Implementing quality management systems in national regulatory authorities:

Examples and practices

World Health Organization

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Contents

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Abbreviations & Glossary

The glossary is the same as that of the WHO Guideline on implementation of QMS for NRAs, Annex 13, WHO Technical Report Series, No. 1025.

Abbreviations

ADR	Adverse drug report
CAPA	Corrective and Preventive Action
CT	Clinical Trial Oversight (GBT regulatory function)
EMA	European Medicines Agency
EU	European Union
GBT	Global Benchmarking Tool
GxP	Good Practices (Manufacturing-M, Clinical-C, Distribution-D, Laboratory-L, Regulatory-R, Review-Rev)
HMA	The Heads of Medicines Agencies
IT	Information Technology
ISO	International Standardization Organization
KPI	Key Performance Indicator
LI	Licensing Establishments (GBT regulatory function)
LR	Lot Release (GBT regulatory function)
LT	Laboratory Access and Testing (GBT regulatory function)
LIMS	Laboratory information management system
LSP	Lot summary protocol
MA	Marketing Authorization (GBT regulatory function)
MAH	Marketing Authorization Holder
MC	Market Surveillance and Control (GBT regulatory function)
MOH	Ministry of Health
NRA	National Regulatory Authority
PDCA	Plan, Do, Check and Act
PV	Pharmacovigilance (equivalent to Vigilance regulatory function)
QA	Quality Assurance
QMS	Quality Management System
RCA	Root cause analysis
RI	Regulatory Inspection (GBT regulatory function)
RS	Regulatory System (GBT regulatory function)
SF	Substandard or falsified
SOP	Standard Operating Procedure
TM	Top management
VL	Vigilance (GBT regulatory function)
WHA	World Health Assembly
WHO	World Health Organization

1. Background

World Health Organization (WHO) has developed a guideline on the implementation of Quality Management Systems (QMS) for National Regulatory Authorities (NRAs), Annex 13, WHO Technical Report Series, No. 1025 (also known as WHO QMS guideline) *(1).* The guideline is intended to assist NRAs in fulfilling their mandates to ensure safety, quality and efficacy of medical products. The QMS supports NRAs in ensuring transparency, effectiveness and efficiency in providing their products or services and in meeting customers' needs and expectations consistently while complying with the national legislations and regulatory requirements.

The aim of the WHO guideline on implementation of QMS for NRAs *(1)* is to assist them in developing, implementing and improving their QMS across the organization. The guideline is aligned with the principles of ISO 9001 Standard requirements *(2)* and with the WHO Global Benchmarking Tool (GBT) *(3)* indicators and sub-indicators which address QMS related aspects of appropriate regulatory functions.

The guideline is expected to promote consistency in regulatory practices within and across NRAs to facilitate harmonization, mutual reliance, and recognition mechanisms among Member States.

This document has been developed to assist NRAs with the practical implementation of the WHO guideline within their respective contexts. The document includes a combination of practices and real examples from QMSs that have been implemented in different NRAs and that are in line with the guideline's recommendations. These examples may assist other NRAs to understand the guideline further and to gain insight on the application of the recommendations within the specific context of an NRA. This version provides examples that have been voluntarily provided by NRAs in the spirit of sharing their experience with other regulators.

2. Objective

The objective of this document is to provide real-life examples and practices to facilitate the understanding and implementation of the *WHO guideline on the implementation of quality management systems for national regulatory authorities (1)*. It is a practical and maintainable document that should be used alongside the WHO guideline for the implementation of QMS as well as other relevant WHO guidelines such as the QMS requirements for national inspectorates, Annex 5, WHO Technical Report Series, No. 1025 *(4)*. WHO, NRAs and partners may use these examples to facilitate the implementation of regulatory strengthening activities on QMS, for example, as part of the implementation of Institutional Development Plans.

3. Scope

The scope of this document is the same as per the *WHO guidelines on the implementation of quality management systems for national regulatory authorities (1).* This document focuses on the QMS requirements that are listed in the subsections of chapter 5 of the WHO guideline under the heading "Quality Management System requirements for NRAs". The intent is to provides examples and practices for all the subsections, although the length of coverage may vary among the subsections. The coverage is related to the needs and challenges faced and identified by NRAs when interpreting or implementing the *WHO guideline on the implementation of quality management systems for national regulatory authorities (1).* Whenever necessary, this version may be superseded by a new version that is prepared in response to other needs as determined by the WHO secretariat or Expert Committee(s), for example, the Expert Committee on Specifications for Pharmaceutical Preparations. The versions of this document shall be maintained and managed by the Regulation and Prequalification Department at the WHO Headquarters with the active participation and support of all WHO Regional Offices.

4. Use of Examples

NRAs can access the current version of this document on the WHO website. This document is to be used alongside the guideline and is intended to provide specific practices and real examples for each of the requirements addressed in the guideline. Each requirement may have one or more examples and additional guidance, as appropriate. The practices and examples contained in this document are based on examples provided by NRAs of different settings and contexts and are intended to stimulate experience-sharing among regulators from different NRAs and to learn from successful cases. Although some of the examples contained in this document may have been adapted to maintain consistency within the document, the content was not changed from that provided by the NRAs in order to keep the examples authentic to the actual QMS practices of the NRA. Therefore, the inclusion of these examples should not be considered a WHO endorsement of these examples as best practices. All examples contained in this document are anonymized as the focus is on the examples and not the source (NRAs). However, the specific NRAs providing examples are acknowledged in each version without specifying which NRA contributed the example. For an easy distinction between examples, the NRAs in this document are designated by a fictitious code that follows the alphabet (e.g., aNRA, bNRA, ..., aaNRA, bbNRA).

The examples and practices provided in this document may be used by WHO, NRAs, and partners, and are provided for training purposes for NRAs that are at different stages of developing, implementing or improving their QMS. In general, examples in this document should not be reproduced and implemented as is, because the context may differ significantly and may lead to inconsistencies, ineffectiveness and inefficiencies within the QMS. However, where practical and possible, NRAs may adopt and adapt the approaches or practices from the examples if they facilitate the understanding and implementation of the QMS within the organization. In addition, the adoption and adaption may contribute towards harmonization, consistency, transparency, reliance and collaboration among regulators.

4.1. Presentation of the examples in this document

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5. QMS requirements for NRAs

5.1. Scope of the QMS

EXAMPLE 1

NRA scope statement

In order to ensure the quality and safety of food, the safety, efficacy and quality of human and animal medicines, and the safety, quality and performance of medical devices and supplies, the QMS at "a" National Regulatory Authority (aNRA) covers all the procedural, executive and supervisory functions of the NRA and promotes the establishment of an effective regulatory body in all sectors of the aNRA and all of its branches in the country.

Integrated with:

1. All technical procedures and tests that are carried out in the laboratories, which will be covered through the application of a QMS for laboratories based on ISO Standard 17025 *(5).*
2. All procedures for sampling during the inspection of establishments and at ports of entry as well as tools for related inspections, which will be covered by the implementation of the quality system of inspection ISO Standard 17020 *(6).*

5.2. Organizational context of the NRA

5.2.1. UNDERSTANDING NRA ORGANIZATION AND ITS CONTEXT

EXAMPLE 2

Example at bNRA for Regulatory Inspection (RI) and Market Surveillance and Control (MC) functions

The bNRA was created by Law XYZ, as an autarchy under a special regime with administrative independence, leadership stability and financial autonomy. The bNRA has the institutional function to promote the protection of the population's health by managing health surveillance of the production and the commercialization of covered products and services, including environments, processes, raw materials and technologies; related activities at ports, airports and borders are also controlled.

Within bNRA's organizational structure, the Inspections Department is responsible for inspections to verify the compliance with good manufacturing practice (GMP) and for investigation of quality deviations of medicines, pharmaceutical ingredients, medical devices, sanitizing products, foods, cosmetics, personal care products and perfumes. The Inspections Department also controls the publicity, advertising and promotion of these products. In addition, the Inspections Department works on quality management of the inspection process within the Health Authorities National System. This is accomplished through audits performed in state, district and local health authorities and organizations that are part of Health Authorities National System and through the coordination of the development of a QMS for Health Authorities National System that covers inspection activities and qualification of those who perform GMP inspections.

The specific responsibilities of each team within the Inspections Department are assigned in bNRA's Internal Regulation and are arranged according to the department organizational structure.

The responsibilities within the scope of the Inspections Department are shared among technicians, analysts, specialists, coordinators, managers and general managers.

Relationship between bNRA's Inspection department and other Health Authorities

The inspection activities of establishments located within the national territory are performed in partnership with local authorities in accordance with established agreements and as described in the laws creating the bNRA.

bNRA is responsible for inspecting the manufacturers of medicines, medical devices of risk class III and IV and active pharmaceutical ingredients from all the country states except for the seven states that have a higher concentration of manufacturers. These seven states have the responsibility within their state; however periodically audits are performed by the bNRA Inspectorate.

Inspection activities of companies located in international territory are the responsibility of bNRA. Internationally, bNRA has increased the information exchange with other health authorities, with the aim of optimizing its international inspections by developing common documents and promoting discussions with neighbor countries, setting up new international arrangements, and participating in international programs covering medical devices, active pharmaceutical ingredients and medicines. Included are programs offered through the International Medical Device Regulators Forum, Pharmaceutical Inspection Co-operation Scheme and European Commission Audits.

Relationship with the National Network of Health Surveillance Laboratories

Quality control analyses for monitoring the quality of products under health surveillance and also for the verification of illicit products are arranged by the National Institute of Health Quality Control and by official local laboratories.

These official laboratories together form the National Network of Health Surveillance Laboratories. At the federal level, the coordination of the National Network is a regimental responsibility of bNRA's Office of Public Health Laboratories.

When a laboratory analysis is necessary to verify a suspicion of quality deviation, samples of the lot of the product under suspicion must be collected and sent to the official laboratory for official analysis, as established in Federal Law.

The legal responsibility for collecting the samples for official analysis belongs to the National Health Authorities (i.e., bNRA or local authority). A sample collection document must be issued.

After analyzing the samples, the official laboratories issue analytic reports that are sent to the competent health authority in order to continue with the investigation process and, if necessary, to take all the appropriate actions.

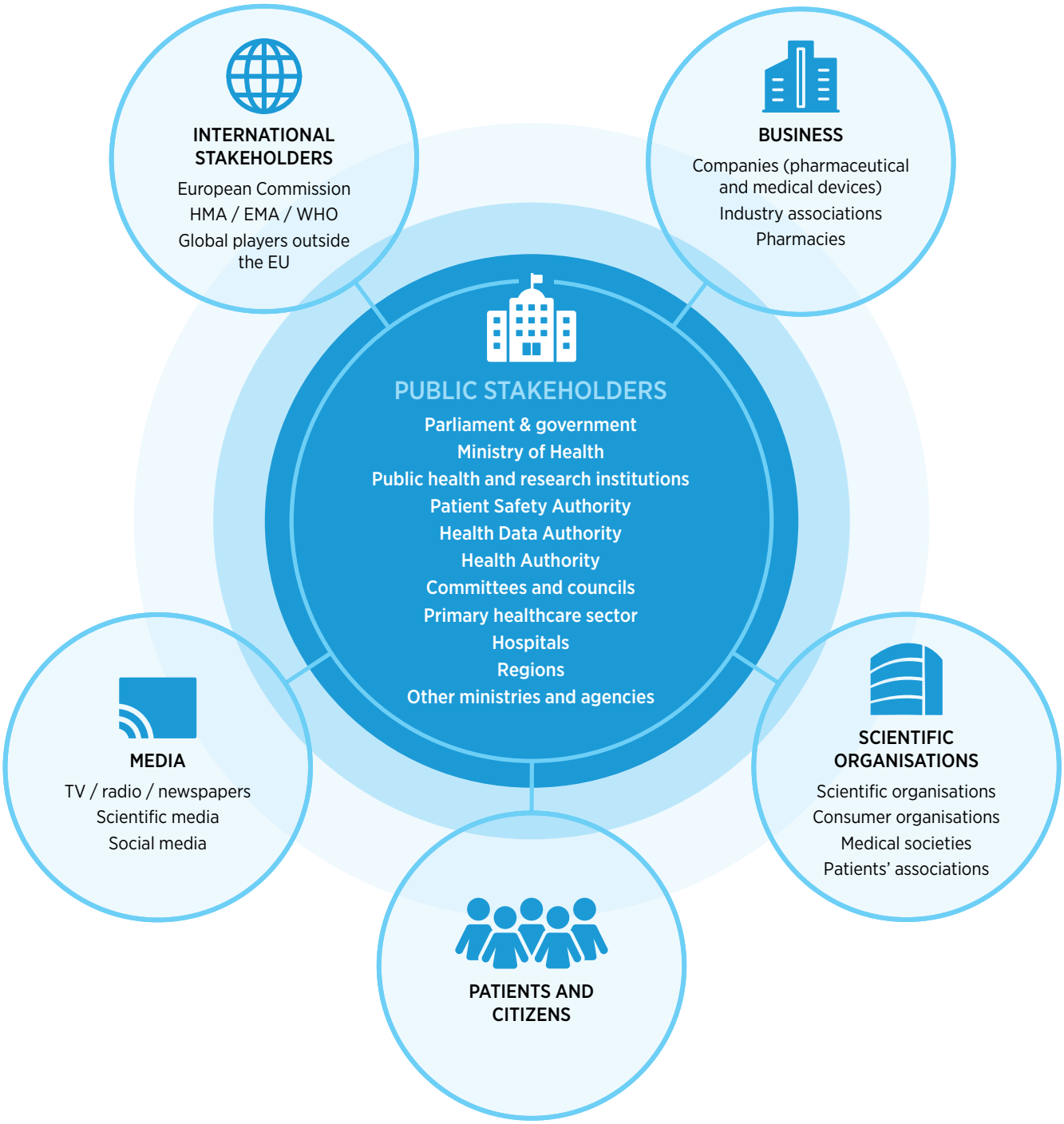
EXAMPLE 3

TABLE 1
Examples of cNRA's interested parties (i.e., customers and stakeholders) and their requirements

