

Guidance for Implementing Risk-Based Post-Marketing Quality Surveillance in Low- and Middle-Income Countries



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About PQM

The Promoting the Quality of Medicines (PQM) program is a cooperative agreement between the U.S. Agency for International Development (USAID) and the U.S. Pharmacopeial Convention (USP). The PQM program provides technical assistance to strengthen medicines regulatory authorities and quality assurance systems and supports manufacturing of quality-assured priority essential medicines for malaria, HIV/AIDS, tuberculosis, neglected tropical diseases, and maternal and child health.

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Abbreviations

GFATM	Global Fund for AIDS, Tuberculosis, and Malaria (Global Fund)
HCP	HIV control program
ISO/IEC	International Organization for Standardization and the International Electrotechnical Commission
LMICs	low- and middle-income countries
MAH	market authorization holders
MNCH	maternal, newborn, and child health
MOH	ministry of health
MQM	medicines quality monitoring
NRA	national regulatory authority
NQCL	national quality control laboratory
PQM	Promoting the Quality of Medicines program
QA/QC	quality assurance and quality control
SOP	standard operating procedure
TB	tuberculosis
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO PQ	WHO Prequalification
WHO	World Health Organization

Glossary of Terms

For the purpose of this document, the following definitions (adapted from the World Health Organization) are used.

epidemiology The study of the various factors influencing the occurrence, distribution, prevention, and control of disease, injury, and other health-related events in a defined population, in an effort to understand the etiology (causes) and course of illness and/or disease.

falsified Medical products that deliberately/fraudulently misrepresent their identity, composition, or source.

medicines quality monitoring (MQM) Originally coined by the Promoting the Quality of Medicines (PQM) program to refer to the sampling and testing of medicines to gather information on medicines quality in countries. The information is used to identify medicines quality issues in countries and advocate for the need to develop medicines quality assurance systems.

post-marketing surveillance Surveillance activities that occur following market approval of a medicine, including maintenance of product authorization and/or registration of variations or renewals; regular inspections of manufacturers, wholesalers, distributors, and retailers; quality control testing; pharmacovigilance; promotion control; public reporting of poor-quality products; handling of market complaints; and removal and disposal of non-compliant products. Post-marketing surveillance is typically considered a key regulatory function and refers to the set of comprehensive quality surveillance activities. *Note: For the purposes of this document, this term is used to refer to aspects of surveillance that pertain specifically to medicines quality rather than pharmacovigilance, though active coordination between quality surveillance and pharmacovigilance efforts is strongly recommended.*

quality assurance	An integrated system of activities involving planning, quality control, quality assessment, reporting, and quality improvement to ensure that a product or service meets defined standards of quality with a stated level of confidence.
quality control	All measures taken, including the setting of specifications, sampling, testing, and analytical clearance, to ensure that raw materials, intermediates, packaging materials, and finished pharmaceutical products conform with established specifications for identity, strength, purity, and other characteristics.
quality survey	Serves as a source of information about the quality of medicines available to patients at a point in time. However, quality surveys rely on laboratory testing and cannot offer complete assurance that medicines are safe and effective.
screening technologies	The qualitative and/or quantitative technologies that could rapidly acquire preliminary analytical information or data on the quality of medical products in the field.
sentinel sites	Communities from which in-depth data are gathered and the resulting analysis is used to inform programs and policies affecting a larger geographic area. Sentinel sites are a limited number of selected reporting sites from which the information collected may be extended to the general population. Sentinel surveillance systems are useful because a rich source of data collected from the sentinel sites enables more accurate estimation of a risk than that available from broader passive surveillance programs.

**simple random
sampling**

Random sampling is a probability-based sampling technique whereby a group of subjects is selected (a sample) for study from a larger group (a population). Each subject is chosen entirely by chance, and each has an equal (or non-zero in the case of complex random sampling) chance of being included in the sample. This technique differs from convenience sampling, which is a non-probability sampling technique and is therefore prone to biases. Convenience sampling may, however, be suitable for identifying potential areas with a high risk of poor-quality medicines so that further sampling can be conducted.

**stratified random
sampling**

A probability sampling method in which the population is divided into non-overlapping subgroups (strata) and then a probability sample (often a simple random sample) is drawn proportionally from within the different strata.

substandard

Also called “out of specification,” refers to authorized medical products that fail to meet either their quality standards or specifications, or both.

unregistered

Medical products that have not undergone evaluation and/or approval by a national or regional regulatory authority for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

Program Background

Since 1992, the U.S. Pharmacopeial Convention (USP) has worked cooperatively with the U.S. Agency for International Development (USAID) to help developing countries address critical issues related to pharmaceuticals. The earliest program, the Rational Pharmaceutical Management Project, implemented and evaluated country-specific drug information resource programs in selected developing countries. The Drug Quality and Information program that followed brought efforts to improve medicines quality control (QC) and quality assurance (QA) systems to the forefront.

Building on these previous efforts, the Promoting the Quality of Medicines (PQM) program helps to ensure the quality, safety, and efficacy of medicines essential to USAID priority health areas, particularly malaria, HIV/AIDS, tuberculosis (TB), and maternal and child health. The PQM program is USAID's response to the growing development challenge posed worldwide by substandard and falsified medicines. There is increasing recognition of the threat these poor-quality medicines pose to public health, especially in low- and middle-income countries (LMICs), and their potential to undermine decades of investments in global health, including those made by USAID.

Using a systems-based approach, PQM offers technical assistance to LMICs that is tailored to the needs of individual countries or regions. This includes building the capacity of national regulatory authorities (NRAs) to review and approve quality-assured essential medicines and strengthening their ability to protect their own population from poor-quality medicines through medicines evaluation, manufacturing inspection, and surveillance. PQM helps NRAs implement or improve post-marketing surveillance programs and trains NRA staff in sampling and testing. Samples are first screened in the field using tools such as GPHF-Minilab™, followed by confirmatory laboratory testing of samples that pass field-based screening. PQM also supports national quality control laboratories (NQCLs) through hands-on training and technical assistance to improve laboratory standards, in part to assist those laboratories in attaining internationally recognized certifications, such as International Standardization Organization (ISO) accreditation and/or World Health Organization Prequalification (WHO PQ). PQM uses a systems-based approach that also extends to medicines manufacturers. PQM helps manufacturing companies improve their compliance with good manufacturing practices and develop dossiers to submit to the WHO PQ program.

Over 25 years of collaboration with USAID, USP has supported more than 40 countries in Africa, Latin America, and Asia to improve the quality assurance of medicines.

01 Introduction

Substandard and falsified medicines can cause treatment failure and adverse reactions, increase morbidity and mortality, and contribute to the development of drug resistance. Vulnerable populations and patients with comorbidities are at particular risk of being harmed from receiving substandard or falsified medicines. These poor-quality medicines also increase health care costs to both patients and the health system as a whole, wasting resources that could otherwise be used to benefit public health.¹

Strong national post-marketing surveillance programs capable of monitoring the overall quality and safety of medical products (e.g., medicines, vaccines, devices, and diagnostic kits) and responding to public health risks can help protect citizens from the threats posed by substandard and falsified medicines. Post-marketing surveillance is fundamental to the effective regulation of medicines and includes all regulatory activities that monitor the effectiveness, safety, quality, and use of medicines on the market.*

The Lancet Commission's article "Essential Medicines for Universal Health Coverage" emphasizes that achieving sustainable development requires a concerted effort to improve the quality and safety of medicines. The Commission identified five critical areas of opportunities for improving the quality and safety of medicines, including enhanced surveillance of medicines in the market and the involvement of several stakeholders, beyond just the NRA, in the surveillance of quality and safety of medicines.²

However, many low- and middle-income countries have regulatory systems that are under-resourced, lack an effective or enforceable legal mandate, and/or have insufficient capacity to address the challenge of keeping substandard and falsified medicines from reaching patients.³ In most LMICs, post-marketing surveillance of medicines quality is often limited to sporadic surveys or the collection of medicines samples as part of routine inspections, and these samples may not be tested properly. In addition, the data collected from these samples are often not analyzed or interpreted appropriately due to poor planning, unclear surveillance objectives, and/or limitations in sampling or testing methodology. This means that while NRAs may be spending significant resources to sample and test medicines, these efforts often result in poor-quality data that cannot be used for evidence-based decision-making.

* Note to the reader: For the purposes of this document, the term post-marketing surveillance is used to refer to aspects of surveillance that pertain to medicines quality rather than pharmacovigilance.

Implementation Challenges for Post-Marketing Surveillance Programs

Major gaps remain in establishing effective and robust post-marketing surveillance programs in LMICs. Many NRAs concentrate their major activities on premarket authorization and inspections, while the post-marketing surveillance component often lacks appropriate planning and resources. Box 1 provides additional detail on the key challenges that may be encountered when establishing and maintaining post-marketing surveillance programs in LMICs.

Box 1. Common challenges for implementing post-marketing surveillance programs in LMICs

Legal mandate and governance

- ▶ Absence of legal basis for post-marketing surveillance in national regulations
- ▶ Post-marketing surveillance is not considered a core regulatory function
- ▶ Regulations do not support a shared sense of responsibility among market authorization holders, manufacturers, importers, and wholesalers in ensuring the quality and safety of products

Financing

- ▶ Limited in-country financial resources allocated for post-marketing surveillance
- ▶ Budget priorities are focused on ensuring the availability of and access to medicines, but often are not allocated to maintain the efficacy, safety, and quality of those medicines

Human resources

- ▶ Lack of qualified personnel to manage post-marketing surveillance programs at NRAs
- ▶ Limited NQCL capacity to properly test medicines samples

Management and planning

- ▶ Medicines safety activities are often limited to adverse drug reactions monitoring and reporting
- ▶ Post-marketing surveillance of medicines is often limited to scattered medicines quality surveys funded mostly by donors, or a number of medicines samples collected randomly as part of inspections by NRAs
- ▶ Efforts to strengthen post-marketing surveillance or related aspects of QA/QC may be conducted by multiple stakeholders, with fragmented, overlapping, or uncoordinated activities
- ▶ Lack of international model guidelines to support LMICs in building integrated, effective, and sustainable post-marketing programs

Sampling and testing methodology

- ▶ Surveillance conducted without predefined objectives or with objectives that are unclear
- ▶ Sampling methodology not well defined, justified, or planned
- ▶ Sampling methodology does not properly account for biases
- ▶ Medicines testing is not performed according to registration specifications or compendial standards and/or does not follow good laboratory practices
- ▶ Data quality is poor and cannot be used for evidence-based decision-making

Coordination and communication

- ▶ Poor coordination and information sharing among involved stakeholders
- ▶ Data are not shared or disseminated appropriately and are not used to inform decision-making

The challenges faced by LMICs are far from uniform, and the challenges encountered in one country may not be present in another. In addition, some countries have invested

more heavily in developing post-marketing surveillance, while others may be just beginning to develop their surveillance capacity. The country profiles described below (Table 1) provide examples of actual challenges faced by countries that are at different stages of developing post-marketing surveillance programs.

