milk and milk products)

(97/C 306/09)

(See notice in Official Journal of the European Communities *No L 360 of 21 December 1982, page 43)*

(ECU/100 kg)

Standing invitation to tender	Tender No	Date of Commission Decision	Minimum selling price	Processing security
Commission Regulation (EEC) No 3398/91 of 20 November 1991 on the sale by invitation to tender of skimmed-milk powder for the manufacture of compound feedingstuffs and amending Regulation (EEC) No 569/88 (OJ No L 320, 22. 11. 1991, p. 16)	94	30. 9. 1997	205,52	45,00

II

(Preparatory Acts)

COMMISSION

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

(97/C 306/10)

(Text with EEA relevance)

COM(97) 369 final — 97/0197(COD)

(Submitted by the Commission on 4 September 1997)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

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

Having regard to the proposal from the Commission,

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

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

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

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

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

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 jeopardizing 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;

(1) OJ 22, 9. 2. 1965, p. 369/65.
(2) OJ L 147, 9. 6. 1975, p. 1.

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 authorized 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 [1];

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;

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:

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.

[1] OJ L 281, 23. 11. 1995, p. 31.

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 organization'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 authorization when used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about an authorized 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 organization 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) impatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Sponsor: An individual, company, institution, or organization which takes responsibility for the initation, 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 investigating team, where further information may be obtained.

Ethics Committee opinion

Article 4

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

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 authorize 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 authorize 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.

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 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.

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 authorization referred to in Article 16 of Council Directive 75/319/EEC [1].

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

3. A person engaging in the activities of a 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.

[1] OJ L 147, 9. 6. 1975, p. 13.

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 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 seven days after first knowledge by the sponsor that a case qualifies. All other serious adverse reactions that are not fatal or life-threatening shall be reported as soon as possible but no later than within 15 days. The sponsor shall also inform all investigators.

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

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

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

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

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.