MINISTRY OF PUBLIC HEALTH

ORDER
for approval of Norms relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

Taking into account provisions of Law No. 95/2006 on Healthcare Reform, Title XVII, The medicinal product, of Government Ordinance No. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved with changes and completions through Law No. 594/2002, with further changes and completions,

on seeing the Approval Report of the Pharmaceutical Directorate No. E.N. 2.399 of 25 July 2006,

based on Government Decision No. 862/2006 on organisation and functioning of the Ministry of Public Health,

The minister of public health hereby issues the following order:

Article 1. - The Norms relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use are approved according to the Annex, which is an integral part of the present order.

Article 2. - The present order shall come into on 28 July 2006, when any other contrary dispositions shall be repealed.

Article 3. - The present order shall be published in the Official Gazette of Romania, Part I.

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Norms provided under Article 1 are a transposition of Directive 2001/20/EC of the European Parliament and Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, published in Official Journal of the European Union No. L 121 of 1 May 2001.

Minister of public health,
Gheorghe Eugen Nicolăescu

Bucharest, 25 July 2006
No. 904.

ANNEX

Norms relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

CHAPTER I
Introduction

Article 1. - These Norms transpose the Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use[1)].

CHAPTER II
General principles

Article 2. – Article 702 (4) of Law No. 95/2006 on the healthcare reform, Title XVII, The Medicinal Product requires that applications for authorisation to place a medicinal product on the market should be accompanied by a dossier containing particulars and documents relating to the results of tests and clinical trials carried out on the product, which have to be submitted according to analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products, approved through Minister oh Public Health Order No. 906/2006.

Article 3**.** - (1) The accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration.

(2) The clinical trial subject's protection is safeguarded through risk assessment based on the results of toxicological experiments prior to any clinical trial, screening by ethics committees and the National Medicines Agency, and rules on the protection of personal data.

Article 4. - (1) Persons who are incapable of giving legal consent to clinical trials should be given special protection.

(2) It is incumbent on the National Medicines Agency to lay down rules to this effect.

(3) Such persons may not be included in clinical trials if the same results can be obtained using persons capable of giving consent.

(4) Normally these persons should be included in clinical trials only when there are grounds for expecting that the administering of the medicinal product would be of direct benefit to the patient, thereby outweighing the risks.

(5) However, there is a need for clinical trials involving children to improve the treatment available to them.

(6) Children represent a vulnerable population with developmental, physiological and psychological differences from adults, which make age- and development- related research important for their benefit.

(7) Medicinal products, including vaccines, for children need to be tested scientifically before widespread use; this can only be achieved by ensuring that medicinal products which are likely to be of significant clinical value for children are fully studied.

(8) The clinical trials required for this purpose should be carried out under conditions affording the best possible protection for the subjects. Criteria for the protection of children in clinical trials therefore need to be laid down.

[1)] JO No. L 121 of 1 May 2001, p. 34.

Article 5. - (1) In the case of other persons incapable of giving their consent, such as persons with dementia, psychiatric patients, etc., inclusion in clinical trials in such cases should be on an even more restrictive basis.

(2) Medicinal products for trial may be administered to all such individuals only when there are grounds for assuming that the direct benefit to the patient outweighs the risks.

(3) Moreover, in such cases the written consent of the patient's legal representative, given in cooperation with the treating doctor, is necessary before participation in any such clinical trial.

Article 6**.** - The notion of legal representative may include natural or legal persons, an authority and/or a body provided for by national law (The Code of the Family, as amended by Law No. 59/1993, published in the Official Gazette of Romania, Part I, No. 177 of 26 of July 1993, Law No. 487/2002, the law of mental health and of the persons with psychic disorders protection, published in the Official Gazette of Romania, Part I, No. 589/08.08.2002, with further changes).

Article 7. - (1) In order to achieve optimum protection of health, obsolete or repetitive tests (analyses) will not be carried out in Romania.

(2) The harmonisation of technical requirements for the development of medicinal products should therefore be pursued through the appropriate fora, in particular the International Conference on Harmonisation.

