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LEGISLATIVE DECREE no. 211 of 24 June 2003

Transposition of Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for clinical use.

(Official Gazette no. 184 of 9/8/2003, Ordinary Supplement no. 130)

THE PRESIDENT OF THE REPUBLIC

Having regard to articles 76 and 87 of the Constitution;

Having regard to Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use;

Having regard to Statute no. 39 of 1 March 2002 containing terms relating to the fulfilment of obligations deriving from Italy's membership of the European Community, and in particular to Annex A and section 1.5 thereof;

Having regard to Presidential Decree no. 439 of 21 September 2001 which simplifies the procedures for checking and testing new systems and experimental therapeutic protocols;

Having regard to the preliminary resolution passed at the Cabinet meeting held on 12 March 2003;

Having regard to the opinion of the Permanent Conference for relations between the State, Regional Councils and the Autonomous Provincial Councils of Trento and Bolzano;

Having heard the opinion of the relevant Commissions of the Chamber of Deputies and the Senate of the Republic;

Having regard to the resolution passed at the Cabinet meeting held on 6 June 2003;

On the proposal of the Minister for Community Policies and the Minister of Health, by agreement with the Foreign Affairs, Justice, Economy, Finance and Regional Affairs Ministers;

HEREBY ISSUES
the following Legislative Decree:

Section 1.

Scope

1. This Legislative Decree establishes specific provisions regarding the conduct of clinical trials, including multi-centre trials, on human subjects involving medicinal products as defined in section 1 of Legislative Decree no. 178 of 29 May 1991, in particular relating to the implementation of good clinical practice. This Decree does not apply to non-interventional trials or observational studies.

2. Good clinical practice is a set of internationally recognised ethical and scientific quality requirements, which must be observed for designing, conducting, recording and reporting clinical trials that involve the

participation of human subjects. Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible.

3. Detailed guidelines conforming to the said principles are established by decree of the Minister of Health, which transposes the principles of good clinical practice adopted by the European Commission into Italian national legislation.

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

5. Incentives and financial benefits may not be offered, paid or requested for participation by subjects in clinical trials; however, compensation may be paid to healthy volunteers. If the trial sponsor is a public body, compensation may only be granted within the limits of the budget allocated to it.

6. The results of clinical trials not conducted in accordance with the rules of good clinical practice will not be considered for the purpose of issuing marketing authorisation.

Section 2.

Definitions

1. For the purpose of this Legislative Decree, the following definitions shall apply:

a) “clinical trial”: any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy. This definition includes clinical trials conducted at a single centre or a number of centres, only in Italy or also in other member states of the European Union;

b) “multi-centre clinical trial”: a clinical trial conducted according to a single protocol but at more than one centre, and therefore by more than one investigator; the trial centres may be located only in Italy, or also in other Member States of the European Union and/or third countries;

c) “non-interventional trial (observational study)”: a study where the medicinal product(s) is (are) prescribed in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data;

d) “investigational medicinal product”: a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form;

e) “trial sponsors”: an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial;

f) “investigator”: a doctor or dentist qualified for investigations, who is responsible for the conduct of the clinical trial at a given centre. If a trial is conducted by a team of individuals at a trial centre, the investigator is the leader responsible for the team and may be called the “principal investigator”;

g) “investigator’s brochure”: a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in human subjects;

h) “protocol”: a document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial; the term “protocol” refers to the protocol, successive versions of the protocol and protocol amendments;

i) “subject”: an individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control;

l) “informed consent”: decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative or by an authority, individual or organisation in accordance with the relevant legislation. If the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in current legislation;

m) “ethics committee”: an independent body, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing 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 investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent;

n) “inspection”: the conduct by the Ministry of Health and/or the regulatory authorities of other countries of an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the said authorities to be relevant. The inspection may be conducted at the trial centre, at the sponsor’s and/or contract research organisation’s facilities, or at other establishments that the said authorities see fit to inspect;

o) “adverse event”: any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment;

p) “adverse reaction”: all untoward and unintended responses to an investigational medicinal product related to any dose administered;

q) “serious adverse event or serious adverse reaction”: any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect;

r) “unexpected adverse reaction”: an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator’s brochure for an investigational product or summary of product characteristics for an authorised product);

s) “collaborating centre”: a centre, other than the one in which the coordinating investigator works, which participates in a multi-centre trial;

t) “competent authority”:

1) The Director-General or Legal Officer, pursuant to current legislation, of the public health facilities at which the clinical trial is conducted, or equivalent facilities, as defined by decree of the Minister of Health;

2) The Ministry of Health:

a) in the cases referred to in the Minister of Health’s decree referred to in section 9.5;

b) in relation to the medicinal products listed in section 9.6;

3) The Higher Health Institute in the case of the newly instituted drugs referred to in Presidential Decree no. 43 of 21 September 2001.

