PQM Promoting the Quality of Medicines

Strengthening Regulatory Systems To Improve Medical Product Quality in Low- and Middle-Income Countries

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USAID FROM THE AMERICAN PEOPLE

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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). Since 1992, USP has worked with USAID to support low- and middle-income countries in addressing critical issues related to medicines information and quality. The PQM program provides technical assistance to build the capacity of medicines regulatory authorities and quality assurance systems in countries with weak health systems. PQM also provides technical support to manufacturers of quality-assured priority medicines for malaria, HIV/AIDS, tuberculosis, neglected tropical diseases , and maternal, newborn, and child health (MNCH).

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Acronyms

AMRH	African Medical Regulatory Harmonization (program)
EAC	East African Community
GMP	good manufacturing practice
GRP	good regulatory practice
LMIC	low- and middle-income country
MRA	medicines regulatory authority
NOMCoL	Network of Official Medicines Control Laboratories
NQCL	national quality control laboratory
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PQM	Promoting the Quality of Medicines (program)
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization
RBA	risk-based approach
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization

Introduction

Progress against the world's most pressing global health threats—including malaria, tuberculosis, and HIV/AIDS—requires broad and concerted efforts to strengthen systems that help ensure uninterrupted access to safe and effective health services, medicines, and supplies. Availability of and access to essential medicines underpins progress against these diseases; however, it is only when these medicines are produced, distributed, and sold in a manner that ensures their quality that they can bring about positive outcomes for patients and public health.

A strong medicines regulatory system is an essential component of the health system that helps protect populations by ensuring that medicines and other medical products are not only safe and effective but also of assured quality. Poor-quality medicines—those that are unregistered, substandard, or falsified—can endanger patients, extend illness unnecessarily, and even result in death. Poor-quality medicines also undermine efforts to improve health and strengthen health systems, erode public confidence in those same systems, and may contribute to antimicrobial resistance.[1]

Box 1. Defining poor-quality medicines

At the 70th World Health Assembly,the World Health Organization (WHO) adopted a change in how poor-quality medicines are categorized and defined. These new definitions help add clarity and accuracy in the global discourse and effort to combat poor-quality medicines.

WHO Definitions:[2]

Unregistered/unlicensed: Medical products that have not undergone evaluation and/or approval by the 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.

Substandard: Also called "out of specification," these are authorized medical products that fail to meet either their quality standards or specifications, or both.

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

In most countries, a medicines regulatory authority (MRA) is responsible for providing regulatory oversight of all medical products (medicines, vaccines, biological and blood products, traditional or herbal medicines, and medical devices).[3] The regulatory authority oversees several key functions, including product registration; control of medicine importing and exporting; inspections of manufacturers, distributors, importers, wholesalers, and retailers; post-marketing surveillance; and control of pharmaceutical promotion and advertising.

In low- and middle-income countries (LMICs), MRAs often have limited capacity and insufficient resources to carry out these critical regulatory functions, which can mean delays in getting medicines to those who need them most, and when medicines are available, their safety and quality may not be fully assured.

As countries work toward achieving Goal 3 of the Sustainable Development Goals, and other major global health initiatives, including Creating an AIDS-Free Generation, Protecting Communities from Infectious Diseases, and Ending Preventable Child and Maternal Deaths, it is critical to continue improving access to safe and effective medicines and medical products of assured quality by strengthening the systems that allow for their effective regulation.[4,5]

Since 1992, USP has worked cooperatively with the U.S. Agency for International Development (USAID) to support LMICs in addressing critical challenges in the pharmaceutical sector. The earliest program, the Rational Pharmaceutical Management project, implemented and evaluated medicine information resource programs in select countries. Subsequently, the Drug Quality and Information program focused on medicines quality control and quality assurance systems. The Promoting the Quality of Medicines (PQM) program (2009–2019) 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. PQM capitalizes on USP's technical know-how in analytical chemistry and microbiology and applies these skills to strengthen the capacity of national quality control laboratories (NQCLs) to assure the quality of medical products in LMICs.

PQM forms strategic partnerships and builds mutual relationships with accreditation bodies, the World Health Organization (WHO), regulatory agencies, implementing partners, manufacturers, contract research organizations, and other national and international organizations that help drive the agenda for quality assurance of medicines.

Purpose and scope of document

This document reviews key regulatory challenges in LMICs, the key areas in which PQM aims to build or strengthen regulatory capacity, and shares lessons learned from the program's extensive implementation experience. Strengthening the capacity of MRAs requires in-depth and ongoing consideration of the broader country context and health system components that interact and influence MRA operations. As such, PQM relies on strategies and interventions rooted in systems thinking to sustainably strengthen regulatory capacity.