Article 8**.** – In case a clinical trial is developed in Romania, information on the content, commencement and termination of a clinical trial should be available to the National Medicines Agency; in the case of a multicenter trial, it is necessary that all authorities involved have access to the same information, with due regard for the rules of confidentiality.

Article 9. - (1) Clinical trials are a complex operation, generally lasting one or more years, usually involving numerous participants and several trial sites, often in different Member States.

(2) It is therefore necessary to simplify and harmonise the administrative provisions governing such trials by establishing a clear, transparent procedure and creating conditions conducive to effective coordination of such clinical trials by the authorities concerned.

Article 10. - The Rules of good manufacturing practice should be applied to investigational medicinal products.

Article 11. - Special provisions should be laid down for the labelling of the investigational medicinal products.

Article 12. - (1) Non-commercial clinical trials conducted by researchers without the participation of the pharmaceuticals industry may be of great benefit to the patients concerned.

(2) These Rules should therefore take account of the special position of trials whose planning does not require particular manufacturing or packaging if these trials are carried out with medicinal products with a marketing authorisation within the meaning of the and are manufactured or imported in accordance with the provisions of Law No. 95/2006 on healthcare reform, Title XVII, The Medicinal Product, and on patients with the same characteristics as those covered by the indication specified in this marketing authorisation.

(3) Labelling of the investigational medicinal products intended for trials of this nature should be subject to simplified provisions laid down in Annex 11 of the Rules of good manufacturing practice for medicinal products, approved through Minister of Health Order No. 1.058/2003, relating to manufacturing of investigational medicinal products.

Article 13. - The verification of compliance with the Good clinical practice rules in clinical trials approved though Minister of Health Order No. 1236/2004 and the need to subject data, information and documents to inspection in order to confirm that they have been properly generated, recorded and reported are essential in order to justify the involvement of human subjects in clinical trials.

Article 14. - (1) The person participating in a trial must consent to the scrutiny of personal information during inspection by the National Medicines Agency and properly authorised persons.

(2) Such personal information is treated as strictly confidential and is not made publicly available.

Article 15. - These Norms are to apply without prejudice to Law No. 677/2001 on the protection of individuals with regard to the processing of personal data and on the free movement of such data published in the Official Gazette of Romania, Part I, No. 790 of 12 December 2001 and to Law No. 46/2003 on the patient rights, published in the Official Gazette of Romania, Part I, No. 51 of 29 January 2003.

Article 16. - It is also necessary to make provision for the monitoring of adverse reactions occurring in clinical trials using the procedures of medicinal product surveillance as provided in Law No. 95/2006 on the healthcare reform, Title XVII, The Medicinal Product, in order to ensure the immediate cessation of any clinical trial in which there is an unacceptable level of risk.

CHAPTER III
Scope

Article 17. - (1) These norms establish specific provisions regarding the conduct of clinical trials, including multi-centre trials, on human subjects involving medicinal products as defined in Article 659 of Law No. 95/2006 on the healthcare reform, Title XVII, The Medicinal Product, in particular relating to the implementation of good clinical practice.

(2) These Norms do not apply to non-interventional trials.

Article 18. - (1) Good clinical practice rules are 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.

(2) 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.

Article 19**.** - (1) The National Medicines Agency shall adopt the principles of good clinical practice and detailed guidelines in line with those principles and, if necessary, revise them to take account of technical and scientific progress.

Article 20. - All clinical trials, including bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the Rules of good clinical practice.

CHAPTER IV
Definitions

Article 21**.** -For the purposes of these Norms 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 includes clinical trials carried out in either one site or multiple sites, whether in one or more than one country;

b) *multi-centre clinical trial* - a clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in Romania only or in several countries;

c) *non-interventional trial* - a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization; 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 authorized form;

e) *sponsor* - 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 a person following a profession agreed in Romania for investigations because of the scientific background and the experience in patient care it requires; the investigator is responsible for the conduct of a clinical trial at a trial site; if a trial is conducted by a team of individuals at a trial site, 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;

j) *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; 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 national legislation;

k) *ethics committee* - an independent body, consisting of healthcare professionals and nonmedical 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;

l) *inspection* - the act by the National Medicines Agency of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the National Medicines Agency sees fit to inspect;

m) *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;

n) *adverse reaction* - all untoward and unintended responses to an investigational medicinal product related to any dose administered;

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

p) *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 unauthorised investigational product or summary of product characteristics for an authorized product

CHAPTER V
Protection of clinical trial subjects

Article 22**.** – The National Medicines Agency shall adopt detailed rules to protect from abuse individuals who are incapable of giving their informed consent.