Section 3.

Protection of clinical trial subjects

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

a) the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A clinical trial may be initiated only if the Ethics Committee and/or the competent authority, if any, comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored;

b) the trial subject or, when the person is not able to give informed consent, his legal representative has had the opportunity, in a prior interview with one of the investigators, to understand the objectives, risks and inconveniences of the trial, and the conditions under which it is to be conducted and has also been informed of his right to withdraw from the trial at any time;

c) the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him in accordance with Statute no. 675 of 31 December 1996 are safeguarded;

d) the trial subject or, when the person is not able to give informed consent, his legal representative has given his written consent after being informed of the nature, significance, implications and risks of the clinical trial. If the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in current legislation;

(e) the subject may without any resulting detriment withdraw from the clinical trial at any time by revoking his informed consent;

f) provision has been made by the trial sponsor for insurance to cover the third-party liability of the investigator and the sponsors in the event of claims for damages by trial subjects;

g) the trial centre informs trial subjects or their legal representatives of a contact person from whom further information can be obtained.

2. The medical care given to, and medical decisions made on behalf of, subjects shall be the responsibility of an appropriately qualified doctor or, where appropriate, of a qualified dentist.

3. The minimum requirements for insurance policies designed to protect subjects participating in the clinical trials referred to in this Legislative Decree will be established by decree of the Minister of Health, issued by agreement with the Minister for Production Activities. Until such time as the said decree has been issued, trial sponsors shall comply with the obligations set out in sub-section 1f) of this section.

4. If the sponsor is a public body, the cost of the insurance referred to in sub-section 1f) of this section shall be covered by the budget allocated to it.

Section 4.

Clinical trials on minors

1. In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if:

a) the informed consent of the parents, the other parent in the absence of one of them, or the legal representative has been obtained in accordance with current legislation; consent must represent the minor's presumed will and may be revoked at any time, without detriment to continuation of the necessary treatment;

b) the minor has received information according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits;

c) the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in paragraph b) to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or the principal investigator;

d) some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors;

e) the relevant scientific guidelines issued by the European Agency for the Evaluation of Medicinal Products (EMEA) have been followed;

f) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored;

g) the Ethics Committee, with paediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol;

h) the interests of the patient always prevail over those of science and society.

Section 5.

Clinical trials on incapacitated adults not able to give informed legal consent

1. In addition to the requirements specified in section 3, inclusion in clinical trials of incapacitated adults who have not given or not refused informed consent before the onset of their incapacity shall be allowed only if:

a) the informed consent of the legal representative has been obtained; consent must represent the subject's presumed will and may be revoked at any time, without detriment to the subject;

b) the person has received information according to his/her capacity of understanding regarding the trial, the risks and the benefits;

c) the explicit wish of a subject who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical trial at any time is considered by the investigator or where appropriate the principal investigator;

d) no incentives or financial inducements are given except compensation that, if the trial sponsor is a public body, may only be granted within the limits of the budget allocated to it;

e) such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods and relates directly to a life-threatening or debilitating clinical condition from which the incapacitated adult concerned suffers;

f) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress shall be specially defined and constantly monitored;

g) the Ethics Committee, with expertise in the relevant disease and the patient population concerned or after taking advice in clinical, ethical and psychosocial questions in the field of the relevant disease and patient population concerned, has endorsed the protocol;

h) the interests of the patient always prevail over those of science and society;

i) there are grounds for expecting that administering the medicinal product to be tested will produce a benefit to the patient outweighing the risks or produce no risk at all.

2. In cases of temporary incapacity, informed consent to continue the trial must be sought when the patient recovers his/her decision-making capacity.

Section 6.

Ethics Committee

1. The Ethics Committee shall give its opinion, before a clinical trial commences, on any issue requested.

2. In preparing the opinion referred to in section 6.1, the Ethics Committee shall consider, in particular:

a) the relevance of the clinical trial and the trial design;

b) whether the evaluation of the anticipated benefits and risks as required under section 3.1a) is satisfactory and whether the conclusions are justified;

c) the protocol;

d) the suitability of the investigator and supporting staff;

e) the investigator's brochure;

f) the suitability of the medical facilities;

g) the adequacy and completeness of the written information to be given to the subject and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research on persons incapable of giving informed consent as regards the specific restrictions laid down in section 3;

h) provision for indemnity or compensation in the event of injury or death attributable to a clinical trial;

f) provision for insurance to cover the third-party liability of the investigator and the trial sponsor in the event of claims for damages by trial subjects;

l) the amounts and, where appropriate, the arrangements for rewarding or compensating investigators and trial subjects and the relevant aspects of any agreement between the sponsor and the trial centre;

m) the arrangements for the recruitment of subjects and information procedures to disseminate knowledge of the trial in accordance with the rules of good clinical practice and in compliance with current legislation.

