# Annex 5

## Quality management system requirements for national inspectorates

### Background

During the Joint Meeting on Regulatory Guidance for Multisource Products (Copenhagen, July 2016), several World Health Organization (WHO) guidance documents were identified for update. In October 2016, the Fiftieth WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) confirmed the need to update the selected guidelines.

Following up on the recommendation from the Fiftieth ECSPP, the WHO Secretariat conducted a detailed analysis of the cluster of guidelines proposed for revision. The outcome of this analysis was discussed during the informal consultation on Good Practices for Health Products Manufacture and Inspection (Geneva, July 2018). In particular, considering that the *WHO Quality systems requirements for national good manufacturing practice inspectorates* (*1*) defines the basic requirements applicable to quality systems for the operation of inspection services within national regulatory authorities (NRAs) concerned with good manufacturing practices (GMP) inspections, the WHO Secretariat proposed a strategy for revision that includes aligning the guidance with the principles of ISO 9001:2015 (*2*) and with relevant Pharmaceutical Inspection Convention/Co-operation Scheme (PIC/S) guidance (*3*), as well as broadening its scope to include all good practices (GXP)-related inspections conducted by an NRA.

The Fifty-second ECSPP endorsed the proposal for revision and recommended the WHO Secretariat to revise the *WHO Quality systems requirements for national good manufacturing practice inspectorates* (1), aligning its content to international standards and the latest quality management systems (QMS) principles, and to expanding the scope.

# 1. Introduction

1.1 This document describes the quality management system (QMS) requirements for the operation of inspection services within national regulatory authorities (NRA) or other state structures (for the purpose of this guidance, the term "NRA" will be used in the text to represent both NRAs and other state structures). It is intended that each inspection service uses these requirements as the basis for developing and implementing its own QMS. Where the inspectorate operates under the umbrella of the NRA QMS, consideration should be given to the *WHO guideline on the implementation of quality management systems for national regulatory authorities* (*4*).

1.2 The adoption of a common standard for QMS requirements is an essential element in achieving consistency in inspection practices and facilitating structured communication with other units of the NRA, as well as enabling mutual confidence and permitting recognition between pharmaceutical inspectorates.

# 2. Scope

2.1 This document outlines the QMS requirements for pharmaceutical inspectorates that are competent for the oversight of GXP operations.

# 3. Glossary

The definitions given below apply to the terms used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts.

**corrective actions.** Steps taken to eliminate the cause of existing nonconformities in order to prevent recurrence. The corrective action process tries to make sure that existing nonconformities and potentially undesirable situations do not happen again.

**good practices (GXP).** The group of good practice guides governing the preclinical, clinical, manufacturing, testing, storage, distribution and post-market activities for regulated pharmaceuticals, biologicals and medical devices, such as good laboratory practices (GLP), good clinical practices (GCP), good manufacturing practices (GMP), good pharmacovigilance practices (GPP) and good distribution practices (GDP).

**internal audit.** An examination and assessment of all or part of a quality system, with the specific purpose of improving it. An internal audit should be conducted by an independent (of the function to be audited) and qualified team of experts designated by the management for this purpose.

**quality indicators.** Selected data intended to be monitored and used in assessing trends in performance.

**quality management system.** An appropriate infrastructure, encompassing the organizational structure, procedures, processes, resources and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

**quality manual.** A document that includes the quality policy and objectives and describes the various elements of the QMS.

**quality policy.** A brief statement that describes the organization's purpose, overall intentions and strategic direction; provides a framework for quality objectives; and includes a commitment to meet applicable requirements.

**rapid alert.** An urgent notification submitted by an NRA participating in the rapid alert system concerning measures taken against a product placed on the market that poses a risk to consumers' health and/or safety.

**risk management.** The systematic application of quality management policies, procedures and practices to the tasks of assessing, controlling, communicating and reviewing risk.

**standard operating procedure (SOP).** An authorized written procedure giving detailed instructions for performing a task or following a process in accordance with legislation, official guidance or internal standards.

## 4. Quality management system

4.1 The concept of a QMS is wide-ranging and covers all matters that are necessary to implement the inspectorate's quality policy and to meet predefined objectives.

4.2 The QMS should define the inspectorate's scope and context within the regulatory mandate, as well as covering all functions, processes and activities.