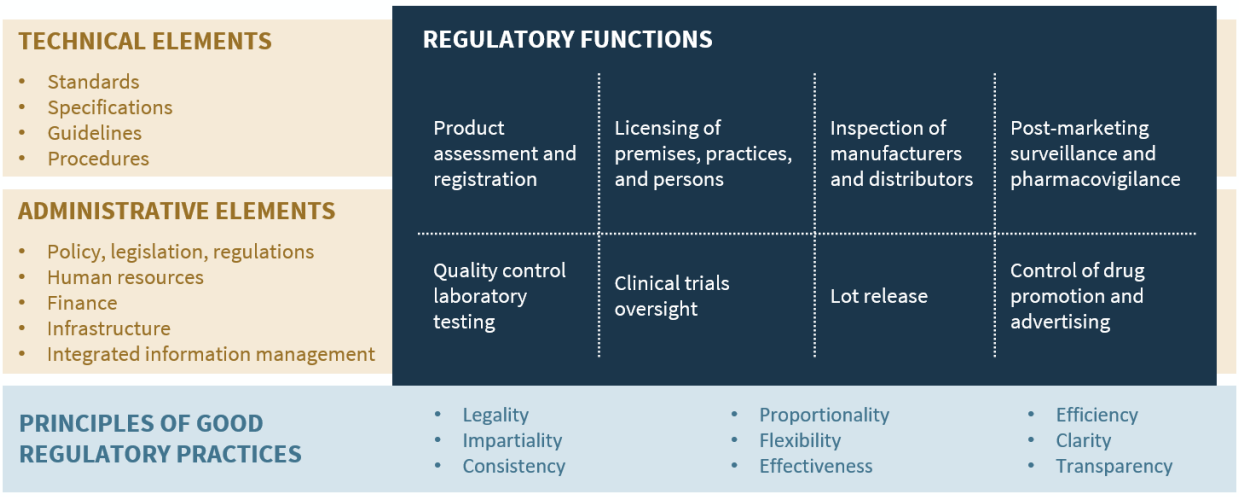
The Role of Medicines Regulatory Authorities in Protecting Public Health

As regionalized and globalized trade expands, new developments in science and medicine continue, and new technologies are introduced, there are unprecedented challenges and opportunities to ensure that regulatory systems are well-equipped to ensure the quality of medicines. Robust and effective quality assurance and regulatory systems are widely recognized as a key aspect to effectively scaling up access to medicines and health services as part of efforts to ensure universal health coverage.

However, many LMICs lack adequate systems, structures, or capacity to ensure the safety, efficacy, and quality of medicines. The consequences of ineffective regulation are not limited to the affected countries but instead, in an era of globalized trade, have far-reaching and worldwide implications. In fragile or poorly regulated systems, medicines that are of poor quality or are falsified can cause treatment failure and adverse drug reactions, can increase morbidity and mortality, and may contribute to antimicrobial resistance. These medicines have negative financial implications on patients, health systems, and national economies. They also undermine advances in public health, confidence in health systems, and decades of investments in health and development.

A well-functioning regulatory system requires the presence of key technical and administrative elements that support and enable essential regulatory functions. Regulatory elements and functions must be mandated through national legislation and policy frameworks that give MRAs the authority and ability to conduct their activities effectively. MRAs may be financed from various sources, including registration and inspection fees, government allocations, foreign aid, or a combination of these. MRAs should also have specific measures in place to avoid conflicts of interest in decision-making, ensure confidentiality, promote transparent and accountable decision-making, and encourage effective consultation with stakeholders. Figure 1 describes the key administrative and technical elements as well as the regulatory functions that compose a typical regulatory authority.

Figure 1. Functional, technical, and administrative components of a regulatory system
(Adapted from Ratanawijitrasin et al. 2002)[6]



Challenges in establishing systems for medicines quality assurance

Although much progress has been made in strengthening regulatory systems around the world, serious challenges remain to ensure the quality and safety of medicines, particularly in LMICs. MRAs in LMICs often have limited capacity and/or insufficient resources to carry out the range of critical regulatory functions effectively. WHO estimates that at least 30 percent of MRAs globally are operating with limited capacity to perform core regulatory functions.[7] In Africa, more than 90 percent of MRAs are operating with minimal capacity.[8]

Assessments across multiple countries indicate inconsistent, outdated, and sometime absent legislative frameworks and policies that can incapacitate an MRA and prevent it from operating effectively.[9,10,11]

Compounding this issue is the overall heterogeneity of regulatory frameworks, policies, and standards across LMICs, which can slow down the process of market authorization for new medicines and hinder access. Additionally, while MRAs use a variety of funding models (including collecting fees for medicines registration and inspections, government allocations, and/or donor funding), many are underfinanced and lack sustainable financing. Regulatory human resource capacity also varies significantly across LMICs, with nearly all MRAs suffering from a shortage of qualified or appropriately trained staff and insufficient numbers of professionals in the pipeline.[12]

The limitations in human and financial resources often impede regulatory functions and can create inefficiencies in regulatory processes. As a result, MRAs in LMICs often face significant backlogs of medicines registration applications and too few resources to effectively carry out inspection, quality control, and post-marketing surveillance activities. Ineffective or absent governance mechanisms and information management systems contribute to a lack of accountability and transparency and the mismanagement of regulatory information and data.

