WHO GUIDELINE ON THE IMPLEMENTATION
OF QUALITY MANAGEMENT SYSTEMS
FOR NATIONAL REGULATORY AUTHORITIES
(January 2019)

DRAFT FOR COMMENTS

Please send any comments you may have to Dr S. Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms (kopps@who.int), with a copy to Ms Sinéad Jones (jonessi@who.int) by 30 March 2019.

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Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms, Department of Essential Medicines and Health Products, World Health Organization, CH-1211 Geneva 27, Switzerland, fax: (41 22) 791 4856, email: kopps@who.int.

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# SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/19.783:

## WHO GUIDELINE ON THE IMPLEMENTATION OF QUALITY MANAGEMENT SYSTEMS FOR NATIONAL REGULATORY AUTHORITIES

<table>
<thead>
<tr>
<th>Activity</th>
<th>Date</th>
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</thead>
<tbody>
<tr>
<td>Prepare and present concept paper to recommend the development of the 'WHO guidelines on implementation of quality management systems (QMS) for national medicines regulatory authorities'.</td>
<td>16-20 Oct 2017</td>
</tr>
<tr>
<td>Develop the TOR for drafting group members, including the selection criteria and invitation letter to join the drafting group.</td>
<td>15 Nov 2017</td>
</tr>
<tr>
<td>Contact selected countries and call for experts to join the drafting group according to selection criteria and follow up on communications. Select and appoint drafting group.</td>
<td>15 Nov 2017 to 15 Jan 2018</td>
</tr>
<tr>
<td>Select and appoint drafting group based on meeting specified criteria and invite them officially to join the group, WebEx conference, and first face-to-face drafting group meeting.</td>
<td>15 Jan 2018</td>
</tr>
<tr>
<td>Kick-off drafting group meetings (WebEx).</td>
<td>13-15 Feb 2018</td>
</tr>
<tr>
<td>First face-to-face meeting with drafting group, Tunis, Tunisia.</td>
<td>12-16 Mar 2018</td>
</tr>
<tr>
<td>QMS workshop in Burkina Faso. Complete self-benchmarking by end of workshop. Run survey and summarize countries' expression of needs for WHO guideline on QMS implementation.</td>
<td>16-20 Apr 2018</td>
</tr>
<tr>
<td>Produce first draft (V1) of the guidelines.</td>
<td>29 Jun 2018</td>
</tr>
<tr>
<td>Review of draft V1 by CRS, rapporteur and ISO expert.</td>
<td>30 Jun to 10 Jul 2018</td>
</tr>
<tr>
<td>Deliver final V1 for review by drafting group.</td>
<td>11 Jul 2018</td>
</tr>
<tr>
<td>Conduct WebEx meetings with drafting group.</td>
<td>7-9 Aug 2018</td>
</tr>
<tr>
<td>Drafting group members submit comments on V1.</td>
<td>31 Jul 2018</td>
</tr>
<tr>
<td>Address comments from drafting group and produce V2 for review by CRS and hand over to TSN.</td>
<td>31 Aug 2018</td>
</tr>
<tr>
<td>ECSPP meeting. Update on status of guidelines development.</td>
<td>15 Oct 2018</td>
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<tr>
<td>Event</td>
<td>Date</td>
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<td>----------------------------------------------------------------------</td>
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<tr>
<td>Submit to TSN for Public Consultation 1.</td>
<td>31 Oct 2018</td>
</tr>
<tr>
<td>Public consultation 1.</td>
<td>31 Oct – 31 Dec 2018</td>
</tr>
<tr>
<td>Address and incorporate comments from public consultation 1, produce draft to share with drafting group, address comments from drafting group, prepare (V3) of the guidelines.</td>
<td>31 Dec 2018</td>
</tr>
<tr>
<td>Provide opportunity for the drafting group to comment on current version via WebEx.</td>
<td>1 Feb 2019</td>
</tr>
<tr>
<td>Organize and conduct informal consultation with international stakeholders and drafting group (three-day meeting)</td>
<td>10 Feb 2019</td>
</tr>
<tr>
<td>Informal consultation on V3, Tunis, Tunisia.</td>
<td>mid-March 2019</td>
</tr>
<tr>
<td>Post-meeting edits/clean up and submit to TSN for public consultation 2 (V4).</td>
<td>15 Mar to 15 Jun 2019</td>
</tr>
<tr>
<td>Public consultation 2.</td>
<td>15 Jul 2019</td>
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<tr>
<td>Collate comments and circulate for final review by drafting group.</td>
<td></td>
</tr>
<tr>
<td>Hand-off to TSN for review by ECSPP in advance to annual meeting in October where the guidelines will be presented for adoption.</td>
<td>31 Jul 2019</td>
</tr>
<tr>
<td>Review guidelines for possible endorsement.</td>
<td>Oct 2019</td>
</tr>
<tr>
<td>Address all comments and requests from ECSPP, produce final version of guidelines (V5).</td>
<td>31 Dec 2019</td>
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Abbreviations

NOTE: This section will be updated in the final stages of guideline development.

CAPA Corrective action and preventive action
CI Continual improvement
DI Documented information
GBT Global Benchmarking Tool
GCP Good Clinical Practice
GMP Good Manufacturing Practice
GRP Good Regulatory Practice
ICT Information and Communication Technology
IMS Integrated Management System
ISO International Standards Organization
KPI Key Performance Indicators
LIMS Laboratory Information Management System
MA Marketing Authorization
M and M Monitoring and Measurements
MC Market Surveillance and Control
MOF Ministry of Finance
MOH Ministry of Health
MRM Management Review Meeting
MS Member States
NCL National Control Laboratory
NRA National Regulatory Authority
PDCA Plan, do, check and act
P and S Products and Services
QMP Quality Management Principles
QMS Quality Management System
SF Substandard and Falsified
SLP Summary Lot Protocol
SOP Standard Operating Procedure
TM Top Management
TRM Technical Review Meeting
VL Vigilance (one of the NRA regulatory functions)
WHO World Health Organization
1. Introduction

1.1 Background

Implementation of the Thirteenth World Health Organization (WHO) General Programme of Work (2019-2023) as adopted by the Seventy-first World Health Assembly (2018) and the WHO Leadership Priorities, has attracted much international public health attention to the theme of Universal Health Coverage (UHC) and increased access to safe and effective medical products.

Several World Health Assembly (WHA) resolutions, including WHA67.20 (2014), mandate WHO to provide support to its Member States (MS) in strengthening national regulatory systems for medical products. It recognizes that “effective regulatory systems are an essential component of health system strengthening and contribute to better public health outcomes; that regulators are an essential part of the health workforce, and that inefficient regulatory systems themselves can be a barrier to access to safe, effective and quality medical products” [1]. Accordingly, WHO’s vision is for all MS to have a regulatory system that ensures medical products and other health technologies in the market meet internationally recognized standards of quality, safety, and efficacy to facilitate access to these products.

National Regulatory Authorities (NRAs) are responsible for facilitating access to safe, quality and effective medical products within the respective MS and for consistently demonstrating that the services they provide meet legal and regulatory requirements; they deliver effective and efficient services; and they can evaluate performance and make improvements. A quality management system (QMS) can ensure that the products or services an NRA provides consistently meet statutory and regulatory standards and meet customers’ expectations. A QMS provides opportunities to enhance customer satisfaction; address context-associated risks and opportunities for continuing improvement; demonstrate conformity to specific QMS requirements; and assure the quality, safety and efficacy of medical products.

In 2015, WHO developed and launched the Global Benchmarking Tool (WHO GBT). This tool assists regulators worldwide in evaluating the developmental status of their regulatory system and its related functions. The GBT includes one indicator that assesses the NRAs’ level of development with respect to QMS.1 Benchmarking results of 43 low and middle-income countries indicate that most NRAs need to establish and implement, or if already established, enhance and maintain QMS.

1 Appendix 1 describes the relationship between QMS and the WHO GBT.
QMS implementation is challenging for NRAs due to the diversity of NRA organizational structures, the different levels of NRA development and the number of regulatory functions that need to be addressed. Several international guidelines on QMS have been published; however, none of these focuses specifically on NRAs. Other existing guidelines are field specific [11-20]. At the request of MS, WHO developed this document to provide tailored guidance to NRAs on QMS implementation.

1.2 Basis for the guideline

ISO Standard 9001:2015 ‘Quality management systems- Requirements’ is a well-known international standard published by the International Organization for Standardization (ISO). The standard is applicable to both products and services and provides requirements for establishing a QMS that can be applied to any organization, public or private, big or small, and to a variety of fields. The WHO GBT QMS sub-indicators are based on this standard. Accordingly, ISO standard 9001:2015 offers a practical model to establish and implement QMS for NRAs [7].

1.3 Objective

The objective of this guideline is to assist NRAs to develop, implement or improve quality systems using ISO Standard 9001:2015, and subsequent updates, as a basis. The expectation is that this will increase the reproducibility of the quality and consistency of the outputs (products and services), customer focus and stakeholder satisfaction.

1.4 Scope

This is an overarching guideline that can be applied across all regulatory functions, including registration and marketing authorization, vigilance, market surveillance and control, licensing establishments, regulatory inspections, laboratory access and testing, clinical trials oversight and lot release.

This guideline, for practical and illustrative purposes, only provides examples for the following four NRA functions:

- Registration and marketing authorization (MA)
- Vigilance (VL)
- Lot release (LR)
Market surveillance and control (MC).

Each of these functions was selected for different reasons: MA is a critical function, but no specific guidance is available; VL is the weakest function as evidenced by the results from WHO benchmarking of NRAs; LR is the vaccine-specific regulatory function and requires particular attention; and MC was selected because sub-standard and falsified medical products are a major issue in developing countries.

Although the examples are specific to these four functions, it is important to note that the principles can be applied to any regulatory function.

This guideline can be utilized by all institutions responsible for regulatory oversight of medical products including the national control laboratory (NCL) and any other agency or institute involved in regulatory oversight, as well as customers and other stakeholders.

1.5 Instructions for using the guideline

This guideline provides interpretation for implementation purposes specific to NRAs. It does not duplicate the text from the ISO Standard 9001:2015, therefore it is important to read this guideline in conjunction with ISO Standard 9001:2015 and its supporting documents.

1.5.1 Required documents

As a first step, NRAs should have the following three documents on hand.

- ISO Standard 9001:2015 is the standard upon which this guideline is based.
- ISO Standard 9000: 2015 provides QMS-related vocabulary (terms and definitions) and describes the fundamentals and principles of QMS [8].
- ISO/TS 9002:2016 provides generic guidance (not specific to NRAs) on how to apply ISO Standard 9001:2015 by describing individual clauses and giving examples of steps any organization can take to meet the requirements [21].

1.5.2 Recommended documents

The additional documents listed below may be of interest to NRAs but are not required.

- Quality management principles (ISO brochure) [34]
1.5.3 Accessing the documents

Complete information on QMS-related ISO standards, free brochures and publications and links for purchase of these documents are available on the ISO website https://www.iso.org/iso-9001-quality-management.html. Alternatively, ISO standards can also be purchased from the national standard body in the NRA’s country.

1.5.4 Guidance for NRAs on the requirements for ISO 9001:2015

This document provides guidance on how the ISO Standard 9001:2015 requirements can be applied to QMS implementation for NRAs. Section 4.3 of this guideline is a clause by clause correlation to Clauses 0 to 10 of ISO Standard 9001:2015. NRAs are advised to use the following step-wise approach:

3. Refer to the corresponding clause in section 4.3 of this guideline, which contains guidance and examples specific to NRAs.

NRAs are referred to ISO Standard 9000: 2015 [8] for terms and definitions. Definitions of some important terms are included in Section 3 of this guideline.

2. General considerations

Use of this guideline is voluntary. NRAs are free to use this guideline or to choose other methods for implementing QMS.
NRA.s from any country can use this guideline regardless of the NRA’s size or organizational structure.

WHO considered three NRA organizational models (centralized, decentralized and discrete)\(^2\) and examined whether the differences in their organizational structure impacted the approach to QMS implementation. WHO concluded that regardless of the organizational structure of the NRA, each institution involved in the regulatory oversight of medical products should establish its own QMS for the products and services it provides.

Preferably, all regulatory institutions in a single country should follow the same standard for consistency and coherency, ideally ISO Standard 9001:2015, since this standard provides the basis (principles and requirements) for adaptation and implementation of QMS to any field.

Certain ISO 9001:2015 standard elements are systemic while others are functional. This guideline discusses them in an integrated manner tailored to the specific needs of NRAs.

WHO does not provide QMS certification services and cannot issue QMS certification or conduct official QMS audits of NRAs. However, as part of the regulatory systems strengthening program, WHO can provide technical support for benchmarking.

Good Regulatory Practices (GRP) provide a means for establishing sound, affordable, and effective regulation of medical products as an important part of health system strengthening. GRP are a set of practices applied to the development, implementation and maintenance of controls, including laws, regulations and guidelines, to achieve a public policy objective. There are nine GRP principles [6].

- **Legality:** Regulation should have a sound legal basis and should be consistent with existing legislation, including international norms or agreements.
- **Impartiality:** Regulation and regulatory decisions should be impartial to be fair and to avoid conflicts of interest, unfounded bias or improper influence from stakeholders.
- **Consistency:** Regulations should be clear and predictable; both the regulator and the regulated party should understand the behaviour and the conduct that are expected and the consequences of noncompliance.
- **Proportionality:** Regulations and regulatory decisions should be proportional to the risk and should not exceed what is necessary to achieve the objectives.
- **Flexibility:** Regulations should not be prescriptive; they should allow flexibility in

\(^2\) A more detailed description of the NRA models is provided in practical help box 1.
responding to a changing regulated environment and different or unforeseen circumstances.

- **Effectiveness**: Regulations should produce the intended result.
- **Efficiency**: Regulations should achieve their goals within the required time, effort and cost.
- **Clarity**: Regulations should be accessible to, and understood by, the users;
- **Transparency**: Regulatory systems should be transparent; requirements and decisions should be made known to affected parties and, where appropriate, to the public in general.

These principles may be used while framing the quality policy and objectives of the NRA and compliance achieved through the implementation of QMS. A WHO guidance document on GRP is in development [6].

### 3. Definition of terms

**NOTE:** This section will be refined and updated in the final stages of guideline development.

The definitions provided below apply exclusively to the terms used in this guidance document.

Terminology and definitions in this document that are specific to NRAs are those of WHO [32, 33]. Additional terms related to QMS can be found in ISO Standard 9000:2015 [8].

**A**
- Activities- project management smallest identified object of work in a project
- Assessment- Systematic, independent and documented process for obtaining assessment evidence and evaluating it objectively to determine the extent to which assessment criteria are fulfilled
- Audit- Systematic, independent and documented process for obtaining objective evidence and evaluating it objectively to determine the extent to which the audit criteria are fulfilled

**B**
- Batch- A defined quantity of product processed in a single process or series of processes and therefore, expected to be homogeneous

**C**
- Certification- The term applied to third party attestation related to products, processes, systems or persons
- Competence- Ability to apply knowledge and skills to achieve intended results. Commitment
- Conformity- Fulfilment of a requirement
- Continual improvement- Recurring activity to enhance performance
- Control- The taking of all necessary actions to ensure and maintain compliance with the criteria established in the statutory and regulatory requirements
- Corrective action- Action to eliminate the cause of nonconformity and to prevent recurrence
• Counterfeit- A counterfeit medicine is one which is deliberately and fraudulently mislabelled with respect to identity and/or source
• Customer- Person or organization that could or does receive a product or a service that is intended for or required by this person or organization
• Customer satisfaction- Customer’s perception of the degree to which the customer’s expectations have been fulfilled
• Customer service interaction of the organization with the customer throughout the life cycle of a product or a service

D
• Defect- Non-fulfilment of a requirement related to a specified use
• Documented information- information required to be controlled and maintained by an organization and the medium on which it is contained

E
• Effectiveness Extent to which planned activities are realized and results achieved
• Efficiency Relationship between the result achieved and the resources used

F
Feedback- customer satisfaction opinions, comments and expressions of interest in a product, a service or a complaints-handling process

G
• Good manufacturing practice That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization
• Good regulatory practice Set of practices that are to be applied to the development, implementation and maintenance of controls – including laws, regulations and guidelines – to achieve a public policy objective
• Governance Refers to the different ways that organizations, institutions, businesses and governments manage their affairs. Governance is the act of governing and thus involves the application of laws and regulations, but also of customs, ethical standards and norms

K
• Key performance indicator- A quantifiable measure used to evaluate the success of an organization, employee, etc. in meeting objectives for performance

M
• Management system- System to establish policy and objectives and to achieve those objectives
• Measurement management system- Set of interrelated and interacting elements necessary to achieve metrological confirmation and continual control of measurement processes
• Medical products- A term that includes medicines, vaccines, diagnostics and medical devices

N
• National Regulatory Authority- WHO terminology for national medicines regulatory authorities. NRAs should promulgate and enforce medicines regulations
• Non-conformity- Non-fulfilment of a requirement

P
• Procedure- Specified way to carry out an activity or a process
• Process- Set of interrelated or interacting activities that use inputs to deliver an intended result
• Process approach- Any activity or set of activities, that uses resources to transform inputs into outputs can be considered a process
• Product - Output of an organization that can be produced without any transaction taking place between the organization and the customer

• Provider (Supplier) - Organization that provides a product or a service

• Qualification - Action of proving that any premises, systems and items of equipment work correctly and lead to the expected results

• Quality - Degree to which a set of inherent characteristics of an object fulfils requirements

• Quality assurance - Part of quality management focused on providing confidence that the quality requirements will be fulfilled

• Quality characteristic - Inherent characteristic of an object related to a requirement

• Quality control - Part of quality management focused on fulfilling quality requirements

• Quality management - Management with regard to quality

• Quality management system - Part of management system (set of interrelated or interacting elements of an organization to establish policies, objectives, and processes to achieve those objectives) with regard to quality

• Quality manual - Specification for the quality management system of an organization

• Quality planning - Part of quality management focused on setting quality objectives and specifying necessary operational processes and related resources to fulfil the quality objectives

• Quality policy - Overall intentions and direction of an organization related to quality as formally expressed by top management

• Regulation - A written instrument containing rules having the force of law. Regulatory requirement - Obligatory requirement specified by an authority mandated by a legislative body

• Release - Permission to proceed to the next step of the process or to the next process

• Requirement - Need or expectation that is stated, generally implied or obligatory. Generally implied means that it is a custom or common practice for the organization, its customers or other interested parties, that the need or expectation under consideration is implied

• Review - Determination of the suitability, adequacy and effectiveness of an object to achieve established objectives

• Risk - Effect of uncertainty

• Service - Output of an organization with at least one activity necessarily performed between the organization and the customer

• Statutory requirement - Obligatory requirement specified by a legislative body

• Validation - Confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application, have been fulfilled.
4. Translation of ISO Standard 9001:2015 to the specific needs of NRAs

4.1 Requirements

This section of the guideline requires NRAs to have access to three standards: ISO 9001:2015, ISO 9000:2015 and ISO/TS 9002:2016 [21] (see 1.5.1 above).