Internal Clients		Needs
1	**Inter Departmental**	• Accurate, effective and timely communication • Submission of agenda items on time • Timely submission of requests • Timely response and feedback to requests (e.g., reports and requisitions) • E-mail contributions must be timely • Effective project collaboration • Good interpersonal relationships
2	**Staff**	• Training and development • Promotion and advancement • Health and safe working environment • Guaranteed job security • Equal opportunities • Fair labor practices

External Clients		Needs
1	**Applicants**	• Timely registration • Timely, clear, scientifically sound, efficient and effective communication • Clear and up-to-date guidance and access to information (e.g., online status updates) • Easy and efficient payment processes
2	**Manufacturers**	• Supportive regulatory authority • Timely resolution of regulatory problems, available guidance on best practices, timely reports following GMP inspections • Preferential evaluations of applications for registration (i.e., from local manufacturers) • Protection from foreign manufacturers (i.e., for local manufacturers)
3	**Distributors**	• Faster registration of medicines • Faster processing of import permits and licenses • Faster processing of applications for amendments
4	**Retailers**	• Timely processing of applications • Communication and guidance • Flexibility in certain situations
5	**Industrial clinics**	• Timely processing of applications • Communication and guidance • Flexibility
6	**Persons (dispensers)**	• Less restrictive access to medicines required by patients • Less cumbersome requirements for acquisition of unregistered essential and life-saving medicines • More suppliers so that costs can be lower
7	**Hospitals and clinics**	• Timely processing of applications • Communication and guidance • Flexibility in certain situations

FIGURE 1
Example of interested parties



5.2.2. QMS PROCESSES

ADDITIONAL GUIDANCE

The processes required by NRAs to carry out the different functions include those needed for service provision and for effective implementation of the system, such as internal audits, management review and others (including processes performed by external providers).

a) *The NRA should determine the inputs required (i.e., what is required for the implementation of the processes as planned) and the outputs expected from its processes (i.e., 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), process control criteria and methods should be determined and applied. Criteria for monitoring and measuring can be process parameters, specifications of services, or performance indicators related to quality objectives.*

d) *The NRA should determine the resources needed for processes, for example, personnel, organizational knowledge, and infrastructure and environment for the operation of the processes.*

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.*

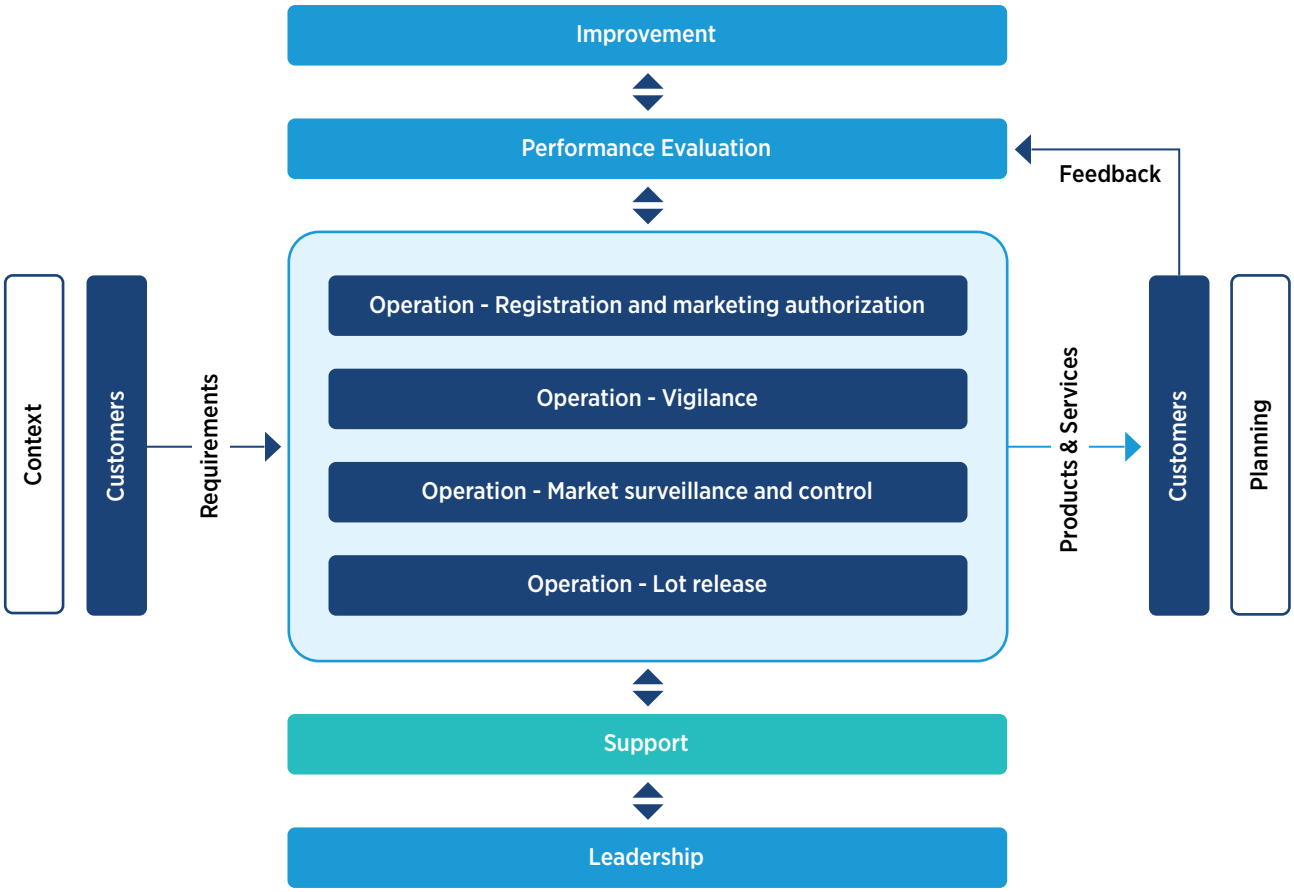
g) *The NRA should analyze and evaluate the results of monitoring and measuring data (see item c above); and implement any changes needed to ensure that these processes consistently achieve their intended results.*

h) *The NRA can use the results of analysis and evaluation (see item g above) to determine the necessary actions for improvement.*

Registration and Marketing Authorization (MA), Lot Release (LR), Vigilance (VL), Market Surveillance and Control (MC) and Regulatory Inspections (RI) are regulatory functions used as model regulatory functions throughout the examples presented in this section; however, a similar approach can be taken to address other regulatory functions. The following information illustrate the processes for carrying out each of the above-mentioned functions. The process flows described below are not intended to serve as the recommended ones; rather they are provided as examples to explain interactions between the processes, the related inputs and outputs, the monitoring points and established controls, the indicators used, the resources needed (including roles and responsibilities), the authorities responsible, and the risks and opportunities for improvement. Different NRAs may have different ways of approaching the functions; hence the steps and the relationships between steps and interrelated processes may differ.

EXAMPLE 4

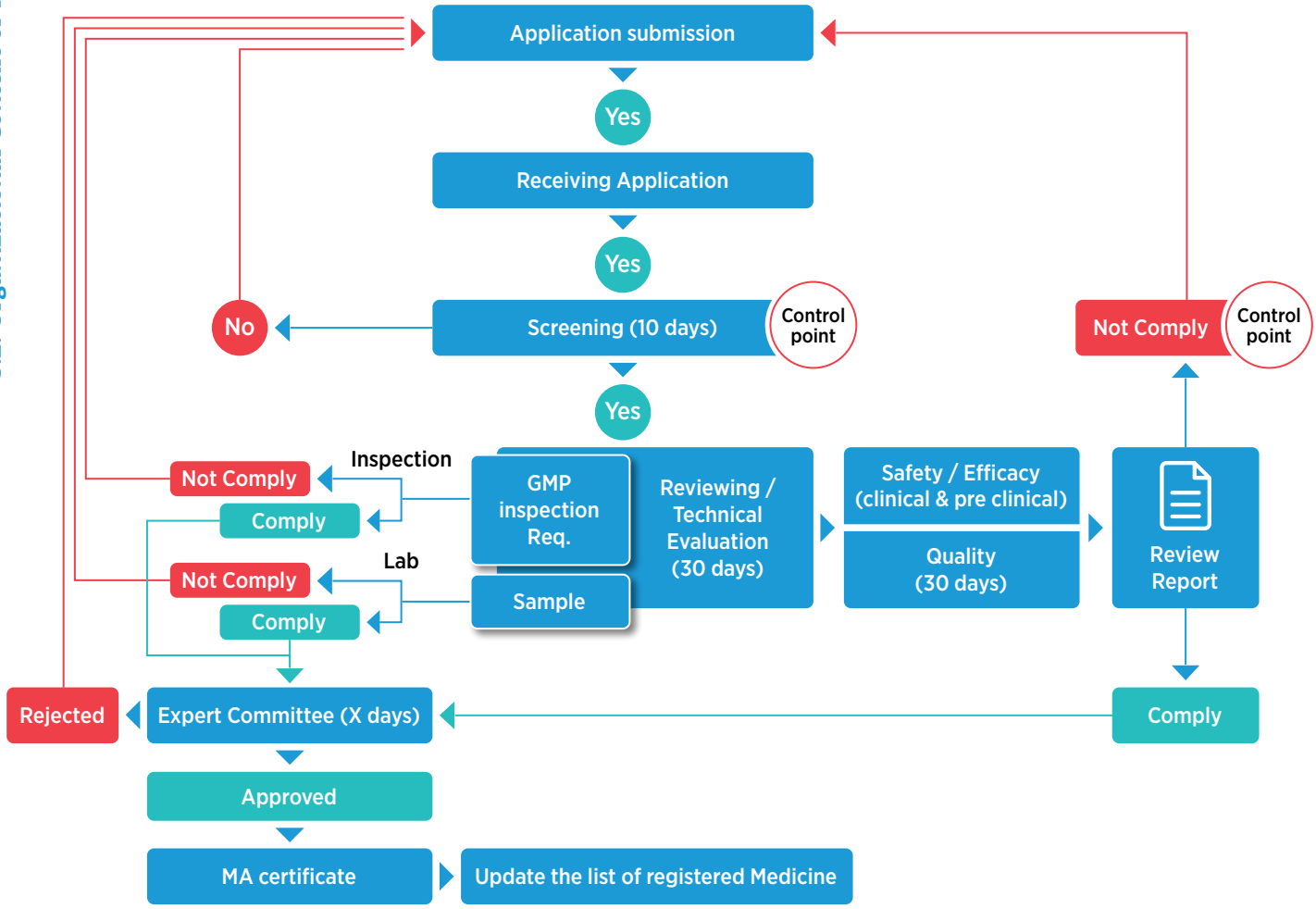
FIGURE 2
Example of interaction of processes at dNRA



For dNRA, business processes related to MA, LR, VL, and MC are taken as examples of key regulatory functions for vaccines and therefore are shown in the center of Figure 2 (operation box). Horizontally, customer requirements are captured to the left of the operation box, and delivery of products and services to the customer are shown on the right. Vertically, top management (TM), at the bottom provides leadership and commitment for QMS to achieve its intended results. Monitoring and measurement data of processes and services and customer feedback data, when analyzed and evaluated, provide information on QMS performance. Output of performance evaluation can be used for initiating improvement of QMS or dNRA services. Two vertical bars on the far left and far right of the figure illustrate that the QMS is based on the context of the organization and QMS planning has been based on the context information.

FIGURE 3
Example of Registration and Marketing Authorization (MA) processes

- **Characteristics of the processes and interrelationships involved in the MA**



- **Inputs**

  Laws, regulations, mandates, guidelines, market authorization applications, product dossiers and site master files, results from laboratory sample testing, and inspection outcomes (e.g., GMP, good clinical practice (GCP), and good distribution practice (GDP) inspections).

- **Steps**

  Dossier screening, dossier evaluation (i.e., quality, safety, and efficacy), laboratory analysis, onsite or desk-based inspection process, expert committee review and decision making, final approval by TM and update of the list of registered medicines.

- **Outputs**

  Screening results (i.e., checklist), dossier acceptance letter, dossier review reports, rounds of questions to the manufacturer and other pertinent communications, test results, inspection reports and certificates, committee decisions, MA approval or rejection, MA certificate, and update of database of registered medicines.

- **Main processes**

  Receipt of application, screening, evaluation (including cycles of questions and responses), laboratory analysis, GMP inspection, expert committee review, documentation (e.g., email communications, meeting minutes, information technology (IT) platform, official files, and letters), expert meetings and granting or rejecting MA.

- **Examples of criteria and methods in place to ensure effective operation and control of processes**

  Criteria that must be monitored to ensure that processes are properly executed will be based on the criticality and steps of the processes. Guidelines and standard operating procedures (SOPs) will define elements such as the target evaluation timeframe. Control points will be defined and indicators chosen to monitor performance parameters.

  Control points: Screening, dossier review and update of registered medicines list.

  Key performance indicators (KPIs) to measure actions and events that lead to a result should be established and the frequency of evaluation should be defined. KPIs, if carefully developed, are an excellent tool to monitor performance of the NRA. When establishing KPIs, use a quantitative method whenever possible and determine appropriate numerators and denominators.