Table 1. Three countries at different stages of developing post-marketing surveillance programs

	Country A	Country B	Country C
Status of post-marketing surveillance program			
Legal mandate/ basis for program?	Yes	Yes	No
Post-marketing program established?	Yes	Post-marketing surveillance directorates exist within NRA, but formalized activities are lacking.	No
Program funded by govt. allocations?	Yes	Activities primarily done as part of inspections. Other post-marketing surveillance activities are mostly donor funded.	Post-marketing surveillance conducted as part of inspections. Some activities occur through donor funding.
Number of accredited QC labs (ISO 17025 or WHO PQ)	30+	<5	1
Key challenges			
Sampling and testing	<ul style="list-style-type: none"> ▶ Limited to a small number of registered medicines ▶ Limited to private facilities ▶ Limited to certain tests (identification, assay, dissolution) 	<ul style="list-style-type: none"> ▶ Sampling of medicines not prioritized/risk- based ▶ Post-marketing surveillance activities lack clear objectives 	<ul style="list-style-type: none"> ▶ Sampling of medicines not prioritized/risk-based ▶ Activities focus mainly on comparing locally produced products to imports
Coordination	Activities occur at central level; little coordination with provincial or other stakeholders	Key stakeholders not involved in post-marketing surveillance activities	Post-marketing surveillance activities conducted by NRA with little coordination among other stakeholders
Data sharing and use	Data not shared with key stakeholders and often not used to inform decisions	Data not managed, shared, or used appropriately	Data not managed, shared, or used appropriately
Efforts to strengthen post-marketing surveillance			
	Post-marketing surveillance being piloted in public sector by working with health programs, other stakeholders		Post-marketing surveillance plans developed for additional priority medicines with extensive consultation with stakeholders.

Table 1 highlights why interventions used in one country may not be suitable in another. It also makes clear that step-wise, incremental changes are preferable, given the limited resources available to strengthen post-marketing surveillance programs. These limited resources, combined with varying levels of in-country capacity, and the staggering volume of medicines to be tested, emphasize the need for risk-based approaches that consider and assess multiple types of risk factors and prioritize activities accordingly. These risks include those that are associated with the product itself, the manufacturing process, the target population, the public health impact, and the geographical area, among several other factors.

PQM's Role in Addressing Medicines Quality Issues

USAID provided funding to USP (first through the Drug Quality and Information program, and later through the PQM program) to support countries in building capacity to monitor the quality of medicines. Using sentinel sites and basic tests, countries were successful in identifying both the presence of substandard and falsified medicines and the extent to which they were infiltrating their markets. In collaboration with WHO, USP generated evidence on the presence of falsified medicines in Southeast Asia and Africa. These medicines quality monitoring (MQM) programs first assessed the quality of antimalarial medicines and were subsequently expanded to include medicines for HIV/AIDS; tuberculosis; and maternal, newborn, and child health (MNCH). In the Greater Mekong subregion, for example, PQM collected and tested nearly 4,000 samples of antimalarial, anti-TB, and antiretroviral medicines (ARVs). The average initial failure rates were around 6 percent, a figure that decreased steadily at the sites monitored.⁴

In parallel, USP provided support to help strengthen the capacity of QC laboratories to achieve compliance with international standards, such as WHO PQ and/or ISO 17025 accreditation. Strengthening regulatory systems and QC laboratories in tandem ensures that the results of quality surveillance are accurate and reliable, and that those results can be used to make informed regulatory decisions and take appropriate enforcement actions.

“ In the Greater Mekong subregion, for example, PQM collected and tested nearly 4,000 samples of antimalarial, anti-TB, and antiretroviral medicines (ARVs). The average initial failure rates were around 6 percent, a figure that decreased steadily at the sites monitored.”

Despite these strides, many countries have yet to incorporate medicines quality activities into a national post-marketing surveillance program as a core regulatory function. Many MQM activities continue to rely on donor funding. Additional donor support is necessary to maintain the achievements to date and to take steps toward making these activities institutionalized and sustainable through post-marketing programs that are incorporated as a core function of the regulatory system.

Risk-Based Approach to Post-Marketing Surveillance

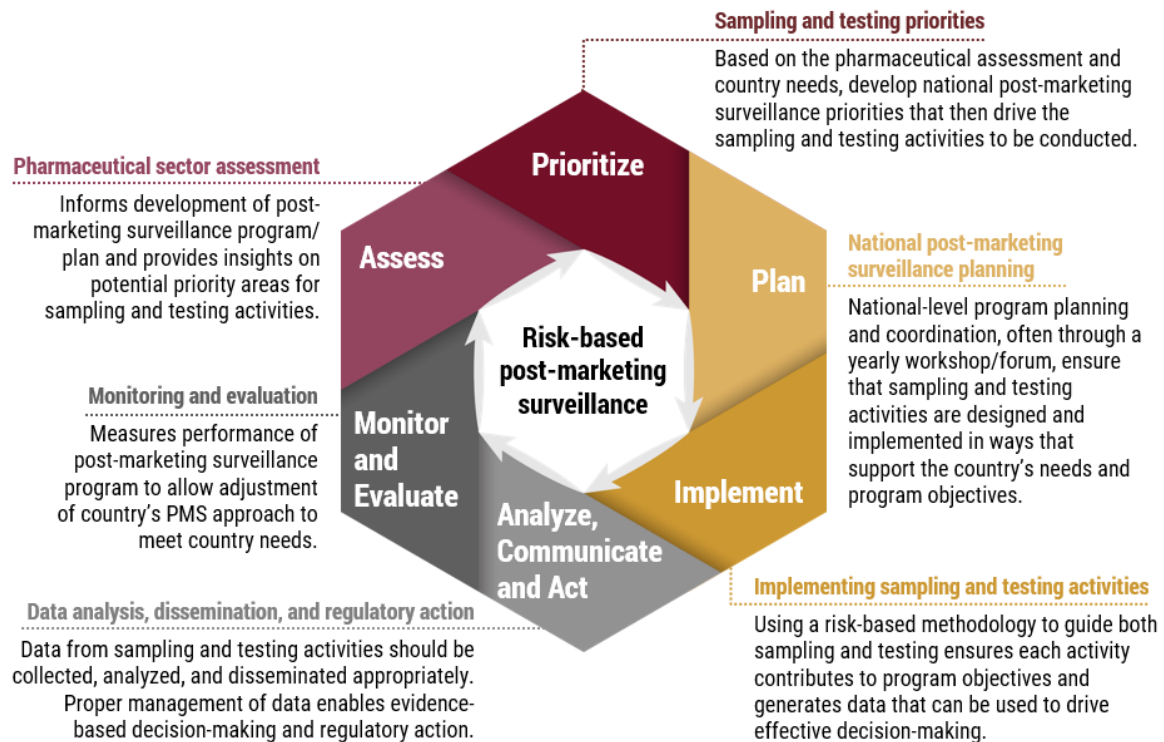
To help address the above gaps, the PQM program, through extensive consultation with international experts, has developed this document to guide the implementation of comprehensive risk-based post-marketing surveillance programs in LMICs. This guidance document is informed by lessons learned from 25 years of USP supporting more than 40 countries in Africa, Latin America, and Asia to improve the quality assurance of medicines. We also draw from published literature on medicines quality and reference guidance from major international organizations and donors, including WHO.

Although some countries may already conduct ad hoc quality surveys, this guidance document is intended to help countries design and implement technically sound, strategic, and sustainable risk-based post-marketing surveillance programs that are responsive to unique country contexts and needs.

Moving from sporadic medicines quality monitoring activities toward robust risk-based post-marketing surveillance programs is critical for a country to ensure the quality of medicines and medical products. Effective risk-based post-marketing surveillance programs can also optimize the use of resources and support countries in transitioning from donor-supported surveys to locally funded and sustainable post-marketing surveillance programs that are integrated and implemented as a core regulatory function.

The graphic below (Figure 1) depicts the key aspects of developing and implementing a risk-based post-marketing surveillance program.

Figure 1. Framework for developing and implementing post-marketing surveillance programs



Purpose of this Guide

This guide provides information for regulatory authorities in LMICs to begin executing post-marketing surveillance as a core regulatory function. It may also be used by regulatory authorities that already have such programs but are looking for ways to optimize resources using a risk-based approach. Each aspect of the risk-based post-marketing surveillance approach is covered in additional detail throughout this document.

- ▶ **Section 2** provides information to help LMICs *Assess* local needs, *Prioritize* post-marketing surveillance objectives, and *Plan* for implementation.
- ▶ **Section 3** describes how the risk-based approach is used to *Implement* post-marketing surveillance programs.
- ▶ **Section 4** introduces and describes a PQM-developed risk-based post-marketing surveillance tool, Medicines Risk-based Surveillance (MedRS), that can assist countries in objectively identifying the most susceptible medicines, determining the number of samples required to achieve statistical significance, and prioritizing sampling at the most vulnerable locations.
- ▶ **Section 5** outlines considerations to *Analyze, Communicate, and Act* on sampling and testing data.
- ▶ **Section 6** describes key indicators that regulatory authorities may use to *Monitor and Evaluate* their post-marketing surveillance programs.

Although this guidance focuses on quality surveillance aspects of post-marketing surveillance, it also recognizes that strong coordination with medicines safety (pharmacovigilance) activities is critical for the effective regulation of medicines.

02

Establishing a Post-Marketing Surveillance Program

This guide proposes the development of a national post-marketing surveillance program that consists of a series of medicines quality sampling and testing activities each with an objective dictated by a country's specific needs. Each sampling and testing activity is established with its own yearly plan developed in consultation with relevant stakeholders. Post-marketing surveillance and the associated sampling and testing activities should be coordinated and owned by the NRA and designed to address predefined objectives. The national post-marketing surveillance program should be reviewed, updated, and revised yearly.

An assessment of the pharmaceutical sector and existing QA/QC capacity is a necessary starting point to identify sampling and testing priorities and to identify the stakeholders to be involved in initial planning. This assessment informs the design of the post-marketing program as a whole and helps identify potential objectives for the sampling and testing of medicines. Risk-based approaches should then be applied at each step to optimize sampling and testing and make the most of resources without compromising data quality.

The WHO document *Guidelines on the Conduct of Surveys of the Quality of Medicines* (WHO-TRS number 996, 2016) describes how to conduct a medicines quality survey.⁵ The WHO guidelines discuss general points of consideration for medicine and site selection and sampling and testing methodology. In this guide, we aim to assist NRAs to establish post-marketing surveillance programs or transition existing medicines quality monitoring activities into coordinated and cohesive national-level risk-based post-marketing surveillance programs based on existing country resources and local needs.

Post-marketing surveillance and the associated sampling and testing activities should be coordinated and owned by the NRA and designed to address predefined objectives.

General Considerations for Effective Post-Marketing Surveillance

Legal Mandate

The legal provisions, regulations, and guidelines that constitute the regulatory framework for implementing national post-marketing surveillance activities must be in place. The law must clearly stipulate the NRA's authority to establish, implement, and periodically update post-marketing surveillance programs. NRAs should consider post-marketing surveillance a key standalone regulatory function with a legal basis in the national laws and regulations and should establish a dedicated post-marketing surveillance department/unit within the NRA. Additionally, a coordination mechanism should be established between the medicines safety and medicines quality teams. Mechanisms should also be put in place to monitor the performance of the NRA and promote transparency, accountability, and communication. Medicines regulations should promote a shared responsibility for assuring the quality, safety, and efficacy of medicines across procurement agencies, manufacturers, importers, wholesalers, and retailers of medicines. Market authorization holders (MAHs) should be held responsible for products on the market.