4.3 The primary aims of an inspectorate's QMS are:

1. to ensure its ability to consistently provide services that meet the organization's objectives, legal requirements and interested parties' expectations; and

2. to facilitate continual improvement and provide a sound basis for sustainable development to comply with statutory and regulatory requirements.

4.4 The QMS should at least describe and manage organizational structure, responsibilities, procedures, systems, processes and resources required, to provide value and achieve results for the inspectorate and relevant interested parties.

4.5 Typically, the legal basis for the establishment of the inspectorate, its mandate, the quality policy and the principles of the QMS should be documented in a quality manual or equivalent document.

4.6 The QMS should enable senior ("top") management to best use available resources and systems in order to achieve the inspectorate's targets and quality objectives. Senior management's commitment and active participation is essential to ensure implementation of the QMS and to support staff within the inspectorate.

## 5. Context of the inspectorate

5.1 The legal basis for the establishment of the inspectorate and its mandate, as well as statutory and regulatory responsibilities and functions, should be clearly defined.

5.2 The inspectorate should determine its scope and strategic direction, in order to achieve the intended objectives.

5.3 The structure and operation of the inspectorate should be such that impartiality and independence are safeguarded. Rules for deontology, confidentiality, ethics and conflicts of interest should be clearly defined and obeyed. Where relevant, the inspectorate should implement a policy that distinguishes between the process of inspection and that of providing an advisory service. This service should be of benefit to all of industry and not solely to individual organizations.

5.4 The relationship of the inspectorate with other departments within the same NRA, and other agencies and organizations outside the inspectorate, as well as any other stakeholders, should be described and documented where relevant.

## 6. Management and leadership

6.1 Senior management should make a formal commitment to the implementation of a documented quality policy that is compatible with statutory requirements and relevant objectives.

6.2 Senior management should ensure that the inspectorate's services and functions are aligned with regulatory requirements and the NRA's objectives, as well as meeting interested parties' expectations.

6.3 Senior management is accountable for the integration of QMS requirements into the inspectorate's processes and functions; for communicating the importance of QMS principles; and for the overall effectiveness of the QMS. In addition, senior management should promote the application of risk management principles and support the engagement and contribution of personnel in improving the QMS.

6.4 Senior management should ensure that the pharmaceutical inspectorate has sufficient and appropriate resources at all levels to enable it to meet its objectives. Responsibilities, authorities and the reporting structure for relevant roles should be clearly defined and documented in the QMS. The structure should be defined in organization charts.

6.5 An appropriately experienced and qualified person should be nominated as a QMS responsible person. This person should have direct access to senior management. If necessary, this task may be assigned to more than one person.

6.6 There shall be a system for periodic management review of the QMS effectiveness, including process improvements. Such reviews should be documented and records should be maintained for a defined period.

## 7. Management system planning

7.1 The inspectorate should establish appropriate objectives for the intended level of service and of its functions, which should be consistent with the quality policy and regulatory requirements. Principles of risk management and sustainable development should be considered for the establishment of these objectives.

7.2 These objectives should be communicated to personnel at all levels and be updated whenever necessary.

7.3 Appropriate resources should be available to meet these objectives. Roles and responsibilities should be defined and, where appropriate, timelines for completion should be established. Systems for monitoring and evaluating results should be established. All necessary information on quality objectives should be maintained.

7.4 A documented change management system should be established, to ensure that change requests are assessed, approved or rejected; that appropriate resources are allocated; and that roles and responsibilities are defined. Any change should be documented, communicated to the personnel and evaluated after implementation, to ensure the objectives are met. The change management system should ensure that continual improvement is undertaken in a timely and effective manner.

## 8. Resources

8.1 The inspectorate should have an organizational structure, required resources (financial, human, facilities and others) and documented procedures that enable it to meet its objectives; to perform inspection activities in accordance with official GXP guidelines and national legislation; and to carry out its functions and operations satisfactorily. Where necessary, measures and resources for the safety of personnel should be available.

### Personnel

8.2 The inspectorate should employ the required personnel possessing the appropriate expertise to perform its functions, including inspections, and to determine whether the inspected entities comply with the principles of current GXP guidelines and with relevant legislation.

8.3 Personnel responsible for inspections should have appropriate qualifications, including education, training, experience and knowledge of the inspection process and subject, and should be periodically evaluated. They should have the ability to make professional judgements as to the conformity of the inspected party with the requirements of GXP and the relevant legislation, and be able to apply risk management principles in their decision-making process.

