MINISTRY OF PUBLIC HEALTH

ORDER
on approval of Principles and guidelines for good manufacturing practice in respect of medicinal products for human use and investigational 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. 2.398 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 guidelines for good manufacturing practice in respect of medicinal products for human use and investigational 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 - The present order shall come into on 28 July 2006, when any other contrary dispositions shall be repealed.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 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 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use, published in the Official Journal of the European Communities No. L 262 of 14 October 2003.

The minister of public health,
Gheorghe Eugen Nicolăescu

Bucharest, 25 July 2006
No. 905

ANNEX

PRINCIPLES AND GUIDELINES
for good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use

CHAPTER I
Introduction

Article 1. – The present document is a transposition of Commission Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.

CHAPTER II
Scope

Article 2. – The present document lays down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use whose manufacture requires the authorisation referred to in Article 748 (1) of Law no. 95/2006 on healthcare reform and in respect of investigational medicinal products for human use whose manufacture requires the authorisation referred to in Article 48 (1) of the Annex to Minister of public health order no. 904/2006 for approval of Norms regarding the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use.

CHAPTER III
Definitions

Article 3. - For the purposes of this document, the following definitions shall apply:
1. '*medicinal product*'. - any product as defined in Article 695 1) of Law No. 95/2006;
2. '*investigational medicinal product*'. - any product as defined in Article 21 d) of Minister of public health order No. 904/2006;
3. '*manufacturer'*. - any person engaged in activities for which the authorisation referred to in Article 748 (1) and (3) of Law No. 95/2006 on healthcare reform or the authorisation referred to in Article 48 (1) of the Annex to Minister of public health order No. 904/2006;
4. '*qualified person*'. - the person referred to in Article 757 of Law No. 95/2006 or in Article 49 of the Annex to Minister of public health order No. 904/2006;
5. '*pharmaceutical quality assurance*'. - the total sum of the organised arrangements made with the object of ensuring that medicinal products or investigational medicinal products are of the quality required for their intended use;
6. '*good manufacturing practice*'. - the part of quality assurance which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use;
7. '*blinding'*. - the deliberate disguising of the identity of an investigational medicinal product in accordance with the instructions of the sponsor;
8. '*unblinding'*. - the disclosure of the identity of a blinded product.

CHAPTER IV
Inspections

Article 4. - By means of the repeated inspections referred to in Article 823 (1) of Law No. 95/2006 on healthcare reform and by means of the inspections referred to in Article 55 of the Annex to Minister of public health order No. 904/2006, the National Medicines Agency shall ensure that manufacturers respect the principles and guidelines of good manufacturing practice laid down by this document. The National Medicines Agency shall also take into account the inspection procedures and information exchange published by the European Commission and transposed in Romania through decisions of the Scientific Council of the National Medicines Agency.

Article 5. - For the interpretation of the principles and guidelines of good manufacturing practice, the manufacturers and the National Medicines Agency shall apply provisions of the detailed guidelines referred to in Article 756 of Law No. 95/2006, approved through minister of public health order, as well as provisions of the Guide to good manufacturing practice for medicinal products and for investigational medicinal products, approved through decision of the Scientific Council of the National Medicines Agency.

CHAPTER V
Conformity with good manufacturing practice

Article 6. - The manufacturer shall ensure that manufacturing operations are carried out in accordance with good manufacturing practice and with the manufacturing authorisation. This provision shall also apply to medicinal products intended only for export.

Article 7. - (1) For medicinal products and investigational medicinal products imported from third countries, the importer shall ensure that the products have been manufactured in accordance with standards which are at least equivalent to the good manufacturing practice standards laid down by Romania and the European Community.

(2) In addition, an importer of medicinal products shall ensure that such products have been manufactured by manufacturers duly authorised to do so; an importer of investigational medicinal products shall ensure that such products have been manufactured by a manufacturer notified to the National Medicines Agency and accepted by them for that purpose.

CHAPTER VI
Compliance with marketing authorisation

Article 8**. -** (1) The manufacturer shall ensure that all manufacturing operations for medicinal products subject to a marketing authorisation are carried out in accordance with the information provided in the application for marketing authorisation as accepted by the National Medicines Agency.

(2) In the case of investigational medicinal products, the manufacturer shall ensure that all manufacturing operations are carried out in accordance with the information

provided by the sponsor pursuant to Article 37 of the Annex to Minister of public health order No. 904/2006, as accepted by the National Medicines Agency.

Article 9. - (1) The manufacturer shall regularly review his manufacturing methods in the light of scientific and technical progress and the development of the investigational medicinal product.