3. In the case of single-centre trials, the Ethics Committee shall have a maximum of sixty days from the date of receipt of a valid application filed by the trial sponsor to give its reasoned opinion to the sponsor, the Ministry of Health and the competent authority. In the case of multi-centre trials, the terms of section 7 shall apply.

4. Within the period of examination of the application referred to in section 6.3, the Ethics Committee may send a single request for information supplementary to that already supplied by the trial sponsor; in such case the period laid down in section 6.3 shall be suspended until receipt of the supplementary information.

5. No extension to the period referred to in section 6.3 shall be permissible except in the case of trials involving products for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms. In this case, an extension of a maximum of thirty days shall be permitted. In the case of these products, the period is extended by a further ninety days pending receipt of the authorisation issued by the Ministry of Health. In the case of xenogenic cell therapy, there shall be no time limit to the application evaluation period.

6. The agreement referred to in section 6.2 l) shall be entered into between the Legal Officer of the trial centre or a person appointed by him and the trial sponsor, within the period specified in section 9 for examination of applications by the competent authority, provided that the entry into force of the said agreement shall be conditional on receipt of the favourable opinion referred to in section 6.1, and on performance of the procedures referred to in section 9.

7. Without prejudice to the terms of section 12-bis, sub-section 9 of Legislative Decree no. 502 of 30 December 1992, as amended, the minimum requirements for the institution, organisation and operation of Ethics Committees for clinical trials on medicinal products shall be updated, without variation in costs, by decree of the Minister of Health, issued by agreement with the Economy and Finance Minister.

Section 7

Single opinion

1. In the case of multi-centre clinical trials conducted only in Italy, or in Italy and other countries, the motivated opinion on the trial shall be expressed by the Ethics Committee of the Italian facility in which the coordinating researcher for Italy works, within thirty days of the date of receipt of a valid application filed by the trial sponsor, as specified in section 8; the trial may not begin at any site until the said opinion has been issued.

2. The Ethics Committees involved in the trial may send its comments to the Ethics Committee referred to in section 7.1. The Ethics Committee referred to in section 7.1 shall notify the trial sponsor, the other Ethics Committees involved in the trial and the Ministry of Health of its opinion within thirty days of receipt of a valid application filed by the trial sponsor, as specified in section 8.

3. The favourable opinion may only be accepted or rejected in its entirety by the Ethics Committees of the other Italian centres participating in the trial; the Ethics Committees of all the trial centres may amend the wording of the informed consent applicable to the trial subjects participating at their centre only, and may make participation in the trial conditional on acceptance of the said amendments. The Ethics Committees of the participating centres are responsible for judging all aspects of the protocol. Duly motivated acceptance or rejection of the opinion of the Committee referred to in section 7.1 shall be notified by the committees of the collaborating centres to the trial sponsor, the other committees of the participating centres and the competent authorities, within a maximum of 30 days from the date on which they received the said single opinion.

4. In the case of multi-centre clinical trials, the extensions referred to in section 6.5 are only applicable to the Ethics Committee referred to section 7.1.

Section 8.

Procedure for filing applications for the Ethics Committee's opinion

1. The Ministry of Health, taking account of the detailed guidance published by the European Commission, shall establish by decree the application format and documentation to be submitted by the sponsor in an application for an Ethics Committee opinion as specified in sections 6 and 7, in particular regarding the information that is given to subjects, and on the appropriate safeguards for the protection of personal data.

2. In the case of multi-centre clinical trials, the application referred to in section 8.1 shall also be filed by the trial sponsor at the same time with the Ethics Committees of the other centres participating in the trial.

Section 9.

Commencement of a clinical trial

1. The sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion and inasmuch as the competent authorities have not informed the sponsor of any grounds for non-acceptance. If reasoned objections are expressed by local authorities, the impossibility of commencing the trial shall relate to the individual health facility concerned; if the competent authority is the one referred to in section 2.1 t), paragraph 2) or 3), the trial may not be conducted at any centre. The procedures to reach these decisions can be run in parallel or not, depending on the sponsor.

2. Before commencing any clinical trial, the sponsor shall be required to submit a valid request for authorisation to the competent authority as specified in section 9.11 a).

3. If the competent authority notifies the sponsor of grounds for non-acceptance, the sponsor may, on one occasion only, amend the content of the request referred to in section 9.2 in order to take due account of the grounds given. The period referred to in section 9.4 shall be interrupted until the requested amendments are received. If the trial sponsor fails to amend the application as specified within thirty days or the period referred to in section 5.5 of Presidential Decree no. 439 of 21 September 2001, it shall be deemed to be rejected, and the trial may not commence.

