DECISION

No. 5/09.03.2007

on approval of Guideline on quality system framework for Good Manufacturing Practice inspectorates

The Scientific Council of the National Medicines Agency,
set up based on Minister of Public Health Order no. 485/09.05.2005, as amended through Minister of Public Health Order No. 159/22.02.2006, No. 1599/12.12.2006 and No. 395/27.02.2007, reunited on summons of the National Medicines Agency President in the ordinary meeting of 09.03.2007, in accord with Article 10 of Government Ordinance No. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law no. 594/2002, as further amended, agrees on the following

DECISION

Single article. – The Guideline on quality system framework for Good Manufacturing Practice inspectorates, according to the Annex which is integral partof this Decision, is approved.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

GUIDELINE

on the quality system framework for the Good Manufacturing Practice Inspectorates

CHAPTER I
Introduction

Art. 1.- This Guideline is a translation into Romanian and an adaptation of the Guideline EMEA/INS/GMP/313500/2006 concerning the quality system framework for Good Manufacturing Practice (GMP) inspectorates, issued by the European Medicines Agency.

Art. 2. – (1) The main requirement for the Pharmaceutical Inspection Department (PID) of the National Medicines Agency (NMA) consists of fulfilling the provisions of the national legislation (Law No. 95/2006 on helathcare reform, Title XVII-The medicinal product and the Minister of Public health Orders which transpose the directives of the European Union concerning the application field of the medicinal product),

(2)The inspection-related specific obligations, as included in the relevant national legislation should also be included in the PID quality system.

Art. 3. – (1) This Guideline mentions the requirements of the PID quality system.

(2) The PID should use this Guideline as the basis for developing and implementing its own quality system and for preparing its own quality manual.

(3) In addition to providing a basis for self-assessment and a reference document for use by external assessors, establishing and maintaining an effective quality system will generate confidence within and between GMP national pharmaceutical inspectorates in the assessment of GMP compliance and/or good wholesale distribution practice.

(4) The PID cooperates with the GMP national pharmaceutical inspectorates of Member States, with the European Commission (EC), EMEA and the Pharmaceutical Inspection Cooperation Scheme (PIC/S) in exchanging experiences in the maintenance and operation of quality systems and in the further development of the community guideline concerning the quality systems for the GMP certificates.

(5) This document could be useful for (other) inspectorates, assessing compliance with other practices than GMP (such as the inspectorates which check the Good practice in pharmacies).

Art. 4.- In preparing this text, the working group was advised by:

EN 45004: 1995	General criteria for the operation of various types of bodies performing inspections;
EN 45012: 1998	General requirements for bodies operating assessment and certification/registration of quality systems;
ISO 9001-2000	Quality management systems-requirements;
ISO 9004-2000	Quality management systems: guidelines for performance improvements;
ISO 19011: 2002	Guidelines for quality and/or environmental managerial systems auditing;
PI 002-1: 2000	Recommendations on quality system requirements for pharmaceutical inspectorates ;

May 2001	Revised Compilation of Community procedures on administrative collaboration and harmonisation of inspections;
1998	Proceedings of the PIC-PIC/S seminar on quality systems for pharmaceutical inspectorates.

CHAPTER II
Purpose

Art. 5. - (1) The main purpose of a quality system is to ensure that adequate quality standards are maintained.

(2) The purpose of adopting a common standard for quality system requirements is to achieve consistency in inspection standards between GMP national pharmaceutical inspectorates and thus to facilitate mutual recognition of those inspectorates: this standard should facilitate implementation of the European Joint Audit Programme and PIC/S Joint Re-assessment Programme.

(3) Each GMP national inspection service should use this document as the basis for developing its own quality system, so that inspection activities within each inspection service are carried out in accordance with a system compatible with those of the other member states.

CHAPTER III
Scope

Art. 3. – (1) This Guideline specifies the quality system requirements for national pharmaceutical inspection services concerned with good manufacturing practice.

(2) The quality system should include all activities involved in the inspection process.

CHAPTER IV
Definitions

Art. 4. – Within this procedure, the following terms are defined as follows:

1. *quality system* - The sum of all that is necessary to implement an organisation's quality policy in an organisation and meet quality objective; it includes organisation structure, responsibilities, procedures, systems, processes and resources. Typically these features will be addressed in different kinds of documents as the quality manual and documented procedures, modus operandi.

2. *quality* - The totality of characteristics which must be periodically assessed in order to evaluate the established indicators in view of meeting the fixed objectives.

3. *pharmaceutical inspectorate* - The national body responsible for co-ordinating and carrying out GMP inspections, including inspections of pharmaceutical manufacturers and/or wholesale distributors; this could include making decisions concerning the issue or withdrawal of establishment licences for the respective site or authorisations for their activities, the issue or withdrawal of GMP certificates, providing advice and handling suspected quality defects of medicinal products.

4. *licence* – for the purpose of this Guideline, a licence is defined as an authorisation to manufacture or distribute medicinal products.