  Examples of performance indicators:

  - *Percentage of applications that have been screened within the specified timeline*
  - *Compliance with defined review timeline*
  - *Quality of the evaluation reports, e.g., evaluation reports from three evaluators of different seniority levels yield similar results*
  - *Number of new products listed in the register in a year vs. the number of applications received.*

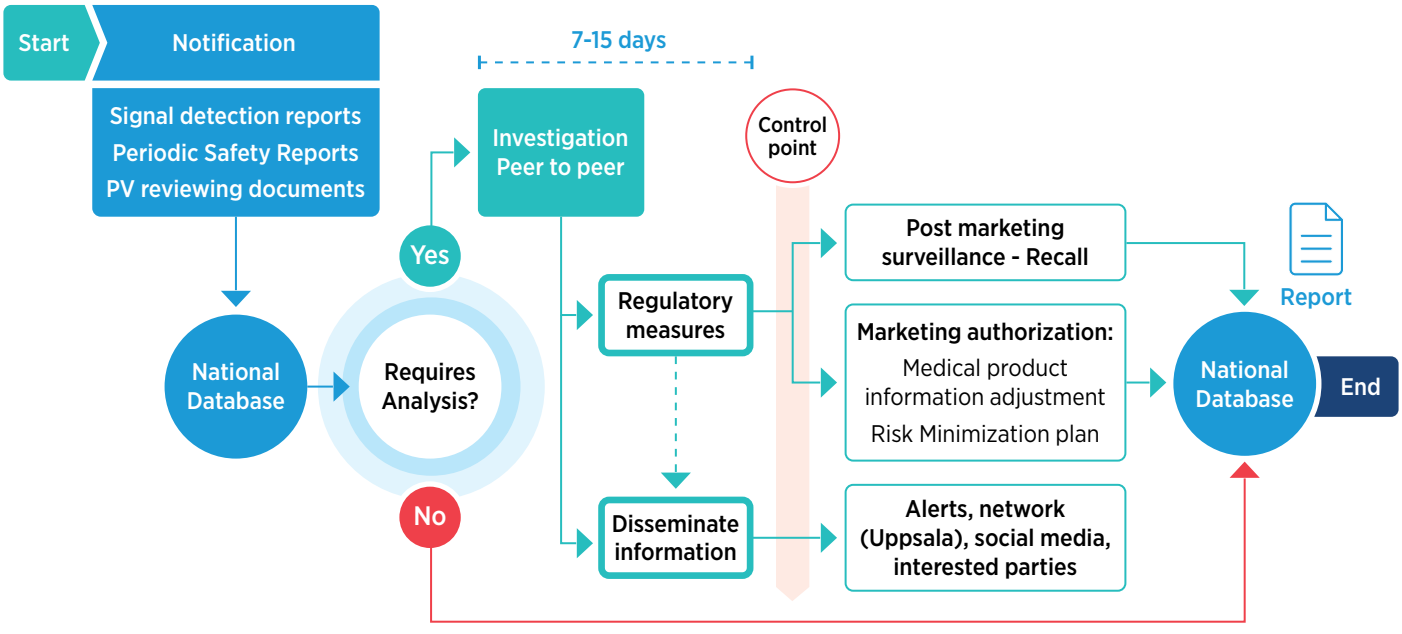
  Potential indicators for other possible control points:

  - *Compliance with overall timeline for registration*
  - *Customer satisfaction as evaluated through metrics such as complaints, surveys, questionnaires, and percentage of approved appeals*
  - *Performance assessments through use of internal audits*

  Otherwise, qualitative KPIs can still serve the purpose and be acceptable when set wisely.

FIGURE 4
Example of Vigilance process

- **Characteristics of the processes and interrelationships involved in the Vigilance system**



- **Inputs**

  Information received from patients, health professionals, international VL networks, industry, and media, risk management plans, clinical trial data, post-market surveillance, suspect product reports, or adverse event reporting.

- **Steps**

  Receipt, analysis, conclusion, reporting, feedback.

- **Outputs**

  Communication of outcome (positive or negative), feedback to reporting source, and regulatory actions including alerts, recalls, risk minimization plans, and provision of medical product information to patients, health professionals, international VL networks, industry, and media.

- **Examples of criteria and methods in place to ensure effective operation and control of processes**

  Criteria that must be monitored to ensure that processes are properly executed will be based on the criticality 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 to monitor performance parameters.

  Considerations for establishing criteria for monitoring performance:

  - *Structural indicators should measure systems and physical infrastructure.*
  - *Assessments, evaluations, and reviews should be timely (consistent with severity of signals).*
  - *Evaluations should address all relevant aspects of the VL system (i.e., 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 pharmacovigilance (PV) documentation and resource compliance with regulatory VL expectations and requirements.*
  - *KPIs should be re-evaluated to assess their relevance as indicators, and targets can be reset when deemed appropriate.*
  - *Because VL system performance is monitored, identified corrective and preventive measures must be implemented; this results in continuous improvements to the VL system.*

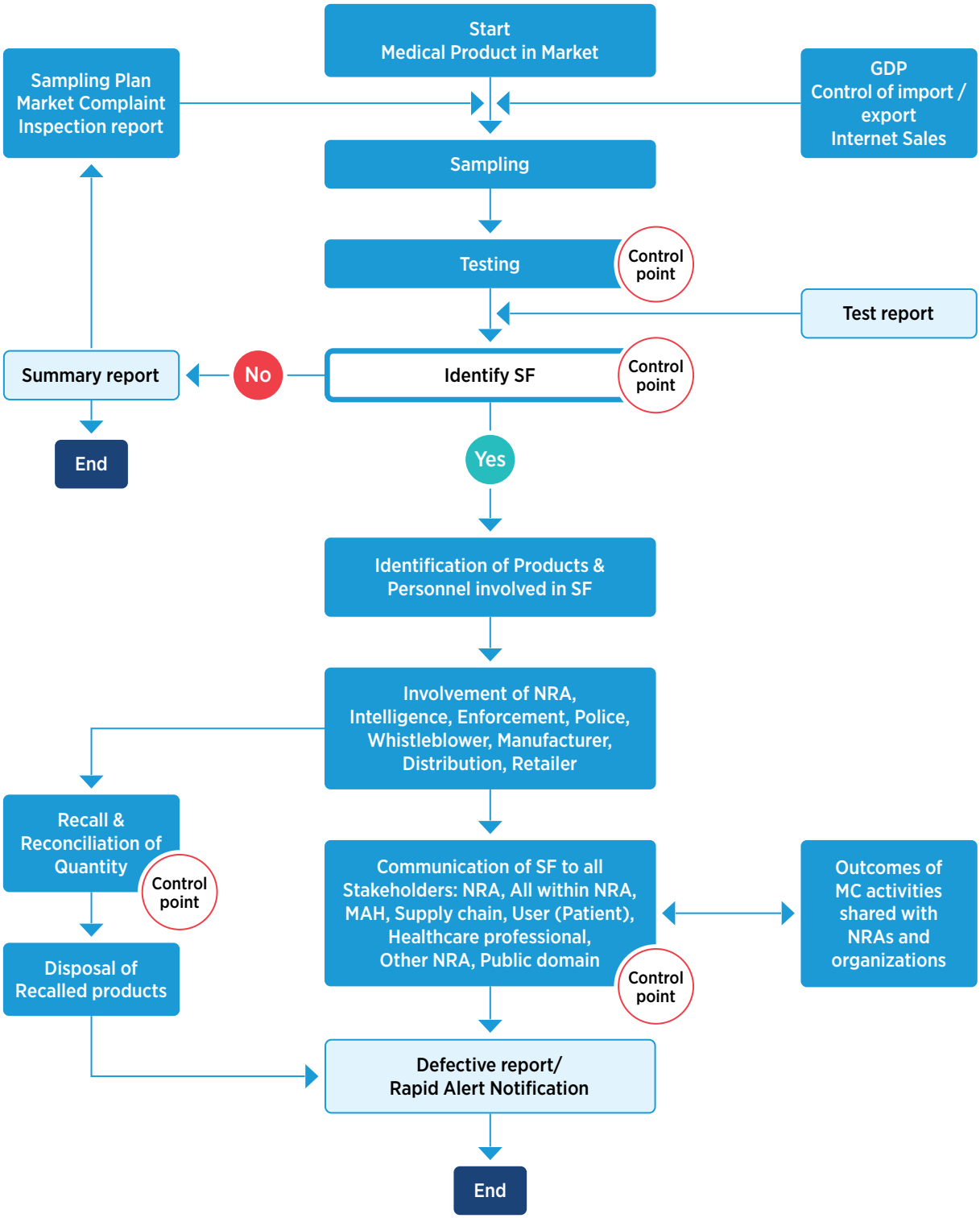
  Control points: Triage and prioritization, data collection and verification, coding of adverse event descriptions, evaluations of the quality of case causality assessments, timeliness of actions, and dissemination of relevant information.

  KPIs that measure the actions and events that lead to a result must be established and the frequency of evaluations must be defined. When setting up KPIs, use a quantitative method whenever possible and determine appropriate numerators and denominators.

  Examples of performance indicators include:

  - *Number of vigilance inspections performed vs. those planned based on inspection prioritization criteria.*
  - *Number of adverse drug reaction (ADR) reports received, for example, from healthcare professionals or from the media.*
  - *Percentage of fatal ADRs analyzed within target timeline, and the percentage of serious ADRs analyzed within target timeline.*
  - *Number of complaints addressed vs. total number of complaints received by the VL department.*
  - *Number of returned products vs. the number of released or distributed products that are subject to recall (also called reconciliation of recalled products).*
  - *Internal audit findings.*

FIGURE 5
Example of Marketing Surveillance and Control (MC) process



- **Characteristics of the processes and their interrelationships involved in the MC system**

  MC requires the NRA (in collaboration with other relevant authorities such as customs) to ensure that substandard and falsified (SF) products do not enter or are removed from the national market. MC function also mandates the NRA to require that all transactions relating to importation and exportation of consignments of medical products be conducted by licensed entities and that GDPs are followed.

- **Inputs**

  Market complaints, market intelligence, inspection reports, sampling plans, and feedback from import and export activities and from internet pharmacies

- **Steps**

  Risk-based sampling, testing, identification of SF products, decisions on recall, and communication to all stakeholders, including, for example, all relevant parties within NRA, MA holders, supply chain participants, health care professionals, patients, and international organizations.

- **Outputs**

  Identification of SF products, alerts, recalls, communications to all stakeholders and addition to a database for the SF.

- **Examples of criteria and methods in place to ensure effective operation and control of processes**

  Criteria that must be monitored to ensure that processes are properly executed will be based on the criticality 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 to monitor performance parameters.

  Control points include sampling and testing, identification of SF products, recalls and related reconciliation, and effective communication to stakeholders.

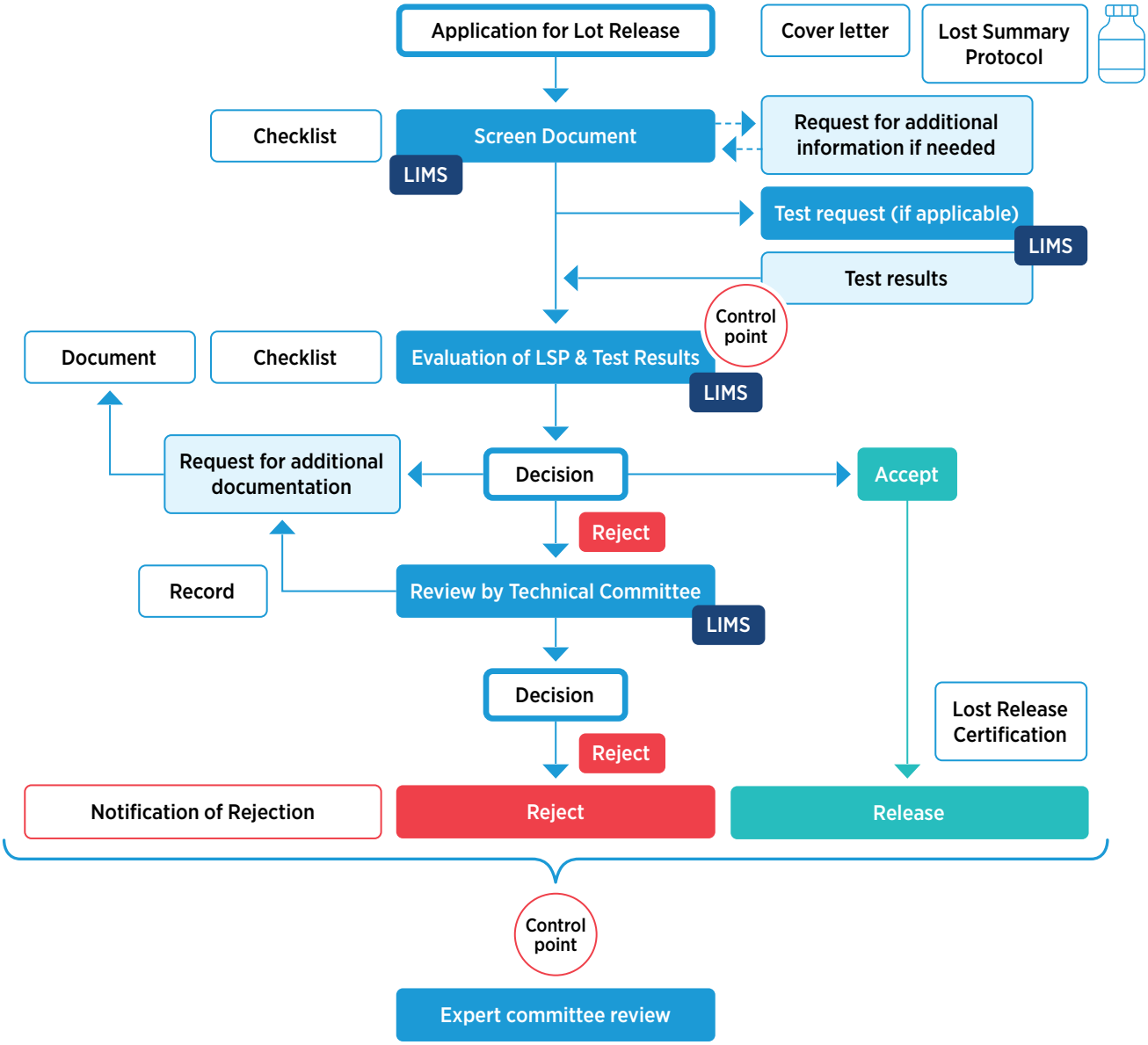
  KPIs that measure the actions and events that lead to a result and that measure the frequency of evaluation must be established. When setting up KPIs, use a quantitative method whenever possible and determine appropriate numerators and denominators.