4.2 High level structure of ISO 9001:2015

ISO Standard 9001: 2015 contains an introduction section (Clause 0) and 10 clauses as presented in Table 1. Clauses 1 to 3 set the stage for the requirements. Clauses 4 to 10 represent the actual requirements, with Clause 4 providing an overview of considerations regarding the context of the organization and how to apply the process approach. These considerations are addressed in detail in Clauses 5 to 10. Table 1 provides an overview of the structure of ISO Standard 9001:2015 and briefly describes the intent of each clause.
Table 1. Structure of ISO 9001:2015, its clauses and brief description of intent for each clause

<table>
<thead>
<tr>
<th>Clause</th>
<th>Description</th>
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<tr>
<td>0 Introduction</td>
<td>Describes benefits of QMS, quality management principles, concept of process approach and Plan-Do-Check-Act (PDCA), concept of risk-based thinking and relationship with other management system standards.</td>
</tr>
<tr>
<td>1 Scope</td>
<td>Provides purpose of QMS for an organization (i.e. NRA)</td>
</tr>
<tr>
<td>2 Normative references</td>
<td>ISO Standard 9000:2015 should be used as the reference standard which defines the terms used in ISO Standard 9001:2015.</td>
</tr>
<tr>
<td>3 Terms and definitions</td>
<td>Terms and definitions are given in ISO Standard 9000:2015.</td>
</tr>
</tbody>
</table>
| 4 Context of the organization | 4.1 To determine issues (strengths and areas for improvement) internal and external to the NRA which may affect its ability to meet the expected results  
4.2 To determine the interested parties (stakeholders) and capture their needs and expectations relevant to the QMS  
4.3 The organization (i.e. NRA) to decide the scope (boundaries) of the QMS  
4.4 Provides a template for process approach (PDCA) and documented information needed for QMS |
| 5 Leadership | 5.1 Responsibilities/actions of/by top management (TM) to demonstrate leadership and commitment towards QMS, including customer focus  
5.2 Development of a quality policy by TM and ensuring its application  
5.3 Definition of roles, responsibilities and lines of authority by TM |
| 6 Planning | 6.1 Determining risks and opportunities (using information from 4.1 and 4.2) and planning actions on risks and opportunities  
6.2 Establishing quality objectives and making plans to achieve them  
6.3 Planning for changes, if any, in QMS |
| 7 Support | 7.1 Providing resources for QMS (people, infrastructure, measuring equipment and organizational knowledge)  
7.2 Ensuring staff are competent  
7.3 Ensuring people are aware of quality policy, quality objectives, importance of their contributions to the effectiveness of QMS and knowing the consequences for not doing work as per QMS  
7.4 Establishing internal and external communication processes  
7.5 Creation and control of documented information (procedures and records) |
| 8 Operation | 8.1 To address operational planning and control |
8.2 Requirements for products and services (P and S) covering communication with customers, developing and reviewing requirements for P and S and to document changes to P and S requirements
8.3 To develop processes for designing and developing P and S
8.4 To develop processes for procurement of the right P and S
8.5 To carry out provision of services under controlled conditions, including post-delivery activities
8.6 To ensure authorized release of P and S
8.7 To ensure outputs (products, services or other) which are not conforming are controlled

| 9 Performance evaluation | 9.1 Monitoring, measurement, analysis and evaluation (Check part of PDCA) covering plan for monitoring and measurements (M and M) of P and S, processes and system and for analysis and evaluation of M and M data and establishing a process for obtaining customer feedback for assessing the degree of customer satisfaction
9.2 Process of planning and conducting internal QMS audits and reporting results internally
9.3 Management review covering purpose of review, inputs to be considered by TM and outputs of review with decisions and actions relating to opportunities for improvement, changes needed in QMS and resource needs |
| 10 Improvement | 10.1 To determine opportunities for improvement with focus on enhancing customer satisfaction
10.2 Nonconformity and corrective action. Actions to control or correct a nonconformity should be taken promptly, this can be achieved by containing the problem while investigations continue to eliminate its cause to avoid its recurrence
10.3 Using outputs from 9.1.3 and improvement decisions taken during management review to initiate continual improvements |

| Annex A | Clarification of new structure of the standard, terminology in the standard and concepts |
| Annex B | Other international standards on quality management and QMS developed by ISO/TC 176 |
| Bibliography | Useful list of supporting ISO standards and websites |
4.3 Clause by clause guidance for NRAs on the requirements for ISO Standard 9001:2015

Clause 0 Introduction

This clause describes the benefits of QMS; quality management principles; the concept of process approach and Plan-Do-Check-Act (PDCA); the concept of risk-based thinking; and relationship with other management system standards.

Clause 0.1 General

ISO Standard 9001:2015 has been adopted by more than 130 countries, it is internationally accepted and has become a world benchmark for good management practice. More than one million certificates of conformity to ISO Standard 9001 have been issued worldwide. ISO Standard 9001:2015 is not a product standard but a system standard. It gives “what” an NRA should do for its QMS and leaves the “how” to be decided by the NRA.

Benefits for NRAs using this ISO standard include:

- the possibility to standardize operations, leading to uniformity;
- availability of up-to-date manuals, instructions and procedures;
- clarity and transparency of responsibilities;
- systematic training and development of human resources;
- structured and smooth vertical and horizontal communication;
- in-built process performance monitoring and improvement mechanism;
- systematic processing of customer feedback;
- standard system of detections, investigation and correction of errors;
- system for addressing customers’ complaints; and
- a means to demonstrate the ability to consistently provide quality products and services.

QMS are influenced by the different policies, objectives, diverse work methods, resource availability and administrative practices specific to each NRA. Therefore, the details of each QMS will be different in each NRA. While the detailed method of QMS implementation is important, what matters most is that the QMS yields effective, consistent and reliable results. The QMS must be as simple and understandable as possible to function properly and meet the quality policies and objectives of the NRA.
An NRA may decide to have its QMS assessed for certification or not. Regardless of whether it seeks assessment and/or certification by a third party, the NRA will still benefit from the implementation and maintenance of an effective QMS.

The ISO Standard 9001:2015 standard adopts the “process approach”, which enables the NRA to plan processes and its interactions. It also incorporates the concepts of the PDCA cycle and risk-based thinking. Risk-based thinking enables an NRA to identify factors that could cause its processes and QMS to deviate from the planned results; put in place preventive controls to minimize negative effects; and leverage opportunities as they arise.

Clause 0.2 Quality Management Principles

ISO Standard 9001:2015 supports the application of the seven quality management principles (QMPs) described in ISO Standard 9000:2005 which are applicable in the context of NRAs.

- Customer focus. The primary focus of quality management is to meet customer requirements and to strive to exceed customer expectations.
- Leadership. Leaders at all levels establish unity of purpose and direction and create conditions in which people are engaged in achieving the organization’s quality objectives.
- Engagement of people. Competent, empowered and engaged people at all levels throughout the organization are essential to enhance the organization’s capability to create and deliver value.
- Process approach. Consistent and predictable results are achieved more effectively and efficiently when activities are understood and managed as interrelated processes that function as a coherent system.
- Improvement. Successful organizations have an ongoing focus on improvement.
- Evidence-based decision-making. Decisions based on the analysis and evaluation of data and information are more likely to produce desired results.
- Relationship management. For sustained success; organizations manage their relationships with relevant interested parties, such as providers.

An ISO brochure titled ‘Quality management principles’ provides the full text of the QMPs. The brochure can be downloaded from http://www.iso.org/iso/pub100080.pdf at no charge. ISO 9000:2005 and the ISO brochure, contain supporting information on the QMPs, including the rationale, key benefits and possible actions associated with each QMP. These principles also provide a sound basis for establishing quality policy and quality objectives.
ISO 9001:2015 advocates the use of a process approach for the development, implementation and enhancement of the effectiveness of a QMS, with the aim of increasing customer satisfaction by meeting their requirements. Understanding and managing the interconnected processes in a regulatory system contributes to the NRA’s effectiveness and efficiency in achieving its quality objectives and intended results. In addition, this approach helps NRAs identify the management capacity needed to produce the desired outputs.

The NRA should identify the following elements for each process:

- the main inputs to the process, for example: information, legal requirements, national and/or regional government policies, materials, energy, human and financial resources;
- the desired outputs, for example, the characteristics of the product/service to be provided;
- controls and indicators needed to verify the process performance and/or results; and
- interaction with other processes (outputs from one process typically form inputs into other processes).

PDCA

The regulatory system, the QMS and related processes can be managed using the Plan-Do-Check-Act cycle (PDCA) cycle with an overall focus on risk-based thinking to leverage opportunities and prevent undesirable results. ISO 9001:2015 provides the following brief description of the PDCA process:

- **Plan**: establish the objectives of the system and its processes, and the resources needed to deliver results in accordance with customers’ requirements and the NRA’s policies, and identify and address risks and opportunities;
- **Do**: implement what was planned;
- **Check**: monitor and, where applicable, measure processes and the resulting products and services against policies, objectives, requirements and planned activities and report the results;
- **Act**: take actions to improve performance, as necessary.

Clauses 6 to 10 each focus on one stage of the PDCA cycle:

- Clause 6 – Planning – Plan
- Clause 7 – Support – Do
Risk-based thinking

According to the ISO standard 9001:2015, risk-based thinking is an essential component of QMS. Risks and opportunities should be identified during the planning stage.

Risk is the effect of uncertainty, and any uncertainty can have positive or negative effects on one or more objectives. Uncertainties can emerge due to changes in the operational environment, political decisions, lack of information or unknown information or a variety of aspects. NRAs should plan and implement actions to address risks and opportunities to prevent negative effects and improve results.

Opportunities can arise due to situations favourable to the achievement of a desirable result. For example, a change in the structure of the NRA can create opportunities to improve the efficiency in the organization. It can also carry some risks. Actions taken to leverage the opportunities should also include consideration of the associated risks.
0.4 Relationship with other management system standards

It is important to note that ISO Standard 9001:2015 was developed following the same high-level structure used in all ISO management systems standards. This structure (10 clauses with the same headings) facilitates the integration between different standards enabling NRAs to develop an integrated management system (IMS) if they wish to implement other management system standards. The following standards may be of interest to NRAs.

- ISO Standard 37001:2016 anti-bribery management systems (24)
- ISO/IEC 27001:2013 information security management systems (25)

ISO Standard 9004:2018 (Managing for sustained success of an organization) (9), provides guidelines which NRAs may use for initiating improvements in the QMS.

Clause 1. Scope

The scope explains the purpose of the standard. This clause states that the ISO 9001:2015 requirements are for a QMS, and not for products or services. It also indicates that ISO Standard 9001:2015 is intended to be generic and applicable to all organizations, regardless of their type, size, or the products and services they provide.

By implementing this standard, the NRA can demonstrate its ability to consistently provide products and services that meet customer, statutory and regulatory requirements and can enhance customer satisfaction. This guideline aims to provide guidance to adapt the ISO Standard 9001:2015 requirements to the needs of NRAs with respect to all of its regulatory functions, including the supporting processes.

Clause 2. Normative references


Clause 3. Terms and definitions

As all terminology required for the use given in ISO Standard 9000:2005, no additional terms are
Specific NRA-related terminology (not included in the ISO standard) is listed and definitions are those provided in the relevant WHO documents.

The ISO 9000 family of standards uses generic terms to describe the relationship between the parties involved. For the purposes of this guideline the term “organization” means NRA. “External providers” are people or companies from whom the NRA receives products and services (e.g. suppliers). “Customers” are people or organizations who receive products and services from the NRA.

ISO’s “Online Browsing Platform” can be used to search for information on terms and definitions included in ISO 9000:2005, see: https://www.iso.org/obp/ui/

Clause 4. Context of the organization

4.1 Understanding the organization and its context

Guidance

The intent of this clause is to understand the external and internal issues relevant to the NRA’s purpose and strategic direction that can impact its ability to achieve the planned quality objectives of its QMS.

There are many sources of information about internal and external issues that can affect the effective implementation of the QMS. The issues are categorized as either related to statutory or regulatory requirements. Statutory issues are considered for both internal and external cases. They provide the boundaries within which the QMS can be implemented while complying with national laws (pieces of legislature). Regulatory issues relate to professional regulatory bodies for personnel, materials, environmental, financial and other areas that affect internal and external implementation of the QMS.

There are many sources for information about external and internal issues, such as internal documented information and meetings, national and international press, websites, publications from national statistics offices and other government departments, professional and technical publications, conferences and meetings with relevant agencies, meetings with customers and relevant interested parties, and professional associations.

External and internal issues can change, and therefore should be monitored and reviewed. The NRA can conduct reviews of its context at planned intervals and through activities such as management review.
An NRA must /should understand the context to provide the foundation for determining the scope of its QMS, quality policy, quality objectives, and risks and opportunities.

**Practical help box 1. Guidance to assist in the interpretation of clause 4.1**

<table>
<thead>
<tr>
<th>Understanding the NRA and its context</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRAs can be organized according to different models:</td>
</tr>
<tr>
<td>- In the centralized model, all regulatory functions are under the same organization and TM.</td>
</tr>
<tr>
<td>- In the decentralized model, a central office is generally located in the capital city and subsidiary offices in states or provinces. The roles and responsibilities of these offices can be different; some functions may be carried out at central level while others are delegated to the decentralized offices.</td>
</tr>
<tr>
<td>- In the discrete model, different institutions are responsible for different regulatory functions. Each of them reports independently, usually to the Ministry of Health.</td>
</tr>
</tbody>
</table>

The specific characteristics of the NRA in question must be carefully analyzed when considering the context of the organization. WHO concluded through discussions with the drafting group, that independently from the organizational structure of the NRA, each institution involved in the regulatory oversight of medical products should establish their own QMS in accordance with their specific processes.

**Examples of internal/external issues**

**Internal issues to be taken into consideration include:**
- resource factors, including infrastructure, governance, environment for the operation of the processes, organizational knowledge, workforce and financial considerations;
- human aspects such as competence of persons, organizational culture and values, relationships with unions;
- operational factors such as process capabilities, performance of the quality management system, customer evaluation; and
- factors in the governance of the organization, such as rules and procedures for decision making or organizational structure.

**External issues to be taken into consideration include:**
- macro-economic factors such as money exchange rate predictions, economic situation, inflation forecast, credit availability;
- political factors such as political stability, public investments, local infrastructure, international trade;
agreements; and

- technological factors such as new sector technology, materials and equipment, patent expirations, professional code of ethics.

NRAs can use tools such as strengths, weaknesses, opportunities and threats analysis (SWOT) and political, economic, social, technological, legal, environmental analysis (PESTLE) to identify issues. Alternatively, simpler approaches can be useful, depending on the size and complexity of the NRA’s operations, such as brainstorming and asking “what if” questions.

### 4.2 Understanding the needs and expectations of interested parties

#### Guidance

The intent of this clause is to ensure that the NRA considers the requirements of relevant interested parties, beyond just those of its direct customers. NRAs should focus only on parties that can have a direct or indirect impact on the NRA’s ability to provide products, and services that meet requirements customer’s and statutory and/or regulatory requirements. The NRA may consider external and internal issues (decided under clause 4.1) for determining relevant interested parties.

The NRA should have a robust system in place to monitor and review the relevant requirements of its interested parties at planned intervals. The information resulting from these activities should be considered when determining the scope of the QMS (see 4.3) and for determining risks and opportunities (see 6.1).