CHAPTER V
Quality Manual

Art. 5. - The PID shall prepare and maintain a quality manual covering the elements described in this Guideline. It is for each PID to decide on the format and style of their quality manual, but it must include, or make reference to, the quality system procedures which define the activities of the Inspectorate and the arrangements for maintaining the quality system; the reference used to complete it (as ISO or EN norms) must be quoted too.

CHAPTER VI
Administrative structure

Art. 6. - (1) The PID should be structured, organised and function shall be such as to enable it to meet the objectives of quality management and to ensure that impartiality is safeguarded.

(2) The PID, including sub-contracted personnel and experts which work according to a contract, shall be free from any commercial, financial and other pressures which might affect their judgement and freedom to act. The pharmaceutical inspectorate shall ensure that persons or organisations external to the inspection organisation cannot influence the result of inspections. The system for obtaining fees should not improperly influence the inspection procedure. Rules for deontology, ethic and conflict of interests should be clearly defined.

(3) The relationship of the PID to other agencies and to other organisations within and outside the Inspectorate shall be described where relevant.

(4) The PID shall implement a policy which distinguishes between the process of inspection and that of issuing a GMP manufacturing authorisation.

(5) Where relevant, the PID shall implement a policy which distinguishes between the process of inspection and that of providing an advisory service to clients; this service should be of benefit to all of industry and not solely to individual organisations.

CHAPTER VII
Organisation and management

Art. 7. - (1) Senior management of the PID shall make a formal commitment to the recommended principles embodied in this Guideline by ensuring that the quality policy of the Inspectorate is documented, that it is relevant to the objectives of that organisation and that it is implemented.

(2) The responsibility, authority and reporting structure of the PID shall be clearly defined and documented; the structure shall be defined in organisation charts and shall be supported by individualized written job descriptions for each member of staff.

(3) There shall be nominated an appropriately qualified and experienced person or persons with responsibility to carry out the quality assurance function, including implementing and maintaining the quality system; this person shall have direct access to senior management of the PID.

(4) The PID should have sufficient resources at all levels to enable it to meet its objectives effectively and efficiently; the senior management of the PID shall ensure that all personnel are competent and qualified to carry out their assigned duties and that they receive appropriate training. Such training shall be documented and its effectiveness assessed.

(5) There shall be a system for periodic management review of the quality system, carried out by the senior management; such reviews shall be documented and records shall be retained for a defined period.

CHAPTER VIII
Documentation and Change Control

Art. 8.- (1) The PID shall establish and maintain a system for the control of all documentation relating to the inspection system; this shall include policies, procedures, guidelines and any documents of external origin such as regulations and directives which may direct the activities of the Inspectorate or influence the quality of its operations.

(2) The document control system shall ensure that documents are authorised by appropriate persons prior to issue and that only current versions are held by nominated individuals. A record of all relevant documents and document holders shall be maintained. The system shall ensure that superseded documents are withdrawn from use. Superseded documents shall be retained for an appropriate and defined period.

(3) The documentation system shall ensure that any changes to documents are made in a controlled manner and are properly authorised. There shall be a means of identifying changes in individual documents.

CHAPTER IX
Records

Art. 9.- (1) The PID shall establish and maintain a system of records relating to its activities which complies with any existing regulations; if relevant, the system shall include documents received from licence applicants and licence holders as appropriate.

(2) Records shall provide detailed information about the planning of inspections, the way in which each inspection was applied, a description of the inspection process, follow-up activities and recommendations to the body responsible for issuing licences.

(3) All records shall be handled in such a way as to prevent their damage or loss and shall be retained for an adequate period consistent with any legal requirements; all records shall be maintained in confidence to the inspected party unless otherwise required under freedom of information legislation, or unless required under exchange of information procedures and arrangements between national pharmaceutical inspectorates, the EU/EEA, the EMEA and Mutual Recognition Agreement (MRA) or PECA partners.

CHAPTER X
Inspection Procedures

Art. 10. – (1) The PID shall conduct repeated inspections of manufacturers and/or wholesale distributors and shall issue inspection reports in accordance with national or European Community requirements as appropriate.

(2) The PID shall have the documented procedures and resources to enable inspection of manufacturing and wholesale distribution operations to be carried out in accordance with the official inspection plan; all instructions, standards or written procedures, worksheets, check lists and reference data relevant to the work of the pharmaceutical inspectorate shall be maintained up-to-date and be readily available to staff.

(3) When more than one inspector is involved in an inspection, a lead inspector shall be appointed to co-ordinate inspection activities; the inspection report shall normally be prepared by the lead inspector and shall be agreed by all participating inspectors.

(4) The inspection report format should be in compliance with the European model.

(5) The report should be sent to the responsible person of the inspected structure (preferably the qualified person); the lead inspector and all concerned inspectors should participate in assessing the reply.

(6) Observations and/or data obtained in the course of inspections shall be recorded in a timely manner to prevent loss of relevant information.

(7) Completed inspections shall be reviewed to ensure that requirements are met.