  Examples of performance indicators:

  - *Number of consignments received through the port of entry*
  - *Number of samples drawn vs. number planned*
  - *Number of samples sent for testing and number tested*
  - *Time taken to generate test report vs. the target timeline*
  - *Time taken to evaluate suspected products vs. the target timeline.*

FIGURE 6
Example of Lot Release (LR) process

- Characteristics of the processes and their interrelationships involved in the LR system



- **Inputs**

  Cover letter, lot summary protocol (LSP), samples, MA specifications, information on adverse events, surveillance data (e.g., test results on samples retrieved from the market).

- **Steps**

  Screen documents, request and perform testing (i.e., if lot is part of the routine release process), evaluate LSP and testing results, make decisions, and refer to technical committee for review.

- **Outputs**

  Notification of rejection or issuance of lot release certificate.

- **Main processes**

  Screen documents (i.e., of cover letter and LSP), evaluate LSP, review by the technical committee, and carry out the decision-making process.

- **Interactive processes**

  Sample testing can be considered an interactive process if it is contracted out to a third-party laboratory or if it is not always performed. Otherwise, it is an process that must be performed to yield an output.

- **Examples of criteria and methods in place to ensure effective operation and control of processes**

  Criteria that must be monitored to ensure that processes are properly executed will be based on the criticality 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 to monitor performance parameters.

  Control points: Evaluation of the LSP and expert committee review (of the report).

  KPIs that measure the actions and events that lead to a result must be established and the frequency of evaluation must be defined. When setting up KPIs use a quantitative method whenever possible and determine appropriate numerators and denominators.

  Examples of performance indicators include:

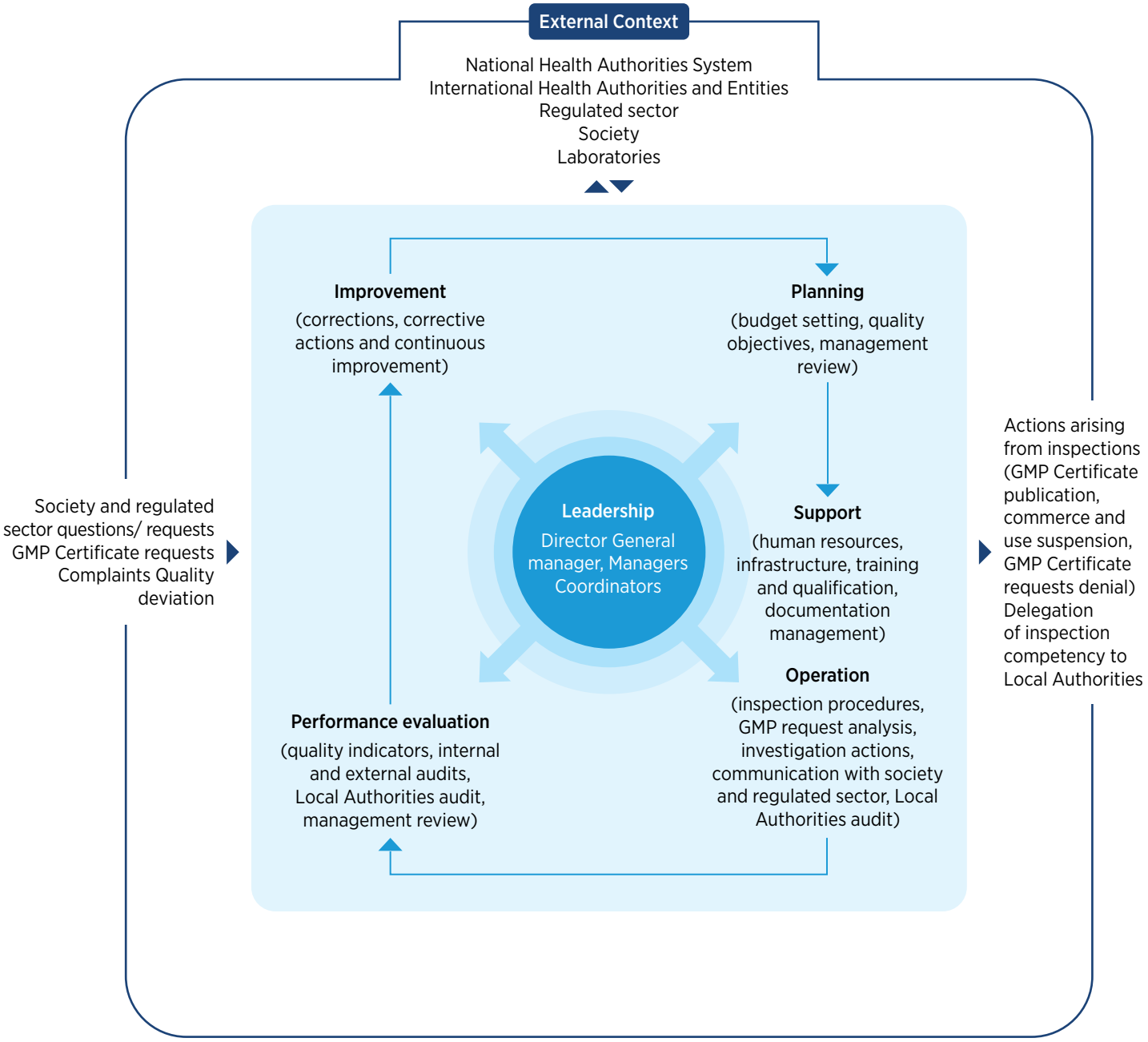
  - *Compliance with evaluation timelines*
  - *Verification of inputs into the laboratory information management system (LIMS)*
  - *Evaluations of checklists*
  - *Verification or validation of outputs (i.e., percentage of outputs verified or validated in quality review).*
  - *Trend analyses for test results*
  - *Percentage of timely reviews by the expert review committee*

  Potential indicators for other possible control points:

  - *Customer satisfaction evaluated through complaints, surveys, or questionnaires*
  - *Use of internal audits to assess performance*

EXAMPLE 5

FIGURE 7
Structure of eNRA Inspection Department's QMS, including its processes and interactions



EXAMPLE 6

Processes are defined in "process clusters" and processes. Each process has an appointed process owner responsible for design of the process (inputs, outputs and subprocesses), including documentation requirements and archiving of data from the process, process description in the QMS, and definition of requirements for and implementation of training, where relevant.

Examples below describe process clusters and processes relevant to MA, VL, MC and LI at fNRA:

Management processes

- *Management review*
- *Performance and effectiveness measurement and reporting*
- *Resource management*
- *Crisis management*
- *Business Continuity Planning*
- *Internal audits*
- *Corrective and preventive action (CAPA) system*

Support processes

- *Record management including data protection*
- *Control of documents*
- *Compliance management*
- *Training*
- *Communication*
- *Facilities and equipment*
- *Delegation procedures*

PV processes

- *PV inspections and PV system master file*
- *Risk management systems; tools, educational materials, and effectiveness measurement for risk minimization*
- *Periodic safety update reports*
- *Post-authorization safety studies*
- *Signal management*
- *Additional monitoring*
- *Safety communication*
- *Handling of cases concerning advertising of medicines and economic benefits*

MA processes

- *Approval of drugs*
- *Approval of variations*
- *Changing, suspending or revoking a MA*
- *Publication of summary of product characteristics and leaflets*
- *Summary of risk management plans as well as risk management programs*
- *Provide dosage and indication texts, short generic names, and other related information.*
- *Receive and process complaints and reports of defective or counterfeit drugs or active substances*
- *Establish requirements for the quality of medicines*
- *Issue compassionate use permits*

MC and LI processes

- *Approval of pharmaceutical companies*
- *Amending, suspending or revoking an approval*
- *Control of pharmaceutical companies*
- *Registration of companies that manufacture, introduce or distribute active substances*
- *Registration of drug intermediaries*
- *Export certificates for medicines*
- *Control of medicines*
- *Securing the drug supply in emergency situations*

5.3. Leadership, management and organization

5.3.1. COMMITMENT OF TOP MANAGEMENT (TM)

EXAMPLE 7

The TM of gNRAs is accountable for the effectiveness of the QMS and for a demonstration of leadership and commitment to the QMS. The commitment of gNRA's TM to the establishment, implementation, effectiveness, development and continuous improvement of the QMS is demonstrated by the maintenance of a dedicated department to coordinate the QMS within gNRA, and by a formal commitment articulated in a Quality Manual that was approved by the General Manager upon prior authorization by the Board of Directors (i.e., TM).

The TM of gNRA makes the commitment to develop administrative and technical conditions for the adoption and maintenance of the established Quality Policy in all levels of the NRA.

Specifically, the gNRA's TM is responsible for:

- *Establishing organizational identity;*
- *Informing the organization about the importance of fulfilling customer requirements;*
- *Complying with statutory and regulatory requirements;*
- *Establishing a Quality Policy and objectives in line with the strategic direction using the process and risk-based approach;*
- *Conducting management reviews;*
- *Providing needed resources and training;*
- *Ensuring that a culture of trust, integrity and teamwork is established and maintained;*
- *Ensuring that shared values, fairness and ethical models for behavior are sustained at all levels of the organization;*
- *Creating an internal environment in which people are engaged and committed to the achievement of the organization's objectives;*
- *Ensuring that leaders at all levels establish and maintain the unity of purpose and direction as given by TM;*
- *Personally and regularly reinforcing the values and expectations; communicating achieved successes internally and externally;*
- *Establishing a basis for effective communication with staff, discussing issues that have general impact on the organization, including financial impact where applicable;*
- *Supporting leadership development.*

5.3.2. QUALITY POLICY

EXAMPLE 8

hNRA quality policy

hNRA is committed to meet the needs and expectations of customers through continual improvement of its processes and quality services by implementing QMS effectively. We will ensure quality, safety and efficacy of food, medicines, cosmetics and medical devices in compliance with the hNRA Drug Act 1:2006. Objectives should be established at the system and departmental level that ensure that the requirements of this policy are met. TM is committed to providing the necessary resources to ensure maintenance and continuous improvement of QMS.

EXAMPLE 9

iNRA quality policy

The iNRA is committed to protect people's health in 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.

iNRA should work in an effective, transparent and timely manner, ensuring implementation of QMS and 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.*

EXAMPLE 10

jNRA quality policy

- **MISSION**

  jNRA regulates and supervises the sectors of medicines for human use and health products, which includes medical devices and cosmetic products, according to the highest standards of protection of public health, and commits to ensuring that health professionals and citizens have access to safe, effective, and high quality medicines and medical products.

- **VISION**

  The Medicines Agency: To be among best in class and to be a reference model worldwide, valuing its employees and expecting from them:

  - *Active dialogue and collaboration; provide value to citizens*
  - *Quality and on-time delivery*
  - *Professional expertise and commitment; provide a fantastic place to work!*
  - *Help boost our country as a leading life science nation*
  - *Driver of collaboration and a strong international position*

- **VALUES**

  jNRA is guided by a set of principles and values that define the framework used for the decision-making process from an ethical and technical point of view. jNRA identified the internal and external issues relevant to its mission and strategy, which are disclosed in various institutional documents, namely in the multi-annual strategic plan and activity plans. These documents also present the strategic objectives that contribute to the achievement of jNRA's mission and vision.

- **STRATEGIC OBJECTIVES**

  To meet our commitments, we must:

  - *Live our social responsibility;*
  - *Believe in transparency;*
  - *Accept the challenge of competence;*
  - *Welcome unconformities;*
  - *Be a team;*
  - *Believe that communicating is the key to success;*
  - *Take responsibility;*
  - *Desire to evolve;*
  - *Be involved.*

Strategic Objectives:

01 - Health System Sustainability: contribute to the sustainability of the health system through the rational use of medicines and health products and the effective and efficient use of resources;

02 - Market Compliance and Risk Management: reinforce the market supervision instruments for inspection, quality assurance (QA) and proactive risk management;

03 - Development of the Pharmaceutical and Health Products Sectors: promoting innovation and competitiveness of the national industry in the pharmaceutical and health products sectors through technical-scientific support and institutional collaboration;

04 - Reinforcing Communication: reinforcing communication with citizens, professionals and entities in the sector, providing more and better information on medicines and health products and consolidating jNRA's image as a regulatory authority;

05 - Continuous Improvement and Internal Efficiency: develop a culture of continuous improvement and value development and creativity for the various NRA clients and for society in general, optimizing processes and ensuring resource efficiency;

06 - Strengthening the position in the International Context: reinforcing the presence of the NRA in the European and international contexts, following scientific innovation and market evolution and developing differentiated resources and skills.

5.3.3. ROLES, RESPONSIBILITIES AND AUTHORITIES

ADDITIONAL GUIDANCE

Ideally, NRAs will have, as a minimum, a responsible officer within each unit, Department or Directorate, who serves as management representative or QMS coordinator and who can report on QMS performance, promote customer focus and maintain the integrity of the QMS when changes are made.

EXAMPLE 11

The Deputy Director of the kNRA has been designated as the agency representative for quality management. His/Her 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 need 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 QA Manager.

Roles, responsibilities, and authorities required to ensure adequate performance of processes for delivery of quality services by kNRA (common to all functions)

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 or her job. Roles and responsibilities and lines of authority should be detailed in the job descriptions and organizational charts. Each process should have appropriate staffing and managers. Staff performance, including performance of managers, should be evaluated regularly and retraining should be provided as needed.

kNRA staff roles may include, but are not limited to, receptionist, administrative staff, screening officer, case investigation experts, evaluators, leaders, process supervisors, laboratory analysts, IT staff, human resources staff, expert committee members, regulatory inspectors, housekeeping staff, and drivers. Proper infrastructure should be in place to carry out the activities (i.e., processes); for example, if adequate laboratory infrastructure is not in place, consideration should be given to contracting with a qualified laboratory.