**Practical help box 2. Guidance to assist in the interpretation of clause 4.2**

#### Interested parties and examples of their requirements

**Examples of NRAs interested parties include:**

- manufacturers, researchers, sponsors for new product development, civil society, consumers, patients, healthcare providers, distributors, exporters, importers, wholesalers, pharmacists, government partners (MOH, MOF, other), parliament members and commissions, national and international pharmacopoeias, health system in general and immunization program in particular, provincial NRA offices in the case of decentralized models, other institutions with regulatory responsibilities as in the case of the discrete model.
Examples of requirements include:
availability of affordable medical products of assured quality, safety and efficacy, effective and efficient service, legality, transparency, good communication skills, confidentiality, courtesy, compliance with laws, regulations and requirements and responsiveness, good governance, impartiality, clarity, consistency and flexibility.

4.3 Determining the scope of the QMS

Guidance

The scope for the QMS should be established based on the following information:

- the external and internal issues as determined by the requirements of clause 4.1;
- the requirements of relevant interested parties (such as regulators and customers) as determined in accordance with the requirements in clause 4.2; and
- the products and services provided by the NRA.

In determining the scope of the QMS, the NRA shall also establish the boundaries of the QMS by considering issues such as: the infrastructure of the NRA; the NRA’s different sites/offices and activities; and centralized, decentralized or externally provided functions, activities, processes, products and services.

The NRA should carefully review each individual requirement within a clause to determine whether it is applicable. Some or all the requirements in a clause may be applicable. NRAs should not decide a clause is not applicable without careful consideration of each requirement. The documented scope should include details of the products and services covered as well as justification for any requirements determined to be not applicable.

The scope should be maintained as documented information using whatever method meets the NRA’s needs, such as in the quality manual or a website.

Practical help box 3. Guidance to assist in the interpretation of clause 4.3

Defining the scope of a QMS in an NRA

The NRA should determine the scope of the QMS based on the services to be provided, requirements of interested parties, processes, infrastructure, and activities and resources available for each organization. The scope should match the roles and responsibilities of the NRA and address all regulatory functions. In the case of a decentralized
or discrete NRA, if a certain institution is responsible for vigilance and another institution is responsible for inspections; the scope for each institution should cover the services each one provides. Both institutions should establish a QMS, preferably using the same standard, ideally ISO Standard 9001:2015.

Example of scope statement:

The Quality Management System at country X National Regulatory Authority (XNRA) covers all the procedural, executive and supervisory functions of the X National Regulatory Authority in order to ensure the safety of food, the safety and quality of the human and animal medicines, and the safety and efficiency of medical devices and supplies through the establishment of an effective regulatory body in all sectors of the XNRA and all of its branches in the country.

Excluding:

1. All the technical procedures and tests carried out in the laboratories, which will be covered through the application of quality management system for the laboratories based on the international standards ISO Standard 17025,

2. All procedures for sampling during the inspection of establishments and at the ports of entry as well as inspection tools used in this regard, will be covered by the implementation of the quality system of inspection ISO Standard 17020.

4.4 QMS and its processes

Guidance

This clause provides a template for the process approach (PDCA). It focuses on the processes needed for the QMS in accordance with ISO Standard 9001:2015 and the related documented information needed.

When referring to the processes required by NRAs to carry out the different functions, it includes not only the processes for service provision, but also the processes needed for the effective implementation of the system, such as internal audits, management review and others (including processes that are performed by external providers).

A process is a set of interrelated or interacting activities that use inputs to deliver intended results.

a) The NRA should determine the inputs required (what is required for the implementation of the
processes as planned) and the outputs expected from its processes (either by the customers or the subsequent processes). Inputs and outputs can be tangible (e.g. materials, components or equipment) or intangible (e.g. data, information or knowledge); b) When determining and organizing the sequence and interaction of these processes, different methods can be used such as process maps or flow diagrams (see figure 2 as example); c) To make sure that processes are effective (i.e. deliver the planned results), the process control criteria and methods should be determined and applied, criteria for monitoring and measurement can be process parameters, or specifications of services; performance indicators related to quality objectives or other; d) The NRA should determine the resources needed for processes such as people, infrastructure and environment for the operation of the processes, organizational knowledge etc; e) The NRA should assign the responsibilities and authorities for its processes by first determining the activities of the process and then determining the persons who will perform the activity; f) The NRA should ensure that any actions needed to address risks and opportunities associated with the processes are implemented; g) The NRA should analyse and evaluate monitoring and measuring data (see c above); and implement any changes needed to ensure that these processes consistently achieve their intended results; and h) The NRA can use the results of analysis and evaluation (see ‘g’ above) to determine the necessary actions for improvement.
Figure 2. Example of interaction of processes

Business processes of the NRAs are shown in the centre of figure 2 (operation box) which includes four processes of NRAs related to MA, VL, MC, & LR. Horizontally, the customer requirements are captured to the left of the operation box and, to the right, delivery of products and services to the customer is shown. Vertically, top management, at the bottom, provides its leadership and commitment for QMS to achieve its intended results. Monitoring and measurement data of the processes/services and customer feedback data, when analysed and evaluated, provide information on performance of QMS. Output of performance evaluation can be used for initiating improvement of QMS/services. Two vertical bars on left and right of the figure demonstrate that the QMS is based upon the context of the organization and planning of QMS has been done based upon the context information.

MA, LR, VL and MC are used as models throughout this guideline; however, a similar approach can be taken to address the other regulatory functions. Practical help boxes 4 to 8 and Table 2 illustrate the processes for carrying out each of the above-mentioned functions. It is worth noting that it is not the purpose of the process flows provided in figures 3 to 6 to represent a recommendation about the steps required to exercise each of these functions. These are just provided as examples to explain the relationship between the processes, the related inputs/outputs, monitoring points and established controls, indicators used, resources needed including roles and responsibilities, authorities and risks and opportunities for improvement described in the help boxes. Different NRAs can have different ways of approaching the functions and, hence, the steps involved and the relationships between steps and/or inter related processes may differ.
Practical help box 4. Guidance to assist in the interpretation of clause 4.4

Characteristics of the processes and their interrelationships involved in the MA function

Figure 3. Processes and their interrelationships in conducting the MA function

Inputs

Laws, regulations, mandate, guidelines, access to laboratory for sample testing, market authorization applications, site master files, outcome of inspections, including: good manufacturing practice (GMP), good clinical practice (GCP), good distribution practice (GDP), others

Steps

Dossier screening, dossier evaluation (quality, safety, efficacy), laboratory analysis, inspection report, expert committee review and decision making, final approval by Top Management and update of the list of registered medicines.

Outputs

Screening results (checklist), dossier acceptance letter, dossier review reports, rounds of questions to the manufacturer and other pertinent communications, test results, inspection reports and certificates. Update of database, committee decision and MA approval or rejection.
Main processes

Receipt of application, screening, evaluation, including cycles of questions and responses, granting MA or rejection

Interacting processes

Laboratory analysis, GMP inspection, review by expert committee, email communications, meeting minutes, IT platform, official files, letters, meetings (expert meetings)

Examples of criteria and methods in place to ensure effective operation and control of processes: control points and performance indicators

Criteria that must be monitored to ensure that processes are properly executed will be based on the criticality of the processes and steps of the processes. Guidelines and SOPs will define elements such as the target evaluation timeframe. Control points will be defined, and indicators chosen in such a way as to allow to monitor parameters of performance.

Control points

Screening and dossier review

Performance indicators

Key performance indicators (KPI) that measure the actions and events that lead to a result as well as the frequency of the evaluation must be established. The KPIs, particularly if they are carefully developed, represent an excellent tool to monitor performance of the NRA. When setting KPIs use a quantitative method whenever possible and determine appropriate numerators and denominators. [27].

Examples of performance indicators include

Percentage of applications that have been screened within the specified timeline.

Compliance with defined review timeline

Quality of the evaluation reports, e.g. evaluation report assessed by three evaluators of different level of seniority yields similar results

Number of new products listed in the register in a year in relation to the number of applications received
### Potential indicators for other possible control points

- Compliance with overall timeline for registration
- Customer satisfaction evaluated through complaints, surveys, questionnaires, percentage of approved appeals, others
- Use of internal audits to assess performance
Practical help box 5. Guidance to assist in the interpretation of clause 4.4

Characteristics of the processes and their interrelationships involved in the VL function

Figure 4. Processes and their interrelationships involved in conducting the VL function

Example of inputs, steps and outputs of processes and processes interrelationships

Inputs

Information received from patients, health professionals, international vigilance (VL) networks, industry, media, risk management plans, clinical trials or PMS, suspect product, adverse event reporting, risk management plan, post-market surveillance, clinical trial data.

Steps

Receipt, analysis, conclusion, reporting, feedback

Outputs

Communication of outcome (positive or negative), regulatory measures, alerts, recalls, risk minimization plan, medical product information provided to patients, health professionals, international VL networks, industry, media and feedback to reporting source.
Examples of criteria and methods in place to ensure effective operation and control of processes: control points and performance indicators

Criteria that must be monitored to ensure that processes are properly executed will be based on the criticality of the processes and steps of the processes. Guidelines and SOPs will define elements such as the target evaluation timeframe. Control points will be defined, and indicators chosen in such a way as to allow to monitor parameters of performance.

Criteria for monitoring performance can include

- Structural indicators should measure systems and physical infrastructure;
- Assessments/evaluations/reviews should be timely (according to severity of signals);
- Evaluation should address all relevant aspects of the VL system (quality of the evaluation);
- The evaluation strategy should include outcomes that can be realistically measured, to avoid inaccurate or misleading data;
- Indicators should provide an assessment of current PV documentation and resource compliance with regulatory VL expectations and requirements.
- KPI should be re-evaluated to assess their relevance as indicators, and targets can be re-set when deemed appropriate.
- As a consequence of monitoring VL System performance, corrective and preventive measures must be implemented, resulting in continuous improvements to the VL System.

Control points

Triage/prioritization, data collection and verification, coding of adverse event descriptions, quality of case causality assessment, timeliness, dissemination.

Performance indicators

Key performance indicators (KPI) that measure the actions and events that lead to a result as well as the frequency of the evaluation must be established. When setting KPIs use a quantitative method whenever possible and determine appropriate numerators and denominators. [27].

Examples of performance indicators include

Examples of performance indicators include the Number of vigilance inspections performed against planned based on prioritization criteria for inspection.
<table>
<thead>
<tr>
<th>978</th>
<th>Number of Adverse Drug Reaction reports received from healthcare professionals, from the media (data collection mechanisms).</th>
</tr>
</thead>
<tbody>
<tr>
<td>980</td>
<td>Percentage of fatal adverse drug reactions analyzed within target timeline, percentage of serious adverse drug reactions analyzed within target timeline.</td>
</tr>
<tr>
<td>984</td>
<td>Number of complaints addressed vs. total number of complaints received by the VL department.</td>
</tr>
<tr>
<td>988</td>
<td>Internal audit findings.</td>
</tr>
<tr>
<td>986</td>
<td>Number of recalled products “controlled” vs recalled products.</td>
</tr>
</tbody>
</table>
Practical help box 6. Guidance to assist in the interpretation of clause 4.4

Characteristics of the processes and their interrelationships involved in the MC function

Figure 5. Processes and their interrelationships involved in conducting the market surveillance and control (MC) function
MC requires the NRA (in collaboration with other relevant authorities e.g. customs) to ensure that substandard and falsified (SF) products do not enter or are removed from the national market. It mandates the NRA to ask for all transactions relating to importation and/or exportation of consignments of medical products to be conducted by licensed entities and that good storage and distribution practices be followed.

**Example of inputs, steps and outputs of processes, processes interrelationships**

**Inputs**

Market complaint, market intelligence, inspection reports, sampling plan outcome, feedback from import and export activities and internet pharmacy.

**Steps**

Risk-based sampling, testing, identifying SF, decision on recall and communication to all stakeholders, including all relevant parties within NRA, market authorisation holder, supply chain, health care professionals, patients, international organisations others.

**Outputs**

Identification of SF, alerts, recalls, communication to all stakeholders and database for the SF.

**Examples of criteria and methods in place to ensure effective operation and control of processes: control points and performance indicators**

**Control points**

Sampling and testing, identification of SF, recalls and related reconciliation and effective communication to stakeholders

**Performance indicators**

Key performance indicators (KPI) that measure the actions and events that lead to a result as well as the frequency of the evaluation must be established. When setting up KPIs use a quantitative method whenever possible and determine appropriate numerators and denominators. [27].

**Examples of performance indicators include**

- Number of consignments received through the port of entry.
- Number of samples drawn against planned.
<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1065</td>
<td>Number of samples sent for testing and number tested.</td>
</tr>
<tr>
<td>1066</td>
<td>Time taken to generate test report against the target timeline.</td>
</tr>
<tr>
<td>1067</td>
<td>Time taken to evaluate suspected products against the target timeline.</td>
</tr>
</tbody>
</table>
Practical help box 7. Guidance to assist in the interpretation of clause 4.4

Characteristics of the processes and their interrelationships involved in the LR function

Figure 6. Processes and their interrelationships involved in conducting the LR function

**Inputs**

Cover letter, summary lot protocol (SLP), samples, marketing authorization specifications, information on adverse events, surveillance data (test results on samples retrieved from the market).

**Steps**

Screening documents, request testing, perform testing, evaluation of SLP and testing results, decision, refer for review by technical committee.

**Outputs**

Notification of rejection, lot release certificate.
Main processes

Screening documents (cover letter and SLP), evaluation of SLP, review by the technical committee, decision-making process.

Interacting processes

Sample testing can be considered an interacting process if this is contracted out to a third-party laboratory. Otherwise, it is a process that must be performed to yield an output.

Examples of criteria and methods in place to ensure effective operation and control of processes: control points and performance indicators

Criteria that must be monitored to ensure that processes are properly executed will be based on the criticality of the processes and steps of the processes. Guidelines and SOPs will define elements such as the target evaluation timeframe. Control points will be defined, and indicators chosen in such a way as to allow to monitor parameters of performance.

Control points

Evaluation of the SLP.
Expert committee review (of the report).

Performance indicators

Key performance indicators (KPI) that measure the actions and events that lead to a result as well as the frequency of the evaluation must be established. When setting KPIs use a quantitative method whenever possible and determine appropriate numerators and denominators. [27].

Examples of performance indicators include

Compliance with evaluation timelines.
Check inputs in laboratory information management system (LIMS), checklist, outputs - percentage of outputs verified/validated in quality review.
Trend analysis for test results.
Percentage of timely reviews by the Expert review committee.
Potential indicators for other possible control points

Customer satisfaction evaluated through complaints, surveys, questionnaires.
Use of internal audits to assess performance.

Practical help box 8. Guidance to assist in the interpretation of clause 4.4 relating to resources

Resources, roles and responsibilities, and authorities required to ensure adequate performance of processes for delivery of quality services by NRAs (common to all functions).

Resources, roles and responsibilities, authorities

Human resources should be allocated in line with the processes to be executed as well as the workload. Each employee has a job description and needs to be trained and qualified to perform his/her job. Roles and responsibilities and lines of authority should be detailed in the job description and organizational chart. Each process should have appropriate staffing and managers responsible for it. Staff performance, including performance of managers, should be evaluated regularly and re-training provided as needed.

Human resources

May include receptionist, administrative staff, screening officer, case investigation experts, evaluators, leadership, process supervisors, laboratory analysts, IT staff, human resources staff, expert committee members, regulatory inspectors, housekeeping staff, driver, other.

Proper infrastructure should be in place to carry out the activities (processes), e.g. if adequate laboratory infrastructure is not in place, consider contracting the service of a qualified laboratory.

Examples of aspects to be considered in terms of infrastructure, including facilities, IT, financial resources, documentation and work environment.

Infrastructure

- Adequate work space
- Equipment as needed
- Fully established lab or access to a contracted laboratory
- Means of transportation
- IT system, computers and software, databases, archiving system
Financial resources

Financial resources to buy appropriate equipment, secure its maintenance and procure consumables. Computer systems and databases need to be validated. Hiring and retaining a sufficient number of qualified staff requires competitive salaries.

Documentation System

Required documents include: strategic direction, vision and mission, laws and regulations, quality policy, guidelines, lot release policy, SOPs, forms, instructions and checklists. The NRA should establish a system for documentation preparation, review and approval as well as documentation control, revision and recordkeeping (see also guidance under clause 7.0).

Work environment

Social, physical and psychological factors all contribute to establishing an environment conducive to quality work; e.g. non-discriminatory, non-confrontational, stress-reducing, physically comfortable (lighting, temperature, ventilation, others).

During the planning stage, the NRA should address risks and opportunities in accordance with the requirements set forth in 6.1.

Table 2. Risks and opportunities affecting MA, LR, VL and MC

NOTE: Text is presented in plain format below to ensure it has line numbers consistent with the rest of the document, thereby facilitating use of the comment form during public consultation. The table will be appropriately formatted in the final stages of guideline development.

Marketing authorization

Transparency of NRAs and their work is one of the principles of GRP. Posting as much information as possible on the internet helps NRAs increase transparency. This information can include the registration procedure steps and timelines, related regulations and guidelines, charts indicating actual level of compliance with the target timelines, evaluation reports, others. Posting sensitive information on the web (e.g. performance charts) constitutes a risk of potential complaints or criticism, but at the same time offers opportunities for improvement, advocacy of the work performed, reliability, others.
The evaluation process should be properly monitored and evaluated, including the experts who conduct the evaluation. Failure to do so can lead to the risk of granting a MA based on an insufficient or inadequate data package. Risks usually also entail opportunities. In this example, if an NRA does not have the adequate expertise / resources to evaluate a certain product, reliance on other agencies can be an option.