Governance

Effective post-marketing surveillance requires good governance mechanisms that are accountable, transparent, responsive, equitable, inclusive, consensus oriented, and effective, and that follow the rule of law. Strong regulations promote good governance and transparency in medicines supply chains. The NRA should have a sound governance structure that promotes an effective organization with clearly defined roles and responsibilities and documented standard operating procedures (SOPs).⁶ Regulators should be accountable to the public while remaining independent from the influence of government or industry in making decisions.

Financing

Governments and NRAs should provide adequate resources for the sustainability of post-marketing surveillance activities, including regulations, processes, budgetary provisions, and human and technical resources for the implementation of an effective post-marketing surveillance strategy. Each sampling and testing activity should have an approved protocol with specific objectives, an approved plan, and a budget. The NRA should mobilize the required funds before starting any sampling and testing activity. The regulatory system and the NRA should use a comprehensive risk assessment to optimize the use of limited resources, including financial and human resources, in the areas that need them the most. Risk-based approaches should be used to determine the types of medicines that will be sampled, the sampling locations, the sample size, and the appropriate analytical test to perform. Using risk-based methods can significantly reduce both sampling and testing costs.

Human Resources and Capacity

Qualified and proficient staff with relevant education, training, skills, and experience should be assigned to perform regulatory activities. The duties, functions, responsibilities, necessary competencies (education, training, skill, and experience), and specific policies should be clearly defined and updated as needed. A code of conduct, including management of conflicts of interest, should be shared with and followed by

NRA staff and external experts. Capacity development is critical in making post-marketing surveillance sustainable and, as such, a training plan for staff should be developed, implemented, and updated periodically. NQCLs that perform medicines quality testing should comply with international standards and guidelines, such as ISO 17025 or WHO PQ, to ensure the reliability and accuracy of test results. Field-level staff should also be trained appropriately by the NRA and/or NQCL to perform field-level visual inspection or testing of medicines. Finally, medicines quality and post-marketing surveillance topics should be incorporated in relevant health-related training programs, including those for pharmacy, laboratory, and regulatory affairs.

Management and Planning

National post-marketing surveillance activities should be planned and executed annually, using a risk-based approach to determine sampling and testing priorities across different medical products in the public, private, and informal medicines supply chains. Post-marketing surveillance activities should also include public reporting of suspected substandard and falsified medical products, handling of market complaints, control of promotion of pharmaceutical products, detection of and action against substandard and falsified medicines, removal and disposal of defective and noncompliant medical products from the market, and implementation of corrective and preventive actions.

Sampling and Testing

Based on the post-marketing surveillance objectives, prioritized according to a country's specific needs, sampling and testing should be conducted using well-defined methodology that is effective and can be rationalized. Risk-based sampling methods should be used to target activities to areas and medicines that are most vulnerable and represent the greatest risk to public health. Similarly, resources should be optimized by using tiered approaches to testing (such as the Three-Level Approach, discussed in Section 3).

Risk-based sampling methods should be used to target activities to areas and medicines that are most vulnerable and represent the greatest risk to public health."

Coordination and Communication

To implement effective post-marketing surveillance programs and activities, NRAs must coordinate closely with all stakeholders involved directly or indirectly with medicines manufacturing, importation, exportation, and wholesale, and also relevant nongovernmental organizations (NGOs), donors, and other partners. For each sampling and testing activity, coordination with relevant stakeholders should lead to establishing a plan with well-defined roles and responsibilities for all parties involved. The plan should cover all post-marketing surveillance activities: sampling, testing, data analysis, data reporting, and follow-up actions.

Mechanisms should be in place to ensure involvement and communication among relevant stakeholders and the various departments/units within the NRA. Similarly, the NRA should hold public consultations during the development or revision of regulations and guidelines relevant to the national post-marketing surveillance program. Published regulations and guidelines should be made available to all stakeholders after publication. Similarly, post-marketing surveillance activities should be communicated within departments of the NRA (e.g., laboratory, inspection, and enforcement) and among relevant stakeholders, countries, and international organizations as appropriate.

Sustainability

Ensuring that a post-marketing surveillance program is supported by appropriate legal frameworks, staffed with a qualified and proficient regulatory workforce, and financed through regular and adequate national budget appropriations, helps ensure continued operational sustainability. Regular strategic planning efforts with key stakeholders are also critical in ensuring that approaches, assumptions, and priorities for the post-marketing surveillance program remain relevant over time.

In some cases, regional cooperation and coordination can strengthen local regulatory capacity where an NRA may not have sufficient resources to fully implement regulatory processes or functions. Official Medicines Control Laboratory (OMCL) networks, for example, can provide medicines quality testing services to several countries within a region to support post-marketing surveillance efforts.

Conducting a Pharmaceutical Sector Assessment

Prior to initiating a post-marketing surveillance program, and periodically as needed during regular planning processes, conducting a pharmaceutical sector assessment can help inform the development of post-marketing surveillance goals, objectives, and activities. The data collected can provide insight on potential medicines, regions, and locations for medicines sampling and testing activities and also serves to ensure post-marketing activities remain relevant to local needs and priorities.

An assessment should include a review of local QA/QC capacity, the systems in place to ensure quality across the life cycle of medicines (including systems that facilitate selection, procurement, registration, storage, distribution, and rational use), the applicable and relevant medicines laws and regulations, and relevant sectors related to medicines quality (e.g., manufacturing, importation, wholesale, and retail medicine markets). Specifically assessing the QC capacity at the NRA is critical and should include a review of the agency's capacity for key regulatory functions, such as licensing; inspections; control of import and export of medicines; enforcement; and control of facilities, practices, and professionals. As part of the assessment, all relevant QA/QC stakeholders in country should be mapped out with each stakeholder's role in quality assurance clearly defined. This list should be reviewed and updated regularly.

The data obtained from the pharmaceutical assessment may be used to identify relevant gaps in capacity that can be studied further through the post-marketing surveillance program and can help begin to develop national surveillance needs and testing priorities.

Determining Medicines Quality Sampling and Testing Priorities

The capacity and effectiveness of medicines quality assurance programs in LMICs vary from country to country; however, there are a number of critical areas where LMICs can consider prioritizing their post-marketing surveillance activities. Based on the results of the pharmaceutical assessment, each country should identify its unique sampling and

testing needs. These priorities form the basis for activities conducted within the post-marketing surveillance program and help shape sampling and testing protocols and study designs.

Below are examples of sampling and testing priorities that may be highly relevant for LMICs:

- ▶ Monitoring medicines that are new to the market, especially brand name products.
- ▶ Monitoring medicines based on the risks associated with manufacturing complexity, dosage form, stability (e.g., temperature sensitivity), safety/efficacy (e.g., narrow therapeutic window), demand (e.g., high-burden diseases), therapeutic indication (e.g., infectious diseases), or other factors.
- ▶ Monitoring the quality of medicines at key ports of entry. This type of monitoring serves as a first-line intervention, has been shown to deter the trading of poor-quality medicines, and requires close collaboration among the regulatory, customs, and law enforcement authorities.
- ▶ Monitoring medicines to meet specific donor requirements (e.g., the Global Fund).
- ▶ Coordinating with ongoing sampling and testing initiatives, such as:
 - Sampling and testing activities conducted by national health programs (e.g., malaria, TB, HIV/AIDS, and MNCH).
 - Donor-led or regional initiatives to address medicines quality issues (e.g., border trading, pilferage from public to private sector).
 - Surveillance activities established by other relevant stakeholders (e.g., manufacturers, importers/exporters, distributors, NGOs).

Based on the results of the pharmaceutical assessment, each country should identify its unique sampling and testing needs.”

Preparing to Implement Post-Marketing Surveillance Programs

The sampling and testing plan must ensure that sampling is unbiased and that data produced are meaningful and accurate in order to be used for decision-making. Sampling and testing programs implemented in countries that follow the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines (e.g., the United States and countries in Europe) typically have the following characteristics:

- ▶ Sampling and testing activities conducted at least once per year.
- ▶ Initial planning under the NRA is coordinated with other stakeholders. The NRA establishes clear procedures and guidelines on how to execute all steps of sampling and testing, including clear definition of roles and responsibilities of all parties involved.
 - NRA leads sampling and testing activity and finalizes the plan of each program.
 - NRA inspectors carry out sampling according to an established and approved plan.

- Official QC laboratories of each country carry out QC tests according to regulations and guidelines (official verified/validated test methods in product dossiers, or pharmacopeial methods).
- Data are analyzed by the NQCL and reported to the NRA which is responsible for sharing with all relevant stakeholders.
- NRA carries out follow-up actions.

A national post-marketing surveillance design workshop can be an effective way of engaging and coordinating with stakeholders before beginning a sampling and testing activity. The objectives of the sampling and testing activity must be clearly identified to ensure that the results can inform regulatory decisions. The roles and responsibilities of all involved parties should be defined, and an appropriate sampling method and protocol should be developed during the planning phase. Medicines sampling must be carried out by trained inspectors according to approved SOPs. The sampling plans should avoid any type of bias or conflict of interest.

The post-marketing surveillance program should be managed by a committee that consists of representatives of the NRA, NQCL, Ministry of Health (MOH), disease programs, and other relevant partners and stakeholders. The committee should be responsible for addressing issues around budget allocation and advocacy for the post-marketing surveillance program. The post-marketing surveillance committee also must establish the task force responsible for implementing the post-marketing surveillance program.



Implementing Risk-Based Post-Marketing Surveillance Programs

Regulatory authorities must constantly balance the risks and benefits of the medicines on their market. In LMICs, the regulatory capacity for evaluating quality risks and applying best practices to mitigate these risks is limited. In addition, financial limitations require LMICs to use resources judiciously when establishing and maintaining systems to ensure patient safety. However, given that countries often face competing issues, medicines quality and safety issues sometimes receive lower priority.

Assuring the quality of medicines is challenging and costly, and requires close collaboration and coordination among many parties. The application of risk-based approaches offers an opportunity for LMICs to establish effective, affordable, and sustainable medicines post-marketing surveillance systems. WHO's *Guideline on the Conduct of Surveys of the Quality of Medicines*[†] and *Draft Guidance on Testing of SSFFC Medicines*[‡] provides normative guidance for conducting medicines sampling and testing surveys.^{7,8} NRAs should see these guidelines for detailed discussion on the selection of medicines, sampling sites, and sampling and testing methodologies. This section complements the WHO guidance and focuses on providing information to assist countries in implementing medicines sampling and testing activities within a national risk-based post-marketing surveillance program. Box 2 reviews key considerations for implementing post-marketing surveillance programs.