Key Strategies for Building Strong Quality Assurance and Regulatory Systems

Strong, robust, and resilient regulatory systems are underpinned by good practices and principles that support effective regulation of medical products.[13] WHO defines good regulatory practice (GRP) as "a set of practices applied to the development, implementation, and maintenance of controls, including laws, regulations, and guidelines to achieve a public policy objective."[14]

WHO also notes that GRPs should be enforceable and built on a foundation of transparent, non-discriminatory, predictable processes backed by rigorous stakeholder engagement and regular assessment and evaluation.[15] Compliance with GRPs must be complemented by strong political commitment to maintaining effective regulatory systems and adequate funding for the system to be truly sustainable and resilient.

WHO's guideline on GRPs provides essential principles (box 2) of effective regulation and key consideration for implementation that help to ensure regulations are transparent, effective, efficient, and flexible enough to respond to a complex and dynamic regulatory landscape.

GRPs provide an enabling regulatory environment that helps good manufacturing practices (GMP), good review practices, and good distribution practices to be applied and enforced. Together, these regulatory practices help safeguard medicines quality during production, distribution, and use.

For regulatory authorities in LMICs, which may have insufficient financial or human resources to carry out the full suite of regulatory functions, consideration and incorporation of risk-based approaches, regional harmonization and reliance, and collaboration across regulatory authorities can help leverage capacity and improve regulatory efficiencies across multiple countries.

Box 2. Principles of good regulatory practices

- Legality
- Impartiality
- Consistency
- Proportionality
- Flexibility
- Effectiveness
- Efficiency
- Clarity
- Transparency

Risk-based regulation of medical products

Regulatory authorities in LMICs sometimes spend a bulk of their financial resources on aspects of quality assurance that may not necessarily yield the greatest benefit to public health. For example, some MRAs spend a disproportionate amount of resources on dossier review, evaluation of current GMP, post-marketing surveillance, and quality testing. In the case of post-marketing surveillance, although substantial resources may be devoted to this function, activities are often undertaken in an ad hoc or non-strategic manner, or may not be based on existing data or indicators of risk. Additionally, a lack of rigorous study methods means that although significant resources may be used for surveillance purposes, ultimately the results may not be reliable enough to use for decision-making purposes.

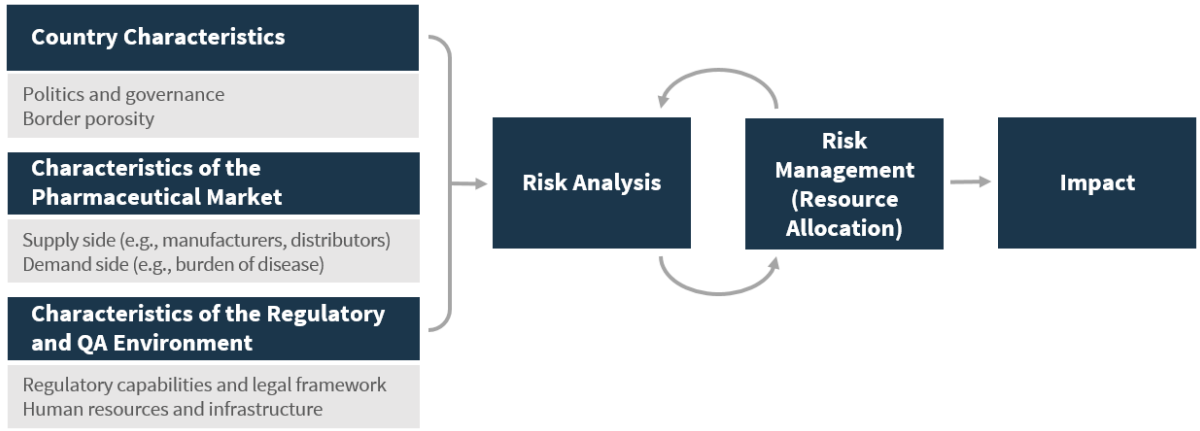
Risk-based regulation of medical products incorporates risk management principles to ensure regulatory resources are used in ways that provide the maximum benefit to the public and that regulatory functions are carried out as efficiently as possible, grounded in evidence-based risks to public health.

Pharmaceutical quality assurance systems should therefore include risk-based strategies to detect and respond to the presence of substandard and falsified medicines, address vulnerabilities in the quality assurance system, and inform the allocation of resources to effectively carry out essential regulatory functions.

Risk-based resource allocation

Many LMICs struggle to allocate adequate resources to build, strengthen, and/or maintain an effective quality assurance system and may rely to some degree on donor support to carry out regulatory activities. Risk-based resource allocation for regulatory and quality assurance systems improves the ability of regulatory agencies to manage and mitigate those risks that pose the greatest threat to the health of their populations.[16] A risk-based approach helps countries to prioritize and optimize use of limited resources. When deployed, a risk-based approach can help facilitate self-reliance and sustainable quality assurance systems, maximizing country investments and enabling countries to increase self-reliance and transition away from dependence on donor support for regulatory systems strengthening. Figure 2 presents a framework for a risk-based approach to allocating regulatory resources.