4. Examination by the competent authority of a valid request for authorisation as specified in section 9.2 shall be concluded within sixty days, without prejudice to the circumstances referred to in sections 5 and 9 of Presidential Decree no. 439 of 21 September 2001, limited to cases in which the competent authority is the

one referred to in section 2.1 t) 3). However, the competent authority may notify the trial promoter that it has no objection before the expiry of the said period. No further extensions to the said period shall be permissible except in the case of trials involving the medicinal products listed in section 9.6, for which an extension of a maximum of thirty days shall be permitted. For these products, the ninety-day period is extended by a further ninety days if technical evaluations need to be obtained from the bodies specified by current legislation. In the case of xenogenic cell therapy, there shall be no time limit to the application evaluation period.

5. Without prejudice to the terms of section 9.6, written authorisation must be obtained by the trial sponsor before the commencement of clinical trials on medicinal products which do not have a marketing authorisation within the meaning of Legislative Decree no. 178 of 29 May 1991, as amended, and which are indicated for that purpose in a specific list adopted by decree of the Ministry of Health. The said list may only contain the medicinal products referred to in Part A of the Annex to Regulation (EEC) No. 2309/93, and other medicinal products with special characteristics, such as medicinal products the active ingredient or active ingredients of which is or are a biological product or biological products of human or animal origin, or contains biological components of human or animal origin, or the manufacturing of which requires such components.

6. The trial sponsor shall also obtain written authorisation before commencing clinical trials involving medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms. No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity.

7. The authorisation referred to in section 9.6 shall be issued without prejudice to the application of Legislative Decree no. 206 of 12 April 2001 on the contained use of genetically modified micro-organisms and Legislative Decree no. 92 of 3 March 1993 on the deliberate release into the environment of genetically modified organisms.

8. In cases where the authority competent to issue authorisation for trials to which this section refers is the Ministry of Health, the said authorisation will be issued by the Drug Evaluation and Pharmacovigilance Department.

9. In the cases referred to in section 9.8, the applicant for authorisation shall pay a fee to be established within thirty days of the date on which this Decree comes into force by decree of the Minister of Health, pursuant to section 5.12 of Statute no. 407 of 29 December 1990. The income therefrom will be used by the Ministry of Health for the purpose of monitoring clinical trials on medicinal products.

10. The income deriving from the fees referred to in section 9.9 shall be paid into the State Treasury and reallocated to a specific Ministry of Health basic budgetary unit. The Economy and Finance Minister is authorised to make the necessary budget variations by decree.

11. A decree of the Minister of Health, which transposes the detailed guidelines published by the European Commission into Italian national legislation, will establish:

a) the format and contents of the request referred to in section 9.2 as well as the documentation to be submitted to support that request, on the quality and manufacture of the investigational medicinal product, any toxicological and pharmacological tests, the protocol and clinical information on the investigational medicinal product including the investigator's brochure, without prejudice to any further additions defined pursuant to section 4.2 of Presidential Decree no. 439 of 21 September 2001;

b) the presentation and content of the proposed amendments referred to in Section 11.1 a) on substantial amendments made to the protocol;

c) the declaration of the conclusion or termination of the clinical trial.

12. Clinical trials shall be conducted at the facilities already specified in decrees issued by the Minister of Health.

Section 10.

Conduct of a clinical trial

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

a) after the commencement of the clinical trial, or after receiving the favourable opinion of the Ethics Committee, the sponsor may make amendments to the protocol. If those amendments are substantial and are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant in relation to the clinical conduct of the trial, the sponsor shall notify the competent authorities and the Ethics Committee or Committees concerned of the reasons for, and content of, these amendments, in accordance with the procedures laid down in sections 6, 7 and 9. Amendments that do not fall within the terms of the preceding paragraph shall require mere notification to the Ethics Committees; specifications in relation thereto will be established by decree of the Minister of Health. On the basis of the details referred to in section 6.2, in the case of single-centre trials the Ethics Committee shall give an opinion within a maximum of thirty-five days of the date of receipt of the proposed amendment in good and due form. In the case of multi-centre trials, the Ethics Committee referred to in section 7.1 shall issue the said opinion within twenty days and the Committees referred to in section 7.3 may only accept or reject it in its entirety within the next fifteen days. If the Ethics Committee's opinion of the proposed amendment to the protocol is unfavourable, the sponsor may not implement the amendment to the protocol. If the opinion of the Ethics Committee is favourable and the competent authorities have raised no grounds for non-acceptance of the above-mentioned substantial amendments, the sponsor shall proceed to conduct the clinical trial following the amended protocol. Should this not be the case, the sponsor shall either take account of the grounds for non-acceptance and adapt the proposed amendment to the protocol accordingly or withdraw the proposed amendment. If the amendment is filed before the issue of a favourable opinion by the Ethics Committee, except in the event of presentation at the same time as the protocol, the period referred to in sections 6.3, 6.6 and 9.4 shall be extended by thirty-five days to allow evaluation of the amendment; in the case of multi-centre trials the period referred to in section 7.2 shall be extended by twenty days, and the period referred to in section 7.3 shall be extended by fifteen days;

b) without prejudice to point (a), in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. The trial sponsor shall immediately inform the competent authorities and the Ethics Committees of these new facts and the measures taken.