Box 2. Key Sampling Considerations

Sampling and testing programs should establish inclusion and exclusion criteria, as well as substitution criteria (including limited or unavailable medicines, and medicines with a limited shelf-life). Substitution criteria should be developed to address the following scenarios when they occur:

- ▶ If the selected sampling outlet is closed
- ▶ If the medicine being sampled is not found in the selected sampling outlet, then the outlet can be substituted by the nearest health institution found in the same area
- ▶ If the medicine is not available or seller is not willing to sell
- ▶ If the medicine in the outlet has less than six months' shelf life
- ▶ When the supply of medicine is limited and the medicine is necessary for life of the patient
- ▶ When the minimum quantity of medicines needed is not available during sampling

[†] WHO-TRS number 996, 2016

[‡] October 2016; WHO Expert Committee on Specification of Pharmaceutical Preparations (WHO QAS/15.635)

Elements of Risk-Based Sampling

Selection of medicines

The number of medicines authorized to be on the market varies from one country to another. Even in small countries, the total number of market authorizations may often be in the thousands. Controlling the quality of all medicines registered is extremely difficult and often unfeasible in LMICs, so applying risk-based approaches to select medicines for sampling and testing as part of a post-marketing surveillance program is imperative. For example, sampling and testing activities could target newly introduced medicines on the market, brand-name medicines with limited safety and efficacy data, medicines with complex formulations, medicines known to have stability issues, medicines to which antimicrobial resistance is increasing, medicines in high demand, or manufacturers or suppliers with previous quality issues. Even within the same disease, risk-based approaches must be applied in selecting the type of medicines to target. The likelihood that poor-quality medicines exist and the potential health impact on patients should be considered.

Selection of geographical area

Controlling the quality of all medicines registered is extremely difficult and often unfeasible in LMICs, so applying risk-based approaches to select medicines for sampling and testing as part of a post-marketing surveillance program is imperative.”

Based on the sampling and testing plan, risk-based selection should first be applied to the geographical areas where the sampling of medicines will be conducted. Such criteria could include poor storage conditions, poor access, high disease burden, population size, porous border zone, level of drug resistance, presence of illicit market, complexity of supply chain, and specific issues reported by prior inspections. Areas with a high risk of compromised medicines quality and/or patient safety should be prioritized. Selection criteria should be identified and applied during the initial planning in

collaboration with key stakeholders and based on NRA knowledge of the medicines supply chain in the country.

Collection sites and sampling methods

Risk-based assessments inform the selection of geographical area and type of medicines to be sampled, and they must be similarly applied to select the sampling sites. Drug distribution in LMICs occurs through public, private, or informal supply chains, each of which carry different risks. Supply chains are also classified as vertical or decentralized based on the proximity (level) of the medicines outlet to the patient. When developing site selection criteria, necessary considerations include the local knowledge of the supply chain for target medicines, the availability and accessibility of target medicines, and information on where patients obtain medicines.

NRAs should map all medicines outlets in the sampling area by name and location. Sampling could be performed using convenience, random, stratified random, or lot quality assurance sampling methods, and may use mystery shoppers or overt sampling depending on the objectives and limitations of the study. Because poor-quality

medicines are regularly found in hard-to-reach and informal outlets in unregulated sectors, it is important to establish sentinel sites in carefully selected locations that pose the greatest risk to the population. Sentinel sites also provide a means for monitoring the impact of interventions aimed at reducing poor medicines quality. It is suggested that samples collected have at least six months until expiry as this allows sufficient time for testing before the product expires.

Number of dosage units per sample, number of samples per medicines per location, total number of samples collected per country, region, or area

Use of the risk-based approaches discussed in previous sections reduces the potential number of samples to collect. However, the number of units to collect per sample depends on the objectives of the sampling and testing activity, the type of medicine, the planned tests to be applied, and the approved medicine specification. Another risk-based approach, the Three-Level Approach,⁹ can assist in prioritizing the number of units needed for testing and reduce the cost associated with testing. The Three-Level Approach is a stepwise process developed by PQM that “extends the QC of medicines beyond an established laboratory by the systematic and successive initial use of two additional levels of assessment—visual/physical inspection and screening testing.”¹⁰ In the Three-Level Approach, Level 1 refers to the initial visual inspection, Level 2 refers to field-based screening, and Level 3 refers to compendial testing.

Handling, storage, and transportation of samples

As part of sample selection criteria, countries should consider the chain of custody required to preserve the integrity of each medicine from the collection sites to the location where quality testing will occur. Inappropriate handling, storage, and transportation of samples affect the overall integrity of medicines and can compromise results. This is particularly true for medicines that have poor stability profiles and/or require cold chain transportation. It is important to observe the following best practices throughout the chain of custody of the products:

- ▶ Avoid excessive mechanical vibration during transportation.
- ▶ Store in original container, where available, and label accordingly.
- ▶ Store away from sunlight and excessive humidity.
- ▶ Label each sample with the location of collection, number of samples collected, name of the sampler and any observation at the time of collection.
- ▶ Samples that are light or heat sensitive may require special handling, transportation, and storage conditions. If cold storage is indicated, store in an appropriate container and monitor the temperature during transportation.

In addition to the general storage and distribution requirement, different levels of the supply chain may require different storage and handling procedures. A public sector supply chain, for example, typically comprises the central medical store, district hospitals, health centers/pharmacies, informal outlets, and virtual outlets. To conduct risk-based sample collection and testing, when quality failure is observed at the central medical store, it may not be necessary to sample at other levels. On the other hand, when quality failure is observed at the district hospital, it may be necessary to sample at the central medical store to determine the effect of transportation on the medicines distribution network in the country.

Lot sampling and testing

Lot sampling and testing is suitable for use at ports of entry, warehouses, manufacturers, and import consignments. In lot sampling, sampling is not limited by the number of units per sample; instead, the individual lots manufactured are sampled for testing. Whenever possible, sampling and testing of medicines lots before distribution establishes a baseline of quality for the product and could lead to a significant reduction of the sampling and testing cost when samples are collected from the supply chain later during post-marketing surveillance. Testing before distribution is feasible only if countries closely coordinate post-marketing surveillance plans with medicines procurement and distribution cycles.

Risk-Based Approach to Testing

Medicines quality testing is an important component of post-marketing surveillance in LMICs. However, due to limited technical capacity and the high cost of establishing a functional NQCL, regulatory agencies can follow a risk-based approach to medicines testing. Because of the reliance on analytical testing results to inform regulatory or public health decisions, testing of medicines should be done by qualified QC laboratories according to authorized specifications. Depending on the objectives of each sampling and testing activity, implementing a tiered approach to testing can drastically reduce the number samples to be collected and the types of tests to be performed without affecting the overall quality of post-marketing surveillance. For instance, if the objective of a specific sampling and testing activity is to assess the stability of medicines at different levels of supply chain (i.e., storage conditions), then it may not be necessary to conduct full compendial testing at each level of the system. If identification, disintegration, and dissolution tests were determined for samples at the central level, samples at the district level may only benefit from testing related substances rather than repeating the previously conducted tests. On the other hand, if the initial screening of the sample from the district level showed discoloration, it may not be necessary to conduct additional compendial testing of the sample.

Most LMICs have limited testing capacities and lack a fully functional NQCL. However, the lack of an NQCL must not be a barrier to developing a robust sampling protocol. As such, some approaches, for example WHO TRS 996 and QAS 15.634, suggest the use of a tiered approach to laboratory testing. In addition, various advanced analytical techniques have been suggested, but these techniques may not be available in developing countries.

This guideline also recommends the use of a tiered approach to testing as part of post-marketing surveillance and builds upon and refines PQM's Three-Level Approach which proposes that testing can occur at three levels: in the field, initially through visual inspection; then through field-based tests (using the Minilab™ or other screening tools); and finally at the laboratory as required (using compendial or other methods accepted by the NRA). Table 2 provides a summary of these tests and the potential product quality issues that can be detected by each test. Use of the Three-Level Approach allows countries to

“ Significant risk to patients can be mitigated with simple cost-effective visual inspection and screening tools.”

screen a large number of samples across many geographic areas at limited cost. The use of basic analytical tests in the field (e.g., GPHF Minilab™) could significantly reduce the number of units required per sample, as only a subset of medicines are tested in QC laboratories using compendial methods. For example, in their effort to institutionalize post-marketing surveillance, some countries have incorporated Minilab™ field-based screening in their sampling and testing activities, while others with a very limited testing capacity have implemented the visual inspection of selected medicines on the market. As a result, several falsely-labeled antimalarial medicines were detected and removed from circulation. This shows that significant risk to patients can be mitigated with simple cost-effective visual inspection and screening tools.

Table 2. Select tests to detect product quality issues

Test	Possible product quality issue	Comments
Visual inspection	Falsely or incorrectly labeled, poor appearance, unregistered	Comparison with innovator or registered products in the country. Medicines Registration Database is a good source of information.
Identification	Incorrect or absent active ingredient	Techniques vary depending on capacity and technology.
Assay Uniformity of dosage unit	Quantity of active ingredient inconsistent with claim on label	See Pharmacopeia sections on uniformity of dosage units, QAS 15.635.
Disintegration Dissolution	Dosage form performance	Harmonized across pharmacopeias – USP, EU, etc.
Related substances/ Impurities	Degradation or impurities	Product specific – Refer to pharmacopeial or other standards.
Endotoxin Sterility Foreign particulate matter Viscosity pH	Toxicity or contamination of liquid and sterile formulation	Microbial testing may be necessary when available or outsourced

Visual inspection (Level 1)

Simple visual inspection may identify important characteristics related to product quality (registration status, expiry, product packaging, etc.) or issues with the physical characteristics of the dosage form (presentation, color, texture, and viscosity, etc.). Testing at this level can be primarily performed in the field at the point of sampling and can be used to identify falsified, substandard, unregistered, or incorrectly labeled medicines. For example, if a box of aspirin is discolored and moldy, immediate action is warranted rather than additional field screening or compendial testing. This initial screen should be mandatory and performed on all collected samples. Failed samples can, in some cases, be omitted from further testing, which reduces the costs associated with post-marketing surveillance.

Figure 2 provides a flow diagram for conducting visual screening. Before assessing other aspects of quality, inspectors should confirm that the product is registered with the appropriate and relevant regulatory authority and has not expired. When unregistered or expired products are detected, inspectors should discuss the findings with the regulatory

authority to determine appropriate next steps. Depending on the objective of the study, further assessment of the quality of the product may be warranted.

Visual inspection can also include an assessment of the product label, packaging, and presentation. Inspectors may review the batch number, scientific name, company logo, number of units per container, dosage form, strength, manufacturer address, presence of a package insert, integrity of packaging, color, texture, presence of particulates, and other characteristics. Ensuring that inspectors have access to a current medicines registry or other visual inspection tools is critical to effectively supporting the detection of quality issues at Level 1.