5.4. Document and data management

EXAMPLE 12

Examples of documented Information that needs to be maintained by INRA

Organizational charts, job descriptions, lists 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, SOPs, instructions, and forms.

Examples of documented Information that needs to be retained by INRA

MA files, LSPs, certificates of compliance or 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 and external audit plans and related reports, agendas and minutes for management review meetings, and records and reports of validations, qualifications and calibrations.

EXAMPLE 13

At mNRA, any changes to the quality documents, including the Quality Manual, must be made through a formal request to the Coordinator of the Inspectorate QMS. Revised versions must be approved by the department manager before they become effective. The quality documents are available (in PDF format) in an electronic file that is accessible, via an electronic platform, to all mNRA personnel. Quality documents are not distributed physically. The Coordinator of the Inspectorate QMS is responsible for maintaining the updated mNRA Document Master List.

Data management

For the management of processes and electronic administrative documents, an electronic information system is used, according to Ordinance No. 1111/mNRA. The electronic information system is used to create processes and documents related to personnel management, bidding, contract management, agreements, finances, budget, accounting, auditing, institutional events, communication, parliamentary matters, strategic management, knowledge management, information management, deliberations of the Collegiate Board of Directors, and international travels (e.g., international relations, inspections and training) and regulations.

The final stage administrative processes, such as medicines registration, GMP certification, and establishment authorization, must be performed according to the Manual of Procedural Instruction, established by Ordinance No. 222/mNRA. There is an electronic system which is the tool used to process the data of the final stage processes.

The data stored in the electronic systems have controlled access such that the reading or updating of information can only be done by authorized personnel.

The mNRA's IT department is responsible for daily backup of the information stored in all electronic systems and is able to restore the data from the backup, if necessary.

5.5. Planning

5.5.1. QMS PLANNING

EXAMPLE 14

The nNRA planning is structured in order to integrate the processes with the goal of continuous improvement of the QMS using the "Plan, Do, Check, and Act" (PDCA) cycle.

The quality objectives are defined through indicators and targets that are evaluated monthly, quarterly and biannually, according to the management review procedure. The results are evaluated and, if necessary, actions are defined to achieve the targets.

If changes to the QMS are required, their purpose of the change, as well as the activities and resources required to perform the change, are discussed and defined at the management review meeting.

Process changes are planned and controlled, and required training is documented, through the document management process procedure.

5.5.2. ACTIONS TO ADDRESS RISKS AND OPPORTUNITIES

EXAMPLE 15[1]

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

An increased demand for release of batches of a certain vaccine is anticipated in the coming year. The analysis of risks and opportunities to meet the increase in demand includes an assessment of the current situation (i.e., 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 review the LSP, and professionals to prepare the report to be reviewed by the technical committee, with the final approval by the head of agency. The risks associated with addressing the increased demand include the possibility that the testing as well as the review capacity may not be sufficient; additionally, since the technical committee meets only once per month, the response capacity may not be sufficient.

As part of the planning process, the team must assess the risk of releasing lots that do not meet specifications, as well as the risk of not releasing a lot that meets the specifications due to limited capacity. In addition, the probability of failure in providing service, the impact on the quality of the products released, the estimated frequency at which errors could happen, the potential impact on customer satisfaction, and the credibility of the institution in the event of inadequate service, 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 could be applied that is based on knowledge of the different products to be released and the track record of the manufacturers. Through this analysis, it may be estimated that by increasing the staff by one analyst and by increasing committee meetings to two per month, the demand could be appropriately addressed and thereby taking advantage of the opportunity to increase resources.

1 This example is linked to the example 20 and may be relevant to read them together.

EXAMPLE 16

TABLE 2
Examples of risks and opportunities affecting MA, LR, VL and MC at pNRA

Risks and opportunities			
Marketing authorization (MA)	**Lot release (LR)**	**Vigilance (VL)**	**Market surveillance and control (MC)**
Transparency of pNRA and its work is one of the principles of good regulatory practice (GRP). Posting as much information as possible on the internet helps pNRA increase transparency. This information can include, for example, the registration procedure steps and timelines, related regulations and guidelines, charts indicating actual level of compliance with the target timelines, and evaluation reports. 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 and reliability. 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 pNRA does not have the adequate expertise or resources to evaluate a certain product, reliance on other agencies can be an option.	Tests to be performed as part of lot release must be appropriately validated (including the equipment used), the consumables properly tested, released and used before expiry, and analysts qualified to perform the tests and regularly requalified and monitored for performance. Failure to meet all these requirements leads to the risk of 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 (i.e., release of lots), while also providing an opportunity for renewing the system (including hardware and software).	The VL function carries a risk of potentially missing important signals because of underreporting or poor analysis and interpretation of the reports. The consequences are harm to the public and loss of reputation for pNRA. Lack of, or poor, communication about safety of a product that has been suspected (as a result of signal analysis), may result in public panic and loss of trust in the NRA. Such failures can simultaneously offer an opportunity to improve and strengthen the system. There is an increase in the number of registered new medicines (e.g., biologicals and biosimilars); hence a robust VL system needs to be in place. To establish this system, a database is developed to monitor implementation of all approved Risk Management Plans and to measure their effectiveness. To track potential safety concerns, the data base is also used for all medicines subject to additional post-marketing monitoring. VL inspection is one of the tools used to monitor and maintain the VL system within local companies and agents.	Failure to test sampled products due to limited capacity for testing may lead to failure in identifying products that have been damaged in the distribution and storage chain. This may adversely impact the reputation of pNRA. 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 for staff. Unclear communication strategy may lead to miscommunicating or neglecting to communicate an SF to relevant stakeholders. This may adversely impact the reputation of pNRA. It provides an opportunity to review the procedures and personnel responsible for communication of such events. In case of product recall, there is a risk not to recall and dispose of the whole batch. Recall from remote areas may be challenging. This provides an opportunity to empower the national vigilance system, to involve and commit other institutions in the dissemination of regulatory measures, and to recall products that are damaged, fail to meet the required quality standards, or are SF.

5.5.3. QUALITY OBJECTIVES AND PLANNING TO ACHIEVE THEM

ADDITIONAL GUIDANCE

TABLE 3
Guidance with practical examples for the development of quality objectives

Requirement	Intent with example
a. Be consistent with the quality policy	Use commitments made in quality policy for setting quality objectives, e.g., setting objectives for continual improvement of QMS as committed in quality policy.
b. Be measurable	Define quantity or period of time, e.g., customer request processing time will be reduced from 2 days to 1 day.
c. Address applicable requirements	For example, setting objectives for applicable regulatory requirements relating to product or service. Use WHO GRP for setting objectives.
d. Be relevant to conformity of products and services and enhanced customer satisfaction	For example, 'On Time and In Full' delivery of service, setting targets for achieving higher level of customer satisfaction.
e. Be monitored	Review 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.
f. Be in communication	For example, through circulation of meeting minutes internally and externally to interested parties, e.g., suppliers who have signed agreements.
g. Be updated as appropriate	Potential or actual changes that can impact the ability to achieve quality objectives that need to be considered and actions that need to be taken, as necessary, to ensure new issues or requirements are addressed.

EXAMPLE 17

Quality objectives for qNRA

Examples of the quality objectives at qNRA

- ***Objective 1:***
  The rate of SF food, medicine, cosmetics and medical devices circulating in the country reduced by 50% by June 2020.
- ***Objective 2:***
  Customer satisfaction for services offered by qNRA increased by 80% for both internal and external customers from 63% and 66%, respectively, by June 2020.
- ***Objective 3:***
  qNRA self-sustained financially from 60% to 80% by June 2020.
- ***Objective 4:***
  90% of human resources recruited and retained by June 2020.

To achieve the timeline for disposal of various applications, each individual responsible for processing of an application shall ensure the disposal of application within the specified time line; this will be reviewed in KPIs and monthly review meetings. The initial objective is to achieve 75% of compliance.

Planning to achieve quality objectives

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

qNRA determines and provides resources (including human, financial, infrastructure, technology, work environment and organizational knowledge) needed to establish, implement, maintain and continuously improve the 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 qNRA services by ensuring the resources, systems and processes needed to implement and improve the QMS and for undertaking management review meetings. All employees are responsible for the quality of their work and for implementation of the policies and procedures applicable to the processes they perform.

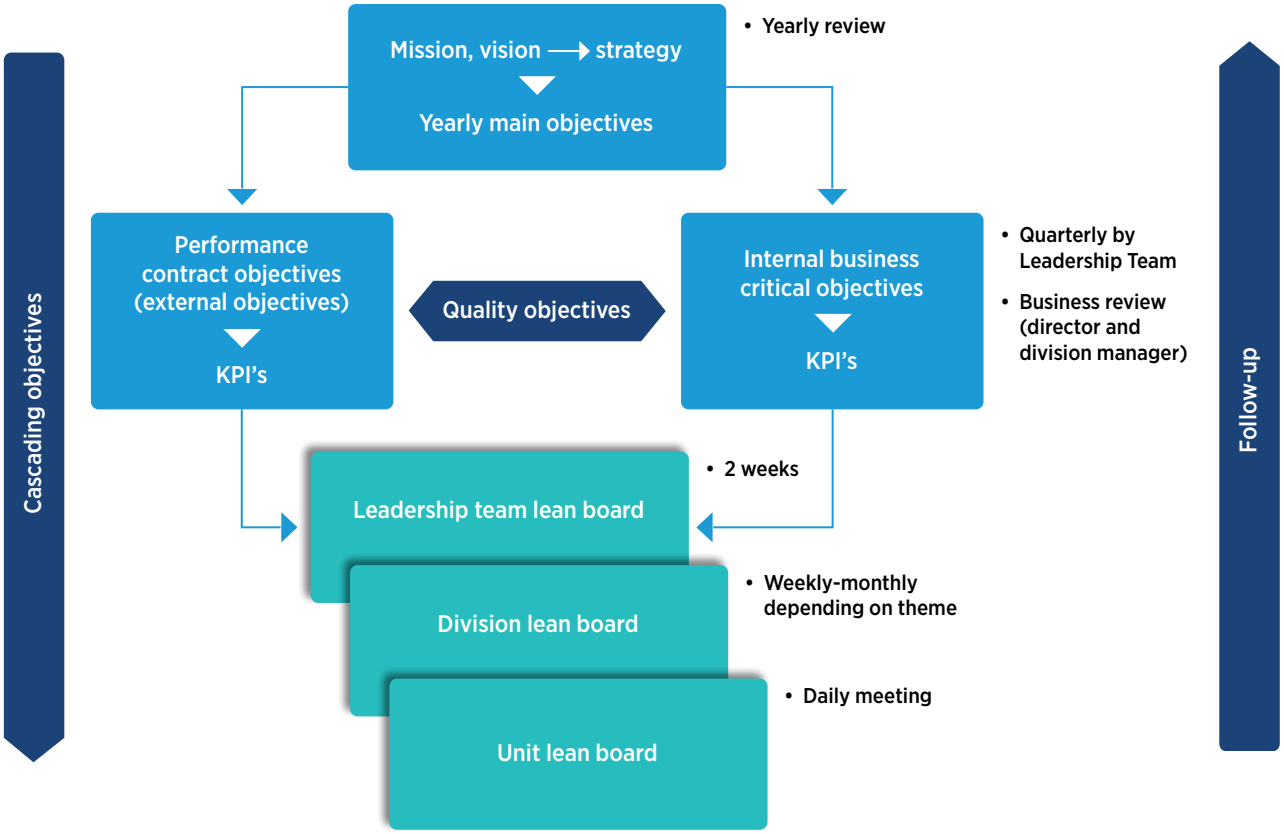
The quality objectives should be achieved by 2020 and will be evaluated by undertaking internal quality audits and by analyzing performance data for continual improvement of the system with the overall aim of meeting customer needs and expectations.

EXAMPLE 18

Development of quality objectives at rNRA

After review of mission, vision, strategy and the performance of the QMS, quality objectives are defined and cascaded down into the organization.

FIGURE 8
Cascading the strategy into quality objectives at rNRA



Development of interviews and performance appraisal

Development interviews and performance appraisals at both individual and managerial levels help to give everyone a clear picture of what is expected, as well as to provide concrete feedback on progress in achieving targets. The individual's competencies and results are assessed and discussed, so that the individual's development contributes to the quality objectives of the Medicines Agency. The interviews allow management to link the overall strategic aim to the individual tasks and to set the direction for the individual employee's development and well-being.

5.5.4. PLANNING OF CHANGES

ADDITIONAL GUIDANCE

In order to benefit from identified risks and opportunities, subsequent changes in an organization may be required. Those changes could be related to any aspect of any process, such as:

- *Inputs*
- *Resources*
- *Personnel*
- *Activities*
- *Controls*
- *Measurements*
- *Outputs*

Changes are intended to be beneficial for the NRA and its employees, but they need to be carried out when deemed relevant, feasible and achievable by the organization. In addition, consideration of newly introduced risks and opportunities should also be taken into account.

To achieve the benefits from changes, the organization should consider all types of changes that may subsequently occur. For example, these changes may be incorporated into:

- *Processes and procedures*
- *Documented information*
- *Infrastructure*
- *Tools*
- *Process equipment*
- *Employees training*
- *Supplier evaluation*
- *Stakeholder management*
- *Interested parties' requirements*

Evidence related to planning and implementation of changes that may impact the QMS should be retained, documented and recorded.

