MINISTRY OF PUBLIC HEALTH

ORDER
on approval of the Principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products

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. 2.400 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 Principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products 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 - The present order shall come into on 28 July 2006, when any other contrary dispositions shall be repealed.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 is to be published in the Official Gazette of Romania, Part I.

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The present order is a transposition of Commission Directive 2005/28/EC of 8 April 2005 regarding Principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products, published in the Official Journal of the European Communities No. L 91 of 9 April 2005.

Minister of public health,
Gheorghe Eugen Nicolăescu

Bucharest, 25 July 2006
No. 903.

ANNEX

PRINCIPLES
and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products

CHAPTER I
Introduction

Article 1. – These regulations transpose Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products[*)].

CHAPTER II
Subject-Matter

Article 2. - (1) These regulations lay down the following provisions to be applied to investigational medicinal products for human use:

a) The principles of good clinical practice and detailed guidelines in line with those principles, as referred to in Article 19 of the Annex to Minister of Public Health Order No. 904/2006 regarding approval of Norms on the implementation of good clinical practice conducted with medicinal products for human use, for the design, conduct and reporting of clinical trials on human subjects involving such products;

b) The requirements for authorisation of the manufacture or importation of such products, as provided for in Article 48 of the Annex to the order provided under a);

c) The detailed guidelines, provided for in Article 57 of the Annex to the order provided under a) on the documentation relating to clinical trials, archiving, qualifications of inspectors and inspection procedures.

Article 3. - When applying the principles, detailed guidelines and requirements referred to in Article 2, the National Medicines Agency shall take into account the technical implementing modalities provided for in the detailed guidance published by the Commission in "The Rules governing medicinal products in the European Union".

Article 4. - When applying the principles, detailed guidelines and requirements referred to in Article 2 to non-commercial clinical trials conducted by researchers without the participation of the pharmaceutical industry, the National Medicines Agency may introduce specific modalities in order to take into account the specificity of these trials as far as Chapters IV and V of these regulations are concerned.

Article 5. - The National Medicines Agency shall establish specific modalities for trials whose planning does not require particular manufacturing or packaging processes, carried out with medicinal products with marketing authorisations in Romania within the meaning of Law no. 95/2006 on Healthcare reform, Title XVII, "The Medicinal Product", manufactured or imported in accordance with the same law and conducted on patients with

[*)] JO No. L 91 of 9 April 2005, p. 13

the same characteristics as those covered by the therapeutic indications specified in the marketing authorisation for the respective medicinal product.

Article 6. - In Romania, labelling of investigational medicinal products intended for trials of that nature is subject to simplified provisions laid down in the good manufacturing practice guidelines on investigational medicinal products.

Article 7. - The National Medicines Agency shall inform the European Commission as well as the other Member States of any specific modalities implemented in accordance with provisions of Articles 5 and 6.

CHAPTER III
Good clinical practice rules for the design, conduct, recording and reporting of clinical trials

III.1. **Good clinical practice rules**

Article 8. - The rights, safety and well-being of the trial subjects shall prevail over the interests of science and society.

Article 9. - Each individual involved in conducting a trial shall be qualified by education, training, and experience to perform his tasks.

Article 10. - Clinical trials shall be scientifically sound and guided by ethical principles in all their aspects.

Article 11. - The necessary procedures to secure the quality of every aspect of the trials shall be complied with.

Article 12. - The available non-clinical and clinical information on an investigational medicinal product shall be adequate to support the proposed clinical trial.

Article 13. - Clinical trials shall be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996).

Article 14. - The protocol referred to in Article 21, h) of the Annex to Minister of Public Health Order No. 904/2006 shall provide for the definition of inclusion and exclusion of subjects participating in a clinical trial, monitoring and publication policy.

Article 15. - The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.

Article 16. - All clinical trial information shall be recorded, handled, and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected.

III.2. **The ethics committees**

Article 17. - Each Ethics Committee established under Article 28 (1) of the Annex to Minister of Public Health Order No. 904/2006 shall adopt the relevant rules of procedure necessary to implement the requirements set out in that order and, in particular, in Chapters VIII and IX.