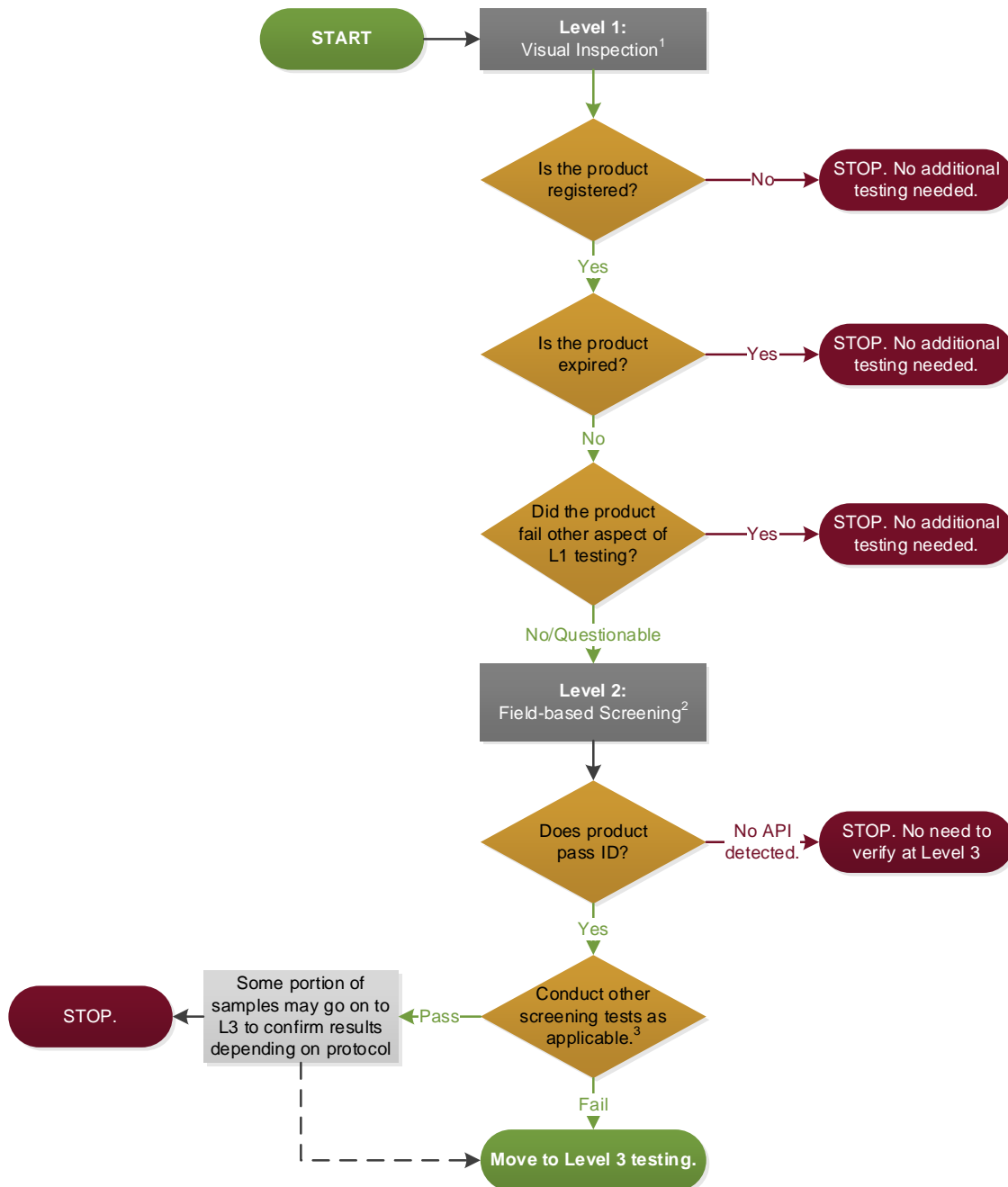
Products that fail some aspect of visual inspection should be discussed with the regulatory authority to determine appropriate action. In some cases, the regulatory authority may choose to seek clarification with the manufacturer, proceed with other aspects of quality testing, or take other decisions based on the results presented at Level 1. If the product passes visual inspection or if a determination cannot be made (e.g., deviations are not clearly discernable against expected product presentation), then the product should proceed to testing at Level 2.

Field-based screening (Level 2)

Level 2 involves analytical testing of product quality using field-based screening technologies. Field-based screening technologies can identify potential product quality issues that may not be apparent at Level 1 and can further reduce the number of samples that require compendial testing (Level 3). Suspicious samples identified by visual inspection may undergo further screening (Figure 2) using one or more advanced screening tests, such as thin-layer chromatography and Raman and/or near infra-red (NIR) spectroscopy (using portable or handheld spectrometers). More information on advanced screening is available in the *Guideline to Establish MQM program, PQM, 2010*.

This level of test is qualitative to semi-quantitative and, depending on the capability of the screening technology utilized, provides information on the identity of the active ingredient, possible degradation, and/or impurities. Depending on the objective of the sampling and testing protocol, a product that passes identification and other applicable field-based screening provides sufficient information and eliminate the need for additional testing. Alternatively, based on which screening tools are used and the tests performed, the regulatory authority may choose to send a portion of the passed samples for compendial testing (Level 3) to confirm the results. Samples that fail field-based screening tests may be retested at the compendial level to confirm results.

Figure 2. Guidance for visual and field-based screening (Levels 1 and 2)



Footnotes:

¹Level 1: Visual inspection to include assessment of registration status, expiration date, labelling, batch number, scientific name, company logo, number of units per container, dosage form, strength, manufacturer's address, presence of a package insert, damage to packaging.

²Level 2: Field-based screening may include assessment of a product's identity (ID) and other screening tests as applicable.

³If a product passes identification, additional tests should be prioritized in the following order: content, disintegration, and impurities.

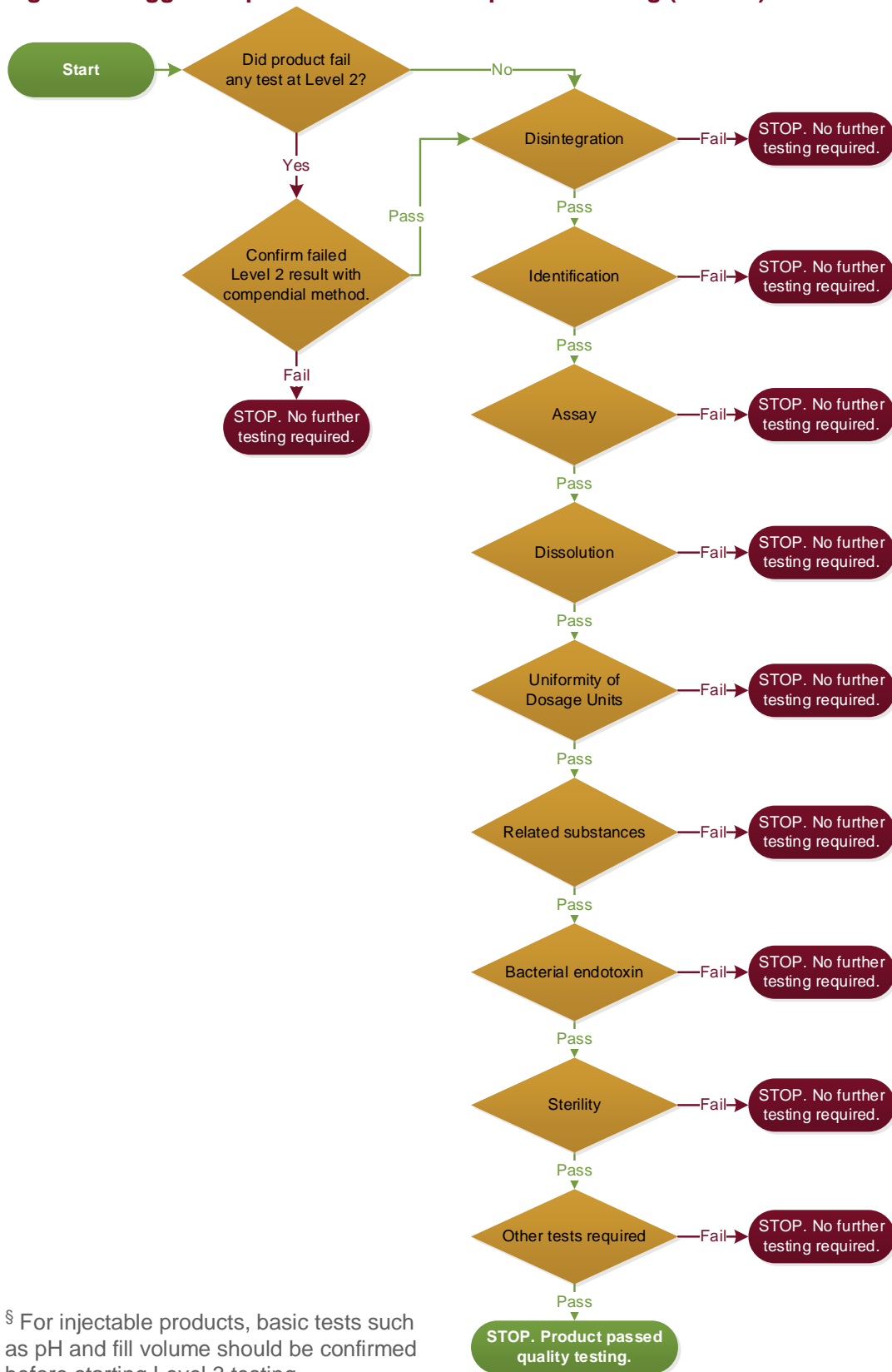
Compendial testing (Level 3)

Compendial testing provides the most extensive information on product quality, but it is also the most complex, expensive, and time-consuming type of testing. Using a risk-based approach in the development of the study protocol, collection of samples, and testing of samples through the Three-Level Approach can reduce the number of samples that need to be tested using compendial methods, and can therefore reduce the costs associated with conducting sampling and testing activities.

Compendial testing should be carried out on suspected samples that fail field-based screening tests and, depending on the protocol, on a portion of samples to confirm the results from Level 2. Figure 3 proposes a scheme for prioritizing compendial testing based on the type of product being tested, the risk associated with samples, the costs associated with particular tests, and the technical complexity. The use of pharmacopeial methods or other validated methods approved by the NRA is recommended. Note that if a product fails a test at Level 2 (for example, the sample does not pass disintegration), the same test should be performed at Level 3 using compendial methods before initiating tests for other quality attributes. If the result from Level 2 is confirmed at Level 3, then no further testing is needed. If, on the other hand, conducting the same test using compendial methods does not confirm the result from Level 2 testing, it is recommended that the analyst proceed with the suggested prioritization of compendial tests as outlined in Figure 3.

The approach described in Figure 3 is not intended as a list of compendial test requirements, and does not include every testing scenario that one may encounter. Rather, the flow diagram is meant to illustrate the *prioritization of analytical tests* to guide the sequence for testing the majority of medicines samples, as applicable. The suggested prioritization takes into consideration the resources, time, materials, and number of samples required to perform each test. Depending on the dosage form, formulation, or other considerations, appropriate adjustments to this sequence may be necessary. For example, if the product being tested is an injectable, disintegration and dissolution tests are not applicable and should be skipped. Additionally, for products procured by the Global Fund or similar organizations with sound quality assurance measures in place (i.e. products are only procured from WHO prequalified or stringent regulatory authority approved sources and pre-shipment lot testing is conducted), a selection of appropriate compendial tests may be considered based on the where in the supply chain samples were collected. For instance, if samples from a Global Fund-procured lot were collected from the port-of-entry, then performing an assay of the sample may be sufficient. Similarly, if the same lot of product is sampled further downstream in the distribution chain (e.g., from the public health facility) then assessing the stability of the product by performing related substance/impurities testing may suffice. Finally, some products may require additional tests that are not listed in Figure 3. Figure 3 should be used together with the applicable pharmacopeial requirements for the product.