Lot release

Tests to be performed as part of lot release must be appropriately validated, including the equipment used (properly calibrated), the consumables properly tested, released and used before expiry, qualified analysts to perform the tests who are regularly re-qualified and test performance monitored. Failure to meet all these requirements lead to the risk of either releasing a lot that does not meet the requirements or rejecting a lot that meets the specifications. Identification of the specific constraints may also bring about opportunities to improve the planning for procurement of consumables or equipment that may be required.

IT failures pose a risk for timely delivery of the service (release of lots), it raises at the same time an opportunity for renewing the system (hardware/software).

Vigilance

VL function carries a risk of potentially missing out on important signals because of underreporting or poor analysis and interpretation of the reports. The consequence is harm to the public and loss of reputation for the NRA. Lack of, or poor communication about, the safety of a product that has been suspected (as a result of analysis of the signals) may result in public panic and loss of trust on the NRA. Such failures can offer at the same time an opportunity for improvement and strengthening of the system.

There is an increase in the number of registered new medicines (biologics, biosimilars, others) so that a robust vigilance system needs to be in place. To establish a robust VL system, a database is developed to monitor implementation of all the approved Risk Management Plans (RMPs) and to measure their effectiveness.

The database is also used for all medicines subject to additional post-marketing monitoring to track potential safety concerns. Vigilance inspection is one of the tools used to monitor and maintain the VL system within local companies and agents.
Market surveillance and control

- Risk of failure to test the sampled products due to limited capacity for testing e.g. reagents, standards, staffing, other. This may lead to failure in identifying products that have been damaged in the distribution/ storage chain. This may adversely impact the reputation of the NRA. At the same time, such an event provides an opportunity to convince TM of the constraints and the need for resources to prevent a recurrence.

- Lack of expertise for SF case investigation poses a serious risk of missing SF products. It provides an opportunity to establish or review methods and training of staff in medicine production facilities.

- Unclear communication strategy may lead to mis-communication or missing communicating an SF to certain relevant stakeholders. This may adversely impact the reputation of the NRA. It provides an opportunity to review the procedures and personnel responsible for communication of such events.

- In case a recall of a product is mandated, there is a risk not to recall and dispose the whole batch. Recall from remote areas may be challenging. It provides an opportunity to empower the national vigilance system, involve and commit other institutions in the dissemination of regulatory measures and recall products that are damaged or do not meet the required quality standards or are SF.

Documented information for QMS

The strategic direction of the NRA, mission, vision, policies, quality objectives, as well as procedures and other information, should be documented (4.4.2). In addition to this, NRAs will also need Documented Information to support its operations. As per definition, documented information is information required to be controlled and maintained by NRAs.

At several places ISO Standard 9001:2015 requires:

a) maintaining documented information (which means a manual, procedure, instruction, checklist, vision/mission/policy/objectives statements, guidelines, specifications, drawings, websites, circulars, government orders etc.); and

b) retaining documented information (which means records, reports, minutes of the meetings or any document which provides evidence that the activity has been performed as per applicable criteria/methods etc.).

Some of the documented information to be retained may be formal (validation reports, audit reports,
and other informal (meeting minutes). NRAs should have such documented information (see clause 7.5 for details of DI).

Practical help box 9. Guidance for interpretation of clause 4.4 relating to documented information

High-level NRA documentation can include the legal basis, regulations, decrees, strategic plan, vision and mission, overall objectives of the organization, quality objectives, quality policy, quality manual, others.

Lower-level NRA documents can be divided into two categories: documents and records.

Examples of documents include SOPs, instructions and forms and checklists. Examples of records include assessment reports, inspection reports, test results, application submissions from manufacturers, marketing authorization dossiers, SLPs, correspondence, trending data and its analysis, validation and qualification protocols and reports, calibration data, training plans and records, analysts and evaluators qualification information, maintenance program, training program and records, internal audit plans and reports, corrective and preventive action (CAPA) plans and compliance reports, others.

Documentation and records must be controlled. A system should be in place whereby documents are reviewed, authorized and approved. Newer versions replace older ones which become obsolete. Documentation should not only be maintained, but also retained for established periods of time, which are defined by each authority according to established rules (generally not less than five years for some documents and not less than 10 years for others). A documentation control system should be established to ensure that all relevant areas have the required documented information and that only the latest (current) version is available at any point in time. (See also clause 7.0).

Clause 5. Leadership

5.1 Leadership and commitment

Guidance

The intent of this clause is to ensure that NRA TM demonstrate leadership and commitment by taking an active role in engaging, promoting, communicating and monitoring the performance and effectiveness of the QMS.

The clause requires TM to demonstrate leadership and commitment with respect to the QMS. To achieve this, TM should comply with conditions (a-j) listed in the standard. In brief, TM is accountable for the effectiveness of the QMS and its integration into the core processes of the NRA by supporting the critical characteristics of the QMS as defined and described in ISO Standard 9001:2015. This
includes promoting the use of the process approach through the PDCA cycle and risk-based thinking to ensure that the quality policy and quality objectives are compatible with the context and strategic direction of the NRA; ensuring that the required resources are available to support staff to contribute to the effectiveness of the system; supporting other managers in their respective roles to demonstrate their leadership; and promoting improvement. Experience shows that leadership and commitment are essential requirements for successful implementation of a QMS.

An important element of the ISO Standard 9001:2015 standard is its emphasis on customer focus. In this respect, TM should demonstrate its leadership and commitment to the QMS by continually identifying the needs and expectations of its customers (Drug importers, Drug manufacturers, Drug outlet operators, Patients, Medical Practitioners, Research institutions etc), as well as ensuring that the NRA fulfils applicable statutory and regulatory requirements.

In many cases, a focus on on-time delivery performance and on customer complaints can provide information on any actions that might be necessary to achieve or improve customer satisfaction.

The NRA also needs to ensure that appropriate actions are implemented to address risks and opportunities that can affect customer satisfaction. To increase customer satisfaction, innovation and best practices can be introduced into the NRA processes.

5.2 Quality Policy

Guidance

Two key aspects are covered in this clause, namely the development of a quality policy and communicating the quality policy to the NRA personnel.

The quality policy is a powerful and highly visible statement of intent towards quality services by the TM signed by the Director or Head of the NRA (in the case of a discrete NRAs, this responsibility may fall in the hands of the Ministry of Health).

While establishing a quality policy, the NRA TM should keep in view its purpose and strategic direction (mission, vision, guiding principles and core values). Good regulatory practices (see 2.0 General considerations of this guideline) and quality management principles (see clause 0.2) can also be used for establishing commitment of the NRA TM towards quality services.

Two commitments should come out clearly in the statement of quality policy:
• Commitment to satisfy customer or stakeholders requirements as well as applicable statutory and regulatory requirements; and

• Commitment to continual improvement of the QMS.

The policy should also provide a framework for setting quality objectives (which means any claims in the quality policy should be measurable when converted into objective).

TM should ensure that the quality policy is communicated, understood and applied by persons of the NRA, so they are able to contribute to the effectiveness of the QMS. The policy can be communicated by different methods such as via noticeboards, screensavers, by the organization’s website, or during routine meetings. In addition, the NRA can make the quality policy available, as appropriate, to relevant interested parties such as external providers (service providers/suppliers), partners, customers and governmental agencies, for example, by displaying it on NRA’s website.

Practical help box 10. Guidance for interpretation of clause 5.2

Example of quality policy for NRAs from countries X, Y and Z.

1) Country X National Regulatory Authority (XNRA) quality policy. (Approved by XNRA management)

XNRA is committed to meet the needs and expectations of customers through continual improvement of its processes and quality services by implementing QMS effectively according to ISO Standard 9001:2015 requirements. We will ensure quality, safety and/or efficacy of food, medicines, cosmetics and medical devices in compliance with the XNRA Drug Act 1:2006. We should establish objectives at system and departmental level that ensure that the requirements of this policy are met. Top Management is committed to providing the necessary resources to ensure maintenance and continuous improvement of QMS.

Executive Director signature

“Together we protect public health”

2) The YNRA is committed to protect the health of people of the country and fulfil its duties with professional and scientific rigor, while ensuring safety, efficacy and quality of Allopathic, Homeopathic and Herbal medicines, vaccines, and biological products according to the Drugs Act and Rules and future amendments. YNRA should work in effective, transparent and timely manner, ensuring implementation of Quality Management System and to ensure its continuing improvement.

To meet our commitment, we must:
Foster a team approach.

— Emphasize appropriate training for all employees.

— Recognize each employee's responsibility for quality.

— Provide regulations with timely written corrective actions.

— Earn recognition of our quality process and progress.

— Provide a framework for establishing and reviewing quality objectives.

— Develop and achieve Quality Improvement Goals.

— Maintain our honesty and integrity by following our Code of Conduct.

— Review and renew this Quality Policy on a regular basis.

3) “ZNRA is committed to provide quality services in response to customer needs and expectations. We should strive to balance the interests of our stakeholders without compromising quality, safety and/or effectiveness of food, drugs, cosmetics and medical devices by managing the Authority with utmost professionalism. We commit ourselves to comply with requirements of the ISO 9001:2008 standard and continually improve effectiveness of Quality Management System. We should manage and provide resources for continuous improvement of our services to ensure customer satisfaction”.

5.3 Organizational roles, responsibilities and authorities

Guidance

The NRA TM will need to establish specific responsibilities and authorities for the assigned roles and ensure that persons of the NRA understand and are aware of their assignments. These could be communicated through job descriptions, work instructions, duty statements, organization charts, manuals, procedures, others. Adequate resources are required to match the needs.

Items a) and b) in the clause - the QMS conforms to the requirements of the ISO Standard 9001:2015 [7] and processes are delivering the intended outputs - describe roles to be assigned to each process owner (managers), while items c) to e) in the clause - reporting on QMS performance, promoting customer focus and maintaining the integrity of the QMS when changes are made - describe roles to be assigned to specific persons. Although certain responsibilities are delegated, the overall responsibility and accountability for the QMS remains with TM.

Practical help box 11. Guidance for interpretation of clause 5.3
Ideally, NRAs will have a QMS unit in place, or a responsible officer as a minimum within each Unit, Department or Directorate, as management representative or QMS coordinator who can report on QMS performance, promote customer focus and maintain the integrity of the QMS when changes are made.

Responsibility for ensuring that the QMS conforms to the requirements of the ISO Standard 9001:2015 and processes are delivering the intended outputs should be included in staff job descriptions and assessed during performance evaluation. Staff should be trained in QMS (conferences, meetings, online platform). Trainings should be relevant to the regulatory functions and reflected in documented information.

**Example of country YNRA**

The Deputy Director of the agency has been designated as the representative of the agency in quality management. His responsibilities and authority include:

- To ensure that the necessary processes for quality management are established, implemented and maintained.
- To inform senior management of system operation, including the needs for improvement.
- To promote awareness of customer requirements at all levels of the organization.

The responsibility of the management representative includes relationships with external parties on matters related to the system. He is the designated Quality Assurance Manager.

**Clause 6. Planning**

**6.1 Actions to address risks and opportunities**

**Guidance**

The intent of clause 6.1 is to ensure that when the NRA plans its QMS processes, it identifies its risks and opportunities and plans actions to address them. The purpose of this clause is to prevent nonconformities, including errors in outputs, and to determine opportunities that might enhance customer satisfaction or achieve quality objectives.

When determining risks and opportunities, the NRA should focus on enhancing desirable effects, preventing or reducing undesired effects (through preventive actions or risk reduction). This is adopting a "risk-based approach" and the NRA should consider the application of this approach to all processes required for its QMS.
The NRA can choose the methods of risk determination that suit its needs. The simpler approaches include techniques such as structured brainstorming, "what if?” method, consequences/probability matrices, etc. For guidance, the NRAs may refer to the international standard ISO/IEC 31010 that provides a list of risk assessment tools and techniques.

When examining opportunities, potential risks to the QMS associated with them should also be determined; the results of such determinations should be used when making decisions on whether to implement the opportunities.

The application of risk-based thinking can also help the NRAs to develop a proactive and preventive culture focused on doing things better and improving how work is done in general.

Once the risks and opportunities are identified, actions must be planned to address them. Actions are planned, implemented, analysed and evaluated to assess their effectiveness.

The actions taken to address risks will depend on the nature of the risk (its probability/frequency and severity), for example:

- a) The risk can be avoided by no longer performing the process where the risk can be encountered (risk is terminated).
- b) The risk can be eliminated by assisting persons in the organization with less experience or by capacity building (risk is treated).
- c) The risk can be shared by outsourcing the process or taking an insurance cover (risk is transferred).
- d) The risk can be accepted, and no action taken, based on its potential effect or the cost of the needed action (risk is tolerated).

The above alternative actions are also termed as 4T (terminate, treat, transfer or tolerate) methods of treating the risks.

Practical help box 12. Guidance for interpretation of clause 6.1

Example of actions to address risks and opportunities for lot release process

It is foreseen that there will be an increased demand for release of batches of a certain vaccine the following year. The analysis of risks and opportunities to meet the increase in demand includes an assessment of the current situation (process capacity), an analysis of the risks of attempting to meet the demand under the present conditions, and the opportunities that arise from this new situation. The release process requires analysts to test the vaccine batches, reviewers to go through the SLP, and professionals to prepare the report to be reviewed by the Technical
Committee, plus the final approval by the Head of Agency. The risks associated with addressing the increased demand include the fact that testing as well as review capacity may not be sufficient, and since the Technical Committee meets only once per month, the response capacity may not be enough.

As part of the planning process, the team needs to assess the risk of releasing lots that do not meet specifications on one hand; and the risk of not releasing a lot that meets the specifications due to limited capacity on the other. In addition, the likelihood (probability) of failure in service providing, the impact on the quality of the products released, the estimated frequency at which errors could happen, the potential impact on customer’s satisfaction and the credibility of the institution (seriousness) in case of not meeting the increased demand, or in case the service provided is inadequate, should all be considered.

The analysis of risk and opportunities provides projections for changes to be introduced in the system to effectively and efficiently address the increased demand. For example, if surge in testing capacity cannot be implemented or is not economically feasible, a new prioritization mechanism based on knowledge of the different products to be released and record of the manufacturers could be put in place.

Through this analysis, it may be estimated that by increasing the staff by one analyst and increasing committee meetings to two per month, the demand could be appropriately addressed (opportunity for increased resources).

6.2 Quality objectives and planning to achieve them

Guidance

The intent of this clause is to ensure that the NRA establishes quality objectives and plans appropriate actions to achieve them. Quality objectives should be established for relevant functions, levels and processes, as appropriate, to ensure the effective deployment of the NRA’s strategic direction (plans) and its quality policy. Whenever possible, they should be SMART objectives (Specific, measurable, achievable, realistic and time bound. The following table provides guidance on implementation of bullets ‘a’ to ‘g’ of clause 6.2

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Intent with example</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Be consistent with the quality policy</td>
<td>Use commitments made in quality policy for setting quality objectives e. g. setting objectives on continual improvement of QMS as committed in quality policy</td>
</tr>
<tr>
<td>b. Be measurable</td>
<td>Define quantity or period e. g. processing time of customer request will be reduced from 2 to 1 day</td>
</tr>
</tbody>
</table>
### Practical help box 13. Guidance for interpretation of clause 6.2

#### Example of mission, vision and quality objectives for an NRA

**XNRA mission statement**

The mission of XNRA is to protect and promote public health by ensuring quality, safety and/or efficacy of food, medicines, cosmetics and medical devices.

**XNRA vision statement**

The vision of XNRA is to provide the best regulatory services to ensure the quality of food, drugs and cosmetics in the southern hemisphere by 2020.

**XNRA quality objectives**

<table>
<thead>
<tr>
<th>c. Address applicable requirements</th>
<th>For example, if certain regulatory requirement relating to product/service are applicable, setting objectives for that Using WHO GRP for setting objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>d. Be relevant to conformity of products and services and enhanced customer satisfaction</td>
<td>For example, ‘On Time and In Full’ delivery of service, setting targets for achieving higher level of customer satisfaction</td>
</tr>
<tr>
<td>e. Be monitored</td>
<td>Means being reviewed for progress being made in achieving the quality objective; this could be carried out through analysis of process monitoring and customer feedback data and comparing results with set targets</td>
</tr>
<tr>
<td>f. Be communicated</td>
<td>For example, through circulation of minutes of meetings internally and to external interested parties viz suppliers by signing agreements</td>
</tr>
<tr>
<td>g. Be updated as appropriate</td>
<td>Potential or actual changes that can impact on the ability to achieve quality objectives need to be considered and action taken as necessary, to ensure new issues or requirements are addressed.</td>
</tr>
</tbody>
</table>
The quality objectives of XNRA are established in line with the goals outlined in the XNRA strategic plan for the period of 2015-2020. These objectives are:

1. Maintain good governance and management of the agency with view at ensuring continuing improvement of QMS.
2. Continuously improve the quality of service through regular training of staff, monitoring of performance and monitoring compliance with set review timelines.
3. Strengthen laboratory services by conducting the validation of all test methods used and the qualification of staff involved in such tests by 2020.
4. Strengthen cooperation and collaboration with relevant organizations and government agencies.