Article 18. - (1) The Ethics Committees shall, in every case, retain the essential documents relating to a clinical trial, as referred to in Article 57 of the Annex to Minister of Public Health Order No. 904/2006, at least three years after completion of that trial.

(2) Communication of information between the ethics committees, the National Medicines Agency and the competent authorities of the Member States shall be ensured through appropriate and efficient systems.

III.3. The sponsors

Article 19. - (1) A sponsor may delegate any or all of his trial-related functions to an individual, a company, an institution or an organisation.

(2) However, in such cases, the sponsor shall remain responsible for ensuring that the conduct of the trials and the final data generated by those trials comply with Minister of Public Health Order No. 904/2006 as well as with these Regulations.

Article 20. - The investigator and the sponsor may be the same person.

III.4. **Investigator's brochure**

Article 21. - The information in the investigator's brochure, referred to in Article 21, g) of the Annex to Minister of Public Health Order No. 904/2006, shall be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician or potential investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial; these provisions shall apply also to any update of the investigator's brochure.

Article 22. - If the investigational medicinal product holds a marketing authorisation in Romania, the Summary of Product Characteristics may be used instead of the investigator's brochure.

Article 23. - The investigator's brochure shall be validated and updated by the sponsor at least once a year.

CHAPTER IV
Manufacturing or import authorisation

Article 24. - (1) As provided for in Article 48 of the Annex to Minister of Public Health Order No. 904/2006, authorisation shall be required for both total and partial manufacture of investigational medicinal products, and for the various processes of dividing up, packaging or presentation.

(2) Such authorisation shall be required even if the products manufactured are intended for export.

(3) Authorisation shall also be required for imports from third countries into Romania.

(4) Authorisation, as provided for in Article 48 of the Annex to Minister of Public Health Order No. 904/2006, shall not be required for reconstitution prior to use or packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in Romania to carry out such processes and if the investigational medicinal products are intended to be used exclusive.

Article 25. - (1) In order to obtain the authorisation the applicant must meet at least the following requirements:

a) specify in his application the types of medicinal products and pharmaceutical forms to be manufactured or imported;

b) specify in his application the relevant manufacture or import operations;

c) specify in his application, where relevant as in the case of viral or non-conventional agents' inactivation, the manufacturing process;

d) specify in his application the place where the products are to be manufactured or have at his disposal, for their manufacture or importation, suitable and sufficient premises, technical equipment and control facilities complying with the requirements of Minister of Public Health Order No. 905/2006 on guidelines for good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use as regards the manufacture, control and storage of the products;

e) have permanently and continuously at his disposal the services of at least one qualified person as referred to in Article 49 of the Annex to Minister of Public Health Order No. 904/2006.

(2) For the purposes of (1), a), *types of medicinal products* include blood products, immunological products, cell therapy products, gene therapy products, biotechnology products, human or animal extracted products, herbal products, homeopathic products, radio-pharmaceutical products and products containing chemical active ingredients.

Article 26. - The applicant shall provide with his application documentary evidence that he complies with Article 25.

Article 27. - The National Medicines Agency shall issue the authorisation only after verifying the accuracy of the particulars provided by the applicant pursuant to Article 25, by the means of an inquiry carried out by its agents.

Article 28. - The National Medicines Agency shall take all appropriate measures to ensure that the procedure for granting an authorisation is completed within 90 days of the day on which the competent authority receives a valid application.

Article 29. - The competent authority of the Member State may require from the applicant further information concerning the particulars supplied pursuant to Article 38, including in particular information concerning the qualified person at the disposal of the applicant in accordance with Article 25 (1), e).

Article 30. - Where the National Medicines Agency exercises that right, the application of the time-limits laid down in Article 28 shall be suspended until the additional data required have been supplied.

Article 31. - In order to ensure that the requirements laid down in Article 25 are complied with, authorisation may be made conditional on the carrying out of certain obligations imposed either when authorisation is granted or at a later date.

Article 32. - An authorisation shall apply only to the types of medicinal products and pharmaceutical forms specified in that application pursuant to Article 25, (1), a).