(2) If a variation to the marketing authorisation dossier or an amendment to the request referred to in Article 37 of the Annex to Minister of public health order No. 904/2006, the application for modification shall be submitted to the National Medicines Agency.

CHAPTER VII
Quality assurance system

Article 10. - The manufacturer shall establish and implement an effective pharmaceutical quality assurance system, involving the active participation of the management and personnel of the different departments.

CHAPTER VIII
Personnel

Article 11.- At each manufacturing site, the manufacturer shall have a sufficient number of competent and appropriately qualified personnel at his disposal to achieve the pharmaceutical quality assurance objective.

Article 12. - (1) The duties of the managerial and supervisory staff, including the qualified person(s), responsible for implementing and operating good manufacturing practice, shall be defined in job descriptions.

(2) Their hierarchical relationships shall be defined in an organisation chart.

(3) Organisation charts and job descriptions shall be approved in accordance with the manufacturer's internal procedures.

Article 13. - The staff referred to in Article 12 (1) shall be given sufficient authority to discharge their responsibility correctly.

Article 14. - The personnel shall receive initial and ongoing training, the effectiveness of which shall be verified, covering in particular the theory and application of the concept of quality assurance and good manufacturing practice, and, where appropriate, the particular requirements for the manufacture of investigational medicinal products.

Article 15. - Hygiene programmes adapted to the activities to be carried out shall be established and observed; these programmes shall, in particular, include procedures relating to health, hygiene practice and clothing of personnel.

CHAPTER IX
Premises and equipment

Article 16. - Premises and manufacturing equipment shall be located, designed, constructed, adapted and maintained to suit the intended operations.

Article 17. - Premises and manufacturing equipment shall be laid out, designed and operated in such a way as to minimise the risk of error and to permit effective cleaning and

maintenance in order to avoid contamination, cross contamination and, in general, any adverse effect on the quality of the product.

Article 18. - Premises and equipment to be used for manufacturing operations, which are critical to the quality of the products, shall be subjected to appropriate qualification and validation.

CHAPTER X
Documentation

Article 19. - (1) The manufacturer shall establish and maintain a documentation system based upon specifications, manufacturing formulae and processing and packaging instructions, procedures and records covering the various manufacturing operations performed; documents shall be clear, free from error and kept up to date.

(2) Pre-established procedures for general manufacturing operations and conditions shall be kept available, together with specific documents for the manufacture of each batch. That set of documents shall enable the history of the manufacture of each batch and the changes introduced during the development of an investigational medicinal product to be traced.

Article 20. - For a medicinal product, the batch documentation shall be retained for at least one year after the expiry date of the batches to which it relates or at least five years after the certification referred to in article 760 (3) of Law No. 95/2006, whichever is the longer period.

Article 21. - For an investigational medicinal product, the batch documentation shall be retained for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used; the sponsor or marketing authorisation holder, if different, shall be responsible for ensuring that records are retained as required for marketing authorisation in accordance with Minister of public health order No. 906/2006 for approval of Analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products, if required for a subsequent marketing authorisation.

Article 22. - (1) When electronic, photographic or other data processing systems are used instead of written documents, the manufacturer shall first validate the systems by showing that the data will be appropriately stored during the anticipated period of storage. Data stored by those systems shall be made readily available in legible form and shall be provided to the National Medicines Agency, at their request.

(2) Data stored by those systems shall be made readily available in legible form and shall be provided to the competent authorities at their request. The electronically stored data shall be protected, by methods such as duplication or back-up and transfer on to another storage system, against loss or damage of data, and audit trails shall be maintained.

CHAPTER XI
Production

Article 23**. -** (1) The different production operations shall be carried out in accordance with pre-established instructions and procedures and in accordance with good manufacturing practice.

(2) Adequate and sufficient resources shall be made available for the in-process controls.

(3) All process deviations and product defects shall be documented and thoroughly investigated.

Article 24. - (1) Appropriate technical or organisational measures shall be taken to avoid cross contamination and mix-ups.

(2) In the case of investigational medicinal products, particular attention shall be paid to the handling of products during and after any blinding operation.

Article 25. - (1) For medicinal products, any new manufacture or important modification of a manufacturing process of a medicinal product shall be validated.

(2) Critical phases of manufacturing processes shall be regularly re-validated.

Article 26. - (1) For investigational medicinal products, the manufacturing process shall be validated in its entirety in so far as is appropriate, taking into account the stage of product development.

(2) At least the critical process steps, such as sterilisation, shall be validated.

(3) All steps in the design and development of the manufacturing process shall be fully documented.

CHAPTER XII
Quality control

Article 27. - (1) The manufacturer shall establish and maintain a quality control system placed under the authority of a person who has the requisite qualifications and is independent of production.