Planning to achieve quality objectives

The achievement of XNRA quality objectives should be through implementation of specific actions as detailed in the current XNRA strategic plan.

XNRA determines and provides resources (including human, financial, infrastructure, technology, work environment and organizational knowledge needed to establish, implement, maintain and continuously improve QMS. The resource requirements are defined through budgeting and other business management processes including planning and management review.

TM is ultimately responsible for quality of XNRA services by ensuring the resources, systems and processes needed to implement and improve QMS and for undertaking management review meetings. All employees are responsible for the quality of their work and implementation of the policies and procedures applicable to the processes they perform.

The quality objectives should be achieved by 2020 and will be evaluated by undertaking quality internal audits and analyzing performance data for continual improvement of the system with the overall aim of meeting customers’ needs and expectations.

Another example - ZNRA Quality objectives

Objective 1: The rate of counterfeit and substandard food, medicine, cosmetics and medical devices circulating in the country reduced by 50% by June 2020

Objective 2: Customer satisfaction for services offered by ZNRA increased by 80% for both internal and external customers from 63% and 66% respectively by June 2020

Objective 3: ZNRA self-sustained financially from 60% to 80% by June 2020

Objective 4: 90% of human resources recruited and retained by June 2020

6.3 Planning of changes
Guidance

The intent of this clause is to determine the need for changes to QMS to adapt to changes in the NRA’s context/business environment, as well as to ensure that any proposed changes are planned, introduced and implemented in a controlled manner.

The purpose of planning the change is to maintain the integrity of the QMS and ensure the NRA’s ability to continue to provide conforming products and services during the change.

The need for changes can result from, changing needs of customers and other relevant interested parties, new products to be evaluated to grant market authorization, changing process methods to improve trends in non-conforming outputs, using new information and communication technology (ICT) for a service or process, outsourcing important processes, persons in key roles leaving (either due to retirement, job change or other), or moving to online service provision.

The NRA should consider the availability of resources and necessary allocation or reallocation of responsibilities for any change. This could be done by assigning persons to a team to manage the change, or by delaying the change until the right resources are available.


In planning for an increased demand for lot release the following year, a risk analysis determines that the NCL will need to add one more SLP evaluator, increase the technical committee meetings to twice per month, and prioritize lot testing. These measures entail a change in the processes which must be planned, documented, integrated to the QMS and properly monitored. In this manner, the organization is considering the potential impact of the change, the availability of resources, and the allocation or reallocation of responsibilities thereby conserving the integrity of the QMS.

Clause 7. Support

7.1 Resources
The intent of this clause is to ensure that the resources necessary for the establishment, implementation, maintenance and continual improvement of QMS are available to the NRA for its effective operation.

In determining the resources that need to be provided, the NRA should consider the current capabilities of its internal resources (e.g. people, capability of equipment, organizational knowledge) and any constraints (e.g. budget, number of resources, schedule). A decision should then be made on the resources needed, including those to be sourced externally, and the necessary actions taken to ensure the resources needed are provided; this applies to all resources listed under sub-clauses of resources from 7.1.2 to 7.1.6 of the Standard.

Three important categories of resources need to be considered; people, infrastructure and environment for the operation of processes. To plan for adequate resources in quality and quantity, three steps are to be followed:

a) Determine what resources are needed (number of people and level of competence required, utilities, facilities, equipment including hardware and software needed as well as good working conditions; physical such as temperature control, level of lightening, etc and human conditions to ensure an adequate work environment).

b) Plan how and when these are going to be provided.

c) Plan for the means to ensure that the resources provided are maintained (periodic preventive maintenance) and controlled as needed.

Monitoring and measurement resources

The intent of the clause is also to ensure that the NRA determines and provides suitable resources (measurement equipment, instruments, etc.) to ensure valid and reliable monitoring and measuring results when evaluating the conformity of its products and services.

Monitoring implies critical observation, supervision and checks to determine the quantitative or qualitative status (or both) of an activity, a process, a product, or a service. Measurement considers the determination of a quantity, magnitude, or speed, by using suitable measuring resources. This can include the use of calibrated or verified equipment that is traceable to national or international measurement standards. For services, it can include the use of known and validated models for service
feedback, for example social service models.

In determining the criticality of monitoring and measurements to ensure valid results, the NRA should determine what needs to be monitored and/or measured for its processes, products and services. It should then determine the resources needed for this monitoring and measuring; ensuring its suitability/fitness for the purpose. Resources used should be maintained for their continuing fitness.

Documented information to be retained can include schedules outlining how often checks are needed to ensure valid results as well as reports of results/outcomes.

Measurements need to be traceable (to national and/or international measurement standards) when it is a requirement or when the NRA determines it to be necessary to have confidence in the validity of the measurement results.

If measuring equipment is used to verify conformity to requirements and to provide confidence in the validity of measurement results, the NRA should consider how the measuring equipment is verified and/or calibrated, identified with calibration status, safeguarded from adjustments, stored, used and maintained.

If measuring equipment is found to be unfit for the intended purpose, the potential impact on compliance with measurement requirements should be reviewed and necessary actions taken. The results of such a review can also indicate that no action is required or, alternatively, that a service needs to be performed, products in stock need to be investigated, relevant customers must be informed, or even that a product recall is required. The level of action needed depends on the conformity of products and services.

Organizational knowledge

The clause also focuses on the need to maintain the knowledge determined as necessary, by the NRA, for the operation of its processes and to achieve conformity of products and services, as well as to encourage the acquisition of necessary knowledge based on changing needs and trends.

Organizational knowledge is the specific knowledge of an organization coming either from its collective experience or from the individual experience of its persons. This knowledge is or can be used to achieve the organization’s intended results.

The NRAs should consider how to determine and manage the organizational knowledge required to
meet NRA’s present and future needs. Persons and their experience are the foundation of organizational knowledge. Capturing their experience and knowledge can generate synergies leading to the creation of new or updated organizational knowledge.

In determining, maintaining and making available organizational knowledge, NRAs can consider:

a) learning from failures, near miss situations and successes;
b) gathering knowledge from stakeholders, experts and partners;
c) capturing knowledge that exists within itself.

The tools for maintenance and distribution of organizational knowledge can include the intranet, libraries, awareness sessions, newsletters, others.

**Practical help box 15. Guidance for the interpretation of clause 7.1 relating to organizational knowledge**

The NRA should safeguard the knowledge necessary for its operation and achievement of conformity of products and services. It should also encourage gaining new knowledge to meet its current and future needs.

Example of measures taken by the NRA of country Y to maintain and update organizational knowledge:

a) YNRA has developed, and updates as needed, detailed job descriptions of personnel responsible for key processes in the chain that leads to their outputs (products and services),

b) YNRA carries out initial training of new staff and refreshment training of staff at different levels with new information relevant to their respective positions to keep their competence up to date,

c) Recruitment of new staff is based on job description, the position posted on the website, and candidates subject to a test and interview before decision-making,

d) In case of staff turnover, and whenever possible, an overlap between the staff leaving the position and the new staff is sought, so that knowledge is properly transferred to the new staff and opportunity is given to the incoming person to practice under advice of the person leaving the position,

e) In case of retirement, succession is properly planned through timely recruitment of successor

f) Organizational knowledge refers not only to processes for service delivery, it also includes the broader perspective (e.g. knowledge of mission, vision, quality policy and objectives, strategic plan and strategic objectives of the NRA, understanding the context, internal and external issues, customers’ expectations, statutory and regulatory requirements, relationship with customers and suppliers and with other relevant organizations or agencies, others). To ensure that this knowledge is maintained and properly communicated to personnel internally, YNRA organizes meetings at regular intervals where issues are discussed; a newsletter is produced and circulated through the intranet on monthly basis; in case of urgency email communications are sent to all relevant personnel,
g) YNRA provides opportunities for training of staff outside the NRA, by participating in technical courses and through attendance to scientific meetings. Personnel that benefits from such opportunities are required to write a meeting or training report and to deliver a lecture to colleagues in the NRA for knowledge/information sharing.

h) Staff benefitting from fellowships abroad are required in addition to g) to stay in the NRA for a time equal to the double of the duration of the fellowship. Monthly seminars are organized in which personnel share experiences from their work with others (e.g. a rejected market authorization application, information on an innovative product, feedback from the field regarding safety profile of recently registered and commercialized vaccines).

7.2 Competence

Guidance

The intent of this clause is to identify the necessary competence required to perform individual roles and responsibilities and to ensure persons carrying out work are competent, based on training, education and/or experience. The term ‘persons’ includes managers, existing employees, temporary employees, sub-contractors and their employees, and outsourced persons.

Competence is the ability to apply knowledge and skills to achieve intended results. Demonstrated competence is sometimes referred to as ‘Qualification’ or ‘licensed person’.

Competence requirements can be determined by, for example:

- Specified performance criteria
- Awareness of specified requirements and acceptance criteria
- Knowledge of processes and controls operated by the organization.

When a person does not meet, or no longer meets, the competence requirements, then actions should be taken; such as, for example:

- Mentoring the employee
- Providing training
- Simplifying the process so that the person can carry it out successfully
- Reassigning the employee to another position.

Evaluation of competence can be done in several ways, including:
• Regular supervisor or manager evaluation of persons performing tasks and the operation of processes; and
• Benchmarking against service performance requirements.

Appropriate documented information that provides evidence of an employee’s competence includes, e.g. diplomas/degrees, completion of training, resumes, performance reviews and licenses should be retained.

**Practical help box 16. Guidance for interpretation of clause 7.2**

The practical help box 15 refers on point c) to the selection and recruitment of staff. The selection process for recruitment is critical to identify persons competent for the job, the requirements of the position, the acceptance criteria and the position specific knowledge are reflected in the job description published on YNRA website. The selection process includes a test and one or more interviews before a decision is made regarding the best candidate. This process is likely to successfully identify competent candidates. YNRA invests in maintaining competence of its employees, and in reducing turnover to the maximum possible extent. It has provisions to update knowledge of personnel through regular refreshment training, participation in scientific/technical meetings and other means. Competence records are kept as part of the process of acquiring competence.

In case a person no longer meets the requirements of the position, YNRA offers mentoring and retraining, and as a last option reassigns the person to a different position. There are instances where reassignment of a person to a different position is not the result of failure but of the initiative of the person to gain experience in a different area of expertise. Rotation of personnel is also a regular practice in YNRA to facilitate the acquisition of additional skills/competencies and to provide incentives.

**7.3 Awareness**

**Guidance**

The intent of this clause is to ensure that persons are aware of the quality policy, relevant quality objectives, their contribution to the effectiveness of QMS and the implications of not conforming to QMS requirements.

Persons can demonstrate their awareness in day-to-day activities by distinguishing between what is acceptable and what is not, and by taking appropriate action when processes, products and services do not meet agreed specifications.
Depending on the nature of the work that the persons perform, the actions for creating awareness can vary. Awareness can be created through regular review meetings, gathering feedback and ensuring this feedback is made known to relevant persons.

NRA staff should be aware of the quality policy and objectives, their role and contribution to an effective QMS and the implications of not conforming to the QMS requirements. A common practice is for the TM to post the mission, vision, quality policy, and quality objectives in the entrance of the NRA or other strategic locations for all staff and customers to see.

Practical help box 17. Guidance for interpretation of clause 7.3

To ensure that personnel are aware of the quality policy and relevant objectives, ZNRA posts them at the entrance of the building, in every bathroom, library and every meeting room. In addition, ZNRA has distributed slogan bottoms stating “I adhere to QM policy and objectives” for every single worker in the organization. ZNRA also placed posters of the Quality Management principles and the benefits of the QMS in improving performance and implications to the health of the public if not conforming to QMS. ZNRA TM speaks in QMS terms.

7.4 Communication

Guidance

The intent of this clause is to establish the process of internal and external communications. NRAs needs to decide what needs to be communicated and who needs this information, to determine the most effective communication method and timing; including who provides the communication.

The NRA should identify those parties with whom they should communicate, to ensure the effective operation of the QMS, such as customers, suppliers, experts, ministry of health, media and other stakeholders.

More formal communication might be required for external interested parties, such as reports, invoices or service level agreements, press briefs, etc. Internal communications can use methods such as regular department meetings, briefing sessions, email or the intranet. More formal methods, such as written reports or minutes of the meetings etc., can also be required for internal communication, depending on the nature of the information and how critical the issues are that need to be communicated.

It is also common for an NRA to designate a specific communication officer who has been trained on what, how, when, and to whom communicate depending on the matter. Communications outside the
NRA, e.g. the media, should be carried out exclusively by communications-trained officers designated by NRA TM.

Practical help box 18. Guidance for interpretation of clause 7.4

Example of internal communication requirements at YNRA

As a minimum internal communication is done through the following channels:

- Meeting with Ministry-Joint Secretary (once in a quarter)
- Senior Staff meetings (monthly)
- Full Departmental meetings (weekly)
- Daily operational meeting of the departments and administrative areas
- Email, internet platform and/or telephone.

Example of communication with the customer at YNRA

Communication with customers is maintained through:

- Internet platform, fax, email or post
- Surveys and interviews are used to obtain customers feedback
- Meetings and exchanges between specialists and managers
- Complaints and grievances are handled in quality management following the instructions for handling complaints and grievances.

7.5 Documented information

Guidance

The intent of this clause is to put the documented information into two categories; information that needs to be maintained and information that needs to be retained. The wording “maintain documented information” means the information contained in documented procedures, manuals, forms, checklists etc. The other examples are QMS scope statement, quality policy and quality objectives statements. These are popularly called ‘documents’.

The wording “retain documented information” means ensuring that information that is used to provide evidence about whether a requirement has been fulfilled needs to be kept/retained. These are popularly called ‘records/ evidences.'
In general, ISO Standard 9001:2015 is not prescriptive in terms of the extent of documented information needed. This will vary from organization to organization depending on the size and complexity of their operations and processes; customers, statutory and regulatory requirements; and the competence of the persons involved.

The following is the typical structure of documented information for QMS:

- Quality manual – a high level document providing intentions and commitments of the NRA about each requirement of ISO Standard 9001:2015 and providing references to lower level documents such as procedures etc. The manual could also include statement of scope of QMS, quality policy and quality objectives.
- System procedures – such as procedures for risk determination and risk control, maintenance of infrastructure, maintenance and calibration of monitoring and measuring resources, creation and control of documented information, internal audit, management review, customer complaints and feedback, corrective action etc.
- Standard operating procedures (SOPs) – for operational processes for each of the regulatory functions
- Forms/formats/templates – as needed in the above procedures
- Records – as evidence of demonstrating conformance to the prescribed requirements

While creating and updating documented information (DI) for QMS, an appropriate identification and format is used, and that DI is duly reviewed and approved.

The Identification and description of DI may be assured by the title, date, author, or reference number (or a combination of these), the format for the DI can be hard copy, electronic or both. It could also be in more than one language, based on the culture of the organization.

The method for the review and approval of DI should be decided, e.g. having an identified person with the authority to review and approve the DI or having one or more reviewers and one person who takes the responsibility for approval.

Documented information should be available in a suitable format and be adequately protected. The DI should also be in a form that is suitable for the intended use, for example, a written technical service agreement for an external service provider, or process parameter information in electronic format that can be used/downloaded at the process interface internally.
Controls on DI include its availability, distribution and protection (for example from loss of data), its confidentiality, improper use and unintended changes. This can be done in many ways, including in electronic systems with ‘read-only’ access and specified permissions to access, password protection or identification (ID) entry. Information security issues and data backup should also be taken into consideration.

The control of documented information also must address distribution, access, retrieval and use, storage and preservation, control of changes, retention and disposition of DI.

Documented information can change and develop as an organization develops its QMS. There is also a need to consider how historical documented information is maintained, stored and retrieved as necessary for subsequent use.

The retention time for documented information could be a statutory or regulatory requirement, a contractual requirement, or can be determined by the NRA.

Documented information of external origin such as customer’s given DI (application files, SLPs), government orders, national/regional/international standards, calibration reports given by outside laboratories etc., as necessary for QMS should be identified appropriately and controlled in line with other DI.

When documented information is retained as evidence of conformity (records), it should be protected from unintended alterations, e.g. in case of soft copies, only giving controlled access (‘read only’) to such information.

**Practical help box 19. Guidance for the interpretation of Clause 7.5**

**Examples of documented information that needs to be maintained by NRAs**

- Organizational chart, job descriptions, list of personnel and their roles and responsibilities, operational processes flow charts, mission and vision policy statements, strategic plans, QMS scope statement, quality manual and quality objectives, standard operating procedures, instructions, forms among others.

**Examples of documented information that needs to be retained by NRAs**
Marketing authorization files, summary lot protocols, certificates of compliance/ non-compliance, lot release certificates, records of test results, reports, annual product review reports, testing methods and related validation reports, reports of adverse events following immunization and case investigation reports, complaints and related reports, personnel qualification records, personnel training records, personnel health records, internal/external audit plans and related reports, management review meetings’ agenda and minutes, validation, qualification or calibration records or reports among others.

More information on good data and record management can be found in the recently published WHO guideline.

Clause 8. Operations

8.1 Operational planning and control

Guidance

The intent of this clause is to ensure that NRAs plan, implement and control the operational processes (MA, VL, MC and LR processes) that are necessary to meet the requirements of service provision, including any externally provided (outsourced) processes.