EXAMPLE 19

sNRA plans the integration and implementation of changes into its QMS processes, always considering the following:

1. The reason for the change; e.g., context of the organization, needs of interested parties, customer feedback, complaints analysis, audit results, performance trends, risk reduction, opportunity identification, continual improvement, organization growth, organization restructuring, or launch of new products or services.
2. Assessment of the purpose of the change(s) and potential impacts using a risk-based approach to ensure that the integrity of the QMS is maintained, for example, by focusing on priorities, avoiding disruptions, ensuring business continuity, maintaining product and service reliability, protecting the customer, maintaining capability, and continuing to meet internal and external requirements.
3. The resources required to enable the change, including, for example, personnel, knowledge acquisition, infrastructure, environment, budget, trials and tests, ongoing monitoring, and structured reviews.
4. Definition of responsibility and authority for the change, e.g., process owner, lead process users, and end-users. Defined responsibilities should include the necessary communication, training and ongoing review to ensure that the change is effective (i.e., the planned activities occur and planned results are achieved).

EXAMPLE 20[2]

At tNRA, an example of planning changes is the following:

For an anticipated increased demand for lot release in the coming year, a risk analysis determined that the National Control Laboratory will need to add one more LSP evaluator, increase the technical committee meetings to twice per month, and prioritize lot testing. These measures would entail a change in processes which must be planned, documented, integrated into the QMS, and properly monitored. In this manner, the organization considers the potential impact of the change, the availability of resources, and the allocation or reallocation of responsibilities, and thereby maintains the integrity of the QMS.

2 This example is linked to the example 15 and may be relevant to read them together.

5.6. Support and resources

5.6.1. RESOURCES

EXAMPLE 21

The inspection department of uNRA has a formal structure, with public employees dedicated to carrying out activities related to the inspection. Within the department structure, there is a specific coordination process for the maintenance of the QMS. The department is located in the uNRA's headquarters and has the necessary infrastructure to carry out its activities.

In relation to financial resources, annual budget planning is drawn up to stipulate the activities required for the following year using a planning system. In the planning system, the budget requirements are defined for national and international inspections, meetings, and staff training.

EXAMPLE 22

The vNRA determines and provides resources through the annual budget for the establishment, implementation, maintenance and continual improvement of the QMS. The process takes into consideration any budgetary constraints and the need to obtain additional resources from external providers.

Resources include personnel, infrastructure, and environment for operation of the processes, laboratory equipment, office equipment (e.g., computers and printers), and organisational knowledge; all these resources will be provided for through the budget.

EXAMPLE 23

Financial resources

The means necessary to finance the activities of wNRA are assured by the NRA's own revenues that result from the collection of various fees that are specified by law.

Funding of the wNRA is totally independent of the state budget, with financing needs completely covered by fees paid by entities operating in regulated and supervised sectors, namely:

- *Fees that are related to sales of medicines and health products, and that are levied on the monthly sales volume of the entities that commercialize the products;*
- *Service fees that are paid by the industry in exchange for a service (e.g., MA requests, MAs, or pharmacy licensing).*

Technological Resources

In recent years, investment in technological resources has been a strategic priority to technologically support a more rational, effective, and efficient model for wNRA.

In this context, during 2020, the Directorate of Information Systems and Technologies will pursue and invest in the implementation of new technologies and in improvements in the existing information systems; these investments will enhance its technological infrastructure to enable the NRA to respond to current and future challenges.

Human Resources

In order to achieve its mission and perform its activities, the wNRA has invested in an additional set of qualified professionals and experts that are in different areas of medical and pharmaceutical sciences and complement the existing in-house knowledge.

As for the learning, development and acquisition of new knowledge, wNRA promoted employee attendance at a total of 95 courses, seminars, congresses and meetings; these activities involved a total of 277 employees for a total of 10,538 hours of training.

5.6.2. PERSONNEL

EXAMPLE 24

The selection process for recruitment of staff at xNRA is critical to identify persons qualified for the job. The requirements for a position, the acceptance criteria and the position-specific knowledge are reflected in the job description published on xNRA 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 qualified candidates. xNRA invests in maintaining competence of its employees and in reducing turnover to the maximum extent possible. xNRA has provisions to update knowledge of personnel through activities such as regular refresher training and participation in scientific and technical meetings. Competence records are kept as part of the process of acquiring competence. In case a person no longer meets the requirements of the position, xNRA offers mentoring and retraining and, as a last option, reassignment to a different position. There are instances where reassignment to a different position is not the result of failure but of the person's initiative to gain experience in a different area of expertise. Rotation of personnel is also a regular practice in xNRA to facilitate acquisition of additional skills and competencies and to provide incentives.

EXAMPLE 25

The inspections department personnel of yNRA must possess the necessary competence to carry out their activities. Training opportunities are distributed among personnel in order to ensure that all personnel meet the minimum qualification requirements for performance of their activities. Job descriptions are described in a work instruction.

The training records specific to the department activities are maintained in the department database (i.e., in a Sharepoint) by the coordinator of the department QMS. The training offered in distance learning is registered in a "In Distance Learning Platform".

Personnel designated for the department activities shall have qualifications, training, experience and knowledge that is appropriate for the type of establishment and product being inspected. The personnel should also have the ability to make professional judgments about the compliance of the inspected company with GMP requirements and other related legislation and be able to perform an assessment of the associated risks.

The specific training requirements for the inspectors are set by the inspector training program. The following are considered as continuing training methods: internships, self-training, workplace training, and participation in courses, seminars, workshops, symposia and conferences (including those carried out through distance education tools).

5.6.3. INFRASTRUCTURE AND WORK ENVIRONMENT

EXAMPLE 26

The zNRA maintains a register of all assets, i.e., physical plant, equipment, electronic equipment and properties. The register is updated each time new acquisitions are brought into the organization and when disposals are done.

The zNRA has approved contracts with various service providers that cover routine and cyclical maintenance of its equipment, infrastructure and physical plant. These contracts are reviewed on an annual basis. A summarized maintenance plan is kept in the administration unit for the scheduled calibration and routine maintenance of plant and equipment; this plan is used to track timely implementation of the activities.

Some of the zNRA's operational areas require a controlled environment. These include, for example, areas for sample analysis, locations for sample storage, offices, server rooms and laboratories. Users determine the optimum conditions as guided by the activities performed in that location. Control parameters include temperature, humidity air flow, and air quality. Access control is provided where required. The zNRA's environmental control and waste disposal is in compliance with National Social Security Authority and Environmental Management Agency requirements.

5.6.4. MONITORING AND MEASUREMENT RESOURCES AND EQUIPMENT

EXAMPLE 27

The aaNRA has obtained monitoring and measuring resources which include laboratory equipment (e.g., balances and high performance liquid chromatography instruments) and office machines (e.g., computers and other IT equipment). Equipment is qualified, calibrated, maintained and verified. Equipment maintenance and calibration schedules are kept in the various departments. Process owners are accountable for the monitoring and measuring equipment used in their respective departments.

5.6.5. ORGANIZATIONAL KNOWLEDGE MANAGEMENT AND AWARENESS

EXAMPLE 28

Example of measures taken by the bbNRA to maintain and update organizational knowledge

1. bbNRA has developed, and updated as needed, detailed job descriptions for personnel responsible for key processes in the chain that leads to their outputs (i.e., products and services).
2. bbNRA carries out initial training of new staff as well as refresher training for staff at different levels; this training provides new information relevant to their respective positions and allows staff to keep their competence up-to-date.
3. Recruitment of new staff is based on job descriptions. Positions are posted on the website, and candidates are subject to a test and interview before decisions are-made.
4. In case of staff turnover, and whenever possible, an overlap between the staff leaving the position and the new staff is sought. This provides for proper transfer of knowledge to the new staff and gives an opportunity for the incoming person to practice under guidance of the person leaving the position.
5. In case of retirement, succession is properly planned through timely recruitment of a successor.

6. Organizational knowledge refers not only to processes for service delivery, but also includes the broader perspective, for example,
   a. *knowledge of mission, vision, quality policy and objectives;*
   b. *strategic plans and objectives of the NRA;*
   c. *understanding of the organizational context, as well as internal and external issues;*
   d. *customer expectations;*
   e. *statutory and regulatory requirements; and*
   f. *relationships with customers, suppliers and other relevant organizations or agencies.*

   To ensure that this knowledge is maintained and properly communicated to personnel internally, bbNRA organizes meetings at regular intervals where issues are discussed and produces and circulates a monthly newsletter through the intranet. In case of urgency, email communications are sent to all relevant personnel.

7. bbNRA provides opportunities for training of staff outside the NRA by participating in technical courses and by attending scientific meetings. Personnel that benefit from such opportunities are required to write a meeting or training report and to deliver a lecture to colleagues in the NRA for knowledge and information sharing.

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

5.6.6. INTERNAL AND EXTERNAL COMMUNICATION

EXAMPLE 29

Example of requirements for internal communications at ccNRA

At a minimum, internal communications are carried out through the following channels:

- *Meetings with Ministry-Joint Secretary (quarterly)*
- *Senior staff meetings (monthly)*
- *Full departmental meetings (weekly)*
- *Operational meeting of the departments and administrative areas (daily)*
- *Email, internet platform and/or telephone (as needed)*

Example of communications with the customers at ccNRA (external communications)

Communication with customers is maintained through:

- *Internet platform, fax, email or postal service*
- *Surveys and interviews to obtain customer feedback*
- *Meetings and exchanges between specialists and managers*

EXAMPLE 30

The activities of ddNRA's inspection unit are communicated in several ways. All official decisions are published in the Government Official Gazette and on the ddNRA website. The actions derived from investigations are made publicly available through the link www.ddNRA.gov-enforcementactions. GMP certificates can be accessed at www.ddNRA.gov-GMPcertificates.

A mechanism for rapid-alert communications between ddNRA and the National Health Authorities System is established in a procedure, while communications with international authorities are defined in a separate procedure.

5.7. Operation

5.7.1. CUSTOMER COMMUNICATION AND REVIEW OF THE REGULATORY PRODUCTS AND SERVICES REQUIREMENTS

EXAMPLE 31

Example of communication with customers at eeNRA

Customer Communications

Communications with customers include collecting information about their needs and expectations as well as receiving doubts, suggestions and complaints about the current work process or the engagement of stakeholders.

- **Phases:**
  - *Meetings with internal customers or managers and their teams to identify problems and propose solutions;*
  - *Meetings with representatives of the regulated sector and other stakeholders to identify difficulties with the products and services offered by the NRA and to seek suggestions for improvements;*
  - *Meetings with managers to present the methodology and schedule of actions.*
- **Products:**
  - *User's journey map: tool to identify a user's points of contact for a product or service and to understand their needs, perceptions and issues related to that product or service in order to promote the necessary improvements;*
  - *Communication plan: a tool that establishes strategies for communicating with customers and other stakeholders involved in all stages of the process improvement initiative and raises awareness of the new way of working.*

Determination and critical analysis of regulatory processes

To analyze the regulatory processes, it is necessary to understand the challenges, make a diagnosis and engage in the problem, throughout five phases.

- **Phases:**
  1. *Definition of the scope of processes;*
  2. *Collection of quantitative and qualitative data;*
  3. *Mapping the current situation of the processes;*
  4. *Definition of performance gains; and*
  5. *Definition of the team allocated to the initiative.*

- **Products:**
  - *Planning the initiative;*
  - *Quantitative and qualitative analysis of processes; and*
  - *Flowcharts and checklists.*

Changes to regulatory processes

When changes to regulatory processes occur, regardless of the reason, process documentation is reviewed, changes are recorded and communicated to all relevant parties.

- **Phases:**
  1. *Meetings with customers to understand the dynamics of the necessary changes;*
  2. *Revision of the documentation (e.g., scope, schedule, responsible individuals, communication plan); and*
  3. *Communication to all those involved.*
- **Product:**
  - *New planning of the process;*
  - *Transformation initiatives (e.g., scope, schedule, responsible individuals, communication plan).*

5.7.2. DESIGN AND DEVELOPMENT OF NEW PRODUCTS AND SERVICES

EXAMPLE 32

An instance in which an NRA may need to go through the design and development process could be when the NRA decides to perform a regulatory function that was not already in place; such a situation would lead to the provision of new products and services. For example, ffNRA currently does not inspect clinical sites, but is now able to introduce this new service to regulate clinical trials. To accomplish this, ffNRA needed to design this service in-house.

5.7.3. EXTERNALLY PROVIDED PRODUCTS AND SERVICES

EXAMPLE 33

External provision of products and services include any processes, supplies or services that the NRA needs to ensure compliance with customer requirements. The hhNRA is responsible for ensuring that externally provided processes, supplies and services conform to the requirements of the QMS.

The hhNRA has determined controls to be applied to externally provided processes, supplies and products. These apply when:

- *Externally provided supplies, components or services either form part of the final product or service, or are critical for provision of service;*
- *A process, or part of a process, is provided by an external provider.*

The hhNRA is guided by the Public Procurement and Disposal of Assets Act (Chapter 22:23) and Statutory Instrument 5 of 2018 Procurement Regulations for selection of external service providers.

The Procurement and Administration Unit and the relevant unit or division are responsible for site visit evaluation of suppliers. The Administration Unit is responsible for monitoring performance of external service providers according to the procedure for purchasing of services and supplies.

5.7.4. SERVICE PROVISION

EXAMPLE 34

The iiNRA implements its service provision under controlled conditions. All departments have documented SOPs that describe how activities for the provision of products and services are conducted. The departments also have documented information in the form of the operational planning and implementation form, which defines the characteristics of the products to be produced and the services to be provided. The document also defines the results to be achieved. On execution of the processes, documented information is maintained.

For example, the iiNRA offers services for the evaluation and registration of medicines and allied substances according to the Medicines and Allied Substances Control Act (Chapter 15:03) and WHO guidance on Good Review Practices (GRevP).

A system of double check and review is required at every stage to monitor and ensure compliance with specified requirements. It is essential to have signatures of two persons (i.e., reviewers) for the review of acceptance criteria and the approval of documents.