8.4 The inspectorate should ensure that induction and continuous training is provided to inspection personnel on administrative, regulatory and technical topics, to maintain the inspectors' competency aligned with current industry practice, technological advancements and regulatory changes. Training should be documented and its effectiveness assessed periodically.

8.5 The inspectorate should maintain documented and up-to-date information on the relevant qualifications, training and experience of each inspector.

8.6 Personnel should have clear, up-to-date and documented job descriptions specifying their duties and responsibilities.

8.7 When products are procured from a third party and/or services are subcontracted to an external body or expert, the inspectorate should ensure that the third party meets predefined documented criteria, qualifications and the relevant requirements of the quality management system. Senior management should ensure that these external bodies or experts are periodically evaluated. Third party responsibilities and liability should be clearly defined in the contract or agreement.

8.8 All personnel employed or contracted by the inspectorate should be bound by the requirements of the quality system, obey the inspectorate's code of conduct and not be subject to any commercial, financial or other pressures that might affect their judgement and freedom to act. They should not be under the control of the pharmaceutical industry and must be assessed for potential conflict of interest. Personnel and third-party declarations of conflict of interest should be maintained, reviewed periodically and updated where necessary. It should be ensured that any decision-making process remains with the inspectorate and is not influenced by any third party.

### Infrastructure

8.9 Personnel should be provided with the necessary infrastructure and appropriate work environment to enable them perform their functions and meet the quality objectives. Infrastructure includes, but is not limited to:

- buildings, workspace and associated facilities;
- qualified equipment, including hardware and software;
- transportation resources; and
- information and communication technology.

## 9. Documentation

### General

9.1 The inspectorate should establish and maintain a system for the control of all documentation, including electronic files, relating to the inspectorate's QMS and activities. This should include policies, procedures, guidelines, records and any documents of external origin, such as legislation, which

may directly or indirectly influence the activities of the inspectorate; or documents received from pharmaceutical companies and relevant organizations, as appropriate.

9.2 The inspectorate should ensure that its functions and operations are described in SOPs that clearly define the required responsibilities, processes and actions. These may include, but not be limited to, training; inspections; reporting after inspections; handling of complaints; licensing (issue, suspension, withdrawal); certification; handling of quality, safety and efficacy issues; documentation control; change and deviation management; inspection planning; risk management; and the handling of appeals.

9.3 The system and activities relating to advising on, issue, withdrawal or suspension of licences, registration or certifications; and the application of other regulatory sanctions on facilities, organizations, products or operations, should be detailed in procedures and be in accordance with relevant guidelines and national legislation.

9.4 The inspectorate should establish procedures describing communication with other NRA units and external interested parties (e.g. industry, media) considering any statutory and regulatory requirements, where appropriate. Similarly, a procedure for exchanging regulatory information with other NRAs or national quality control laboratories should be available.

9.5 Activities relating to the sampling and testing of pharmaceutical products and raw materials should be described in a procedure that should also include the process for handling nonconforming products (e.g. substandard or falsified medical products).

9.6 The inspectorate should have procedures on handling quality, safety and efficacy issues that may lead to recall or withdrawal of products from the market. Where applicable, the inspectorate should establish and maintain a system for communicating rapid alerts. Records of recalls and withdrawals should be maintained in accordance with national legislation.

9.7 The inspectorate should have documented procedures for dealing with complaints arising from its activities or those of its personnel and any contracted person or organization. A record should be maintained of all complaints received and the actions taken by the inspectorate. These records should be retained for a specified period of time.

9.8 The inspectorate should have procedures for consideration of appeals against its decisions.

9.9 The documentation control system should ensure that:

- documents are identified by title, author, reviewer, approver and unique identification. They should be dated and authorized by the appropriate persons prior to issue;
- current versions of documents are held by nominated personnel;
- a register of all relevant documents and document holders is maintained;
- superseded documents are withdrawn from use but are retained for defined periods of time;
- any changes to documents are made in a controlled manner and are properly authorized. There should be a means of identifying changes in individual documents;
- records relating to the inspectorate's activities and functions are readily available and are retained for an adequate period, in line with legal requirements or internal standards;
- records comply with the relevant obligations under national legislation;
- records are safely stored during their retention period and held under conditions that guarantee their security and confidentiality unless otherwise required by national legislation. The destruction of records after their retention period should follow a predefined procedure; and
- electronic documentation and record management systems provide at least the same level of assurance, compliance, accuracy and security as a manual system.