The following are the components of the plan:

- Determining requirements for products and services - consider customer, statutory and regulatory requirements, organizational requirements including requirements relating to relevant interested parties (stakeholders).
- Establishing criteria (methods/procedures/KPIs) for the control of processes and acceptance of products and services consider; a) risks and opportunities; b) quality objectives; c) requirements for products and services.
- Determining what resources are needed and if the current resources suffice.
- Planned and potential unintended changes, and how these changes can affect the operations.
- Determining documented information that needs to be maintained and that which needs to be retained.

The output of the above planning should be used as inputs to operations. It should be kept in suitable format and media for those who need to use it. Practical help boxes 5 to 8 give examples of the details of the processes involved in MA, LR, VL and MC, and possible KPIs, and required resources.
8.2 Requirements for products and services

Guidance

The first part of the clause refers to communication with customers and focuses on five communication areas:

a) detailed communication of the products and services offered so that the customer understands the requirements, to be provided to the customer through the website, pre-submission meetings, scientific advice, telephone or other,

b) clear communication on how the customer can contact the NRA in case of questions or other services, or how the NRA would contact the customer in case of questions or other,

c) establishing channels to gain information from customers such as concerns, complaints, positive and negative feedback, for example a web-based platform, phone calls, surveys, etc.,

d) inform customers how the customer property (documents, samples, dossiers etc.) is handled, where appropriate, and

e) ensure that the NRA is proactive in communicating with the customer about possible contingency actions that can be taken, if the need occurs, such as natural disasters, epidemics, shortfall of staff or others.

Proactive communication enables the customer to understand what the NRA can or intends to provide and enables the NRA to understand or confirm the needs and expectations of the customer and bring greater transparency and public accountability.

The second part of the clause refers to determining the requirements of products and services, which in the case of NRAs are mostly statutory and regulatory requirements such as the Food and Drugs Act, the pharmacopoeia, monographs, etc.; but also, timelines for service delivery, fees charged for service, hours for customers service, acceptable waiting/or response time, etc. This information should be transparently communicated to customers and the public in general, usually through the NRA website.

The NRA should review the commitments it makes to a customer and ensure it can meet them. The review allows to reduce the risk of issues arising during operations.

The NRA should ensure that request for service received from customer is complete and is in conformity with service requirements. When there is a difference between the requirements for products or services
as requested by customer and the one prescribed by the NRA, the same should be communicated to the customer and resolved before processing the request. Any verbal request/change in the requirements, either by the NRA or by the customer, should be confirmed before service is provided.

When the requirements for products and services are changed due to any reason, the NRA should take measures to inform all relevant interested parties.

The NRA should retain evidence of the results of the revisions to the requirements of products and services and any new requirements for the products and services that are provided.

**Practical help box 20. Guidance for the interpretation of Clause 8.2**

**Example of communication with customers**

**a) Customer Communication**

Communication with customers aims at collecting information about their needs and expectations, as well as the reception of doubts, suggestions and complaints about the current work process and the engagement of stakeholders.

**Phases:**

- meetings with internal customers - managers and their teams - to identify problems and propose solutions;
- meetings with regulated sector and other stakeholders to identify difficulties with the products and services offered by the regulatory authority and seek suggestions for improvements;
- meeting with managers, to present the methodology and the schedule of actions.

**Products:**

- user's journey map: tool to identify all the points of contact of a user with a product or service and understand their needs, feelings, desires and pains related to the product or service, to promote the necessary improvements;
- communication plan: a tool that establishes strategies for communicating with customers and other stakeholders involved during all stages of the process improvement initiative and raising awareness of the new way of working.

**b) Determination and critical analysis of requirements**
To determine the requirements, it is necessary to understand the challenges, make the diagnosis and immerse in the problem, through five stages.

Phases:

- definition of the scope of processes;
- collection of quantitative and qualitative data;
- mapping the current situation of the processes;
- definition of performance gains;
- definition of the team committed to the initiative.

Products:

- planning the initiative;
- quantitative and qualitative analysis of processes;
- flowcharts and checklists AS IS (as it is).

c) Changes on requirements

When changes of requirements occur, regardless of the reason, process documentation is reviewed, changes are recorded as well as communicated to all those involved in the chain.

Phases:

- meetings with customers to understand the dynamics of the necessary changes;
- revision of the documentation (scope, schedule, actors, communication plan);
- communication to all those involved.

Product:

- new planning of the process; transformation initiatives (scope, schedule, actors, communication plan).

8.3 Design and development of products and services

Guidance

The intent of this clause is to ensure that NRAs establish, implement and maintain a design and development process in order to ensure that new products and services meet requirements. The design and development process define the characteristics of the products and services.
The design and development of products and services consists of a set of processes that use ideas or requirements for a product or service. These ideas or requirements can come from customers, end-users, regulations, the organization or other interested parties including WHO. The ideas or requirements are processed to develop more detailed requirements that finally define the characteristics of the product or service. An example of an instance where an NRA may need to go through design and development process is in case it decides to perform a regulatory function that was not in place until then, or a new process within a function. For example, NRA from country X does not inspect clinical sites and is now able to introduce this new process within their activities to regulate clinical trials. To introduce this process, they will follow international guidance, however specificities of the process to be followed will be designed in-house. If an organization only uses ideas or requirements provided by regulation, customers or end-users, without adding more detail, it does not have design and development activities. In such cases, an explanation as to why the NRA is not applying clause 8.3 in its QMS can be included in the QMS scope statement (see clause 4.3).

The design and development of products and services requires several phases or steps:

- **Design and development planning:** to determine the necessary design and development activities and tasks. This plan should include, required process stages; design inputs, design review, design verification and design validation, resource needs; as well as a clear definition of roles and responsibilities.

- **Design and development inputs:** determines the inputs for design and development projects. These inputs need to be unambiguous, complete, and consistent with the requirements that define the characteristics of the product or service. It is important to consider the functional and performance requirements, statutory and regulatory requirements as well as additional standards or codes of practice.

- **Design and development controls:** to ensure that once the inputs have been determined, the design and development activities and controls are implemented in accordance with the planning, to ensure process is effective.

- **Design and development outputs:** to ensure that design and development outputs (service provision, standard operating procedure or service provision manual) give the necessary information for all the processes needed to provide intended products and services (including information to be provided by service recipients, service provision process, and post-delivery activities, if any).

- **Design and development changes:** to determine, review and control changes made during or after the design and development process. Changes can arise during the design and development process (because of design review, verification or validation activity), after the release and approval of the
design and development outputs and during implementation of the same, as a result of monitoring
customer satisfaction and interested parties’ feedback or as result of changes, or new, statutory and
regulatory requirements.

Once these development phases are completed, a review by person(s) who are not involved in design
activity) is required to ensure that design and development planning stages and the output of each stage
are in place. Verification (comparing the new design with a similar proven design) and validation
(testing under intended user conditions) activities are essential for controlling the design and
development process and need to be implemented effectively.

NO EXAMPLE AVAILABLE AS YET

8.4 Control of externally provided processes, products and services

Guidance

The intent of this clause is to control processes, products and services that are provided by an external
provider. External providers could include Government’s central procurement agency, suppliers of
products and services, experts and consultants or someone to whom the NRA decides to outsource a
process.

The NRA is responsible for ensuring that externally provided processes, products and services conform
to requirements (e.g. through incoming goods inspection, or surveillance of an outsourced service
provider).

The NRA should clearly identify its requirements (specifications) for the product and service to be
purchased to ensure that externally provided processes, services or products do not have a negative
effect on its operations or on customer satisfaction.

The NRA should ensure, its requirements are complete, clear and address any potential issues. It should
clearly communicate the requirements and controls to be applied to the external provider and both
parties should agree as to what is required. This understanding of requirements is usually reflected in
a technical service agreement and/or through a purchase order/contract.

The NRA needs to determine and apply criteria for the evaluation, selection, monitoring of performance,
and re-evaluation of external providers. The type and extent of control to be exercised is based on how
much effect the externally provided process, product or service can have on the conformity to
requirements of the NRA’s products or services. The NRA should determine which specific controls
are to be implemented to an external provider. Control activities that may be considered include
inspections, certificates of analysis or testing, second party audits, evaluation of statistical data and
performance indicators.

The NRA should maintain up-to-date information related to its external providers, evaluated on their
ability to comply with purchasing requirements both in terms of conformity of the product and service
provided and delivery performance. A list of providers could serve as a basis for external provider
selection and management of relation with current external providers.

**Practical help box 21. Guidance for the interpretation of clause 8.4**

For the MA process, the NRA has as external provider with the figure of “Third Authorized Party” (TAP), which
are persons authorized by the NRA to perform a preliminary review of marketing authorization dossiers and to
issue, if applicable, a Favorable Technical Reports (FTR) for registration, modification or extension of medicines
MA based on compliance with the requirements established by the Ministry of Health in the corresponding
regulations for the completion of procedures.

The process of selection of a TAP by the NRA is done through an announcement published by the Ministry of
Health in which the requirements that must be fulfilled by interested candidates are established. The authorization
to act as a TAP has a validity of two years. TAPs can be individuals or companies.

The NRA recognizes the technical competence of the TAP ensuring that the process of evaluation and release of
an FTR is managed effectively in accordance with the provisions of the current regulations through the
establishment of policies, responsibilities and activities to be fulfilled by the TAP. The TAP is also subject to
controls for evaluation and monitoring.

The controls applied by the NRA fall under the following categories:

- Technical supervision
- Supervision of the records reviewed by the TAP

Verify the technical qualification, training and experience of the personnel involved in the review.
Verify the documented training system that ensures competencies in the technical aspects.
Verify that there are adequate tools, references and bibliography that allow technical activities.
Review of the technical procedures and the homologation criteria of the reviewers (TAP).
Follow up on the corrective or preventive actions derived from the non-conformities detected in the supervision visits.

TAP verification actions allow to detect FTR with inconsistencies or non-compliance with the regulatory provisions.

The qualification of the TAP has been assigned a level of confidentiality from I to IV, being I "highly reliable" and IV "not reliable", which will provide the level of review (reduce, regular or strict) by the NRA of the procedures entered with FTR of the TAP.

**8.5 Production and service provision**

*Guidance*

The intent of this clause is for the NRA to establish controls to ensure that the intended results are achieved (products and services), by reducing the potential for errors/nonconforming outputs. The clause also focuses on the preservation of data and physical property, traceability, control of changes and the responsibility for post-delivery activities.

Items a) to h) of clause 8.5.1 provide suggested controls to be applied to service provision to ensure that the criteria determined in clause 8.1 are met. These include documented information about the procedures used and the results of monitoring activities including measurements if applicable; checks to ensure that the necessary infrastructure is in place as well as availability of competent personnel, that processes are validated, actions taken to prevent human error including appropriate training of personnel provided, and controls are in place for release, delivery and post-delivery activities including confirmation that authorized personnel for these activities is in place.

To properly monitor the status of product and service provision throughout the service provision process, products and services should be identified (reference number of service request, batch number for drugs, code no of product, others) and traceability ensured. Product and service identification prevents unintended mix up of the service requests and allows tracing of the events for processing service requests, updating customer about status of service delivery, investigation of customer complaints, etc.

The NRA, due to its mandated role and responsibilities, has access to property that does not belong to the NRA, but which is under the NRA’s control; this property can be tangible or intangible. Examples
include marketing authorization dossiers, SLPs, vaccine samples for testing, intellectual property or 
personal data, others. The NRA should make provisions to ensure the protection of such property.

The actions taken to protect it, will depend on the type of property. The owner of the property should 
be clearly identified and made known within the NRA. Protection of data could be ensured through a 
specific password protected electronic location or file with restricted access to store customer’s 
intellectual data, patent information, performance and sales figures, etc. Data integrity can be ensured 
by regular back-ups and virus protection, storage of magnetic media (e.g. video tapes, audio tapes and 
computer disks) in a non-magnetic environment, others.

When the NRA takes control of the property its verification is important (e.g. state or physical condition, 
accuracy of personal data, completeness of the dossier).

The customer or external provider should be accurately informed if property is lost, damaged or 
otherwise found to be unsuitable or incapable of use. This will require to be documented.

Outputs from different processes and products and services, should be preserved from damage or loss 
at all stages during service provision. The NRA should determine which are the outputs, products and 
services that can deteriorate or degrade and implement appropriate preservation methods.

In case that changes occur during service provision, these must be reviewed and controlled.

There may be numerous reasons why changes occur; for example, a change initiated by an external 
provider (e.g. delays in getting expert’s opinion or test reports from external labs), due to internal issues 
(e.g. critical equipment failure, internet connectivity issues) or to an external issue (e.g. new or modified 
customer or statutory and regulatory requirements).

Changes must be controlled, and the relevant documented information retained. Examples include: a) 
minutes of the review activities; b) description of the change; c) details of the person(s) or a customer 
authorizing the change.

The responsibility of the NRA does not end with product and service delivery, the clause also 
emphasizes the need to determine the post-delivery activities in which the NRA is engaged. For this, it 
should consider if the post-delivery activity is part of a contractual requirement or is a regulatory 
requirement such as marketing authorization renewals, approval of changes (variations), market 
surveillance or to address a potential complaint from customers (customers dissatisfaction).
Other examples of post-delivery activities include:

- Engagement with customers to determine if the products or services were to their satisfaction through customer feedback, resolving customer complaints, customer compliments, media reports etc; and
- Customer access to on-line information required after delivery.

**Practical help box 22. Guidance for the interpretation of clause 8.5 relating to preservation of physical property**

**Example of infrastructure required for the preservation of vaccines until their expiry**

An NRA may receive vaccine samples for visual inspection or testing during the lot release process, and in some cases also during the marketing authorization evaluation process, although at this stage this is not required.

In case samples are requested, these need to be properly stored and kept until the expiry date. The NRA needs adequate infrastructure to keep vaccines at 2-8°C during the whole shelf life. Adequately validated and regularly monitored refrigerators are needed. Back up measures are required such as an alarm system (ideally centralized), which ensures that in case of electricity failure or break down of the equipment, a responsible officer is immediately informed. A back up refrigerator or electricity generator, depending on the source of the failure, must be available for such situations

**8.6 Release of products and services**

**Guidance**

The intent of this clause is to ensure that products and services are checked for conformity for all applicable requirements, at appropriate stages of the service provision process, before they are released for delivery to the customer, for example, issue of market authorization certificate/letter.

Approval by a relevant authority may be required when all checks for conformity have not been satisfactorily completed - in some cases, this could be the customer.

The release of products and services should be suitably documented (DI). The DI should include evidence that the product or service conforms to all acceptance criteria and be traceable to the person authorized to release products and services.
The person(s) who authorize(s) final release of the product or service should be suitably defined by, for example, their job description or authority level.

**Practical help box 23. Guidance for the interpretation of clause 8.6**

Products of XYN Drug Authority include reports, certificates, licences, permits and authorization letters. These are checked by the respective supervisors and signed by the Executive Director or other senior officer(s) authorised by the Governing Board to do so as per section XX of the National FDA Act, before delivery to the applicant or entity that requests them. The list of authorised persons (Authorised Persons to Release the XYN Drug Authority products to applicants) is updated from time to time and communicated to all staff via the posted on the XYN Drug Authority Intranet.

The release of reports, certificates, licences, permits and delivery to the applicants does not proceed until the requirements have been satisfactorily met (e.g. certificates for GMP compliance are not issued until the evidence of corrective and preventive actions taken by the manufacturer are submitted and evaluated by the XYN Drug Authority and found to be satisfactory).

**8.7 Control of non-conforming outputs**

**Guidance**

The intent of this clause is to prevent non-conforming outputs from progressing to the next stage or to the customer.

There are different ways to control non-conforming outputs:

- Correcting (rework, repair) the nonconformity to ensure it does conform
- Removing the nonconformity from the process entirely (rejecting or scrapping the output/product)
- Obtaining authorization for release under concession

The extent of control that an organization needs to take depends on the nature of the nonconformity and its potential effects.

If the nonconformity is discovered after it has progressed to the next stage, or been delivered to the customer, the NRA should take appropriate actions to prevent unintended use or undesired consequences, and take measures such as issuing a re-call, suspension, re-processing, eliminating or
reducing the NC to acceptable level (concession). In case of concession, authorization should be given by the appropriate person(s) or, where relevant, the customer.

The NRA should ensure that the documented information retained includes details of the nonconformity, the actions taken to correct, mitigate or communicate it, any concessions obtained (e.g. agreement with the customer that the product or service could be used despite the nonconformity) and who authorized the actions taken.

Retaining documented information on the above ensures that processes are improved and optimized; corrected work instructions, processes and procedures are detailed for future use.

Practical help box 24 Guidance for the interpretation of clause 8.7 Control of non-performing outputs

When a nonconforming output is detected before or after delivery to the customer, it is registered by the process owner and an investigation form e.g. complaint investigation in-process form (in case of market/customer complaints); or the OOS investigation form (in case of the QC Laboratory); or the corrective action request (CAR) form (for others, e.g. arising out of quality audits); is raised for investigation to be initiated in order to find out the root cause or assignable cause. Correction and corrective action are then taken by the respective process owner.