Article 23**.** - 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 the National Medicines Agency come 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 the investigator or a member of the investigating team, 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 the provisions of Law No. 677/2001 and of Law No. 46/2003 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 individual is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national 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 for insurance or indemnity to cover the liability of the investigator and sponsor.

Article 24. - The medical care given to, and medical decisions made on behalf of, subjects shall be the responsibility of an appropriately qualified doctor.

Article 25. - The subject shall be provided with a contact point where he may obtain further information.

CHAPTER VI
Clinical trials on minors

Article 26. - In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if:

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

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 this information to refuse participation 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;

e) Some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validated 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;

f) The corresponding scientific guidelines of the National Medicines Agency have been followed;

g) 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;

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

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

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

Article 27. - (1) In the case of other persons incapable of giving informed legal consent, named hereafter *incapacitated adults*, all relevant requirements listed for persons capable of giving such consent shall apply.

(2) In addition to these requirements, 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 not able to give informed legal consent 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;

e) Such research is essential to validated 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) An 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.

CHAPTER VIII
Ethics Committee

Article 28. - (1) For the purposes of implementation of the clinical trials, ethics committees must be established.

(2) The ethics committee shall give its opinion, before a clinical trial commences, on any issue requested.

(3) In preparing its opinion, 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 Article 23(a) 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 quality of the facilities;

g) The adequacy and completeness of the written information to be given 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 Chapter IV;

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

i) Any insurance or indemnity to cover the liability of the investigator and sponsor;

j) 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 site;

k) The arrangements for the recruitment of subjects.

Article 29. - The ethics committee shall have a maximum of 60 days from the date of receipt of a valid application to give its reasoned opinion to the applicant and the National Medicines Agency.

Article 30. - (1) Within the period of examination of the application for an opinion, the ethics committee may send a single request for information supplementary to that already supplied by the applicant.

(2) The period laid down in Article 29 shall be suspended until receipt of the supplementary information.

Article 31. - (1) No extension to the 60-day period referred to in Article 29 shall be permissible except in the case of trials involving medicinal products for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms; in this case, an extension of a maximum of 30 days shall be permitted.

(2) For these products, this 90-day period may be extended by a further 90 days in the event of consultation of a group or a committee of experts.

(3) In the case of xenogeneic cell therapy, there shall be no time limit to the authorisation period.

CHAPTER IX

Single opinion

Article 32. - For multi-centre clinical trials limited to the territory of Romania, the National Medicines Agency shall establish a procedure providing, notwithstanding the number of Ethics Committees, for the adoption of a single opinion for Romania.

Article 33. - In the case of multi-centre clinical trials carried out in more than one country simultaneously, a single opinion shall be given for each country concerned by the clinical trial.

CHAPTER X
Detailed guidance

Article 34. – (1) The National Medicines Agency takes part in consultations with the European Commission for the elaboration of detailed guidance on the application format and documentation to be submitted in an application for an ethics committee opinion, in particular regarding the information that is given to subjects, and on the appropriate safeguards for the protection of personal data.

(2) The National Medicines Agency shall publish all guidelines mentioned under (1).

CHAPTER XI
Commencement of a clinical trial

Article 35. – The National Medicines Agency shall take the measures necessary to ensure that the procedure described in this chapter is followed for commencement of a clinical trial.

Article 36. - (1) The sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion and inasmuch as the National Medicines Agency has not informed the sponsor of any grounds for non-acceptance.

(2) The procedures to reach these decisions can be run in parallel or not, depending on the sponsor.