2. Within 90 days of the end of a clinical trial the sponsor shall notify the Ministry of Health, the other competent authorities and the Ethics Committees concerned that the clinical trial has ended by the procedures laid down by decree of the Ministry of Health, taking account of the detailed guidance published by the European Commission. If the trial has to be terminated early or interrupted, this period shall be reduced to 15 days and the reasons clearly explained.

3. A decree issued by the Minister of Health will establish the details of the results of the trial, including trials terminated early, which must be notified to the Monitoring Unit referred to in section 11 for the purpose of making them available to the scientific community, without prejudice to rights of patentability and intellectual integrity.

Section 11.

Exchange of information

1. The Ethics Committees and sponsors shall notify the competent authority, and the Ministry of Health in any event, for the purpose of entry of the following data into national and European databases:

a) extracts from the request for authorisation referred to in section 9.2;

b) any amendments made to the request, as provided for in section 9.3;

c) any amendments made to the protocol, as provided for in section 10.1 a) and b);

d) the favourable opinion of the Ethics Committee;

e) the declaration of the end of the clinical trial.

2. At the substantiated request of any Member State, the European Agency for the Evaluation of Medicinal Products (EMEA) or the Commission, the Ministry of Health shall supply all further information concerning the clinical trial in question other than the data already in the European database, obtaining it from the competent authority to which the request for authorisation was submitted. The Ministry of Health shall enter details of the inspections conducted in accordance with the rules of good clinical practice in the European database.

3. The format, data and procedures for data entry into the European databases operated by the European Commission with the assistance of the European Agency for the Evaluation of Medicinal Products (EMEA), as well as the methods for electronic communication of the data, shall be established by decree of the Ministry of Health, taking account of the detailed guidance published by the European Commission. The detailed guidance thus drawn up shall ensure that the confidentiality of the data is strictly observed.

4. The Clinical Trial Monitoring Unit already operating under the Drug Evaluation and Pharmacovigilance Department as part of the National Monitoring Unit on the Use of Medicinal Products set up pursuant to section 68.7 of Statute no. 448 of 23 December 1998 shall be responsible for the following tasks, using the existing personnel of the said Department and without any additional cost to the State:

a) monitoring and analysis of clinical trials on medicinal products in Italy and drawing up the corresponding reports with regional data to be transmitted to individual regions;

b) liaison with the European central database;

c) support for the activities of local Ethics Committees;

d) drafting of annual and partial reports designed for regional councils and healthcare professionals which describe the state of clinical drug research in Italy in a qualitative and quantitative manner, including on regional and local basis;

e) the conduct, by agreement with regional councils, of training courses for personnel involved in clinical trials on medicinal products.

Section 12.

Suspension of the trial or infringements

1. Where the Ministry of Health has objective grounds for considering that the conditions in the request for authorisation referred to in section 9.2 are no longer met, it may revoke the authorisation and shall notify the sponsor thereof. Where the Ministry of Health has information raising doubts about the safety or scientific validity of the clinical trial, it may suspend or prohibit the clinical trial and shall notify the sponsor thereof. Before the Ministry of Health reaches its decision it shall, except where there is imminent risk, ask the sponsor or the investigator for their opinion, to be delivered within one week; when that period has elapsed, the Ministry of Health shall take its decisions independently.

2. In this case, the Ministry of Health shall forthwith inform the other competent authorities of the other Member States, the Ethics Committee(s) concerned, the European Agency for the Evaluation of Medicinal Products (EMEA) and the European Commission of its decision to suspend or prohibit the trial and of the reasons for the decision.

3. On the grounds and by the procedures referred to section 12.1, the competent authority referred to in section 2.1 t), paragraph 1, may suspend or prohibit the clinical trial at local level after consultation with the authorities of the other centres participating in the trial.

4. In the cases referred to in section 12.3, the competent authorities shall inform the Ministry of Health of their decisions within three working days.

5. Where the Ministry of Health has objective grounds for considering that the sponsor or the investigator or any other person involved in the conduct of the trial no longer meets the obligations laid down, it shall forthwith inform him thereof, indicating the course of action which he must take to remedy this state of affairs. The Ministry of Health shall forthwith inform the Ethics Committee concerned, the competent authorities of the Member States and the European Commission of the said course of action.

6. On the grounds stated in section 12.5, the competent authority referred to in section 2.1 t) paragraph 1 will adapt the same precautionary measures as specified in section 12.5, and shall forthwith inform the Ethics Committee concerned and the Ministry of Health, which will notify the European Commission and the competent authorities of the other Member States.

