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Quality systems framework for GMP inspectorates

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1. Introduction

1.1 It is important to establish and maintain a system for mutual recognition of national inspections in respect of the manufacture and, where relevant, wholesale distribution of medicinal products and for the administrative collaboration between Member States (MS) of the European Economic Area (EEA). The general requirements for national pharmaceutical inspectorates are to fulfil the requirements of national legislation and of the relevant European Directives for EEA countries. Specific obligations of inspections as contained in national law and if any European Directives must be included in the national Inspectorate's quality systems.

1.2 This document outlines the quality system requirements for GMP pharmaceutical inspectorates. It is intended that each GMP pharmaceutical inspectorate uses the document as the basis for developing and implementing its quality system and for preparing the quality manual. 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 compliance with good manufacturing practice and/or good wholesale distribution practice.

1.3 National GMP pharmaceutical inspectorates, the European Commission, the European Medicines Agency (EMA) and the Pharmaceutical Inspection Cooperation Scheme – (PIC/S) should co-operate with one another in exchanging experiences in the maintenance and operation of quality systems and in the further development of this document.

1.4 Only on voluntary basis, this document could be useful for (other) inspectorates assessing compliance with GXP or for the inspection of pharmacies.

1.5 The preparation of this text was advised by:

EN ISO/IEC 17020:2005	General criteria for the operation of various types of bodies performing inspections;
EN ISO/IEC 17023:2006	General requirements for bodies operating assessment and certification/ registration of quality system;
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 (Pharmaceutical Inspection Cooperation/Scheme) seminar on quality systems for pharmaceutical inspectorates.

2. Purpose

2.1 The primary purpose of a quality system is to ensure that adequate and equivalent quality standards are maintained throughout all Member States . 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. 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.

3. Scope

3.1 This document specifies the quality system requirements for national pharmaceutical inspection services concerned with good manufacturing practice.

3.2 Where wholesale inspections are required by national legislation to be carried out by GMP national pharmaceutical inspection service, this document specifies the quality system requirements for national pharmaceutical inspection services concerned with good wholesale distribution practice of medicinal products.

3.3 The quality system should include all activities involved in the inspection process.

4. Definitions

4.1 Quality system:

The sum of all that is necessary to implement an organisation's quality policy and meet quality objectives. 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.

4.2 Quality:

The totality of characteristics of an entity that bear on its ability to satisfy stated and implied needs.

4.3 Pharmaceutical Inspectorate:

The national body responsible for co-ordinating and carrying out GMP and GDP inspections, including inspections of manufacturers and/or wholesale distributors. If relevant, this could include making decisions concerning the issue or withdrawal of authorisations for their activities, the issue or withdrawal of GMP and GDP certificates, providing advice and handling suspected quality defects.

4.4 Licence:

For the purposes of this document, a licence is defined as an authorisation to manufacture or distribute medicinal products.

5. Quality manual

5.1 The pharmaceutical inspectorate shall prepare and maintain a quality manual covering the elements described in this document. It is for each pharmaceutical inspectorate 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.

6. Administrative structure

6.1 The structure, membership and operation of the GMP pharmaceutical inspectorate shall be such as to enable it to meet the objectives of quality management and to ensure that impartiality is safeguarded.

6.2 The personnel of the inspection service, including sub-contracted personnel and experts, 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.

6.3 The relationship of the pharmaceutical inspectorate to other agencies and to other organisations within and outside the Inspectorate shall be described where relevant.

6.4 The pharmaceutical inspectorate shall implement a policy which distinguishes between the process of inspection and that of issuing a GMP manufacturing authorisation.

6.5 Where relevant, the pharmaceutical inspectorate 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.

7. Organisation and management

7.1 Senior management of the pharmaceutical inspectorate shall make a formal commitment to the recommended principles embodied in this document 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.

7.2 The responsibility, authority and reporting structure of the pharmaceutical inspectorate shall be clearly defined and documented. The structure shall be defined in organisation charts and shall be supported by written job descriptions for each member of staff.

7.3 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.

7.4 Senior management of the competent authority shall ensure that the pharmaceutical inspectorate has sufficient resources at all levels to enable it to meet its objectives effectively and efficiently. The senior management of the pharmaceutical inspectorate 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.

7.5 There shall be a system for periodic management review of the quality system. Such reviews shall be documented and records shall be retained for a defined period.

8. Documentation and change control

8.1 The pharmaceutical inspectorate 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.

8.2 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.

8.3 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.

9. Records

9.1 The pharmaceutical inspectorate 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.

9.2 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.

9.3 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 EMA and Mutual Recognition Agreement (MRA) partners.