Figure 3. Suggested prioritization for compendial testing (Level 3)[§]



[§] For injectable products, basic tests such as pH and fill volume should be confirmed before starting Level 3 testing.

Table 3. Summary of information needed for risk-based sampling and testing

	Selection of area to sample	Selection of medicines	Selection of collection sites	Selection of sampling method	No. of dosage units/sample, No. of samples/medicine, Total number of samples/area	Sample testing
Information required	Administrative and health structure, updated demographic information, disease prevalence, medicines supply chain, pharmaceutical sector information (number of outlets for each sector).	Most-used medicines, most-sold medicines, higher-risk medicines (stability, storage). Cost of medicines per unit, locally produced vs. imported, generics vs. brand names, medicines imported from countries with stringent regulations, supply system of targeted medicine, known points of distribution.	Complete data on supply systems for targeted medicines. Complete and up-to-date information about the pharmaceutical sector in the area (number of outlets, levels of distribution, type of outlets, type of available sectors for supplies, geographical and administrative structure (e.g., number of provinces, number of districts), demographic information.	Sampling methods depend on the type of medicine, its supply system, and the objectives of sampling and testing activity. Data and knowledge of the pharmaceutical sector, the supply chain systems, and the known practices and behaviors of consumers and dispensers are required.	Based on the objectives and testing methodology of the activity, data on the specifications for the medicine and its dosage form are required and should be available at the NRA. The number of samples is determined based on the objectives and information about the area.	QC test to be applied or selected must be determined by QC experts based on objectives of the sampling and testing activity. Requires understanding of medicine specifications as prescribed in pharmacopeia or manufacturers' dossiers.

	Selection of area to sample	Selection of medicines	Selection of collection sites	Selection of sampling method	No. of dosage units/sample, No. of samples/medicine, Total number of samples/area	Sample testing
Source of Information	Country profiles (WHO, UN, USAID, World Bank and others), disease situations (MOH, WHO), concept notes, and country strategies (GFATM), assessment reports from the pharmaceutical sector (NRA, MOH), climatic and seasonal information related to incidence of certain diseases, (e.g., malaria) and seasonal distribution challenges (e.g., no roads during rainy season).	Registration dossiers from NRA; import information from importers and wholesalers; supply and stock management from wholesalers and central medical stores; reports from organizations such as IMC; reports from central procurement agencies; disease profiles and country health indicators (MOH); compendial and other information about medicines efficacy, safety, and quality issues from literature.	NRA should provide most information about pharmaceutical sector. Central medical store, wholesalers should provide information about supply systems (often different among public, private, and informal). Information is also available from USAID, GFATM, WHO, and other partners. Administrative and health structure data are available at MOH and health programs. The best sources for demographic information are documents related to the country's recent strategies and major health initiative.	NRA (pharmaceutical sector information and data, such as assessment reports and studies sponsored by government and supporting partners); information from other surveys; data from supply systems in the country; data from donors and partners (such as implementation mapping–GFATM). The supply system (vertical or not) will define the levels of sampling.	NRA dossier of registration and pharmacopeial monographs (e.g., USP, British Pharmacopeia, International Pharmacopeia); WHO and other existing guidelines on sampling; other surveys and literature data, which could be used to apply a risk-based approach to sampling.	QC lab, NRA, pharmacopeial monographs, manufacturer's dossier of registration (validated test methods). Data on the capacity of the laboratories where the tests will be performed should also be considered.

Quality Surveillance of Global Fund-Supplied Medicines

The Global Fund for AIDS, TB, and Malaria (GFATM) funds approximately half of all HIV medicines imported and used in Country X. GFATM medicines are managed through the country's procurement and supply mechanisms. The country utilizes 4 regional warehouses and a central medical store to supply the 14 public HIV centers that treat the majority of confirmed cases in the country. The HIV Control Program (HCP), a GFATM Principal Recipient, uses an online medicines management tool to monitor the stock levels of ARVs. The NQCL has attained ISO 17025 accreditation from the European Directorate for the Quality of Medicines and Healthcare and is also prequalified by WHO. The GFATM asked the NRA to design a sampling and testing activity to survey the quality of GFATM-procured anti-HIV medicines across all levels of the supply chain. Key stakeholders involved in a sampling and testing activity are outlined in Table 4.

Table 4. Roles and responsibilities of involved parties in sampling and testing activity in Country X

Involved parties	Roles and responsibilities
NRA	<ul style="list-style-type: none"> • Lead planning of the sampling and testing activity • Finalize plan with involved parties and execute according to SOPs • Coordinate sampling and testing across all stakeholders • Sample products according to study protocol/plan (NRA inspectors) • Check storage conditions and ARV management system • Share data and results with HCP and all other stakeholders • Take regulatory actions when products, practices, and facilities are found to be noncompliant with regulations and standards
HCP	<ul style="list-style-type: none"> • Provide data on treatment, medicine use, and epidemiology • Support NRA in collecting product samples according to study protocol/plan • Support NRA in checking storage conditions across supply chain
GFATM	<ul style="list-style-type: none"> • Provide funding for sampling and testing • Provide donor policy/recommendations on QA
Procurement agency	<ul style="list-style-type: none"> • Provide information on procurement cycles, product specifications, and suppliers

Involved parties	Roles and responsibilities
Central medical stores and warehouses	<ul style="list-style-type: none"> • Provide information on storage conditions and stock management
Importers, wholesalers	<ul style="list-style-type: none"> • Provide information on suppliers, quality specifications, storage, and distribution • Support NRA and HCP to collect data on storage and distribution
HIV treatment centers	<ul style="list-style-type: none"> • Provide information on storage, stock management, patient use, and safety-related issues
NQCL	<ul style="list-style-type: none"> • Provide technical information on QC tests to be used, specifications of the products, number of units per sample to collect for each medicine, information related to product stability, and proper handling of medicines during sampling • Carry out tests according to official compendial standards • Report data to NRA
Market authorization holders	<ul style="list-style-type: none"> • Market authorization holders should be held responsible for all aspect of their products on the market including swift action during recall, etc., resulting from PMS.

In this case, Country X could design a sampling and testing activity which assesses product quality at each relevant strata of the health system (central medical store, regional warehouses, HIV treatment centers, and patient level). Because GFATM products are required to be procured from quality assured sources which have received approval from the WHO Prequalification Program or from an appropriate stringent regulatory authority, a consideration of the level of the health system from which the product is being sampled can help determine the appropriate risk-based measures to take. More specifically, if the NRA collects samples immediately upon the product's entry into the country, it may choose to rely upon the quality-assured procurement measures put in place by GFATM and simply test the product for assay to confirm its quality, with the assumption that stability issues may not be as critical at this point in the supply chain. However, stability testing would be an important measure of quality for samples collected further downstream in the supply chain (i.e., at the central medical store, regional warehouses, and other storage points). In these instances, following the sampling and testing guidelines provided earlier in this section and using the Three-Level Approach could help reduce the number of samples tested at Level 3, reduce the overall cost of the exercise, while also ensuring appropriate quality testing is conducted.

04

Risk-Based Post-Marketing Surveillance Tool

Sampling of medicines during post-marketing surveillance studies are often not conducted systematically and may have limited usefulness due to a poorly designed study protocol, leading to ungeneralizable or non-statistically significant conclusions.^{11,12} Little agreement exists on appropriate sampling methods, but a majority of studies rely on convenience sampling, as extensive nationwide random sampling can be expensive, complex, and time consuming.¹³ To help address these challenges, PQM has developed a tool, MedRS, to help NRAs develop risk-based sampling strategies to support national post-marketing surveillance programs while maximizing available resources. MedRS integrates and automates the science and practice of a risk-based post-marketing surveillance into a single platform. An online version of the tool is under development. The pilot version can be viewed at the following link:

<https://drive.google.com/file/d/0B6mAAO0Fp82fa2xwMEMyZFF1ZVE/view?usp=sharing>.

MedRS enables countries to consistently implement risk-based approaches to answer important questions for post-marketing surveillance, including (1) which geographical locations and outlets should be sampled, (2) how many geographical locations and outlets should be sampled, and (3) how many samples should be collected.

Figure 4 depicts the conceptual framework for the surveillance tool and shows the three dimensions of risk considered—medicines, geographic area, and supply chain—that are assessed to help countries identify the most susceptible medicines, determine the number of samples required, and prioritize sampling at the most vulnerable locations. The tool is designed to perform stratified randomized sampling of facilities based on their risk profile. If needed, the tool can also accommodate less rigorous sampling methods such as convenience sampling.

MedRS combines statistical methods and risk evaluation techniques to determine the number and location of outlets for sampling that will provide statistically representative coverage for outlets that pose the greatest risk to patients (see Table 5 for an additional description of the risk model and methodologies used). The risk factors used for evaluating the risks in the tool are derived in part from the WHO guideline on the conduct of surveys of the quality of medicines and the European Directorate for the Quality of Medicines and HealthCare's general document on the incorporation of a risk-based approach in medicines testing.^{14,15}

In LMICs, the distribution of medicines is often classified into public, private, and informal supply chains. To effectively use this tool, countries should map medicines outlets within the public and private sectors. It is recognized that a sizable amount of poor-quality medicines are found in the informal sector, sometimes in hard-to-reach areas. It is therefore important to carefully select sentinel sites and/or use purposeful sampling methods based on the risk posed to the population. Sentinel sites can also provide a means to monitor the impact of interventions aimed at reducing poor medicines quality. Sentinel sites can be treated as any facility within the supply chain and incorporated into MedRS.