Article 37. - Before commencing any clinical trial, the sponsor shall be required to submit a valid request for authorisation to the National Medicines Agency, expressing the intention to perform the clinical trial.

Article 38. - (1) If the National Medicines Agency notifies the sponsor of grounds for non-acceptance, the sponsor may, on one occasion only, amend the content of the request referred to in Article 37 in order to take due account of the grounds given.

(2) If the sponsor fails to amend the request accordingly, the request shall be considered rejected and the clinical trial may not commence.

Article 39**.** - (1) Consideration of a valid request for authorisation by the competent authority as stated in Article 37 shall be carried out as rapidly as possible and may not exceed 60 days.

(2) The National Medicines Agency can nevertheless notify the sponsor before the end of this period that it has no grounds for non-acceptance.

Article 40. - (1) No further extensions to the period referred to in the first subparagraph shall be permissible except in the case of trials involving the medicinal products listed in Article 42, for which an extension of a maximum of 30 days shall be permitted.

(2) For these products, this 90-day period may be extended by a further 90 days in the event of consultation of a group or a committee of experts.

(3) In the case of xenogeneic cell therapy there shall be no time limit to the authorisation period.

Article 41. - Without prejudice to Article 42, written authorization may be required before the commencement of clinical trials for such trials on medicinal products which do not have a marketing according to Law No. 95/2006 on the healthcare reform, Title XVII, The Medicinal

Product, and which are obtained through recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammal cells, monoclonal antibody methods, as well as 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.

Article 42. - (1) Written authorisation shall be required before commencing clinical trials involving medicinal products for gene therapy, somatic cell therapy including xenogeneic cell therapy and all medicinal products containing genetically modified organisms.

(2) No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity.

Article 43. - This authorisation shall be issued without prejudice to the application of the national legislation on the contained use of genetically modified micro-
organisms on the deliberate release into the environment of genetically modified organisms.

Article 44. – (1) The National Medicines Agency takes part in consultations with the European Commission for the elaboration of detailed guidance on:

a) The format and contents of the request referred to in Article 37 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;

b) The presentation and content of the proposed amendment referred to in point (a) of Article 45 on substantial amendments made to the protocol;

c) The declaration of the end of the clinical trial.

(2) The National Medicines Agency shall publish all guidelines mentioned under (1).

CHAPTER XII
Conduct of a clinical trial

Article 45. - Amendments may be made to the conduct of a clinical trial following the procedure described hereinafter:

a) After the commencement of the clinical trial, 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, the sponsor shall notify the National Medicines Agency of the reasons for, and content of, these amendments and shall inform the ethics committee or committees concerned in accordance with Chapters VII and X.

- On the basis of the details referred to in Chapter VIII, Article 28 (3) and in accordance with Chapter IX, the Ethics Committee shall give an opinion within a maximum of 35 days of the date of receipt of the proposed amendment in good and due form; if this opinion is unfavourable, the sponsor may not implement the amendment to the protocol.

- If the opinion of the Ethics Committee is favourable and the National Medicines Agency has raised no grounds for non-acceptance of the abovementioned 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;

b) Without prejudice to (a) and 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 sponsor shall forthwith inform the National Medicines Agency of those new events and the measures taken and shall ensure that the Ethics Committee is notified at the same time;

c) Within 90 days of the end of a clinical trial the sponsor shall notify the National Medicines Agency and the Ethics Committee that the clinical trial has ended; if the trial has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.

CHAPTER XIII
Suspension of the trial or infringements

Article 46. - (1) Where the National Medicines Agency has objective grounds for considering that the conditions in the request for authorization referred to in Article 37 are no longer met or 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.

(2) Before the National Medicines Agency reaches its decision it shall, except where there is imminent risk, ask the sponsor and/or the investigator for their opinion, to be delivered within one week; in this case, the National Medicines Agency shall forthwith inform the other competent authorities; in the case of a multicentre trial which is carried out in more than one country, the National Medicines Agency shall also inform the ethics committee concerned of its decision to suspend or prohibit the trial and of the reasons for the decision.

Article 47**.** - Where the National Medicines Agency 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.