Figure 2. Framework for risk-based pharmaceutical quality assurance in LMICs



The risk-based framework helps guide allocation of resources for pharmaceutical quality assurance, leveraging limited regulatory resources while still protecting public health. In the framework, the characteristics of the country, pharmaceutical market, and regulatory quality assurance environment are identified as the sources of potential risk for poor-quality medicines. Using risk analysis of these attributes, a risk management and resource allocation strategy can be developed that may feed back into the risk analysis as needed. The final step in the framework is an assessment of the impact of resource allocation. Risk-based resource allocation for pharmaceutical quality assurance is an ongoing process that needs to be flexible in its response, capable of adapting to the changing risk environment and pharmaceutical market.[17]

Risk-based dossier review and product evaluation

MRAs must evaluate product dossiers for quality, safety, and efficacy and must inspect the manufacturing facilities and clinical trial sites before registering medicines. Dossier evaluation is a time- and resource-intensive process. Countries with limited resources have a backlog of generic and new drug applications, which prevents timely delivery of medicines to patients in need of treatment.

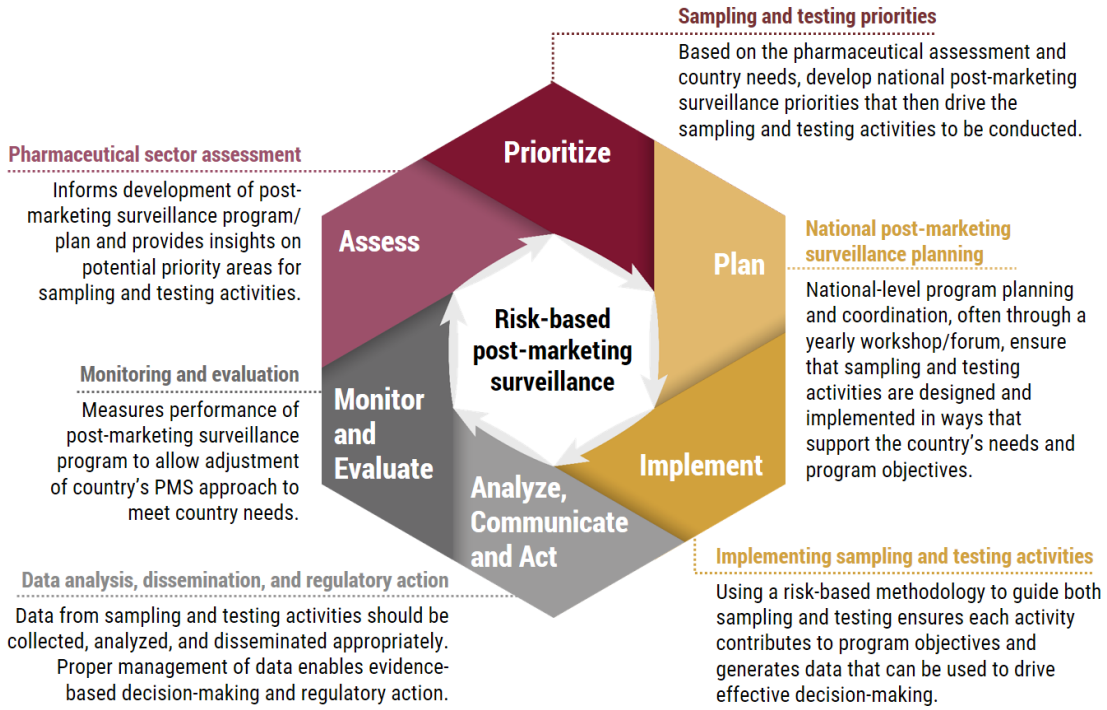
Using a risk-based approach to dossier evaluation, MRAs can accelerate the process by considering those dossiers that may be eligible for an expedited review rather than a traditional full review. Often, if the product has previously been assessed by a competent regulatory authority or WHO, a country may be able to prioritize the product as "low risk." MRAs can also adopt WHO's procedures for expedited registration and can register medicines evaluated and inspected by WHO or a stringent regulatory authority without repeating dossier evaluations. If WHO or another competent regulatory authority already assessed the quality, safety, and efficacy of a drug product; inspected the manufacturing facilities and clinical site; and agreed with the applicant to provide the complete assessment reports to the MRAs, then MRAs can save time by reviewing the assessment reports instead of reviewing entire dossiers.

Risk-based post-marketing surveillance

As mentioned previously, although some countries may already conduct intermittent quality surveys, technically sound, strategic, and sustainable risk-based post-marketing surveillance programs that are responsive to unique country contexts and needs are lacking in many LMICs. 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 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.[18]

Figure 3 depicts a roadmap for developing and implementing a risk-based post-marketing surveillance program. As illustrated, this is an iterative process meant to revert back to regular prioritization and planning informed by lessons from previous cycles of surveillance.