Figure 4. Framework for risk-based post-market surveillance tool

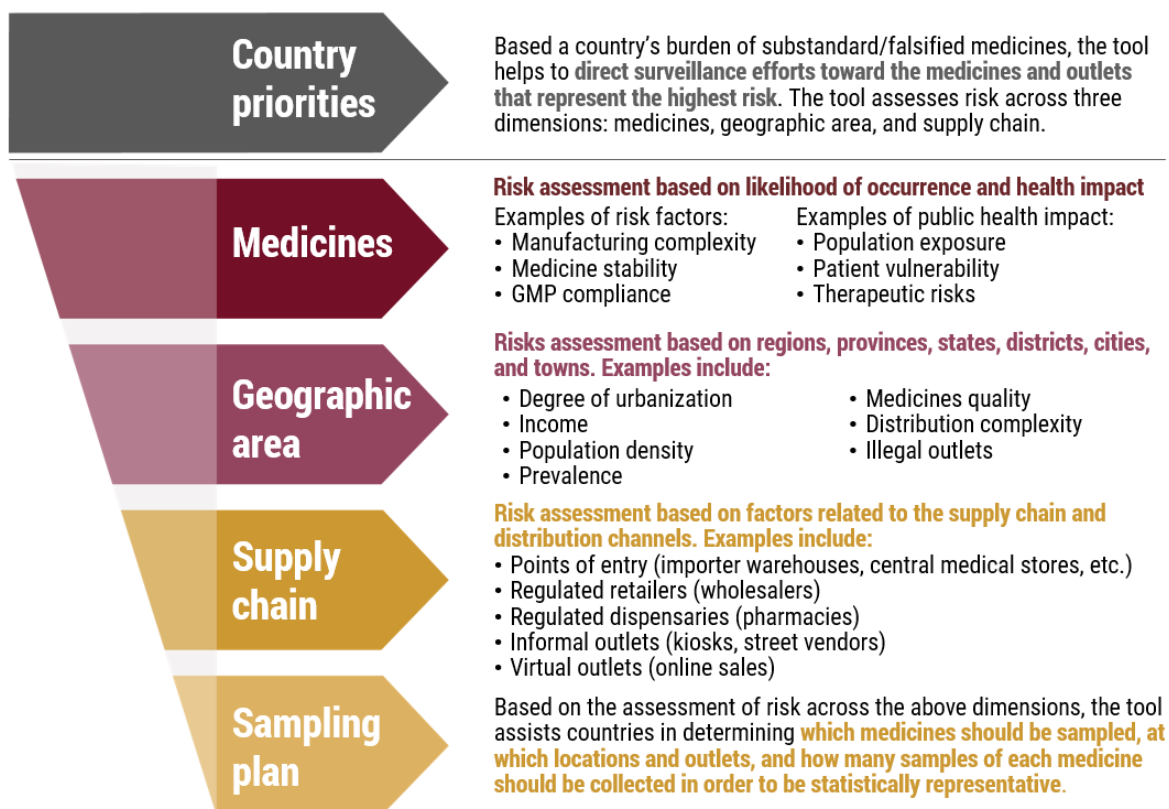


Table 5. Description of MedRS risk-based methodology

Model	Model utility	Input	Methodology	Output
Risk model for medicines	Model computes the risk for a list of medicines of interest and rank orders the medicines based on their risk.	Risk factors. See WHO Technical Report Series No. 996, Annex 7, 2016 for references.*†	Risk scoring is used to determine the overall risks posed by individual risk factors. The final medicines risk score is then determined as a SUM of probability (likelihood) × SUM of impact (consequence) of all risk factors. ‡.§	List of medicines to sample based on rank order of their individual risk scores.
Risk model for location and outlets	Model computes the respective risks associated with a list of regions, cities, and outlets, based on user input.	List of regions, cities, and outlets. Map of country's medicines distribution chain. Risk factors for region, cities, and outlets.*†	Risk analysis is used to determine the risk posed by individual risk factors for location and outlet, respectively. The final risk score for location and outlet is then computed as the SUM of their risk scores.	List of regions, cities, and outlets, and their individual risk scores.
Statistical model for location, outlets, and products	Model estimates statistically representative sample size of outlets (per medicine) to sample. The model stratifies the outlets according to their risk, and then performs a randomized selection of the required number of outlets within each stratum. The number from each outlet is proportionally distributed based on the risk of the outlet.	Input Z, p, and d. Previously computed risk scores for regions, cities, and outlets.	Sample size (Cochran 1977): $n = \frac{n_0}{1 + \frac{(n_0 - 1)}{N}}$ Where: $n_0 = \frac{Z^2(p)(1 - p)}{d^2}$ Population size (N), Critical value (Z), Prevalence (p), Confidence Interval (d) Outlets are stratified by risk score, followed by randomized sampling. Samples to be collected are distributed proportionally based on the risk of the outlets.	Number of outlets that should be sampled per medicine. Model calculates risk associated with each outlet and stratifies outlets accordingly. The algorithm performs randomization to identify the outlets for sampling. Once the outlets have been identified, then the corresponding city and region are known.

* See WHO Technical Report Series No. 996, Annex 7, 2016.

†

https://www.edqm.eu/sites/default/files/omcl_incorporation_of_a_rb_approach_in_ms_testing_at_omcls.pdf

‡ Risk management framework (ISO/IEC 31000:2009, ISO/TR 31004:2013)

§ <https://www.fda.gov/downloads/Drugs/Guidances/ucm073511.pdf>

05

Analyze, Communicate, and Act

Field inspectors and laboratory analysts should report results to the NRA as soon as confirmed data or results are available. If an organization other than the NRA is leading the sampling and testing activity or survey, the lead should report results to the NRA as soon as possible and prior to publication so that appropriate action can be taken.¹⁶

Depending on the data presented to the NRA and the potential public health importance of the findings, the authority may take a variety of actions, including—but not limited to—further testing of samples and requesting additional information or clarification from market authorization holders, or other appropriate regulatory action such as recall.

It is also necessary to share results with other stakeholders, both those involved in the sampling and testing exercise, and other relevant groups including WHO, Interpol, local police, scientists, the wider pharmaceutical industry, other national governments and regulatory authorities, and the general public.¹⁷ Results from post-marketing surveillance exercises may be captured and collated through online publicly available databases such as the Medicines Quality Database (<http://www.usp.org/global-health/medicines-quality-database>) or WHO's Global Surveillance and Monitoring System (GSMS; <http://www.who.int/medicines/regulation/ssffc/surveillance/en/>). Data shared via these mechanisms help country stakeholders to report and share information on substandard and falsified medicines while shedding light on the global scale of the problem. Sharing this information publicly can have a direct impact on the health and wellbeing of patients and populations. As a case in point, the lives of patients in South America were saved after the data from GSMS helped determine that they were affected by the same product that had resulted in several patient deaths in Asia during previous months. The antidote was promptly administered to the patients and, after additional alerts were issued, the product was found and removed from the market in other countries as well.¹⁸

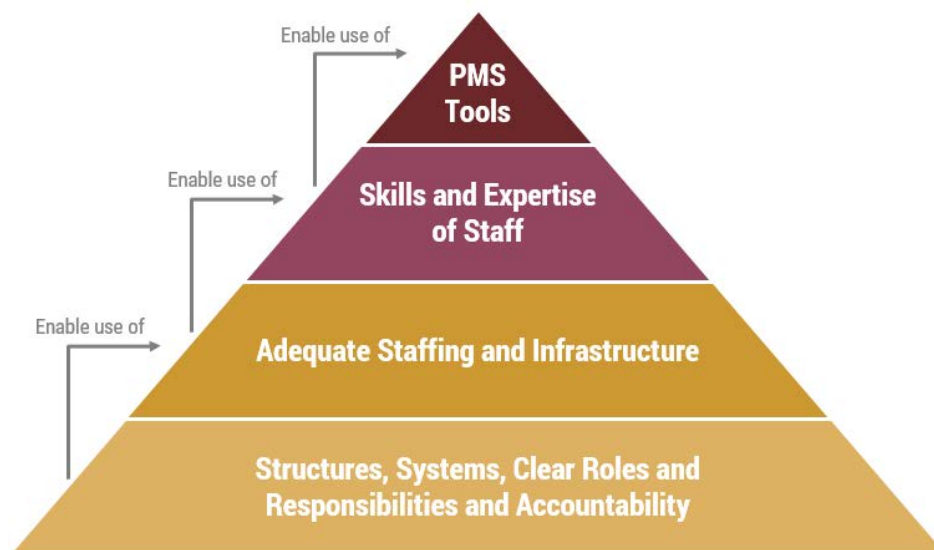
Finally, data from sampling and testing activities within post-marketing surveillance programs can be used to strengthen the programs themselves and should be used to continuously shape, refine, and improve future activities and national post-marketing surveillance priorities.

Sharing this information publicly can have a direct impact on the health and wellbeing of patients and populations."

06 Measuring Post-Marketing Surveillance Capacity

Post-marketing surveillance capacity varies from one country to another, and the effectiveness of these programs depends on many interconnected factors. In building post-marketing surveillance capacity, it is important to consider the existing available legal provisions; infrastructure; systems; governance; roles and responsibilities of each stakeholder; and human resource skills, expertise, and ability to utilize available tools (e.g., gap assessment tools, including that of WHO Global Assessment Tool,¹⁹ sampling guidelines, testing technologies, and training materials). Due to these complexities, measuring the post-marketing surveillance capacity of a country (as described in Figure 5) can be difficult.²⁰ Each of these components should be measured using an appropriate methodology and set of indicators. The approach to building a country's post-marketing surveillance capacity should, as much as possible, be systematic as well as pragmatic in its design, implementation, and monitoring, all of which would help optimize the use of limited resources.

Figure 5. Systematic capacity building in hierarchical needs
(adapted from Potter and Brough)



It is also important to consider establishing a consensus-based set of indicators among the key stakeholders (e.g., regulators and consumers). For example, in 2013, the U.S.

Food and Drug Administration (FDA) and concerned experts suggested the use of a quality metrics program (Table 6) with the objective to promote responsible practices and a quality-driven corporate culture in the pharmaceutical industry. This focus on quality leads to fewer recalls and shortages for the general public/consumers and less extensive regulatory oversight on the part of FDA.

Table 6. Examples of consensus metrics applicable to a distributor company

Quality metrics indicator	Description/definition
Product quality complaint rate	Number of quality complaints / Number of units released (e.g., 1 million)
Recall rate	Number of product recalls / Number of lots released or distributed

In the example in Table 6, the product quality complaint rate and the recall rate are inversely correlated with the company's compliance with good manufacturing practices and quality practices. It is worth noting that these indicators cannot be collected and measured if a regulatory authority does not possess the appropriate infrastructure and human and financial resources and if the inspectorate does not take responsibility for the post-marketing surveillance program.

Using well-designed and selected indicators enables decision-makers to assess whether or not progress is being made toward expected outputs, outcomes, objectives, and goals.²¹ In other words, the indicators should measure the existence and performance of key post-marketing surveillance structures and processes; identify the strengths and weaknesses; and reveal achievements, growth, or lack thereof. Indicators should also measure the degree to which strategic objectives and activities bring about results.

What, How, When, and Why to Measure?

To date, few methods for measuring post-marketing surveillance capacity exist. Developing standardized indicators can support the collection of standardized data to measure capacity. To calculate indicators, data are needed about the specific post-marketing surveillance program. These data should be available within the regulatory information management system. Ideally, the indicators should follow the **RUSMART** format:

1. **R**elvant
2. **U**nderstandable
3. **S**pecific
4. **M**easurable
5. **A**ttainable
6. **R**ealistic
7. **T**ime-bound

Post-marketing surveillance indicators should be able to evaluate the baseline situation (structure, systems, infrastructure, tools, and human resource capacity), track progress made during a specific period of time, and support the assessment of services and interventions. Indicators should be appropriately measured and used to support a continuous improvement process that ensures the post-marketing surveillance program becomes an effective part of the NRA's regulatory activities. The common types of indicators and their definitions are provided in Table 7.