Issuing MA:

1. *Regulatory officer enters the approved product into a logbook giving product a numeric registration number;*
2. *A registration certificate is prepared along with a checklist form for confirming correctness of certificate;*
3. *Second review of the draft certificate;*
4. *Registration certificate is sent to the Director-General for signature;*
5. *Registration certificate is dispatched to the applicant.*

The inspectorate department for the iiNRA offers services for GMP inspections for local and international pharmaceutical manufacturers. The inspection reports are reviewed by the chief regulatory officer or designee. The final GMP approval letters are signed by the head licensing and enforcement office before being released to the customer.

The inspectorate department also conducts inspections of licensed and approved premises to ensure compliance with the Medicines and Allied Substances Control Act (Chapter 15:03). Inspection reports are numbered using the reference number on the cover letter of the inspection report. This number will be unique to the report.

Regulatory officers are trained and deemed competent for conducting inspection according to the procedure for training and development of staff. A competence matrix developed for each department is used for this purpose.

The iiNRA's laboratory facilities are appropriately designed and maintained (e.g., with adequate lighting, ventilation and air conditioning) to facilitate a conducive environment for performance of tests and to assure validity of results.

The laboratories have procedures in place which stipulate the required environmental conditions for the conductance of tests according to the Global procedure TR 5.3: Accommodation, Environmental Conditions, Housekeeping and Safety and Health. The laboratory information files illustrate the design of the facilities and list their specifications.

In situations in which they could influence the quality of the results, the environmental conditions of iiNRA's laboratories are monitored and controlled as required by relevant specifications. The environmental conditions monitored include temperature and humidity which are defined specifically for each laboratory. Each laboratory maintains a record of the environmental conditions in that laboratory. Limits for the parameters measured are found in the SOPs for each specific unit or division because the degree of environmental control and monitoring varies among the locations.

There is controlled access to laboratory areas where tests are done. Entry restriction labels are mounted at each entrance to the laboratory areas. The NRA ensures that there is effective separation between neighbouring areas in which there are incompatible activities. Isolators, biosafety cabinets and chemical fume hoods are housed in the relevant laboratories. Measures are taken to prevent cross contamination by restricting access to authorized personnel according to information communication technology access control procedures.

The iiNRA's laboratories have procedures in place for safe handling, transport, storage, use and planned maintenance of measuring equipment to ensure proper functioning and prevent contamination or deterioration. All equipment is qualified prior to and during use where necessary. After the maintenance and repair of defective equipment, the appropriate checks, calibrations and requalification steps are done before using the equipment again.

The laboratory equipment at iiNRA is properly calibrated by qualified metrologists whose reference documents and calibrators are traceable to international standards. The laboratory has calibration schedules which are monitored by senior laboratory analysts. Maintenance of equipment is done by qualified engineers.

The calibration status of equipment is indicated on the equipment through use of stickers that highlight the identifying name of the equipment, the date of calibration and the next date for calibration.

Any equipment giving inconsistent results is investigated and, if necessary, taken out of service and marked according to its status. Corrections and corrective actions will be taken appropriately.

Intermediate checks on equipment are performed by competent, authorized senior analysts according to the laboratory procedures. System suitability tests and equipment verification tests are performed before analysis.

The iiNRA's laboratories have procedures in place for the application of any correction factors that are to be applied after calibration and service and during routine testing to ensure specified requirements are met. All laboratory equipment is operated by competent and authorized personnel whose access to the equipment is password controlled; different levels of access are used to prevent the invalidation of results due to unintended adjustments of equipment.

The iiNRA's laboratories have equipment records (i.e., in the form of logbooks and hardcopy and electronic folders) to document equipment details, which include, but are not limited to, equipment identification, manufacturer details, evidence of verification, current location, maintenance records and details of any malfunctions.

5.7.5. PROPERTY BELONGING TO CUSTOMERS OR EXTERNAL PROVIDERS

EXAMPLE 35

Example of infrastructure required for the preservation of vaccines until their expiry at jjNRA

The jjNRA receives vaccine samples for visual inspection or testing during the lot release process; in some cases, samples also are received during the MA evaluation process, although that is not required at this stage.

In case samples are requested and received, they need to be properly stored and retained 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 cold rooms are needed. Back up measures, such as an alarm system (ideally which is centralized), are required to ensure that a responsible officer is immediately informed in case of electricity failure or break down of the equipment. A back up refrigerator or electricity generator, depending on the source of the failure, must be available for such situations.

EXAMPLE 36

When needed, the kkNRA has possession of customers' property, e.g., intellectual property and subcontractors' equipment. In such cases, the kkNRA identifies, verifies, protects and keeps customers' property secure.

Intangible information in the dossiers whose rights remain with applicant cannot be shared with anyone. Records of dossiers are kept by the filing clerk, and verification of their condition and state is also conducted daily by filing clerk. Dossiers are always stored in the filing room. Electronic CDs are kept in a locked cupboard. No visitors are permitted in the Evaluations and Registrations department.

Application forms from customers are checked and stamped upon receipt; the stamp is checked every time it is used. Applications and the stamp are securely kept in the in the Chief Regulator's office.

Although submitted medicine samples belong to the customer, the kkNRA does not return samples to customers. Instead, they are kept as retention samples in case of investigations. Retention samples are kept at controlled temperatures in secure conditions.

Condoms shall be stored below 40°C in the Medical Devices Laboratory. After analysis, the customer is free to collect the remainders.

When the property of a customer or external provider is lost or damaged, the kkNRA reports this to the customer or external service provider and retains documented information on the case.

5.7.6. RELEASE AND COMPLIANCE CONTROL OF PRODUCTS AND SERVICES

EXAMPLE 37

Products of llNRA include reports, certificates, licenses, permits and authorization letters. Before delivery to the applicant or entity that requests them, these are checked by the respective supervisors and signed by the Executive Director or other senior officer(s) authorized by the Governing Board to do so as per section XX of the National FDA Act. The list of authorized persons (i.e., persons authorized to release the llNRA products to applicants) is updated from time to time and communicated to all staff via posts on the llNRA Intranet.

The release of reports, certificates, licenses, 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 CAPAs taken by the manufacturer is received and evaluated by the llNRA and found to be satisfactory).

5.8.
Performance evaluation

5.8.1. MONITORING AND MEASUREMENT[3]

EXAMPLE 38

In order to determine if intended results are being achieved, the mmNRA monitors and measures all its processes. Where necessary, the departments develop SOPs for monitoring, measuring, analyzing and evaluating their processes. The SOPs indicate:

- *The parameters or indicators that need to be monitored and measured;*
- *The methods to be used to analyze and evaluate the performance and effectiveness of the QMS;*
- *The frequency of the monitoring and measurement activities.*

3 WHO guidance on the development and implementation of KPIs for NRAs is begin developed; this document can provide further guidance for this QMS requirement.

KPIs for key processes are documented on the Operational Planning and Implementation form for each department. Management determines the frequency of monitoring, measurement, analysis and evaluation of processes. Records are maintained. Results of monitoring and measurement are presented at relevant committee meetings and quality management review meetings.

Responsibility for the KPIs is assigned to individual unit heads, and the main indicators for defining performance are the completion of specific regulatory activities within specified timelines and with adherence to SOPs. Although the goal is to achieve a 100 percent score for maintaining timelines and compliance with SOPs (e.g., for team composition for inspection activities, planning and conducting inspections, categorization of deficiencies, and reviews by inspectorate head), 75 % shall be the threshold value. Possible input data parameters for evaluating KPIs include dates for each of the following steps: receipt of application, review, communication with applicant, inspection (if any), and completion of decision making activities.

5.8.2. MONITORING OF CUSTOMER SATISFACTION

EXAMPLE 39

Examples of how to obtain customer feedback at nnNRA

The nnNRA obtains feedback from its customers to determine whether needs and expectations have been met. This is guided by SOPs for Service to the Customer and Handling Customer Complaints. Customer satisfaction and perception is monitored through use of:

- *Customer feedback forms or customer satisfaction surveys*
- *Customer complaint forms*
- *Public perception survey forms*
- *Stakeholders meetings*
- *Feedback from social media sites*

Indicators evaluated include, for example, number of claims and complaints received; time to respond to customers; and time to complete investigations and corrections. Assessments include comparisons with previous years' results, analyses for common causes of claims, and focus group discussions and analyses.

The public relations office provides guidance to customers and engages the public regularly by providing information related to regulatory products and services. Feedback from surveys is analyzed and the identified gaps addressed by the relevant department.

Analyses of survey results include, for example, identification of actions to sustain positive and improve negative opinions about services, examinations of customer opinion about the services provided, information on registered products published on internet, marketing surveillance and the regulatory legal bases, and assessments of the completeness and timeliness of the updates to publicly-available information.

EXAMPLE 40

Example of obtaining customer feedback and complaints at ooNRA

Purpose

The purpose of having a process for customer complaints is to use the complaints for continuous improvement of the quality within the Medicines Agency, which was designated as the responsible authority by the relevant legislature.

The procedure defines how all complaints to the Medicines Agency are received from customers and are registered and handled consistently.

Definitions

Customer: The definition is broad and may include, in general, citizens and patients, pharmaceutical companies and industry organizations, health care providers, the Ministry of Health (MOH) as a political client, and organizations with which the Medicines Agency has collaborative relationships, e.g., other authorities and partners in the region where the country is located.

Complaint: A complaint means a request from a customer who is dissatisfied with the output or product that the Medicines Agency has delivered, and who wishes to have this output assessed again, either by the Agency itself or by the appellate body.

The customer must always receive a reply to a complaint from the Medicines Agency, unless the complaint was directed specifically to the department or the MOH.

Customer complaint process

- **Registration**

  All employees who receive a complaint are responsible for ensuring that the following data is available before handover to a complaint officer:

  - *The office or department against which the complaint was raised;*
  - *Title of the complaint;*
  - *Date of receipt of the complaint;*
  - *Description of the complaint.*

  The complaint officer is responsible for ensuring that:

  - *Customer communications and related documents are archived.*
  - *A reply is sent to the customer confirming receipt of the complaint no later than three business days after receipt. The confirmation reply states when the customer's response is expected; the timing should be chosen to ensure that the customer receives a response to the complaint as soon as possible. If the processing time is longer, the customer is advised.*
  - *Information is communicated to responsible manager.*
  - *Analyses are initiated.*

- **Analysis**

  Manager initiates a root cause analysis (RCA), and the facts related to the complaint are clarified by the officer of the department that is the subject of the complained. All necessary information is collected and verified to validate the complaint, and to determine the root cause and the extent to which corrections to the customer are required.

  The extent of the impact of the complaint and any observed deviation on previous work must also be assessed (i.e., a "look back").

  Investigation and conclusion must not result in discriminatory acts.

- **Handling**

  Correction is made to the customer where relevant, e.g., a new decision or report is provided to the customer. In cases where the complaint is due to a defect in the quality system, the complaint officer initiates an improvement via the CAPA system. The manager, together with the quality manager, must ensure that relevant processes and related documents in the quality system are adjusted in accordance with the outcome of the RCA.

- **Closing**

  Clarifying answers and correction of the delivery to the customer (where relevant) must be approved by the manager before the complaint officer sends a reply to the customer.

Customer surveys

Purpose: The purpose of customer surveys is to ensure further development of quality within the Medicines Agency, which as designated as the responsible authority by the relevant legislature. This procedure determines the methods for obtaining, monitoring and reviewing customers' perceptions of the extent to which their needs and expectations have been met.

- **Questionnaires: Planning and Implementation**

  Annual questionnaire surveys must be conducted in order to follow progression in the customers' perception of the Medicines Agency's work on both the strategic and the detailed delivery plan.

  The studies must be simple, generic and, as far as possible, identical from year to year, so that development can be recognized and conclusions for further actions can be reached. However, efforts should always be made to improve the quality of the wording of the individual questions where necessary.

  EXAMPLE 1:

  Are you satisfied with your recent delivery on [.....] from the Medicines Agency?

  - *Very good*
  - *Good*
  - *Medium*
  - *Improvement desirable*
  - *Improvement very desirable*
  - *Do not know*

  Comment on why:

EXAMPLE 2:

Are you satisfied with your recent contact with [.....] in the Medicines Agency?

- *Yes*
- *Both yes and no*
- *No*
- *Don't know*

Comment on why:

Questionnaire surveys can be conducted as an annual event or as ongoing queries. If ongoing queries are used, the survey should also be collected on an ongoing basis.

In order to get the optimal benefit from questionnaire surveys, they should be directed to a specific segment or category of customers. This is done so that the survey questions are relevant to the customer and so that it is clear regarding which of the Medicines Agency's services the customers are being asked to offer an opinion. In connection with the questionnaire survey, customers should be informed that it has been sent out for general improvement and not for routine complaint processing. Customers should be reminded that specific complaints should be submitted directly to the Medicines Agency, for example. via mail with the term complaint stated in the text.

5.8.3. ANALYSIS AND EVALUATION

EXAMPLE 41

The ppNRA inspection department established multiple performance indicators that are tracked and evaluated monthly, quarterly and biannually. This process includes the evaluation of the effectiveness of the QMS. The indicators and its evaluation and tracking frequency are established in the management review procedure.

Examples of indicators monitored monthly:

- *Time to issue GMP certificates*
- *Time to renew GMP certificates*
- *Time to finalize investigations*

Examples of indicators monitored quarterly:

- *Number of open corrective actions*
- *Number of open corrective actions which exceeded due date*
- *Time to respond to questions from the public or the regulated sector*
- *Results of feedback from inspected companies*
- *Percentage of the internal audits performed in comparison to the planned internal audits*
- *Internal audit recommendations that exceeded the due date*
- *Percentage of inspection reports delivered on time*
- *Percentage of inspections performed on time in accordance with the established inspection frequency*
- *Percentage of rapid alerts issued on time in accordance with the established procedure*
- *Percentage of enforcement actions completed on time*
- *Percentage of GMP certificates issued using risk assessment and international reliance programs*
- *Percentage of increase of on-site investigation activities*

Biannually, the results of the external audits and the status of the corrective actions raised from these audits are evaluated.