Figure 3. Framework for developing and implementing post-marketing surveillance programs[19]



An assessment of a pharmaceutical sector informs development of post-marketing surveillance program and provides insights on objectives and potential priority areas. Post-marketing surveillance and the associated sampling and testing activities should be coordinated and owned by the MRA and designed to address predefined objectives through the establishment of a rigorous and agreed-upon methodology. Using a risk-based methodology to guide both sampling and testing activities ensures each contributes to program objectives, makes the most of resources, and generates quality data that can be used to drive effective decision-making. The application of risk-based approaches offers an opportunity for LMICs to establish effective, affordable, and sustainable medicines post-marketing surveillance systems.

Taking data-driven regulatory actions

Conducting post-marketing activities in a manner that ensures the resulting data are timely, relevant, and reliable enables regulatory authorities to take actions that effectively protect their populations from poor-quality medicines (see example in box 3). Beyond the data generated during post-marketing surveillance activities, access to data is critical for regulatory authorities to be able to effectively conduct other regulatory functions, including dossier evaluation and medicines registration, inspection, and licensing. Central to strengthening regulatory capacity in LMICs are the establishment and implementation of data standards, integrated regulatory information management systems, and protocols to ensure data integrity.

Box 3: Regulatory actions in Ethiopia fight substandard medical devices

In 2014, with training and support from the USAID-funded Promoting the Quality of Medicines (PQM) program, the national quality control laboratory (NQCL) of Ethiopia's Food, Medicine and Health Care Administration and Control Authority (FMHACA) successfully achieved ISO/IEC 4074 accreditation and expanded its testing scope to include testing the quality of medical devices. This was the first laboratory in sub-Saharan Africa to achieve accreditation for testing of medical devices, a critical step forward in ensuring product quality and creating an AIDS-free generation in East Africa.

In 2016, the laboratory randomly tested 60 batches of male condoms for quality and found that some were incorrectly sized, contained less than the stated amount of lubricating gel, and/or tore when under pressure. As a result, FMHACA issued a recall for 9 lots of condoms—69 million condoms—from a single manufacturer in India. The condoms were destroyed, and the manufacturer was blacklisted. The NQCL, with its new testing capabilities, was able to catch these products and prevent the public from using faulty condoms that may have resulted in unintended pregnancies and sexually transmitted diseases.

Regional harmonization, reliance, and cooperation

Pharmaceutical trade is becoming ever more globalized, both in terms of manufacturing and distribution, which is creating increasingly complex pharmaceutical supply chains. Additionally, the increase in both the number and complexity of pharmaceutical products and formulations presents major challenges for even the most robust MRAs. As a result, regulatory authorities in all regions of the world are capitalizing on and leveraging regulatory harmonization, reliance, and cooperation to help offset these evolving challenges.[20]

Box 4. Key terms related to regulatory harmonization, reliance, and cooperation

Definitions below are from WHO's *Good regulatory practices: guidelines for national regulatory authorities for medical products*:

Collaboration: working with others to achieve shared goals. Collaboration involves informal peer-to-peer information-sharing between experts. It may be supported by International Regulatory Cooperation agreements that provide for the sharing of confidential information between MRAs.

Recognition: the routine acceptance by an MRA in one jurisdiction of the regulatory decision of another MRA or other trusted institution. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B. Recognition may be unilateral or multilateral.

Regulatory convergence: a voluntary process whereby the regulatory requirements in different countries or regions become more similar or "aligned" over time. The process results from the gradual adoption of internationally recognized technical guideline documents, standards and scientific principles, and common or similar practices and procedures, or the establishment of appropriate domestic regulatory mechanisms that align with shared principles to achieve a common public health goal.

Regulatory cooperation: a practice between MRAs aimed at efficiently regulating medical products. The range of formal mechanisms includes the creation of joint institutions and treaties and conventions such as mutual recognition agreements, while the less formal practices include sharing of information, scientific collaboration, common risk assessment, joint reviews, and development of standards. Regulatory cooperation may also include work with international counterparts to build regulatory capacity or provide technical assistance, thus contributing to the improvement of international regulatory governance practices.

Regulatory harmonization: the process by which technical guidelines are developed in order to be uniform across participating authorities in multiple countries.

Reliance: the act whereby the MRA in one jurisdiction may take into account and give significant weight to—i.e., totally or partially rely upon—evaluations performed by another MRA or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken, even when it relies on the decisions and information of others.

Regulatory harmonization (see relevant definitions in box 4) promotes the alignment of regulatory standards across multiple countries to facilitate greater efficiency in key regulatory functions, such as medicines registration, dossier review, and inspection. If regulatory requirements are harmonized, it helps eliminate barriers manufacturers face in seeking market authorization and helps set uniform expectations across multiple parties. In the case of market authorization, the net effect can be shorter registration and authorization times, meaning that a new medicine can reach the patients who need it faster.

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), the African Medical Regulatory Harmonization (AMRH) initiative, and WHO are

among those leading key efforts toward harmonization. ICH's development of the Common Technical Document (CTD) format for submitting product dossiers and WHO's Collaborative Review Procedure are key examples of effective regulatory harmonization. In the East African Community (EAC), AMRH efforts have helped to decrease dossier review times by 40 to 60 percent (down to 7 months from 1–2 years).[21] Boxes 5 and 6 highlight additional examples of successful regulatory harmonization.