Section 13.

Manufacture and import of investigational medicinal products

1. The manufacture and import of investigational medicinal products shall be authorised by the Ministry of Health as specified in Legislative Decree no. 178 of 29 May 1991, where applicable, and in other cases as specified by specific decree of the Minister of Health. In order to obtain the said authorisation, the applicant, and subsequently the authorisation holder, shall meet requirements at least equivalent to those to be established by decree of the Minister of Health, taking account of the detailed guidance published by the European Commission. The said requirements shall also be met for the purpose of authorisation to import the said medicinal products.

2. The holder of the authorisation referred to in section 13.1 shall permanently and continuously employ a Plant Manager, who shall be responsible in particular for compliance with the obligations laid down in section 13.3, and shall possess the qualifications laid down in section 4 of Legislative Decree no. 178 of 29 May 1991.

3. The Plant Manager referred to in section 13.2, without prejudice to his relationship with the manufacturer or importer, is responsible for ensuring:

a) in the case of investigational medicinal products manufactured in Italy, that each batch of medicinal products has been manufactured and checked in compliance with the requirements of good manufacturing practice for medicinal products for human use laid down by Community legislation, the product specification file and the information notified pursuant to section 9.2;

b) in the case of investigational medicinal products manufactured in a third country, that each production batch has been manufactured and checked in accordance with standards of good manufacturing practice at least equivalent to those laid down in Community legislation, in accordance with the product specification file, and that each production batch has been checked in accordance with the information notified pursuant to section 9.2;

c) in the case of an investigational medicinal product which is a comparator product from a third country, and which has a marketing authorisation, where the documentation certifying that each production batch has been manufactured in conditions at least equivalent to the standards of good manufacturing practice referred to above cannot be obtained, that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality in accordance with the information notified pursuant to section 9.2.

4. The terms of Annex 13 to the European rules of good manufacturing practice (GMP) shall be complied with when evaluating the products for the purpose of release of the batches. Insofar as the provisions laid down in paragraph (a), (b) or (c) are complied with, investigational medicinal products shall not have to undergo any further checks if they are imported into another Member State of the European Union together with batch release certification signed by the qualified person pursuant to Directive 75/319. In all cases, the Plant Manager must certify in a register that each production batch satisfies the provisions of this section. The said register shall be kept up to date as operations are carried out and shall remain at the disposal of the inspectors who perform the checks referred to in section 7 of Legislative Decree n. 178 of 29 May 1991, for the period of 5 years.

5. The trial authorisation documents to be annexed to the import documentation for investigational medicinal products shall be established by decree of the Minister of Health.

Section 14.

Labelling

1. The particulars to appear at least in Italian on the outer packaging of investigational medicinal products or, where there is no outer packaging, on the immediate packaging, shall be published in the annex to the rules of good manufacturing practice relating to the manufacture of investigational medicinal products.

Section 15.

Verification of compliance of investigational medicinal products with good clinical and manufacturing practice

1. To verify compliance with the provisions on good clinical and manufacturing practice, the Ministry of Health, in the ambit of the administration's existing human resources, shall appoint inspectors to inspect the sites concerned by any clinical trial conducted, particularly the trial centre or centres, the manufacturing site of the investigational medicinal product, any laboratory used for analyses in the clinical trial and/or the sponsor's premises, and any other facilities involved at any stage of the activities connected with trials. The inspections shall be conducted by the Ministry of Health, which shall inform the European Agency for the Evaluation of Medicinal Products (EMEA); they shall be carried out on behalf of the Community and the inspections and results shall be recognised by all the other Member States. The inspectors must undergo a specific training process without any additional cost to the State.

2. The inspections shall be coordinated by the European Agency for the Evaluation of Medicinal Products (EMEA) within the framework of its powers as provided for in Regulation (EEC) no. 2309/93; a Member State may request assistance from another Member State in this matter.

3. Following inspection, an inspection report shall be prepared; it must be made available to the sponsor and the facilities involved while safeguarding confidential aspects. It may be made available to the other Member States, to the Ethics Committee and to the European Agency for the Evaluation of Medicinal Products (EMEA), at their reasoned request. On receipt of the report the competent office of the Ministry of Health will issue any instructions to be followed to ensure that the trial conforms to the rules of good clinical practice.

4. At the request of the European Agency for the Evaluation of Medicinal Products (EMEA), within the framework of its powers as provided for in Regulation (EEC) no. 2309/93, or of one of the Member States concerned, and following consultation with the Member States concerned, the Commission may request a new inspection should verification of compliance with this Directive reveal differences between Member States.