Article 33. - The holder of the authorisation shall at least comply with the following requirements:

a) To have at his disposal the services of staff that comply with the legal requirements existing in Romania both as regards manufacture and controls;

b) To dispose of the investigational/authorised medicinal products only in accordance with the legislation of Romania;

c) To give prior notice to the National Medicines Agency of any changes he may wish to make to any of the particulars supplied pursuant Article 25 and, in particular, to inform the National Medicines Agency immediately if the qualified person referred to in Article 49 of the Annex to Minister of Public Health Order No. 904/2006 is replaced unexpectedly;

d) To allow agents of the National Medicines Agency access to his premises at any time;

e) To enable the qualified person referred to in Article 49 of the Annex to Minister of Public Health Order No. 904/2006 carry out his duties, for example by placing at his disposal all the necessary facilities;

f) To comply with the principles and guidelines for good manufacturing practice for medicinal products as laid down by national law.

Article 34. – (1) The National Medicines Agency applies the provisions of the detailed guidelines in line with the principles referred to in Article 33, f) that will be revised where necessary to take account of technical and scientific progress.

(2) The National Medicines Agency publishes guidelines mentioned under (1).

Article 35. - If the holder of the authorisation requests a change in any of the particulars referred to in Article 25, (1) a) and e), the time taken for the procedure relating to the request shall not exceed 30 days; in exceptional cases, this period of time may be extended to 90 days.

Article 36. - The National Medicines Agency shall suspend or revoke the authorisation, as a whole or in part, if the holder of the authorisation fails at any time to comply with the relevant requirements.

CHAPTER V
The Trial Master File and Archiving

Article 37. – The documentation referred to as *trial master file* in Article 57 of the Annex to Minister of Public Health Order No. 904/2006 shall consist of essential documents, which enable both the conduct of a clinical trial and the quality of the data produced to be evaluated; those documents shall show whether the investigator and the sponsor have complied with the principles and guidelines of good clinical practice and with the applicable requirements and, in particular, the requirements of the Analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products, approved through minister of public health order.

Article 38. - The trial master file shall provide the basis for the audit by the sponsor’s independent auditor and for the inspection by the National Medicines Agency.

Article 39. - The content of the essential documents shall be in accordance with the specificities of each phase of the clinical trial.

Article 40. – (1) The National Medicines Agency shall apply additional guidance in order to specify the content of these documents as provided and published by the European Commission.

(2) The National Medicines Agency publishes guidelines mentioned under (1)

Article 41. - (1) The sponsor and the investigator shall retain the essential documents relating to a clinical trial for at least 5 years after its completion.

(2) The sponsor and the investigator shall retain the documents for a longer period, where so required by other applicable requirements or by an agreement between them.

(3) Essential documents shall be archived in a way that ensures that they are readily available, upon request, to the National Medicines Agency.

(4) The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

Article 42. - Any transfer of ownership of the data or of documents shall be documented; the new owner shall assume responsibility for data retention and archiving in accordance with Article 41.

Article 43. - (1) The sponsor shall appoint individuals within its organization who are responsible for archives.

(2) Access to archives shall be restricted to the named individuals responsible for the archives.

Article 44. - The media used to store essential documents shall be such that those documents remain complete and legible throughout the required period of retention and can be made available to the National Medicines Agency upon request.

Article 45. - Any alteration to records shall be traceable.

CHAPTER VI
Inspectors

Article 46. - The inspectors appointed by the National Medicines Agency according to Article 55 of the Annex to Minister of Public Health Order No. 904/2006 shall maintain confidentiality whenever they gain access to confidential information as a result of good clinical practice inspections in accordance with applicable Community requirements, national laws or international agreements.

Article 47. - The National Medicines Agency shall ensure that inspectors have completed education at university level, or have equivalent experience, in medicine, pharmacy, pharmacology, toxicology or other relevant fields.

Article 48. - The National Medicines Agency shall ensure that inspectors receive appropriate training, that their training needs are assessed regularly and that appropriate action is taken to maintain and improve their skills.

Article 49. - The National Medicines Agency shall also ensure that the inspectors have knowledge of the principles and processes that apply to the development of medicinal products and clinical research.

Article 50. - Inspectors shall also have knowledge of applicable national and Community legislation and guidelines applicable to the conduct of clinical trials and the granting of marketing authorisations.