A non-conforming output may include any of the following items that is found to have an error, mistake or defect before or after delivery to the applicant (customer):

a) Marketing authorization certificate, GMP certificate, import/export permit, manufacturing licence, licence to sell drugs, or a laboratory test report or certificate of analysis,

b) Published adverse event report,

c) Clinical/field trial assessment monitoring report,

d) Promotional material vetting report.

In all cases, correction and corrective action are taken and the certificate, permit, licence or report that has an error, mistake or defect is either cancelled or withdrawn (without prejudice), or both and replaced with a corrected one. However, the validity period and the applicable conditions remain the same.

Clause 9. Performance evaluation

Practical help box 25 Guidance for the interpretation of clause 9
A monitoring and evaluation framework that tracks process activities, targets, key performance indicators, and outputs is used to monitor progress of processes. Performance reports (quarterly, semi-annual, and annual) are made and their information analyzed and used as input in management reviews.

9.1. Monitoring, measurement, analysis and evaluation

Guidance

The intent of this clause is to ensure that NRAs conduct monitoring, measurement, analysis and evaluation to determine if the intended results are being achieved. The NRAs should determine what needs to be monitored and measured (according to the characteristics of processes, products, services and risks involved) and the methods to be used to analyse and evaluate the performance and effectiveness of QMS. The NRAs should also determine how and when the monitoring, measurement, analysis and evaluation will be carried out, and the resources that will be needed for the same.

The NRAs should decide on what documented information relating to monitoring, measurement, analysis and evaluation will need to be retained as evidence of the results.

One way of monitoring performance is through feedback from customers. It allows to evaluate the degree of customers’ satisfaction and to determine opportunities for improvement. The NRA may choose to seek feedback from a selected population of customers or from every customer at the end of a transaction. Means to obtain feedback are offered through the social and published media such as web sites and message boards, opinion surveys and compliments or complaints.

The NRAs should be able to determine the degree of customer satisfaction after the results are analysed and evaluated; and act based on this information. This information should be an input to management review (9.3) and can be used for determining if actions are necessary to improve customer satisfaction.

The results of monitoring and measurement (data and information) must be analysed to determine if processes, products and services meet requirements and whether there are any needed actions and opportunities for improvement. The purpose of analysis and evaluation of data from monitoring and measurement activities include assessing the level of customer satisfaction, assessing whether plans are being met, assessing performance of external providers, how successful the NRA has been in addressing risks and opportunities, status of performance and effectiveness of QMS and need for improvements.
Data sources that could be used for analysis and evaluation include the monitoring of customer perception (9.1), feedback from media and the public in general (9.1), monitoring quality objectives (6.2), timeliness of service delivery (8.5), data related to corrective or preventive actions taken (8.7), non-compliances detected during internal audits (9.2), others.

The output from analysis and evaluation is generally in the form of documented information such as trend analyses or reports and becomes an input to management review (see clause 9.3).

EXAMPLE NOT AVAILABLE AS YET

9.2 Internal audit

Guidance

The intent of the clause is, for the management of NRA, to obtain information through internal audits about continued conformance and effectiveness of QMS.

The internal audits are conducted at planned intervals to verify if the NRA’s activities and processes continue to meet the prescribed system as defined in NRA’s documented information (e.g. Quality manual, quality policy, quality objectives, procedures, instructions, risk control plans and other plans), if the QMS continues to meet the requirements of ISO Standard 9001:2015 standard and if QMS is effectively implemented and maintained.

Internal audits should be planned, results reported and timely actions on the audit findings taken.

Items a) to f) under clause 9.2.2 of the ISO Standard 9001:2015 provide details on how audits must be planned. The planning process includes developing the audit programme (calendar of audits over a period of time - for example, one year - which also means setting the frequency of audit of each area and related processes over a one-year time), defining the criteria to be used (standard, requirements), the scope of the audit and the methodology to be used during the audit (interviews, documented information review, results, trends, etc.). Auditors should be selected, usually from sectors within the regulatory agency not affected by that particular audit (cross functional audit) who have been trained in QMS auditing. Sometimes external auditors may be used if independence within the NRA is difficult to ensure. Corrective actions must be taken promptly to address the findings of the audit. Documented information of the programme and audit results should be maintained.
Responsibility for planning of audits lies with the person who is directing and managing the internal audit process (audit manager) such as QMS coordinator or some other person as authorized by management of NRA.

While developing the programme, the audit manager should apply risk-based thinking and consider how often the process is performed as well as its maturity and complexity, whether any changes in the process were introduced, or other changes affecting the NRA, the process performance, results from previous audits and history of complaints.

After each internal audit is completed, the results should be reported to relevant management. Based on these results, appropriate correction and/or corrective actions can be necessary. Typically, organizations establish a time to respond and correct nonconformities to ensure they are fixed in a timely manner.

During the audit, auditors might bring up a potential weakness in the QMS, which may represent opportunity for improvement. Such information can help management to decide if it is appropriate to initiate action for improvement.

It is important that management of NRA fosters an open-minded culture where quality audits are perceived as a means to improve performance and not to assign blame for any non-conformities found.

**Practical help box 25. Guidance for the interpretation of clause 9.2**

Planning internal audits by ANRA, the NRA from Country A

Scope of the auditing programme: legal services, internal audit, procurement management, communication and public education, finance and accounts, information and communication technologies and statistics, human resources and administration, planning monitoring and evaluation, food inspection and enforcement, food registration food risk assessment, clinical trials control and pharmacovigilance, medicines and complementary products inspection and enforcement, medicines registration, medical devices, diagnostics and cosmetics control

Timelines: November and December 2018

Processes being audited clearly defined, methodology applied is interviews and documented information review.

Audit duration: One day for each section/unit.

Auditors: Two internal auditors (cross functional) are selected based on expertise.

ANRA is a decentralized authority with five zonal offices. The auditing programme is the following:
Scope: The five zonal offices

Processes: QMS, premises licensing, inspection and enforcement, import and export control, registry, customer complaints and procurement and finance

Audit duration: One day for each zonal office

Timelines: October 2018

Auditors: Two internal auditors (cross functional) are selected based on expertise.

Summary of the procedure for conducting internal audits by ANRA

The purpose is to provide details on how internal audits should be conducted to check and evaluate the efficacy and effectiveness of the QMS for continual improvement.

The quality manager (QM) appoints the auditors and prepares the audit programme for HQ and Zone offices. The QM informs auditors and auditees in writing about the programme. The audit team prepares the audit checklist based on previous audit findings and QMS documentation. During the audit it is the responsibility of the team leader to open the audit and to verify attendance. The audit team should collect and verify information for specific processes, procedures, functions, sites, areas and activities. It records the findings and prepares the audit report. The audit team leader closes the audit. Non-conformities are categorized in minor, major and opportunity for improvement. The audit report is reviewed and agreed upon by auditors and auditee. This is then forwarded to the QM. The auditee should prepare a CAPA and the QM will take measures for timely follow up. If corrective or preventive actions are properly implemented, the audit is closed, otherwise another follow up form is opened.

The audit reports, corrective and preventive actions reports, attendance register, checklists and audit programme should be kept at QM office and maintained for a period of five years and then destroyed by tearing, shredding, burning or other appropriate means.

9.3 Management review

Guidance

The intent of this clause is to ensure that NRA’s top management conducts periodic review of performance of its QMS. The purpose of such review is to determine if NRA’s QMS continues to be suitable (fitting the purpose), adequate (sufficient), effective in achieving the intended results and continues to be aligned with the strategic directions of the NRA.

Management review should be conducted at planned intervals; this could be daily, weekly, monthly, quarterly, semi-annually or annually, depending on the situations facing the NRA. If various levels of
the management carry out management review activities, the results should be made available to its top management for final decision/approval.

Management reviews could be a standalone activity or in a combination of related activities (e.g. strategic planning, business planning, annual meeting, operations meetings, other management reviews).
Table 4. Management Review Meetings (MRM) inputs and outputs

<table>
<thead>
<tr>
<th>INPUTS</th>
<th>OUTPUTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review implementation of actions to be taken following previous review meetings</td>
<td>• Decisions and actions related to opportunities for improvement (10.1)</td>
</tr>
<tr>
<td>Updated analysis of internal and external context of NRA (4.1)</td>
<td>• Decisions and actions related to changes required in the QMS (6.3)</td>
</tr>
<tr>
<td>Performance and effectiveness of QMS (9.1) through: Customers satisfaction (9.1), feedback from interested parties (4.2), implementation of quality objectives (6.1), monitoring processes through KPIs (8.5), conformity of products and services (8.6), status of non-conformities including response to complaints and corrective or preventive actions (10.2), monitoring and measurement results (9.1), audits outcome (9.2) and performance of external providers (8.4)</td>
<td>• Need for additional resources to implement improvement initiatives and changes suggested in QMS and for other areas where resources (including human resource) are not adequate (7.1).</td>
</tr>
<tr>
<td>Adequacy of resources (7.1)</td>
<td>• Progress towards quality objectives (6.2)</td>
</tr>
<tr>
<td>Data about the effectiveness of the actions to confront risks and opportunities (see 6.1)</td>
<td>• Management review meeting minutes to be retained as documented information and communicated in an adequate way to all concerned.</td>
</tr>
<tr>
<td>Opportunities for improvement (10.1 and 10.3)</td>
<td>• Outputs from MRM will be inputs for the following meeting</td>
</tr>
</tbody>
</table>

Practical help box 25. Guidance for the interpretation of clause 9.3

Country A NRA Summary Procedure for Management Review Meetings

The QM should call management review meetings at a minimum once per year but should attempt to conduct them quarterly. Attendees must include the Director General, Directors of Units, Management representative, Legal counselor and any other personnel as deemed necessary by the management to attend. The QM should record the minutes of the meeting. Analysis of data presented (according to table 4) should be performed to look for areas of improvement. Improvement items and follow up actions should be implemented as Action items. The agenda should include status of action of previous MRM and changes in internal and external issues that are relevant to the QMS.

Some NRAs have two types of review meetings:

1. Technical review meetings (TRM) membership is QM focal points in different technical units. They take place frequently (usually monthly) and focus specifically on technical aspects such as KPIs, implementation...
of corrective or preventive actions, conformity of products and services, monitoring and measurement results including trends, audit outcomes and performance of external providers

2. Management review meetings membership is as for the (TRM) plus higher-level management as indicated for Country A above. These take place on quarterly, bi-annual or annual basis. Outputs from the TRM are inputs for MRM as well as other QMS related aspects not addressed in the TRM (see table 4)
XYN Drug Authority Management Review Flow Chart

Management Review Inputs (Agenda)
1) The status of actions from previous management reviews;
2) Reports on process performance, conformity of services and the adequacy of resources (including effectiveness of processes; monitoring and evaluation results and trends; changes in external and internal issues; resources available e.g. human resource, time, equipment and technology used, financial, etc.) with respect to the following key drug regulatory processes:
   a) Assessment and registration of medicines;
   b) Inspection and licensing/certification of pharmacies, medicine shops, pharmaceutical manufacturers (Good Manufacturing practice);
   c) Control of pharmaceutical imports and exports;
   d) Pharmacovigilance;
   e) Clinical Trials;
   f) Vetting of drug promotional materials;
   g) Post-marketing surveillance; and
   h) Enforcement.
3) Report and trends on quality objectives (extent to which objectives related to customer satisfaction, e.g. service delivery objectives have been met) for the key drug regulatory processes listed in 2 above and all the support processes, e.g. Finance and administration, human resource, procurement, legal services, information technology, internal audit, quality management, and public relations;
4) Report and trends on client/customer complaints (market complaints, including appeals)
5) Information from the recent customer satisfaction survey report;
6) Internal quality audit results (from Internal quality audit reports, including second party audits);
7) Report on nonconformities and corrective actions;
8) Performance of external providers;
9) Effectiveness of actions taken to address risks.

Management Review Outputs
- Opportunities for improvement;
- Changes to the QMS;
- Resource needs.
Clause 10. Improvement

10.1 General

Guidance

The intent of this requirement is to ensure that the NRA determines opportunities for improvement, plans and implements actions to achieve the intended results and to enhance customer satisfaction.

Improvements can help the NRA to keep meeting customer requirements and expectations by improving its products and services, correcting or preventing undesired effects, and improving the performance and effectiveness of QMS.

There are different methods to conduct improvement, such as correcting existing nonconformities and taking actions on their causes to prevent recurrence, or making small-step-ongoing improvement activities or through breakthrough projects leading to innovation, revision and improvement of existing processes or the implementation of new processes;

10.2 Non-conformity and Corrective Action

Guidance

The intent of this clause is to ensure that the NRA manages nonconformities, and implements corrective action, appropriately.

Non-conformity means ‘non-fulfilment of a requirement’ related to a product, service, process or QMS. These requirements may come from the customers, from relevant interested parties, from statutory and regulatory requirements, or they may be internal requirements defined by the NRA in its policies, manuals, procedures, quality objectives, etc.

A non-conformity could be identified from customer complaints or from non-conforming outputs, problems arising from relevant interested parties, audit results, the effects of unplanned changes, etc.

The immediate action needed is to control or correct any non-conformity. This can be achieved by containing the problem while the investigation continues. For example, making customers aware of a non-conformity and to provide information about the potential or actual effects on the product provided
or service delivered and also correcting the situation.

To make corrections and introduce corrective or preventive actions, the NRA should follow the following steps:

1. Review and analyse the non-conformity to determine its cause by using methods such as, 5-why method or cause-and-effect-analysis diagrams or simply by brainstorming with a cross functional team. Examples of typical root causes include lack of understanding of requirement, lack of resources, process not well-defined, etc.

2. Determine the extent of the actions that need to be taken to eliminate the cause determined at 1 above. There might be instances where the cause of the non-conformity cannot be eliminated, therefore the NRA should consider taking actions to detect and minimize the effects of the non-conformity if it were to occur again.

3. Implement any needed actions as decided at 2 above. This may include making changes in process/procedure, providing resources, retraining persons, ensuring better adherence to defined process, etc. It should be ensured that corrective action taken in one area should not cause adverse effects in another area of the NRA.

4. Review the effectiveness of corrective or preventive actions taken by confirming (through evidence) that the actions have been implemented. This may be accomplished by observing the performance of processes or reviewing documented information or verifying during internal audits that the same non-conformity is not repeated. This review should be done after a reasonable time needed to implement corrective action has elapsed.

5. After the review of corrective or preventive actions, the NRA should consider whether there is a new risk or opportunity that was not determined during planning (see 6.1) and planning should be updated as necessary.

The NRA should retain documented information showing what correction or corrective or preventive actions were taken, including the nature of the non-conformity (e.g. nonconformity statement); examples include corrective action forms or databases and evidence demonstrating that actions have been taken.
Practical help box 26. Guidance for the interpretation of clause 10.2

An example of dealing with nonconformity using a Corrective Action Request Form.

XYN Drug Authority Corrective Action Request (CAR) Form

(To be used to request for corrective action of a nonconformity in the NRA quality system)

<table>
<thead>
<tr>
<th>Nonconformity</th>
<th>Root Cause (from 5-Why Root Cause Analysis Form attached)</th>
<th>Corrective Action</th>
<th>The steps that have or will be taken for the demonstration of effectiveness of the actions taken</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 There was no evidence of monitoring of the quality objective in the Post Marketing Surveillance department, contrary to the requirements of the standard.</td>
<td>The parameters to be monitored and the tool to be used had not been established.</td>
<td>Develop a format for monitoring the quality objective clearly indicating the parameters.</td>
<td>1. Developed a format with key parameters as listed&lt;br&gt;a) Products&lt;br&gt;b) Annual and Quarterly targets&lt;br&gt;2. Create a database on the NRA server for monitoring the quality objectives and train the NRA staff in using it.</td>
<td>Oct 2018 - Nov 2018</td>
</tr>
</tbody>
</table>

A root cause analysis must be attached. See example below:

XYN Drug Authority Root Cause Analysis Form

Directorate/Department/Area: Inspection & Licensing Dept. Representative: Dr. Brian Harvey Date: 7th Nov 2018

Category of Problem: Nonconformity ✓ Nonconforming output □ Market Complaint □ Other (please specify) □

(Click applicable box above by double clicking on it)

<table>
<thead>
<tr>
<th>Problem / Issue</th>
<th>Why 1</th>
<th>Why 2</th>
<th>Why 3</th>
<th>Why 4</th>
<th>Why 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 There was no evidence of monitoring of the quality objectives in for the Inspection and Licensing (I&amp;L) processes</td>
<td>Why was there no evidence of monitoring of the quality objectives?</td>
<td>Why was monitoring of the quality objectives not yet started?</td>
<td>Why were the quality objectives not yet communicated to the relevant personnel at all levels?</td>
<td>Why was the system of monitoring the quality objectives not well established?</td>
<td>Why was the system of monitoring the quality objectives not well established?</td>
</tr>
<tr>
<td></td>
<td>Because the quality objectives had just been developed and monitoring them had not started.</td>
<td>Because the quality objectives had not been communicated to the relevant personnel at all levels.</td>
<td>Because the system of monitoring them was not well established.</td>
<td>Because the parameters to be monitored and the tool to be used had not been established.</td>
<td>Because the parameters to be monitored and the tool to be used had not been established.</td>
</tr>
</tbody>
</table>

Note: Although this technique is called “5 Whys,” you may need to ask the question fewer or more times than five before you find the root cause of the problem or non-conformity.
10.3 Continual improvement

Guidance

The intent of this clause is that NRA should continually improve the suitability, adequacy and effectiveness of its QMS.