5. Subject to any arrangements which may have been concluded between the Community and third countries, the Commission, upon receipt of a reasoned request from a Member State or on its own initiative, or a Member State may propose that the trial centre and/or the sponsor's premises and/or the manufacturer established in a third country undergo an inspection. The inspection shall be carried out by duly qualified Community inspectors.

6. Guidelines on the documentation relating to the clinical trial, which shall constitute the master file on the trial, archiving, qualifications of inspectors and inspection procedures to verify compliance of the clinical trial in question with this Legislative Decree shall be established by decree of the Ministry of Health taking account of the detailed guidance published by the European Commission.

7. The decree referred to in section 15.6 shall be updated and take account of the revisions adopted by the European Commission.

8. If inspectorates from third countries propose to conduct the inspections referred to in this section at the sites referred to in section 15.1, they shall on each occasion notify the Inspectorate referred to in section 15.14 at least one month before the date scheduled for the inspection; for this purpose, the clinical trial sponsor which receives the inspection shall notify the appropriate inspectorates of the said procedure.

9. The costs of inspections of clinical trials on medicinal products conducted abroad, the results of which are submitted for marketing authorisation in Italy, shall be payable by the company applying for authorisation.

10. The costs of inspections of private organisations to which the sponsor may delegate all or part of its entitlement to conduct clinical trial for industrial purposes, as laid down by the rules of good clinical practice, shall be payable by the said organisations.

11. The terms of section 7.5 of Legislative Decree no. 178 of 29 May 1991 shall apply to personnel who perform the inspections referred to in sections 15.1, 15.2, 15.4, 15.9 and 15.10, including by way of specific differentiated provisions in the periodic updates to the corresponding Ministerial Decree; the costs thereof shall be payable by the pharmaceutical companies and organisations referred to in section 15.10.

12. The fees payable under sections 15.9, 15.10 and 15.11 shall be determined by decree of the Minister of Health, to be issued within thirty days of the date on which this Decree comes into force, pursuant to section 12.5 of Statute no. 407 of 29 December 1990; the proceeds thereof shall be paid into the State Treasury and reallocated to a specific Ministry of Health basic budgetary unit. The Economy and Finance Minister is authorised to make the necessary budget variations by decree.

13. The income deriving from new fees to be established by subsequent decree of the Minister of Health, which shall be subject to the regimen referred to in section 5.12 of Statute n. 407 of 29 December 1990, relating to the inspections referred to in section 7 of Legislative Decree n. 178 of 29 May 1991, shall be used to cover the costs of inspections relating to monitoring of trials whose sponsor is a public or non-profit agency or facility or a non-profit scientific association, and to cover all the costs of implementing the said monitoring which are not otherwise provided for in this section.

14. Activities relating to inspections of the clinical trials of medicinal products referred to in this section shall be performed by the relevant Department, which shall be supported for this purpose by the existing human and material resources of the Ministry of Health, including in the performance of the following tasks:

a) participation in Community activities and those of the European Agency for the Evaluation of Medicinal Products (EMEA), and liaison with other inspectorates in Member States and third countries for the purposes of this section and for the purpose of mutual recognition of inspections in Europe and elsewhere;

b) promotion and implementation of projects designed to provide information for personnel subject to Community inspections.

15. Personnel belonging to private facilities who intend to make use of the activities referred to in section 15.14 b) shall pay a fee to be established by decree of the Minister of Health to be issued within thirty days of the date on which this Decree comes into force, pursuant to section 5 of Statute no. 407 of 29 December 1990. The income deriving from the said fees shall be used to cover the costs referred to in section 15.14 b); the proceeds thereof shall be paid into the State Treasury and reallocated to a specific Ministry of Health basic budgetary unit. The Economy and Finance Minister is authorised to make the necessary budget variations by decree.

Section 16.

Notification of adverse events

1. The investigator shall report all serious adverse events immediately to the sponsor except for those that the protocol or investigator’s brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports.

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

3. For reported deaths of a subject, the investigator shall notify the sponsor and the Ethics Committee and supply any additional information requested.

4. The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator. These records shall be submitted to the Ministry of Health on request.

5. In every communication referred to in this section and in sections 17 and 18 the patient shall always be identified by a unique code.

Section 17.

Notification of serious adverse reactions

1. The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the Ministry of Health and to the Ethics Committee(s) concerned, and in any case no later than seven calendar days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

2. All other suspected serious unexpected adverse reactions shall be reported to the Ministry of Health and to the Ethics Committee(s) concerned as soon as possible, and in any case not later than fifteen days after the date on which they came to the sponsor's knowledge.

3. The investigator shall notify the sponsor forthwith of the reactions referred to in this section.

4. The sponsor shall record all suspected serious unexpected adverse reactions to an investigational medicinal product which come to its knowledge.