Article 51. - The inspectors shall be familiar with the procedures and systems for recording clinical data, and with the organisation and regulation of the healthcare system in Romania, Member States and, where appropriate, in third countries.

Article 52. - The National Medicines Agency shall maintain up-to-date records of the qualifications, training and experience of each inspector.

Article 53. – At any time, each inspector shall have at his disposal a document setting out standard operating procedures and giving details of the duties, responsibilities and ongoing training requirements; standard operation procedures shall be maintained up to date.

Article 54. - Inspectors shall be provided with suitable means of identification.

Article 55. - Each inspector shall sign a statement declaring any financial or other links to the parties to be inspected; these statements shall be taken into consideration when inspectors are to be assigned to a specific inspection.

Article 56. - In order to ensure the presence of skills necessary for specific inspections, the National Medicines Agency may appoint teams of inspectors and experts with appropriate qualifications and experience to fulfil collectively the requirements necessary for conducting the inspection.

CHAPTER VII
Inspection Procedures

Article 57. - Good clinical practice inspections may take place on any of the following occasions:

a) Before, during or after the conduct of clinical trials;

b) As part of the verification of applications for marketing authorisation;

c) As a follow-up to the granting of authorisation.

Article 58. - In accordance with Articles 55 and 56 of the Annex to Minister of Public Health Order No. 904/2006, inspections may be requested and coordinated by the European Medicines Agency (EMEA) within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council, especially in connection with clinical trials relating to applications through the procedure established by these Regulations.

Article 59. - Inspections shall be conducted in accordance with the inspection guidance documents developed to support the mutual recognition of inspection findings within the Community.

Article 60. - The National Medicines Agency shall contribute to the improvement and harmonisation of inspection guidance through joint inspections, agreed processes and procedures together with the European institutions and homologue authorities and sharing of experience and training.

Article 61. - (1) The National Medicines Agency make publicly available in Romania, the documents relating to the adoption of good clinical practice rules.

(2) They shall establish the legal and administrative framework within which their good clinical practice inspections operate, with definition of the powers of inspectors for entry into clinical trial sites and access to data; in so doing they shall ensure that, on request and where appropriate, National Medicines Agency own inspectors as well as inspectors of the other Member States also have access to the clinical trial sites and data.

Article 62. - The National Medicines Agency shall provide for sufficient resources and shall in particular appoint an adequate number of inspectors to ensure effective verification of compliance with good clinical practice rules.

Article 63. - (1) The National Medicines Agency shall establish the relevant procedures for verification of good clinical practice compliance.

(2) The procedures shall include the modalities for examining both the study management procedures and the conditions under which clinical trials are planned, performed, monitored and recorded, as well as follow-up measures.

Article 64. - The National Medicines Agency shall establish the relevant procedures for the following:

a) Appointing experts for accompanying inspectors in case of need;

b) Requesting inspections/assistance from other Member States, in line with Article 15(1) of Directive 2001/20/EC and for cooperating in inspections in another Member State;

c) Arranging inspections in third countries.

Article 65. - The National Medicines Agency shall maintain records of national and, if applicable, international inspections including the good clinical practice compliance status, and of their follow-up.

Article 66. - (1). In order to harmonise the conduct of inspections by the inspectors of the National Medicines Agency with those conducted by the inspectors of the competent authorities of the different Member States, The National Medicines Agency shall attend consultations organized by the European Commission; the National Medicines Agency shall apply the guidance documents containing the common provisions on the conduct of those inspections, published by the Commission.

(2) The National Medicines Agency shall ensure that national inspection procedures are in compliance with the guidance documents referred in (1).

(3) The guidance documents referred to in (1) may be updated regularly according to scientific and technical development.

Article 67. - The National Medicines Agency shall lay down all necessary rules to ensure that confidentiality is respected by inspectors and other experts.

Article 68. - With regard to personal data, the requirements of 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, with later changes.

Article 69. - The National Medicines Agency shall ensure access to the inspection reports only to the recipients referred to in Article 56 of the Annex to Minister of Public Health Order No. 904/2006, in accordance with national regulations and subject to any arrangements concluded between the Community and third countries.