## Inspection process and documents

9.10 An inspection should be categorized in accordance with GXP guidelines (e.g. GMP, GDP, GCP) and its scope (e.g. product, process) and type (e.g. triggered, routine, follow-up) should be appropriately defined and documented.

9.11 The inspectorate should plan inspections in advance and elaborate a written programme as part of the inspectorate's annual workplan. Risk management principles should be considered when establishing an inspection programme and prioritizing inspections, as well as when conducting an inspection. Where repeated inspections of a company or organization have to be carried out, the frequency should be determined based on risk management principles defined in a procedure.

9.12 Inspection-related documents and records, as defined in relevant inspection procedures (e.g. inspection plan, aide-mémoire, checklists, worksheets and company documents and records), should be maintained for a defined period.

9.13 When more than one inspector is involved in an inspection, a lead inspector should be appointed to coordinate inspection activities. The inspection report should be prepared by the lead inspector, with the assistance of all participating inspectors and/or experts, and should be agreed upon by all participating inspectors and/or experts.

9.14 The inspection report should follow a pre-approved format. Observations and/or data obtained in the course of inspection should be recorded in a timely manner, in order to prevent loss of relevant information.

9.15 The inspection report should be sent to the inspected company or organization within the inspectorate's established timelines. The lead inspector and all concerned inspectors and/or experts should participate in assessing the company's response, to determine the appropriateness of corrective and preventive actions as well as the GXP compliance status of the company or organization.

9.16 Completed inspections should be reviewed to ensure that all reporting and regulatory requirements are met.

## 10. Operational planning and performance evaluation

10.1 An annual workplan should be developed, documented and periodically reviewed by senior management, including all the inspectorate's activities, in accordance with a written procedure. Regulatory, statutory and scientific requirements should be taken into account during the planning of operations and services. Consideration should also be given to the availability of required resources and the ability to consistently provide services that meet legislative requirements and stakeholder expectations. Risk management principles should be used during planning, to determine, monitor and manage risks and to identify opportunities for process improvements. Any changes to the workplan should follow the inspectorate's change management system.

10.2 Appropriate quality indicators and methods should be established, in order to monitor and periodically evaluate the inspectorate's processes and level of improvement and service (including contracted-out services) and demonstrate that they were carried out as planned and met predefined

quality objectives. These quality indicators, methods, analyses and results should be documented.

10.3 The results of the analyses should be used to evaluate the performance and effectiveness of the QMS, the adequacy of actions taken to address risks, and the need for further improvements.

## Internal audits

10.4 The inspectorate should implement a system of periodic and documented internal audits of its operations, to assess compliance with the requirements of the QMS. Internal audits should be conducted at least once a year.

10.5 Internal audit processes, criteria, scope and documents should be defined. Auditors' qualifications and selection criteria should be documented. Internal audit records, including the findings, conclusions, recommendations and follow-up actions, should be retained for a defined period.

10.6 Corrective actions corresponding to audit findings should be identified, documented and implemented in a timely manner. The effectiveness of these actions should be evaluated and the risk plan should be updated to take note of the root causes of the nonconformances.

## Management review

10.7 Senior management should review the inspectorate's QMS at planned intervals, to ensure its continuing suitability, adequacy, effectiveness and alignment with the inspectorate's strategic direction and legislative requirements. Management reviews should be conducted at least once a year.

10.8 A management review should include, but not be limited to:

- the status of the actions from previous management reviews;
- any internal or external changes affecting the QMS;
- any deviations affecting the functionality of the QMS;
- the extent to which quality objectives have been met;
- process performance analyses;
- audit results and the effectiveness of corrective actions;
- complaints and appeals;
- the adequacy of resources;

- any identified risks and mitigation measures; and
- opportunities for improvements.

## 11. Publications

11.1 The inspectorate should issue and maintain an up-to-date list of inspected and licensed facilities and organizations, including information on the outcome of inspections. This list may become publicly available in accordance with national legislation.

11.2 The inspectorate should ensure that other relevant publications, such as technical guides, GXP guidelines and regulatory requirements, are publicly available.

## References


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## Further reading


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