(2) That person shall have at his disposal, or shall have access to, one or more quality control laboratories appropriately staffed and equipped to carry out the necessary examination and testing of the starting materials and packaging materials and the testing of intermediate and finished products.

Article 28. - (1) For medicinal products, including those imported from third countries, contract laboratories may be used if authorised in accordance with this document and Article 725 b) of Law No. 95/2006.

(2) For investigational medicinal products, the sponsor shall ensure that the contract laboratory complies with the content of the request referred to in Article 37 of the Annex to Minister of public health order No. 904/2006, as accepted by the National Medicines Agency; When the products are imported from third countries, analytical control shall not be mandatory.

Article 29. - During the final control of the finished product before its release for sale or distribution or for use in clinical trials, the quality control system shall take into account, in addition to analytical results, essential information such as the production conditions, the results of in-process controls, the examination of the manufacturing documents and the conformity of the product to its specifications, including the final finished pack.

Article 30. - Samples of each batch of finished medicinal product shall be retained for at least one year after the expiry date.

Article 31**.** – For an investigational medicinal product, sufficient samples of each batch of bulk formulated product and of key packaging components used for each finished product batch shall be retained for at least two years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer.

Article 32. - (1) Samples of starting materials, other than solvents, gases or water, used in the manufacturing process shall be retained for at least two years after the release of product.

(2) That period may be shortened if the period of stability of the material, as indicated in the relevant specification, is shorter.

(3) All those samples shall be maintained at the disposal of the National Medicines Agency.

Article 33. - Other conditions may be defined, by agreement with the National Medicines Agency, for the sampling and retaining of starting materials and certain products manufactured individually or in small quantities, or when their storage could raise special problems.

CHAPTER XIII
Work contracted out

Article 34. - Any manufacturing operation or operation linked thereto which is carried out under contract shall be the subject of a written contract between contract-giver and contract-acceptor.

Article 35.- The contract shall clearly define the responsibilities of each party and shall define, in particular, the observance of good manufacturing practice to be followed by the contract acceptor and the manner in which the qualified person responsible for certifying each batch is to discharge his full responsibilities.

Article 36. - The contract-acceptor shall not subcontract any of the work entrusted to him under the contract without written authorisation from the contract-giver.

Article 37. - The contract-acceptor shall comply with the principles and guidelines of good manufacturing practice and shall submit to inspections carried out by the National Medicines Agency, pursuant to Article 823 of Law No. 95/2006 and Articles 55, 56 and 57 of the Annex to Minister of public health order No. 904/2006.

CHAPTER XIV
Complaints, product recall and emergency unblinding

Article 38. - (1) In the case of medicinal products, the manufacturer shall implement a system for recording and reviewing complaints together with an effective system for recalling, promptly and at any time, medicinal products in the distribution network.

(2) Any complaint concerning a defect shall be recorded and investigated by the manufacturer.

(3) The manufacturer shall inform the National Medicines Agency of any defect that could result in a recall or abnormal restriction on supply and, in so far as is possible, indicate the countries of destination.

(4) Any recall shall be made in accordance with the requirements referred to in Article 840 of Law No. 95/2006.

Article 39. - (1) In the case of investigational medicinal products, the manufacturer shall, in cooperation with the sponsor, implement a system for recording and reviewing complaints together with an effective system for recalling promptly and at any time investigational medicinal products which have already entered a trial programme.

(2) The manufacturer shall record and investigate any complaint concerning a defect and shall inform the National Medicines Agency of any defect that could result in a recall or abnormal restriction on supply.

(3) In the case of investigational medicinal products, all trial sites shall be identified and, in so far as is possible, the countries of destination shall be indicated.

(4) In the case of an investigational medicinal product for which a marketing authorisation has been issued, the manufacturer of the investigational medicinal product shall, in cooperation with the sponsor, inform the marketing authorisation holder of any defect that could be related to the authorised medicinal product.

Article 40. - (1) The sponsor shall implement a procedure for the rapid unblinding of blinded products, where this is necessary for a prompt recall as referred to in Article 39 (1).

(2) The sponsor shall ensure that the procedure discloses the identity of the blinded product only in so far as is necessary.

CHAPTER XV
Self-inspection

Article 41. - The manufacturer shall conduct repeated self-inspections as part of the quality assurance system in order to monitor the implementation and respect of good manufacturing practice and to propose any necessary corrective measures; records shall be maintained of such self-inspections and any corrective action subsequently taken.

CHAPTER XVI
Labelling

Article 42. - In the case of an investigational medicinal product, labelling shall be such as to ensure protection of the subject and traceability, to enable identification of the product and trial, and to facilitate proper use of the investigational medicinal product.