In 2018, regulatory harmonization in Africa took a major step forward with the establishment of the Africa Medicines Agency, which aims to "promote the adoption and harmonization of medical products regulatory policies and standards, and scientific guidelines, and coordinate existing regulatory harmonization efforts."[22]

Harmonization also helps to facilitate work sharing and collaboration among technical experts at different national or regional regulatory authorities and helps lay the foundation for mutual

Box 5. Knowledge sharing and cooperation to build capacity at quality control laboratories

With support from USAID, in 2009 USP established a Network of Official Medicines Control Laboratories (NOMCoL) in Africa to provide a forum for sharing best practices on medicines quality issues at regional and national levels. The network offers unique interlaboratory testing for participating laboratories to improve performance and harmonize their drug analysis methodologies.[23] Since 2009, USP has developed robust networks in sub-Saharan Africa (NOMCoL-SSA), the Middle East/North Africa (NOMCoL-MENA), and Southeast Asia (NOMCoL-SEA). In 2018, USP, together with the New Partnership for Africa's Development (NEPAD) and AMRH, transitioned NOMCoL-SSA into the African Medicines Quality Forum (AMQF), which will continue to strengthen and harmonize regional capacity for quality control testing, post-marketing surveillance, bioequivalence studies, and proficiency testing.[24]

Box 6. Support for harmonization efforts in the East African Community (EAC)

As a development partner in the EAC, PQM has provided technical support to the six partner states to build local capacity for adopting and operationalizing harmonized registration standards. To increase access to priority medicines, PQM supported WHO in providing technical leadership to build the capacity of partner states in conducting joint dossier review sessions. Once dossiers are approved through this joint process, EAC partner states are able to use the decision to register products in their respective countries without additional reviews. From October 2015 through March 2017, 34 products were submitted for registration: 4 have been registered, 2 have been recommended for approval, and 26 have been queried with requests for more information.

Recognizing additional gaps in the capacity of member states to effectively adopt the guidelines, PQM engaged in a series of technical and capacity-building activities to strengthen critical areas, including evaluating dossiers using the Common Technical Document, validating and qualifying air handling systems, and conducting a first-of-its-kind workshop for EAC partner states on assessment of in vivo bioequivalence data with a hands-on practical component at the Regional Bioequivalence Center in Ethiopia.

recognition and reliance activities. In general, reliance implies that the work done is shared by the trusted authority (e.g., through assessment or inspection reports), while the receiving authority uses this work accordingly to advance its own scientific knowledge and regulatory procedures and retains its own regulatory responsibilities.[25] Reliance helps streamline and reduce the workload of the regulatory personnel, which allows them to focus on other critical areas of work.

Developing professionals for medicines quality assurance and regulatory careers

Quality assurance and regulatory systems that help to ensure medicines and medical products are safe, effective, and quality assured can only be effective if a qualified, experienced, and appropriately staffed workforce is in place. Too often, regulatory authorities in LMICs face budget and staffing shortages, suffer from persistently high attrition, lack professional development and learning opportunities, and receive insufficient numbers of qualified applicants for key positions.

To help address the dearth of qualified professionals the regulatory and quality assurance workforce, many stakeholders are working to increase the number and strengthen the quality of preservice training programs at academic institutions (box 7). For example, USP, through its training programs for university students in Ghana and India, seeks to incorporate pharmaceutical manufacturing and quality assurance fundamentals at the university level to build the foundation for a career in the pharmaceutical sector. The training programs offered by USP provide theoretical and hands-on training to help build the necessary knowledge and skills in dossier assessment, medicines regulation, GMP, quality control, and analytical testing.

Box 7: Investing in tomorrow's pharmaceutical workforce at the University of Addis Ababa

A skilled workforce for pharmaceutical quality assurance and regulation is a critical piece of the overall health system. A strong health system ensures access to safe, effective, and essential medicines for the public. In most low- and middle-income countries, there exists a pharmaceutical management skills gap.

In order to address the skills gap in Ethiopia, PQM collaborated with Addis Ababa University's School of Pharmacy to launch a master's program in regulatory affairs in 2016. PQM has been involved since the early stages of developing content through implementation. The first cohort of students was admitted for matriculation in October 2016. PQM continued to support building the skills of academic leadership by sponsoring two School of Pharmacy management team members to attend regulatory affairs professional meetings in the United States. The team also visited Howard University, George Washington University, and the U.S. Food and Drug Administration. During the visits, the team was able to identify teaching materials and reference textbooks for the master's program. The team also identified areas of collaboration with the different institutions and reached an agreement on signing memorandums of understanding with the University of Southern California, George Washington University, and University of Washington. Based on the agreement, U.S. professors will travel to Ethiopia to teach a number of courses. PQM plans to continue promoting the development of regulatory affairs skills in Ethiopia by supporting technical review of teaching materials.