(2) The National Medicines agency shall forthwith inform the Ethics Committee and the other competent authorities, if the trial is multicenter and is carried out in more than one country of the infringements found and of the remedy measures to be taken.

CHAPTER XIV
Manufacture and import of investigational medicinal products

Article 48**.** - (1) The National Medicines Agency shall take all appropriate measures to ensure that the manufacture or importation of investigational medicinal products is subject to the holding of authorisation.

(2) In order to obtain the authorisation, the applicant and, subsequently, the holder of the authorisation, shall meet the provisions of Law No. 95/2006 on the healthcare reform, Title XVII, The Medicinal Product.

Article 49. - The National Medicines Agency shall take all appropriate measures to ensure that the holder of the authorisation referred to in Article 48 has permanently and continuously at his disposal the services of at least one qualified person, responsible in particular for carrying out the duties specified in Article 50, satisfying the conditions provided for in the Rules on good manufacturing practice for medicinal products, approved through a decision of the Scientific Council of the National Medicines Agency.

Article 50. – (1) The National Medicines Agency shall take all appropriate measures to ensure that the qualified person referred to in the Rules on good manufacturing practice for medicinal products, without prejudice to his relationship with the manufacturer or importer, is responsible, for ensuring:

a) In the case of investigational medicinal products manufactured in Romania, that each batch of medicinal products has been manufactured and checked in compliance with the

requirements of the Rules on good manufacturing practice for medicinal products, the product specification file and the information notified pursuant to Article 37;

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 the Rules on good manufacturing practice for medicinal products, in accordance with the product specification file, and that each production batch has been checked in accordance with the information notified pursuant to Article 37;

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 Rules on good manufacturing practice for medicinal products 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 Article 37.

(2) Depending on compliance with provisions of (1) a), b) and c), investigational medicinal products imported to Romania are not subject to additional verifications if imported together with the batch release certificate by the qualified person.

Article 51. - Detailed guidance on the elements to be taken into account when evaluating products with the object of releasing batches within Romania shall be drawn up pursuant to the Rules on good manufacturing practice for medicinal products, and in particular Annex 1 to the said guidelines.

Article 52. - (1) In all cases, the qualified person must certify in a register or equivalent document that each production batch satisfies the provisions of this chapter.

(2) The said register or equivalent document shall be kept up to date as operations are carried out and shall remain at the disposal of the National Medicines Agency for a period of at least 5 years.

(3) Provisions of Article 759 (1) of Law No. 95/2006 on the healthcare reform, Title XVII, The Medicinal Product shall apply to the qualified person in what concerns investigational medicinal products.

CHAPTER XV
Labelling

Article 53**.** - The particulars to appear in the Romanian language on the outer packaging of investigational medicinal products or, where there is no outer packaging, on the immediate packaging, are specified in Annex 11 of the Rules of good manufacturing practice for medicinal products, approved through Minister of Health Order No. 1.058/2003, relating to manufacturing of investigational medicinal products.

Article 54. - In addition, these Rules of good manufacturing practice for medicinal products shall lay down adapted provisions relating to labelling for investigational medicinal products intended for clinical trials with the following characteristics:

a) The planning of the trial does not require particular manufacturing or packaging processes;

b) The trial is conducted with medicinal products which, in the Member States concerned by the study, have a marketing authorization within the meaning of Law No. 95/2006 on the healthcare reform, Title XVII, The Medicinal Product and are manufactured or imported in accordance with the provisions of the above-mentioned law;

c) The patients participating in the trial have the same characteristics as those covered by the indication specified in the abovementioned authorisation.

CHAPTER XVI

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

Article 55. – (1) To verify compliance with the provisions on good clinical practice and the Rules on good manufacturing practice for medicinal products, the National Medicines Agency shall appoint inspectors to inspect the sites concerned by any clinical trial conducted, particularly the trial site or sites, the manufacturing site of the investigational medicinal product, any laboratory used for analyses in the clinical trial and/or the sponsor's premises.