Table 7. Indicator types and definitions

Indicator type	Definition
Structural	Measure key aspects of regulation, infrastructure, NRA functions and structure, QA/QC systems, supply chains, storage, and distribution in the pharmaceutical sector. Structural indicators assess the existence of key post-marketing surveillance structures, programs, and mechanisms in the environment being measured. They also assess the existence of basic infrastructure, policy, and a regulatory framework required for enabling post-marketing surveillance operations. Many structural indicators may be qualitative.
Process/ Input	Measure the resources needed for the implementation of an activity or intervention and may include policies, human resources, materials, and financial resources. Process indicators measure whether planned activities took place. Examples include meetings held, training courses conducted, medicines distributed, and materials developed.
Output	Measure the direct results of an intervention and are mainly quantitative. Output indicators add more detail on the product (“output”) of the activity. For example, the output of a training course on sampling and testing of pharmaceutical products may be the number of officers trained and, consequently, the number or proportion with improved knowledge/skills in sampling and testing.
Outcome	Measure the achievement of common objectives of each country’s NRA to address poor-quality medicines. Outcome indicators are used to demonstrate the degree to which post-marketing surveillance objectives are being met (e.g., the reduction of poor-quality anti-TB or antimalarial medicines over time).
Impact	Measure the extent to which post-marketing surveillance program objectives contribute to safeguarding the public from harmful medicines. Measuring these indicators can be difficult due to multiple factors, interventions, and externalities that also affect impact.

Data collection methods and techniques

Data should be collected using pre-defined indicators; a proposed list is provided (see Table 9). Selected indicators have been adapted from the WHO Global Assessment Tool. A combination of techniques should be used to collect data, including the following:

1. *Desk review*: Review technical documents and records, which could include drug laws, executive orders, post-marketing surveillance inspection records, and NRA and NQCL annual or mid-term reports.
2. *Semiformal or formal discussions and consultations*: Discussion should be held with responsible officials within the NRA, government, procurement agencies, healthcare providers, key NGOs, medicines testing laboratories, and key pharmaceutical establishments (manufacturers, importers, wholesalers/distributors, and retailers).
3. *Field inspection*: To collect data, including pharmaceutical product samples for quality testing as appropriate, to gain information on supply and distribution chains.
4. *Existing post-marketing surveillance data*: For countries with a medicines quality monitoring program in place, quantitative data on samples and test results from field operations can also be considered, and these data should be obtained.

Methods for data analysis, reporting, and data presentation

Both qualitative and quantitative data collected for each indicator should be examined, analyzed, and (where appropriate) computed into percentages by the appropriate personnel under the supervision of a qualified officer. Where necessary and appropriate, these data should be presented in tables or other graphic depictions for better visual data comparisons among various geographical areas in the country. In the analysis, both the number and proportion (numerator/denominator) expressed as a percentage (%) should be used for selected indicators. Most indicators are expressed in numbers to explicitly reflect the actual data, which may not provide a true picture if expressed as a percentage. If a percentage is expressed, it may enhance the reader's understanding if numerical numbers are also provided (e.g., between 2010 and 2015, an average of 3 percent ($n=9$ of 300) of Company Z's distributed products were recalls). This percentage does not indicate how many products were actually recalled. The percentage also does not indicate whether the recall occurred in a 1-, 2-, or 3-year period. In this example, it is important that the inspectorate delves deep into the data from each year and assesses what corrective and preventive actions have been performed by the company to address the problem identified by the NRA. A hypothetical breakdown of a 3 percent recall rate by year is shown in Table 8.

Table 8. Breakdown of the numbers and % of product recalled by year for Company Z

	N = products distributed	n= products recalled	%
Total	300	9	3.0
2010	80	4	3.8
2011	50	3	6.0
2012	30	1	6.7
2013	60	1	1.7
2014	40	0	0.0
2015	40	0	0.0

The data above illustrate serious quality issues with a product Company Z procured and distributed—data that would be detected through an effective post-marketing surveillance program. These data prompt the post-marketing surveillance inspectorate to include Company Z on the list of at-risk establishments, which warrant closer scrutiny for at least 2 to 3 years. The NRA inspectorate should consider taking actions, which may include but are not limited to the following (in no particular order):

- ▶ Issue notice of warning to the company with specific corrective and preventive action recommendations.
- ▶ Introduce sanctions in various forms as necessary and require the company to sign an agreement for commitment to address fully the corrective and preventive actions.
- ▶ Develop/revise and implement a voluntary recall process and SOPs and report to NRA.
- ▶ Declare to NRA detailed information for recalled products on the total quantity procured (lot size), quantity distributed (chains and clients), quantity recalled, method of disposal, etc.

The post-marketing surveillance data analysis attempts to address the following key questions:

- ▶ Does the country have an adequate post-marketing surveillance system in place? If not, why, and how it can be improved?
- ▶ What is the magnitude of the problem of good vs. poor-quality medicines in the public, private, and informal sectors?
- ▶ What problems with QA/QC systems related to post-marketing surveillance need to be addressed, and by whom? How and when will they be addressed?

Key Indicators

The indicators discussed below are intended to serve as a guide. Each country may adapt, adjust, and/or further develop these indicators to suit its local setting in terms of the regulatory and QA/QC systems environment and the development status of its pharmaceutical sector.

Table 9. Key indicators for measurement of post-marketing surveillance capacity

No.	Indicator
Structural (STL) Indicators	
STL1	Existence of a statutory provision (national policy, legislation, and regulation) for post-marketing surveillance
STL2	Existence of post-marketing surveillance as a key function of the NRA
STL2a	Existence of concrete plans to carry out post-marketing surveillance activities as evidenced in quarterly or annual operational plans
STL2b	Existence of post-marketing surveillance within the regulatory system
STL3	Roles, responsibilities, and organizational structure for post-marketing surveillance program
STL3a	Number, skills, and experience of staff for post-marketing surveillance program
STL4	Existence of any regular financial budget for the post-marketing surveillance program or activities
STL5	Existence of any mechanisms (e.g., coordination, task group, intelligence) for coordination of key stakeholders (e.g., police, customs)
STL6	Existence of post-marketing surveillance program targeted to national priority health programs/products
STL7	Existence of evidence-based decision-making practice through the use of post-marketing surveillance data (e.g., evidence of regulatory actions taken against poor-quality medicines based on post-marketing surveillance data)
STL8	Existence of risk management and communication and enforcement
STL9	Existence of written SOPs for post-marketing surveillance relative to planning, execution, and reporting

No.	Indicator
STL10	Existence of key post-marketing surveillance tools
	STL10a Sampling strategies and guidelines
	STL10b Quality control and access to testing
	STL10c Sample and test results information sharing and reporting
	STL10d Intervention and enforcement (e.g., administrative, regulatory, policy)
Process/Input (PRS) Indicators	
PRS1	Number of procedures established and implemented to perform market surveillance and control
PRS2	Percentage change in the number of dedicated human resources for post-marketing surveillance program
PRS3	Percentage change in financial resources for post-marketing surveillance activities
PRS4	Percentage of licensed pharmaceutical establishments covered by post-marketing surveillance program in private sector, disaggregated by distributors, wholesalers, importers, retail pharmacy outlets, consultancy rooms
PRS5	Percentage of licensed pharmaceutical establishments covered by post-marketing surveillance program in public sector, disaggregated by central medical stores, distributors, wholesalers, importers, health facilities dispensaries, public retail pharmacy outlets
Output (OUT) Indicators	
OUT1	Number of public reports of suspected falsified and substandard medical products
OUT2	Percentage of medical product samples that failed Level 1 (screening test) that undergo confirmatory analysis
OUT3	Number of individuals trained/certified on topics related to post-marketing surveillance by year
OUT4	Percentage of total post-marketing surveillance reports attributed to product quality defect are recorded in database compared to the previous calendar year
Outcome (OUE) Indicators	
OUE1	Cost savings (in local or US\$) attributed to risk-based post-marketing surveillance activities
OUE2	Percentage change in the number of licensed pharmaceutical establishments that sell falsified and substandard medical products
OUE3	Percentage of substandard or falsified medical products circulated in the market identified in the current year (each year there should be a decrease in percentage compared to previous years)
OUE4	Percentage of batches or lots medical products failing quality testing removed from the national programs or market (the percentage should increase over time; i.e., the nominator and denominator should gradually come close to equal as a result of effective post-marketing surveillance)
OUE5	Percentage change in the number of poor-quality medical products used in the national priority health program and in the market over time
OUE6	Percentage change in the number of post-marketing surveillance inspections in terms of frequency from high-risk to low-risk areas as a result of effective risk-based post-marketing surveillance
OU7	Percentage of failed samples followed by the government with regulatory actions

No.	Indicator
Impact (IMT) Indicators	
IMT1	Percentage of regulatory enforcement actions taken in the preceding year as a consequence of post-marketing surveillance activities
IMT1a Timely information sharing and investigation	
IMT1b Timely enforcement interventions and actions (e.g., issues of warnings, quality defect product withdrawal and recall, fine and other sanctions including license suspensions and revocation, imprisonment)	
IMT2	Percentage change over time in medicine-related hospital admissions resulted from product quality defects
IMT3	Percentage change in medicine-related deaths caused by medicines quality defects
IMT4	Change in behavior of supplier, distributor, and retailer handling pharmaceutical products to embrace the quality and safety as a key criterion in their practice
Continuous improvement (COI)	
COI1	Existence of a mechanism to promote transparency, accountability and communication in post-marketing surveillance program (WHO GAT)
COI2	Existence of continuous improvement process (Plan > Do > Check > Act)

Key Resources

WHO Pharmacovigilance Indicators: A Practical Manual for the Assessment of Pharmacovigilance Systems. World Health Organization:
http://www.who.int/medicines/areas/quality_safety/safety_efficacy/EMP_PV_Indicators_web_ready_v2.pdf.

Measuring Pharmaceutical Quality through Manufacturing Metrics and Risk-Based Assessment. Brookings, Engelberg Center for Health Care Reform:
<https://www.brookings.edu/wp-content/uploads/2014/05/Quality-Metrics-Meeting-Summary.pdf>.

PRAC Strategy on Measuring the Impact of Pharmacovigilance Activities. EU Pharmacovigilance Risk Assessment Committee:
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/01/WC500199756.pdf.

WHO Guideline on the Conduct of Surveys of the Quality of Medicines (WHO-TRS number 996, 2016, Annex 7). World Health Organization:
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_web.pdf

OMCL Network of the Council of Europe: General Document PA/PH/OMCL (06) 3 9R. European Directorate for the Quality of Medicines and HealthCare:
https://www.edqm.eu/sites/default/files/omcl_incorporation_of_a_rb_approach_in_ms_testing_at_omcls.pdf

Guidance for Industry. Q9 Quality Risk Management (ISO/IEC 31000:2009, ISO/TR 31004:2013). U.S. Department of Health and Human Services, Food and Drug Administration:
<https://www.fda.gov/downloads/Drugs/Guidances/ucm073511.pdf>

A Risk-based Identification of Essential Medicines for Local Manufacturing in Low- and Middle-Income Countries. World Health Organization:
http://www.who.int/medicines/areas/quality_safety/quality_assurance/Local-manufacturing-risk-QAS16-682_24082016.pdf?ua=1

WHO Guidelines for Sampling of Pharmaceutical Products and Related Materials (WHO 631 Technical Report Series, No. 929, 2005, Annex 4). World Health Organization:
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- ⁵ World Health Organization. WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fiftieth report, WHO Technical Report Series No. 996, Annex 7. 2016. Accessed: 22 Jan 2018. Available at: <http://apps.who.int/medicinedocs/documents/s22404en/s22404en.pdf>.
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