Building workforce capacity at central and decentralized levels is also a critical requirement for strengthening regulatory systems. Students and staff in the field require opportunities to learn from and engage with a wide range of stakeholders on essential and emerging quality assurance topics, including good clinical practices, GMP, bioequivalence study design, quality control, and laboratory calibration and equipment maintenance.[26,27] Support for in-service training programs must leverage a variety of modalities, including hands-on and practical exercises, mock audit and inspections, training-of-trainer workshops, and remote support to help translate knowledge into practice (see example in box 8).

Box 8: Amplifying the effect of technical assistance: examples from Nigeria, Myanmar, and Kazakhstan

PQM provided simultaneous technical assistance to multiple laboratories in Nigeria, Myanmar, and Kazakhstan in support of attaining compliance with international standards, recognized by either ISO/IEC 17025 accreditation or WHO prequalification. In each of these countries, this parallel approach encourages sustainability and is made possible through strong participation on the part of MRAs. The parallel capacity building also works to harmonize medicines quality testing throughout each country.

As PQM provided technical assistance to one laboratory, typically the strongest performing, each of these countries engaged staff from other laboratories to participate in capacity-building activities, which in turn amplified PQM's technical assistance as laboratories worked toward complying with international accreditation requirements. The unique circumstance of each of these countries underscores that the approach is highly replicable, given the prerequisite of strong MRA support and participation.

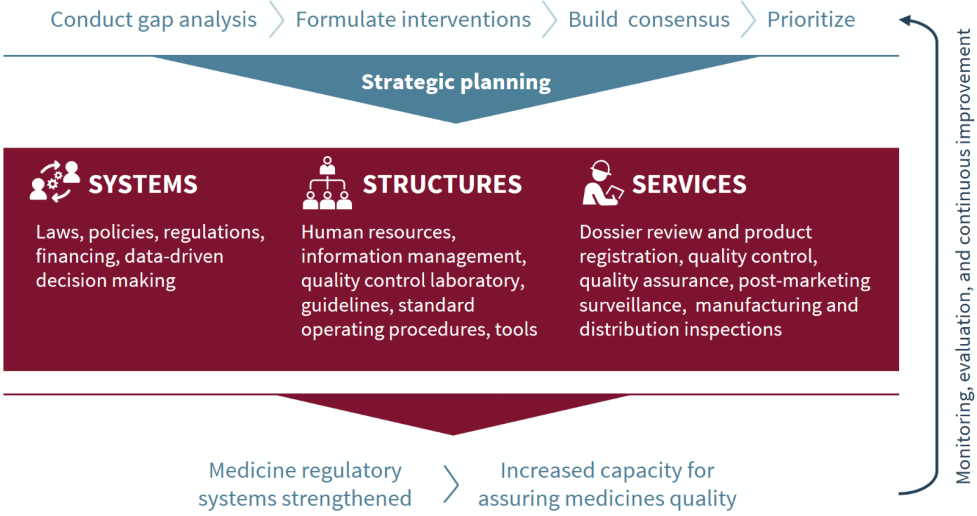
In Nigeria, PQM focused technical assistance on the laboratory with the strongest capability, Agulu laboratory, while staff from Kaduna laboratory visited to benefit from the support. Agulu laboratory successfully attained ISO accreditation in 2016, and Kaduna followed in 2017. In Myanmar, similar to the approach taken in Nigeria, the most advanced laboratory, Nay Pyi Taw, was the first to receive PQM's technical assistance beginning in 2015. The other two laboratories, Mandalay and Yangon, began sending their quality assurance and quality control managers to build simultaneous capacity. Nay Pyi Taw successfully obtained ISO accreditation in 2016.

In Kazakhstan in 2016, PQM performed initial assessments of three NQCLs in Karagancia, Pavlodar, and Kostanay to gauge their compliance with WHO prequalification requirements. During assessments of each laboratory, staff from the other two laboratories attended to learn from each other's experience and to facilitate consistent progress across all three laboratories.

The PQM Approach

The goal of the PQM program is to strengthen quality assurance systems to sustainably ensure the quality and safety of medical products. A critical component of this work involves collaborating with MRAs to build and strengthen regulatory systems and improve regulatory functions. Figure 4 illustrates the framework PQM uses to guide its regulatory systems strengthening work.

Figure 4. PQM implementation approach to building regulatory capacity in LMICs



The framework above guides overall implementation of PQM's work with MRAs; however, PQM tailors specific areas of assistance to fit the needs of individual countries or regions and works with the regulatory authorities to build sustained capacity for implementation of best practices, standardized procedures, effective organizational management, and strong and resilient systems for essential regulatory functions.

Based on implementation experience and field study, PQM has identified critical priority areas (see table 1) that support strengthening of regulatory agencies in LMICs. The priority areas are interconnected and together help to ensure the quality of medicines during manufacturing, assessment, registration, importation, and throughout the supply chain.

PQM's approach (figure 4) begins with a detailed situational assessment and gap analysis that informs the development of pragmatic and proportionate strategic and institutional development plans. Consensus-driven interventions are prioritized based upon potential risks to public health and designed to strengthen the systems, structures, and services that contribute to robust and resilient regulatory capacity within a country. PQM provides hands-on and follow-up support in line with current regulatory best practices and regional harmonization efforts, while seeking complementarity and collaboration among key partners. PQM's approach fosters sustainability by linking to national health and pharmaceutical strategies, actively engaging stakeholders and seeking buy-in from partners, addressing financing and human resources, and advocating for accountability and transparency.