CHAPTER XI
Inspection resources

XI.1 Personnel

Art. 11. – (1) The PID shall possess the required personnel, expertise and other resources to perform inspections of manufacturers and/ or wholesale distributors (if appropriate) to determine their compliance with the principles and guidelines of good practices in force and with the relevant legislation.

(2) The staff responsible for inspections shall have appropriate qualifications, training, experience and knowledge of the inspection process. They shall have the ability to make professional judgements as to the conformance of the inspected party with the requirements of good practices and the relevant legislation and be able to apply an appropriate degree of risk assessment. They shall have knowledge of current technology, including computerised systems and information technology.

(3) The PID shall establish a documented system for recruiting and training its personnel and shall carry out a regular review of the training received and the training needs for each member of staff. Individual training and qualification records shall be maintained.

XI.2 Resources and equipment

Art. 12. - The PID shall have available the necessary resources and equipment to enable it to carry out its obligations effectively and efficiently.

CHAPTER XII
Internal Audit

Art. 13. - (1) The PID shall carry out and document periodic internal audits of its operations to assess compliance with the requirements of the quality system; results of internal audits and associated corrective actions shall be reviewed as part of the management review process.

(2) Internal audit processes and documents, auditors qualifications should be clearly defined (e.g. reference to ISO 19011 : 2002).

(3) Internal audit records shall be retained for a defined period.

CHAPTER XIII
Quality Improvement and Corrective/Preventive Action

XIII.1 Quality indicators

Art. 14. – (1) The PID should establish and maintain quality indicators related to its activities notably in the area of timeframe mentioned in existing EU or national regulations (e.g. licensing system for manufacturing or marketing authorisations) and/or documentation (e.g. writing reports).

(2) Quality indicators should be reviewed as part of the management review process.

XIII.2 Corrective/preventive action

Art. 15. – (1) The PID shall establish and maintain a procedure for the investigation of non-compliances with the quality system which are identified through internal or external audit of its activities. The procedure shall include the prescribing, implementation and verification of corrective action. The procedure shall also cover corrective actions arising from the investigation of complaints and other observations relating to the activities of the PID.

(2) The system shall include a description of the steps to be taken in assessing the need for quality improvement and preventive action.

(3) Corrective and preventive actions shall be documented and records shall be retained for a defined period.

CHAPTER XIV
Complaints

Art. 16. – (1) The PID shall establish and maintain a procedure for dealing with complaints relating to its activities, or those of its personnel, and any contracted persons or organisations. The procedure shall describe the application and verification of corrective action arising from the investigation of complaints.

(2) Records shall be maintained of all complaints received and actions taken and shall be retained for a defined period.

CHAPTER XV
Issue and Withdrawal of Licences and GMP Certificates

Art. 17. – (1) The PID shall establish and maintain a system for the issue and withdrawal of licences and GMP certificates.

(2) Licence and GMP certificate applications shall be assessed and determined in a timely manner and within any time limits imposed by national or European Community requirements: where time limits are imposed, inspection activities shall be included in the total time taken to determine the application.

(3) There shall be a documented system for taking appropriate action against a licence and/or a GMP certificate notably in the event of an adverse inspection report. The system shall include descriptions of the actions available to the PID; such actions may include suspension or revocation of the licence and/ or the GMP certificate(s). There shall be a system for assessing compliance of an organisation with the imposed licensing action concerning authorisation.

(4) The system shall include a description of the appeals procedure available to authorisation holders.

CHAPTER XVI
Handling Suspected Quality Defects and Rapid Alert System

Art. 18. – (1) The PID shall establish and maintain a system for handling of reports of suspected quality defects in medicinal products as defined in the related Community procedure.

(2) The PID shall establish and maintain a system for issuing Rapid Alerts as defined in the related Community procedure.

(3) The PID shall establish and maintain an updated list of all performed recalls.

CHAPTER XVII
Liaison with the Official Medicines Control Laboratory (OMCL)

Art. 19. - The PID should establish and maintain a defined liaison with the OMCL(s) of Romania (Control Department of primary materials and finished materials and the Evaluation and Control Department – biological products from the NMA) in order to exchange information concerning the quality of medicines on the national market; In particular, a validated SOP shall define sampling processes for starting materials and medicinal products.

HAPTER XVIII
Sub-Contracting and Assessing

Art. 20. – (1) The PID shall normally carry out the inspections for which it is responsible. Sub-contracted personnel or experts may be employed as part of an inspection team to assist or advise in a technical capacity, but that team shall normally be led by a GMP lead inspector.

(2) Experts shall be free from any commercial or financial pressures which might affect their freedom to act; they should follow defined rules to avoid conflict of interests and regarding ethic and deontology.

(3) Senior management of the pharmaceutical inspectorate shall ensure that these persons are appropriately qualified and experienced and that they are independent of any organisations which they might be asked to inspect.

CHAPTER XVIII
Publications

Art. 21. - The PID should have at its disposal an updated list of licensed manufacturers and/or wholesale distributors; the list shall be made available on demand made by authorised bodies.