(2) The National Medicines Agency informs the European Medicines Agency on such inspections; inspections are carried out in the interest of the European Community;

(3) The National Medicines Agency recognises outcomes resulted from inspections carried out by competent authorities in Member States;

(4) Inspections are developed under the coordination of the European Medicines Agency.

Article 56. - (1) Following inspection, an inspection report shall be prepared.

(2) This report must be made available to the sponsor while safeguarding confidential aspects. If the study is multicentre and carried out in more than one country, the report must be made available on reasoned request to the other countries involved, to Member States, the European Medicines Agency and to the Ethics Committee.

Article 57. – The National Medicines Agency shall adopt detailed guidelines on the documentation relating to the clinical trial, which shall constitute the master file on the trial, archiving, qualifications of inspectors and inspection procedures to verify compliance of the clinical trial in question with these norms.

CHAPTER XVII
Notification of adverse events

Article 58. - (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.

(2) The immediate report shall be followed by detailed, written reports.

(3) The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter.

Article 59. - 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.

Article 60. - For reported deaths of a subject, the investigator shall supply the sponsor and the Ethics Committee with any additional information requested.

Article 61**.** - The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators. These records shall be submitted to the countries in whose territory the clinical trial is being conducted, if they so request.

CHAPTERX VIII
Notification of serious adverse reactions

Article 62. - (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 competent authorities in all the countries concerned, and to the Ethics Committee, and in any case no later than seven 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 competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor.

(c) The National Medicines Agency shall ensure that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are recorded.

(4) The sponsor shall also inform all investigators.

Article 63. - Once a year throughout the clinical trial, the sponsor shall provide the National Medicines Agency and the Ethics Committee with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.

Article 64. - The National Medicines Agency shall take all necessary measures that all serious unexpected adverse reactions suspected in an investigational medicinal product that are bought to its knowledge are forthwith introduced in a European data base only accessible to competent authorities in Member States, the European Medicines Agency and the Ethics Committee.

CHAPTER XIX
Guidelines on the procedures for adverse reaction reporting

Article 65. – (1) On request by the European Medicines Agency, the National Medicines Agency takes part in consultations with the European Commission for the elaboration of guidance on the collecting, checking and presenting of the reports on adverse events/reactions, as well as on the procedures of decoding for the serious unexpected adverse reactions.

(2) The National Medicines Agency shall publish all guidelines mentioned under (1).

CHAPTER XX
General provisions

Article 66. - (1) The National Medicines Agency introduces the following information into a European data base only accessible to competent authorities in Member States, the European Medicines Agency and the Ethics Committee:

a) Excerpts from the application for authorisation provided for under Article 38;
b) Any changes in application, according to Article 38;
c) Any changes in protocol, according to Article 45, a);
d) The favourable opinion of the ethics committee;
e) The statement on closure of the clinical trial;
f) A reference to verifications of compliance with good clinical practice rules.

(2) On request by any Member State, the European Medicines Agency or the European Commission, the National Medicines Agency shall provide any other information on the clinical trial in case in addition to those already introduced in the European data base;

(3) The National Medicines Agency shall take part in consultations organised by the European Commission for the design and publication of guidelines related to relevant data to be introduced in the European data base working with support from the European Medicines Agency as well as methods for the electronic communication of data. Guidebooks thus devised shall insure strict observance of data confidentiality.

(4) The National Medicines Agency shall publish all guidelines mentioned under (1).

CHAPTER XXI

General provisions

Article 67. – (1) These Norms are without prejudice to the civil and criminal liability of the sponsor or the investigator.

(2) To this end, the sponsor or a legal representative of the sponsor must be established in Romania or the European Community.

Article 68. - Investigational medicinal products and, as the case may be, the devices used for their administration or those necessary according to the protocol of the clinical trial shall be made available free of charge by the sponsor.

CHAPTER XXII
Adaptation to scientific and technical progress

Article 69. - These Rules shall be adapted whenever necessary to take account of scientific and technical progress.

CHAPTER XXIII
Transitory and final provisions

Article 70. – Provisions of Articles 64 and 66 shall come into force on the first day after Romania’s accession to the European Union.