Continual improvement can include actions to increase consistency of process outputs and products and services; improve process capability and reduce process variation. This is done to enhance the NRA’s performance and benefit its customers and interested parties. The results from analysis (9.1) and evaluation and management review (9.3) are used to decide whether continual improvement actions are needed and what they should be.

Examples of CI include reducing errors, rework, complaints, non-conformity, breakdown of equipment, delays of promised services etc. and improving customer satisfaction, improving employees’ involvement, etc.

There are several methodologies and tools that NRA can consider to initiate continual improvement activities, for example, Kaizen, benchmarking, use of self-assessment models etc.

Practical help box 27. Guidance for the interpretation of clause 10.3.

As part of continual improvement, XYN Drug Authority uses trending of quarterly, semi-annual and annual performance of the key drug regulatory process and all support processes; and from results of management review, to determine areas of underperformance and to identify any opportunities for improvement.

5. QMS implementation methodology

For the successful implementation of QMS, full commitment of Head of NRA (top management) will be necessary with respect to provision of timely resources (human and others) for implementation of QMS and by demonstrating his/her leadership, commitment and customer focus (see guidance under clause 5.1 of this guideline) through all stages of the implementation of QMS.

A systematic way of implementing the QMS will include the following steps:
<table>
<thead>
<tr>
<th>Step</th>
<th>Activity</th>
<th>Refer guidance under clause</th>
<th>Responsibility within the NRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.</td>
<td><strong>Documenting QMS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Appoint a Core Team (CT) with members from various functions of NRA with</td>
<td>-</td>
<td>Head of the NRA</td>
</tr>
<tr>
<td></td>
<td>one person as team leader, who subsequently could be designated as QMS</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Coordinator - Head of the NRA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Persons in CT should fully understand the QMS requirements either through</td>
<td>Full guideline</td>
<td>CT</td>
</tr>
<tr>
<td></td>
<td>study of this guideline or undergo a formal training on the subject</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Develop current Context statement (SWOT analysis) of NRA or use one,</td>
<td>4.1</td>
<td>CT</td>
</tr>
<tr>
<td></td>
<td>if already available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Determine and document requirements (needs and expectations) of</td>
<td>4.2</td>
<td>CT</td>
</tr>
<tr>
<td></td>
<td>interested parties/stakeholders (both external and internal) relevant</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>to QMS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Determine and document the Scope of QMS (could be whole NRA or specific</td>
<td>4.3</td>
<td>CT and Head of NRA</td>
</tr>
<tr>
<td></td>
<td>functions) with NRA’s products and services within the scope listed in</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>it. If any of the requirements of ISO 9001 is not applicable,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>provide its justification within scope statement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Develop and document Quality Policy, keeping in view the purpose (vision</td>
<td>5.2</td>
<td>CT and Head of NRA</td>
</tr>
<tr>
<td></td>
<td>and mission), context and strategic direction of NRA.</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Policy statement could be communicated through display within NRA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>office(s) or otherwise communicated to all, for its understanding and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>application.</td>
<td></td>
<td></td>
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<tr>
<td>7.</td>
<td>Develop and document QMS related responsibilities and authorities at</td>
<td>5.3</td>
<td>CT and Head of NRA</td>
</tr>
<tr>
<td></td>
<td>different levels of NRA staff and communicate to all concerned.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Use information from step 3 and 4 above, as input, to determine risks</td>
<td>6.1</td>
<td>CT</td>
</tr>
<tr>
<td></td>
<td>and opportunities and develop risk control plan.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>Develop and document measurable and time bound quality objectives</td>
<td>6.2</td>
<td>CT and Head of NRA</td>
</tr>
<tr>
<td></td>
<td>including plan for monitoring and achieving them and communicate quality</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>objectives to all concerned.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>Carry out a gap analysis with respect to support processes covering</td>
<td>7.1, 7.2, 7.4</td>
<td>CT</td>
</tr>
<tr>
<td></td>
<td>human resources, infrastructure (equipment, hardware, software,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>facilities etc.), process environment (heating, lighting etc),</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>measuring equipment, organizational knowledge and communication and</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>fill the gaps, if any.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Develop new or harmonize existing Standard Operating Procedures (SOPs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>for control of measuring equipment, organizational knowledge, training</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>and communication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>For internal support services provided by viz administration, HR, ICT</td>
<td>7.1, 7.2, 7.4</td>
<td>CT</td>
</tr>
<tr>
<td></td>
<td>systems, maintenance, logistics, procurement etc., it is good to develop</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>and practice Service Level Agreements (SLAs) covering service standards</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(time lines) and responsibilities of each party (internal service</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>provider and service recipient)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Conduct gap analysis to assess the extent to which the existing NRA</td>
<td>8.1, 8.2, 8.3, 8.4,</td>
<td>CT</td>
</tr>
<tr>
<td></td>
<td>policies, procedures/manuals and practices relating to regulatory</td>
<td>8.5, 8.6 and 8.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>functions (MA, VL, MC, LR or others) are in line with service provision</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>processes (8.1 to 8.7) of ISO 9001 and harmonize existing SOPs or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>develop</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
additional processes and related SOPs and SLAs with customers. Also integrate risk control plan in the relevant SOPs. Guidance under clause 4.4.1 will facilitate to harmonize SOPs with ISO 9001 requirements.

| 13. | Develop quality system procedures (QSPs) for monitoring of customer satisfaction, internal audit, management review, complaints handling, correction and corrective actions, improvement; and put them in practice. | 9.1.2, 9.2, 9.3, 10.1, 10.2 and 10.3 | CT |

| 14. | Develop and document a Quality Manual (QM) stating as to how NRA intents to meet each requirement of ISO 9001 with scope and quality policy statement (at 5 and 6 above) included into it. All other documents viz. SOPs, QSPs, SLAs, forms/formats/templates referred in QSPs/SOPs/SLAs may be added as annexes to QM or kept separately as standalone folders. All above documented information (DI) including records could be either in hard or soft version. A QSP for creation, updating and control of DI will also be needed and also a QSP on Planning for changes. | 7.5, 6.3 | QMS Coordinator |

### B. Practicing QMS

| 15. | It is good practice that documents as they get developed are communicated to all concerned and put into implementation mode. | - | QMS Coordinator and all concerned |

| 16. | Formal awareness sessions may be held by CT for people to understand and apply the policies, objectives, SOPs, QSPs, SLAs etc and if necessary train people on how to use new QSPs/SOPs/SLAs | 7.3 | CT/QMS Coordinator and all concerned |

| 17. | Monitoring of products, services and processes should continue to happen against defined KPIs, risk control plan, and through monitoring of applicable quality objectives. The monitoring data should be analysed and evaluated. | 9.1.1 & 9.1.3 | CT/QMS Coordinator and all concerned |

| 18. | After formal implementation of QMS, for at least a period of 3 months, an internal audit, followed by corrections/corrective actions on the audit findings and management review should be carried out | 9.2, 10.2 & 9.3 and related QSPs | QMS Coordinator, all concerned and Head of NRA |

| 19. | After each management review there will be follow up actions on the decisions taken during review and taking forward improvements where ever identified during review. | 9.3, 10.1, 10.2 & 10.3 and related QSPs | QMS Coordinator |

| 20. | Steps 17 to 19 are ongoing | - | All concerned |

2729 It will be realistic to give a time frame of 9 to 12 months for completing all the above steps well.

2730

2731 If the NRA considers necessary to take help of a QMS consultant for implementation of ISO 9001 QMS, the NRA may appoint one.
C. Certification of QMS

Although not mandated by ISO 9001, if the NRA management wishes to obtain a third-party certification, the NRA may select an accredited Registrar/Certification body (data available on ISO website) at an appropriate time, for example during step 18 above.

The selected certification body (CB) will first examine the NRA’s documents (quality manual, QSPs, SOPs & other documents) for their conformity to ISO 9001. Thereafter once NRA has completed all activities satisfactorily (i.e. up to step 19 above), the CB will arrange an audit of the NRA’s QMS and based upon the audit results will issue the certificate. Certification is generally valid for a period of 3 years and for the maintenance of certification, annual surveillance audits are also carried out by same CB after certification.

6. Considerations to ensure integrated implementation of QMS in NRA

Implementing ISO Standard 9001:2015 in departments or institutions of the NRA is feasible; however, integration of several functions of NRAs into one comprehensive and effective system represents a challenge. Executive coordination between different departments or offices in the decentralized model or institutions in the discrete model is critical and challenging. This is not just a question of regulatory affairs because the challenges are widespread. Capacity building and strengthening is essential for coordinating efforts between institutions involved in achieving good implementation of drug policies, frameworks, others.

Potential mechanisms that can help in QMS implementation:

- Strong coordination mechanism is established including communication,
- High level support from TM for QMS implementation,
- Assembly of a high-level executive committee to enforce understanding and commitment to QMS implementation and maintenance,
- Empowerment of the NRA by the MoH with authority to drive QMS implementation,
- Sustainability of QMS would be facilitated if part of the legal framework, e.g. a decree/mandate- or other legal means supported it,
- Including QMS in the national medicine policy,
- Including responsibility for contributing to QMS in staff job description,
• Training all staff in QMS via courses, conferences, meetings, online platform. Trainings should be relevant to the regulatory functions,

• Creation of a QMS unit in the NRA or as a minimum appointment of a QMS responsible officer with the appropriate level of authority,

• Engagement of all stakeholders,

• Creation of a portal for information-sharing among different stakeholders which would allow NRAs to share their procedures for QMS implementation, documentation, models, frameworks, tools. It would provide an opportunity for QMS networking among NRAs,

• Coordination of KPIs between different functions so that all in the NRA speak the same QMS language, integrated and responsive to achieving the strategic plan and the establishment and maintenance of the QMS,

• Monitoring of the process flow between each party, e.g. MA sharing data with NCL and other functions as needed,

• WHO recommendation for the TM to enforce QMS for all parties of the NRA,

• As a part of the enforcement concept, and for some NRA models, creation of a high level (e.g. in the MOH) QMS unit with an external audit team,

• Creation of a technical unit with one representative from each organization or department which meets at regular intervals for coordination, communication and data analysis,

• Practice by many vaccine producers is to have a two-level system: a management review team which is high-level management who meet once a year and a quality management team which is more technical. The technical team meets and discusses KPIs monthly or quarterly. A similar approach could be considered by NRAs.
**References and further reading**

*NOTE: References listed in this section, and their numbering throughout the guideline, will be corrected and updated in the final stages of guideline development.*


[16] Quality systems requirements for national good manufacturing practice inspectorates.

[17] WHO good practices for pharmaceutical quality control laboratories.


European Centre for Environment and Health, Bilthoven


Civil Aviation Organization. First Edition-2010
https://www.icao.int/APAC/Meetings/2011_AAITF6/QMS%20manual%20formatted%20for%20edit


[23] ISO/IEC 17025: 2017 General requirements for the competence of testing and calibration laboratories


[27] ISO 37001:2016 Anti-bribery management systems- Requirements with guidance for use


Authors and acknowledgements

Mr Y. Al-Nujaym, Saudi Food and Drug Authority, Saudi Arabia; Dr O.A.M.A. Badary, National Organization for Drug Control and Research, Egypt; Ms G.F. Ferreiro, Centro para el Control Estatal de Medicamento, Equipos y Dispositivos Médicos, Cuba; Ms A. Julsing, Medicines Control Council, South Africa; Ms Y. Lee, Ministry of Food and Drug Safety, Republic of Korea; Dr R. Lino de Brito, Agencia Nacional de Vigilancia Sanitaria, Brazil; Ms L. Margaryants, Scientific Centre of Drug and Medical Technology Expertise, Armenia; Ms G. Mkomagi, Tanzania Food and Drug Authority, Tanzania; Ms M. Muñozcano Quintanar, Comisión Federal para la Protección contra Riesgos Sanitarios, Mexico; Mr G. Muthuri Francis, Pharmacy and Poisons Board, Kenya; Ms A. Olivares, Comisión Federal para la Protección contra Riesgos Sanitarios, Mexico; Mr P. Osatapirat, Thailand Food and Drug Administration, Thailand; Ms H. Qorani, Jordan Food and Drug Administration, Jordan; and Dr C. P. Alfonso, Mr S. Arora, Dr R.O.A. Dehaghi, Dr N. Dellepiane, and Ms S. Ramirez, World Health Organization, Switzerland.
Appendix 1. Integration of QMS into the WHO Global Benchmarking Tool

The WHO Global Benchmarking Tool (GBT) is used to assess the level of implementation of QMS in NRA. The QMS indicator consists of 14 self-scored sub-indicators to identify the degree of QMS implementation and the existing gaps across the NRA. The equivalence of the 14 sub-indicators in the GBT with the ISO 9001: 2015 requirements is shown in Table 1.

The concept of maturity level (ML) from ISO 9004:2009 into the stratification of QMS scores is incorporated in the GBT and has been implemented for some time by the Benchmarking of the European Medicines Agencies (BEMA). Maturity levels take into account the criticality of indicators and the minimal required capacity of a regulatory system to control and implement proper oversight of health products.

The maturity level indicates the status at which each sub-indicator performs. As maturity level one addresses the legal framework of the regulatory system, the QMS gap analysis starts at maturity level two. In maturity level two, an organization operates in a reactive mode with an evolving national regulatory system that partially performs essential regulatory functions. In maturity level three, an organization has a stable, well-functioning and integrated regulatory system which is accompanied with essential capacity implemented in all functions. Maturity level four implies a regulatory system that performs at advanced level with continual improvement which support all implemented regulatory functions. The basis for climbing the maturity level ladder for robust regulatory systems strengthening is for NRAs to fill the gaps at the lowest level before taking a step up. Maturity level three is currently being considered as the target performing level of national regulatory authorities for implementation of the WHA Resolution 67.20.

Table 1. Equivalence of the 14 GBT sub-indicators with the ISO 9001: 2015 requirements

<table>
<thead>
<tr>
<th>Sub-indicator</th>
<th>Description</th>
<th>ISO 9001:2015 Clause</th>
<th>Requirements</th>
<th>ML</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS05.07</td>
<td>Requirements for documentation management as well as traceability of regulatory activities are established</td>
<td>7.5</td>
<td>Documented information</td>
<td>2</td>
</tr>
<tr>
<td>RS05.01</td>
<td>Top management demonstrates commitment and leadership to develop and implement QMS</td>
<td>5.1.1</td>
<td>Leadership and commitment</td>
<td>3</td>
</tr>
<tr>
<td>RS05.02</td>
<td>Quality policy, objectives, scope and action plans for establishment of the QMS are in place and communicated to all levels</td>
<td>4.3, 5.2.1, 5.2.2, 6.2</td>
<td>Quality policy, objectives, scope, and action plans</td>
<td>3</td>
</tr>
<tr>
<td>RS05.03</td>
<td>Organizational chart, roles and responsibilities to establish the QMS are defined and in place</td>
<td>5.3</td>
<td>Organizational roles, and responsibilities</td>
<td>3</td>
</tr>
<tr>
<td>RS05.04</td>
<td>Enough competent staff is assigned to develop, implement and maintain the QMS</td>
<td>7.1.2, 7.2</td>
<td>Human resources and competency</td>
<td></td>
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<tr>
<td>RS05.09</td>
<td>The externally provided products and services relevant to regulatory activities are controlled through established mechanisms</td>
<td>8.4</td>
<td>Control of externally provided process, products and services</td>
<td></td>
</tr>
<tr>
<td>RS05.11</td>
<td>Internal and/or external audits of the QMS are established and conducted at planned intervals</td>
<td>9.2 and ISO 19011</td>
<td>Internal audit</td>
<td></td>
</tr>
<tr>
<td>RS05.05</td>
<td>The regulatory authority establishes required mechanisms to continually improve the QMS</td>
<td>10.3</td>
<td>Continual improvement</td>
<td></td>
</tr>
<tr>
<td>RS05.06</td>
<td>The NRA has identified its regulatory processes, determined their interactions and defined the methods needed to control these processes</td>
<td>4.4, 8.3, 8.5.1</td>
<td>Operation</td>
<td></td>
</tr>
<tr>
<td>RS05.08</td>
<td>External and internal issues including relevant potential risks are defined and assessed periodically for proper risk mitigation</td>
<td>6.1, 4.1</td>
<td>Actions to address risk and opportunities</td>
<td></td>
</tr>
<tr>
<td>RS05.10</td>
<td>A mechanism to evaluate the satisfaction of internal and external customers and other interested parties is in place for system improvement</td>
<td>9.1.2, 9.1.3</td>
<td>Customer satisfaction</td>
<td></td>
</tr>
<tr>
<td>RS05.12</td>
<td>Corrective actions, and actions to address risks and opportunities, are implemented and documented and their effectiveness is verified</td>
<td>9.1.3, 10.2</td>
<td>Non-conformity and corrective action</td>
<td></td>
</tr>
<tr>
<td>RS05.13</td>
<td>Top management reviews and documents the organization’s QMS at planned intervals (management review)</td>
<td>9.3</td>
<td>Management review</td>
<td></td>
</tr>
<tr>
<td>RS05.14</td>
<td>A mechanism is established to evaluate and demonstrate the effectiveness of training activities</td>
<td>7, 7.2</td>
<td>Training</td>
<td></td>
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</tbody>
</table>