10. Inspection procedures

10.1 The pharmaceutical inspectorate shall conduct repeated inspections of manufacturers and/ or wholesale distributors and shall issue inspection reports in accordance with national or European Union requirements as appropriate.

10.2 The pharmaceutical inspectorate 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 guidelines, EU and national legislation and in accordance with a formal 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.

10.3 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.

10.4 The inspection report format should be in compliance with the European model.

10.5 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.

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

10.7 Completed inspections shall be reviewed to ensure that requirements are met.

11. Inspection resources

11.1 Personnel

11.1.1 The pharmaceutical inspectorate shall possess the required personnel, expertise and other resources to perform inspections of manufacturers and/ or wholesale distributors

to determine their compliance with the principles and guidelines of current good practices and with the relevant legislation.

11.1.2 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.

11.1.3 The pharmaceutical inspectorate 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.

11.2 Resources and equipment

11.2.1 The pharmaceutical inspectorate shall have available the necessary resources and equipment to enable it to carry out its obligations effectively and efficiently.

11.3 Risk management

11.3.1 The pharmaceutical inspectorate should implement risk management for assigning resources and prioritizing tasks and activities to carry out its obligations (e.g. planning of inspections).

11.3.2 The pharmaceutical inspectorate should also implement risk approach in the conducting of inspection.

12. Internal audit

12.1 The pharmaceutical inspectorate 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.

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

12.3 Internal audit records shall be retained for a defined period.

13. Quality improvement and corrective/preventive action

13.1 Quality indicators:

13.1.1 The pharmaceutical inspectorate should establish and maintain quality indicators related to its activities including timeframes mentioned in existing EU or national regulations (e.g. licensing system for manufacturing or marketing authorisations) and/ or documentation (e.g. writing reports).

13.1.2 Quality indicators should be reviewed as part of the management review process.

13.2 Corrective/ preventive action:

13.2.1 The pharmaceutical inspectorate 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 cover also corrective actions arising from the investigation of complaints and other observations relating to the activities of the Inspectorate.

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

13.2.3 Corrective and preventive actions shall be documented and records shall be retained for a defined period.

14. Complaints

14.1 The pharmaceutical inspectorate 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.

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

15. Issue and withdrawal of licences and GMP certificates

15.1 The pharmaceutical inspectorate shall establish and maintain a system for the issue and withdrawal of licences and GMP certificates, or for advising about the issue and withdrawal of licences and GMP certificates, as appropriate.

15.2 Licence and GMP certificate applications shall be assessed and determined in a timely manner and within any time limits imposed by national or European Union requirements. Where time limits are imposed, inspection activities shall be included in the total time taken to determine the application.

15.3 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 and for notifying other Member States. The system shall be based on QRM and include descriptions of the actions available to the Inspectorate; such actions may include suspension, variation 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.

15.4 The system shall include a description of the appeals procedure available to licence holders.

15.5 If the licensing system is not part of the pharmaceutical inspectorate, the latter should establish and maintain a defined liaison with it to obtain and guarantee the objectives mentioned above.

Marketing authorisation

15.6 The pharmaceutical inspectorate should establish and maintain a defined liaison with units responsible for marketing authorisation in order to facilitate actions against marketing authorisation following an inspection, if appropriate.

15.7 Other Member states should be informed with such actions, if appropriate.

16. Handling suspected quality defects and rapid alert system

16.1 The pharmaceutical inspectorate shall establish and maintain a system for handling of reports of suspected quality defects in medicinal products as defined in the related Union procedure. This system shall be based on QRM.

16.2 The pharmaceutical inspectorate shall establish and maintain a system for issuing Rapid Alerts as defined in the related Union procedure.

16.3 The pharmaceutical inspectorate shall establish and maintain an updated list of all performed recalls.

16.4 If the organization in charge of handling suspected quality defects and the rapid alert system is not part of the pharmaceutical inspectorate, the latter should establish and maintain a defined liaison with it to obtain and guarantee the objectives mentioned above.

17. Liaison with the official medicines control laboratory (OMCL)

17.1 The pharmaceutical inspectorate should establish and maintain a defined liaison with the OMCL(s) of its own MS 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.

18. Sub-contracting and assessing

18.1 The pharmaceutical inspectorate shall normally carry out the inspections for which it is responsible and whilst it may sub-contract some of its work it cannot sub-contract any of its responsibility. 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. Sub-contracted personnel shall be bound by the requirements of the quality system and there shall be a written contractual agreement between the parties.

18.2 Persons or organisations to whom inspection activities are contracted out and 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. 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.

19. Publications

19.1 The pharmaceutical inspectorate 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.