5.8.4. INTERNAL AUDIT

EXAMPLE 42

Example of qqNRA internal audit plan

The work processes within qqNRA are the subject of periodic audits conducted under NRA's responsibility and according to the procedures for internal audits. These audits are performed for the purpose of verifying conformity with current directives of the QMS. The audits are a management tool to monitor and verify the effective adoption of a quality management policy. The results of internal audits and the corresponding corrective actions are formally documented and analyzed as part of the management review process.

Annually an internal audit plan is prepared and approved by all coordinators, managers and general managers of the qqNRA. All departments are audited annually. The scope of the internal audit can be reduced to defined processes of the department based on the evaluation of the department performance of the previous years.

The corrective action system is used to address the nonconformities identified during internal audits.

EXAMPLE 43

Example of rrNRA Internal audit plan

The rrNRA conducts internal audits to obtain information about the performance and effectiveness of the QMS as guided by the procedure for internal audits. The internal audits determine whether the QMS conforms to the relevant statutory and regulatory requirements and continues to meet stakeholder needs and expectations.

The Quality Manager develops the internal audit schedule using a risk-based approach considering the following:

- *Importance of the processes*
- *Management priorities*
- *Performance of the processes*
- *Changes affecting the organization*
- *Results from previous audits*
- *Trends in customer complaints and non-conformities*
- *Statutory and regulatory issues*

The rrNRA's internal audits assess all elements of the QMS, and examine documented information (e.g., SOPs, records generated and statutory and regulatory requirements).

QMS internal auditors are drawn from the authority's departments and must have served in the organisation for at least 12 months. The auditors are deemed competent based on relevant training and experience.

Heads of departments ensure appropriate correction and corrective actions are taken without undue delay. The audit results and trends are reported at the quality management review meetings.

CAPAs are recorded on the Non-Conformity Report Form and the CAPA register is retained as evidence of the implementation of the audit programme and audit results.

Audit Procedure

Procedures: Accountability is with the head of the organization or the head of unit for zonal or sub-zonal offices.

Audit team: Persons having regulatory experience and holding the position of XX (level of officials) in a cross functional division shall be nominated as audit team members. Lead auditor should be an upper level or mid-level official with regulatory experience and should hold a position from cross functional division.

Administrative structure: The accountable head shall be responsible to ensure that the personnel who are nominated and approved for the audit team for the internal audit activities that are conducted to improve standards of the regulatory functions and activities should have following characteristics:

- *They shall not be influenced by assessed area or person during their inspection of that area.*
- *They shall not be directly involved in the day to day functions of inspected area.*
- *They should have sufficient experience and expertise to carry out the audits in the areas assigned.*
- *The responsibility, authority and reporting structure should be clearly defined and documented.*
- *The internal audit team should proceed with the objective of identifying all pros and cons of the running system and, accordingly, make suggestions to assure an effective and efficient drug regulatory organization.*

Internal audits covering all the functional sections shall be planned twice in a year, preferably in the months of January and July. Assigned official shall prepare an audit plan as per current version of the internal audit procedure. Each internal audit shall be assigned a specific audit number and that audit number should be referenced in all documents related to that audit. The Head of the division to be audited, as well as the members of audit team, should be informed in writing about the audit plan with proposed date, names of audit team members, and scope of the audit at least one week in advance. The head of the division shall nominate those personnel from the division to be audited and provide, for each auditee, an audit plan form. An opening meeting shall be conducted between auditors and auditees before initiating the audit. The following aspects should be discussed at this meeting: the purpose and scope of audit, audit procedures, including access to documentation, and clarifications on any aspect of audit plan. The audit shall be conducted as per the current version of the audit checklist.

Note: *Apart from items on the checklist, additional points may be considered at the discretion of the audit team. All observations during the audit shall be documented in the comments column of the checklist and the lead auditor shall report them to TM and to the head of the audited area, who shall initiate and take necessary CAPAs. After the completion of the audit and before preparing the final report, the audit team shall have a closing meeting with the auditees to discuss the points observed as deviations. After the closing meeting, the audit report shall be prepared by audit team according to the current version of the procedure and within a period of time not more than 7 days after the closing meeting. The final report of the audit shall be reviewed by the assigned lead and communicated to concerned personnel of the division in order that they initiate CAPAs to eliminate deficiencies found during the audit. Audit team shall perform a follow up to confirm that the CAPAs have been taken and causes have been eliminated effectively. All the audits shall be planned and performed as per the current version of the flow chart for internal audit.*

EXAMPLE 44

Example of ssNRA Internal audit process

Lead Auditor	Auditor Team	Process Owner
1. Call audit team to prepare audit	2. Develop audit plan	
3. Call for the audit and submit audit material to involved parties		
		4. Prepare for the audit
5. Call for planning the audit in detail	6. Plan the audit in detail	
	7. Perform the audit	8. Be audited
	9. Prepare the closing meeting with presentation of the findings and non-conformities	
	10. Execute the closing meeting and discuss disagreements. - Are there critical concerns?	11. Participate in the closing meeting and discuss disagreements.
12. If yes to critical concerns, contact General Director and reach agreement on how to follow up, e.g., a re-audit of the subject of concern		
	13. Prepare a draft audit report and submit it to process owner	14. Prepare comments to the audit report
	15. Finalise audit report	
16. Distribute audit report		17. Suggest corrections, corrective actions and preventive actions to all the findings and non-conformities and submit to lead auditor
18. Approve or reject the CAPA's. When all CAPA's are approved, close the audit		

- **Audit plan template**

Date/time:	
Place:	
Auditee / organisation:	
Audit team: **Lead auditor:** **Auditor:** **Technical expert:**	
Auditee process owner / management:	
Auditee responsible quality manager:	

General Remarks

The audit should verify the appropriateness of the implementation and the efficiency of the operation of [.....] (the process under audit) in the Medicines Agency.

Audit Purpose:

- To check the implementation of and compliance with [.....] legislation.
- To check compliance with documents and processes specified in the Medicines Agency's quality management system (QMS).

Audit scope and demarcation:

Audit includes audit of [.....]

Audit requirements:

The internal audit is based on:

- [.....](Provide specifics where relevant)

Times and order may change during the audit. Document review will be performed during the audit.

Date:	Time:	Activity:	Participants:

5.8.5. MANAGEMENT REVIEW

EXAMPLE 45

Management reviews are performed according to established procedures. Evaluation of the indicators for the final working processes are assessed on a monthly frequency, while overall evaluation of the quality system is performed on a quarterly and biannual frequency.

The management reviews include the evaluation of:

- *Results of the ttNRA internal audits*
- *Results of external audits*
- *CAPAs*
- *Suitability of the QMS policies and procedures*
- *Changes that may affect the QMS*
- *Regulatory changes that have an impact on ttNRA*
- *Feedback from regulated sector and other stakeholders*
- *Performance of the responses to stakeholders and the regulated sector*
- *Results of the quality indicators and KPIs*

The output of the management review is documented and includes:

- *CAPAs as well as improvement recommendations*
- *Required changes in QMS*
- *Resource needs*
- *Training needs*
- *ttNRA progress in relation to the quality objectives*
- *General performance of the processes and QMS*

5.9. Improvement

EXAMPLE 46

Example of dealing with nonconformity using a corrective action request form at uuNRA

uuNRA Corrective Action Request (CAR) Form

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

Nonconformity	Root Cause (from attached Root Cause Analysis (RCA) Form)	Corrective Action	The steps that have or will be taken for the demonstration of effectiveness of the actions taken	Timeline
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.	The parameters to be monitored and the tool to be used had not been established.	Develop a format for monitoring the quality objective clearly indicating the parameters.	1. Developed a format with key parameters as listed a) Products b) Annual and quarterly targets 2. Create a database on the NRA server for monitoring the quality objectives and train the NRA staff to use it.	Oct 2019 Nov 2019

A RCA must be attached. See example below:

uuNRA Root Cause Analysis (RCA) Form

Directorate / Department / Unit / Area: Inspection & Licensing Dept.
Representative: Dr. XX, Date: 7th Nov 2018

Category of Problem:

- ☐ Nonconformity
- ☐ Nonconforming output
- ☐ Market Complaint
- ☐ Other (please specify)

(Check applicable box above by double clicking on it)

Problem / Issue	Why 1	Why 2	Why 3	Why 4	Why 5
1.1 There was no evidence of monitoring of the quality objectives for the Inspection and Licensing processes	Why was there no evidence of monitoring of the quality objectives? Because the quality objectives had just been developed and monitoring of them had not started.	Why was monitoring of the quality objectives not yet started? Because the quality objectives had not been communicated to the relevant personnel at all levels.	Why were the quality objectives not yet communicated to the relevant personnel at all levels? Because the system for monitoring them was not well established.	Why was the system of monitoring the quality objectives not well established? Because the parameters to be monitored and the tool to be used had not been established. This is the root cause that has to be taken to the CAR form above to determine the corrective action	

Note: *Although this technique is called "5 Whys," you may need to ask a question fewer than or more than five times before the root cause of the problem or non-conformity is identified.*

EXAMPLE 47

As part of continual improvement, vvNRA analyzes trends for quarterly, semi-annual and annual performance of indicators for the key regulatory processes and for all support processes, as well as for the results from management reviews. This information is used to determine areas of underperformance and to identify any opportunities for improvement.

Internal and external audit processes (e.g., the management review processes) provide information for corrective actions and continuous improvement.

The procedures for recording, monitoring and evaluating these activities are described for internal audits, for corrective actions, and for management reviews.

EXAMPLE 48

Example of handling of non-conformities at wwNRA

Non-conformities can be identified in two ways.

A – From daily work

B – During an audit

The below overview reflects the small differences in the handling of non-conformities. In this situation, the lead auditor is involved only in those non-conformities initiated during an audit.

Lead Auditor	Case officer	Manager	Responsible Quality Manager
	1. **A** - At daily work: recognise and register the non-conformity and make an immediate correction, if needed. Inform your manager.	2. **A** - Be informed about the non-conformity from the daily work. Accept or reject it. If accepted, delegate the actions to be made to a case officer.	
1. **B** - Register the audit non-conformity that was agreed on during an audit closing meeting and then submitted to relevant management.		2. **B** - Receive the audit non-conformity and delegate to a case officer the actions to be taken.	
	3. Perform an RCA and plan corrective actions, preventive actions, and an efficiency check to confirm that the non-conformity will not happen again. Submit the plan for approval to the responsible quality manager.		4. Approve the plan. **B** - Submit plans regarding audit non-conformities to lead auditor for approval.
5. **B** - Approve the plan and inform the involved parties.			
	6. Implement the plan and submit for approval to the responsible quality manager.		7. Approve the implementation and close the non-conformity.
	8. Perform efficiency check and inform the responsible quality manager.		9. Accept the efficiency check and close it.

Definitions for non-conformities

- **Non-conformity**

  A Non-conformity is a failure to meet requirements. The following are considered non-conformities:

  - *A relevant provision in current legislation or current standards that is not included in or described in NRA documentation or that is not complied with.*
  - *A described requirement in the QMS that is not followed in practice.*
  - *A situation which, on the basis of objective evidence, may cast doubt on the quality of the service or product provided by the Medicines Agency.*
  - *A number of minor discrepancies which are not significant as isolated cases, but which, when occurring in a larger number, indicate that the presence of systematic errors that may have an impact on QMS performance and efficiency.*

- **Critical non-conformity**

  A critical non-conformity is a fundamental weakness of one or more processes or practices that adversely affect the entire QMS or patients' rights, safety or well-being, that constitute a potential public health risk, or that represent a serious violation of applicable laws and guidelines.

- **Major non-conformity**

  A major non-conformity is a significant weakness in one or more processes or practices in the QMS or a fundamental weakness in parts of one or more processes or practices that are detrimental to the processes or that could potentially adversely affect patients' rights, safety or well-being, that could pose a potential public health risk, or that represent a violation of existing legislation and guidelines. Major non-conformities are considered as less serious than critical non-conformities.

- **Minor non-conformity**

  A minor non-conformity is a weakness in part of one or more processes or practices that are not expected to affect the QMS, patients' rights or safety and well-being negatively, or represent a violation of existing legislation and guidelines.

References

1. WHO guideline on the implementation of quality management systems for national regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty fourth report. Geneva: World Health Organization; 2020: Annex 13 (WHO Technical Report Series, No. 1025; https://www.who.int/publications/i/item/978-92-4-000182-4, accessed 10 July 2020).
2. ISO 9001:2015(en). Quality management systems – requirements (https://www.iso.org/obp/ui/#iso:std:iso:9001:ed-5:v1:en, accessed 10 July 2020).
3. WHO Global Benchmarking tool (GBT) Rev 6: (https://www.who.int/publications/i/item/9789240020245, accessed 30 June 2020).
4. Quality management system requirements for national inspectorates. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty fourth report. Geneva: World Health Organization; 2020: Annex 5 (WHO Technical Report Series, No. 1025; https://www.who.int/publications/i/item/978-92-4-000182-4, accessed 10 July 2020).
5. ISO/IEC 17025(en). Testing and calibration laboratories (https://www.iso.org/ISO-IEC-17025-testing-and-calibration-laboratories.html, accessed 10 July 2020)
6. ISO/IEC 17020:2012(en). Conformity assessment — Requirements for the operation of various types of bodies performing inspection (https://www.iso.org/standard/52994.html, accessed 10 July 2020)

Further reading

- Guidance on development and implementation of Key Performance Indicators (KPIs) in National Regulatory Authorities (NRAs) (under development)
- WHO Quality management system requirements for national inspectorates. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 5 (WHO Technical Report Series, No. 1025; https://www.who.int/publications/i/item/978-92-4-000182-4, accessed 10 July 2020)

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