5. The sponsor shall also notify the other investigators.

6. Once a year throughout the clinical trial, as specified in section 18, the sponsor shall provide the Ministry of Health and the Ethics Committees concerned with a listing of all suspected serious adverse reactions that have occurred over this period and a report of the subjects' safety.

7. The Ministry of Health shall see to it that all suspected unexpected serious adverse reactions which are brought to its attention are immediately entered in a European database to which, as stated in section 11(1), only the competent authorities of the Member States, the European Agency for the Evaluation of Medicinal Products (EMEA) and the Commission have access.

Section 18.

Guidance concerning reports

1. By decree of the Ministry of Health, taking account of the detailed guidance published by the European Commission, procedures will be established for the collection, verification and presentation of adverse event/reaction reports, together with decoding procedures for unexpected serious adverse reactions.

Section 19.

Obligation to transmit information

1. The sponsor shall promptly transmit the information relating to the clinical trial requested by the competent authorities referred to in section 2.1 t) and by the Ethics Committees.

Section 20.

General provisions

1. The sponsor or a legal representative of the sponsor must be established in the Community.

2. Investigational medicinal products and, as the case may be, the devices used for their administration shall be made available free of charge by the sponsor; no additional cost for the conduct and management of the trials to which this Decree relates shall be charged to public funds.

3. The minimum requirements which must be met by private organisations to which the sponsor delegates all or part of its entitlement to conduct clinical trials as laid down by the rules of good clinical practice, without prejudice to the sponsor's liability for the trial, shall be established by decree of the Minister of Health.

4. General terms and conditions relating to the conduct of clinical trials on medicinal products may be established by decree of the Minister of Health in compliance with European Union directives and recommendations.

Section 21.

Transitional provisions

1. From the date on which this Decree comes into force, administrative deeds which order the exemption of a medicinal product from the checks laid down for the newly instituted medicinal products referred to in the Minister of Health's decree of 18 March 1998, published in the Official Gazette no. 122 of 28 May 1998, shall be revoked.

Section 22.

Sanctions

1. Any party who acts in breach of the prohibition referred to in the first sentence of section 1.5 shall be liable to pay an administrative fine of 50,000 to 150,000 euros.

2. Any party who acts in breach of the terms of section 3.1 a), b), c), d) or f) shall be liable to pay an administrative fine of 20,000 to 60,000 euros.

3. Any party who acts in breach of the terms of section 4.1 a), d) or g) shall be liable to pay an administrative fine of 30,000 to 90,000 euros.

4. Any party who acts in breach of the terms of section 5.1 a) or g) or 5.2 shall be liable to pay an administrative fine of 30,000 to 90,000 euros.

5. A sponsor who commences a clinical trial without obtaining the favourable opinion of the competent Ethics Committee or despite reasoned objections from the competent authorities shall be liable to pay an administrative fine of 100,000 to 500,000 euros.

6. Any party who acts in breach of the terms of section 9.5 or 9.6 shall be ordered to pay an administrative fine of 100,000 to 500,000 euros.

7. Any party who conducts clinical trials in facilities other than those specified in section 9.12 shall be liable to pay an administrative fine of 50,000 to 250,000 euros.

8. Any party who continues a clinical trial on the basis of substantial unauthorised amendments to the protocol shall be liable to pay an administrative fine of 100,000 to 500,000 euros.

9. Any party who acts in breach of the terms of section 12.1 or 12.2 shall be liable to pay an administrative fine of 100,000 to 500,000 euros.

10. The owner or legal representative of a company which commences manufacture of an investigational medicinal product without obtaining the authorisation referred to in section 13.1, or continues its manufacture after revocation or suspension thereof, shall be liable to the sanction laid down in section 23 of Legislative Decree no. 178 of 29 May 1991.

11. A Plant Manager responsible for performing the obligations set out in sections 13.3 a), b) and c) and 13.4 who fails to perform the supervision and certification obligations set out therein shall be liable to pay an administrative fine of 10,000 to 30,000 euros.

12. A sponsor who fails to record some or all of the adverse events reported to it by the investigator pursuant to section 16.4 shall be liable to pay an administrative fine of 20,000 to 60,000 euros.

13. A sponsor who breaches the terms of section 17.1, 17.2 or 17.4 shall be liable to pay an administrative fine of 50,000 to 250,000 euros.

Section 23.

Entry into force

This decree shall come into force on 1 January 2004.

This Decree, bearing the State seal, shall be incorporated in the Official Collection of Legislation of the Republic of Italy. It shall be observed and caused to be observed by all those to whom it applies.

Rome, this 24th day of June 2003

CIAMPI
Berlusconi, Prime Minister
Buttiglione, Minister for Community Policies
Sirchia, Minister of Health
Frattini, Foreign Minister
Castelli, Justice Minister
Tremonti, Economy and Finance Minister
La Loggia, Minister for Regional Affairs

Signed, Lord Chancellor: Castelli