Table 1. PQM technical priority areas

Technical support area	Description
Development of national and pharmaceutical sector profiles	Developing profiles of the pharmaceutical sector and regulatory capacity, and assesses the impact on regulatory governance, access to medicines, and distribution of falsified and substandard medicines.
Review of pharmaceutical laws, regulations, and policy documents	Supporting the development and revision of regulations and policies related to pharmaceutical quality, as well as best practice guidelines and procedures for registration, inspection, and quality control activities.
Adoption of CTD and good review practices	Building local capacity to enable countries to adopt the CTD format to streamline dossier submission and review processes in line with good review practices.
Standards for transmission of regulatory information	Providing technical advice on data integrity and other relevant standards for the appropriate management of regulatory information related to product registration, manufacturing, laboratory inspections, licensing, post-marketing surveillance, and other regulatory functions.
Dossier evaluation and GMP	Conducting trainings and providing consultation on dossier evaluation and GMP inspections to build capacity for efficient and effective risk-based assessment of product dossiers, inspection of facilities, and issuance of market authorization/registration.
Pharmaceutical Inspection Cooperation Scheme (PIC/S)	Strengthening inspection capability to adhere to common inspection standards and, where applicable, supporting countries with PIC/S ascension.
Post-approval support to manufacturers and regulators	Helping countries to navigate the implications of WHO prequalification on procurement, treatment guidelines, essential medicine lists, and local manufacturing plans.
Post-marketing surveillance	Strengthening or establishing coordinated, strategic, and risk-based post-marketing surveillance programs.
Risk-based quality assurance for effective regulatory systems	Providing guidance to countries in adopting risk-based regulatory practices as models for self-sufficiency and sustainability.
Laboratory quality management system strengthening	Developing or strengthening laboratory managerial and technical capacity, and improving processes and procedures required to comply with ISO 17025, WHO prequalification, and ICH 10.
Analytical instrumentation support	Supporting NQCLs in managing and maintaining their analytical instrumentation and building expertise of NQCL staff, national metrology institutes, and/or contract service providers to share resources and reference standards.
Official medicine control laboratories	Developing classroom and hands-on technical training for the analysis of active pharmaceutical ingredients and finished pharmaceutical products to build individual and institutional capacity in pharmaceutical inspection and confirmatory testing.
Collaborative Learning Model	Using a train-the-trainer model to encourage peer-to-peer knowledge sharing and allow laboratory personnel to mentor and build capacity of personnel from other laboratories, thus promoting sustainability of the laboratory network.

Box 9. Key PQM publications on strengthening quality assurance systems

- A Risk-Based Resource Allocation Framework for Pharmaceutical Quality Assurance for Medicines Regulatory Authorities in Low- and Middle-Income Countries
- Guidance for Implementing Risk-Based Post-Marketing Quality Surveillance in Low- and Middle-Income Countries
- Strengthening National Quality Control Laboratories in Low- and Middle-Income Countries to Improve the Quality of Medicines
- Analytical Instrumentation Support for National Quality Control Laboratories
- Monitoring the Quality of Medicines: Results from Africa, Asia, and South America
- The Three-Level Approach: A Framework for Ensuring Medicines Quality in Limited-Resource Countries
- Ensuring the Quality of Medicines in Resource-Limited Countries: An Operational Guide

Gap analysis

PQM structures its gap analysis to capture qualitative and quantitative data that help identify national, sectoral, and international trends within the context of the specific agency. Conducting a gap analysis helps PQM to understand the status of current regulatory quality assurance/quality control systems, how they are functioning, and opportunities for improvement. The purpose of the gap analysis is to identify gaps and needs, in terms of both technical and human resources, to help strengthen the capacity of the country's medicines quality assurance and regulatory systems.

PQM's gap analysis consists of planning, desk review, field assessment, analysis, and dissemination of findings and recommendations.

- **Planning:** setting up a competent assessment team or working group that is approved by the relevant authority and is made up of individuals with a relevant combination of skills and expertise.
- **Desk review:** review of relevant information on pharmaceutical laws, regulations, policies, and guidelines concerning the quality assurance and quality control of pharmaceutical products, including the supply, distribution, and sale of medicines in the country, as well as the key functions of the MRA, NQCL, and other quality control laboratories.
- **Field-based regulatory assessment:** creating a customized tool adapted from the WHO Global Benchmarking Tool and PQM assessment tools to conduct detailed field-based assessments of MRAs.
- **Analysis:** analyzing the components of medicines regulatory, quality assurance, and quality control systems to determine the needs for capacity strengthening.
- **Dissemination of findings and recommendations:** suggesting key strategic priorities and interventions to strengthen national or regional regulatory and quality assurance systems.

Strategic planning

A strategic plan helps the MRA reach its overarching organizational goals in a strategic manner and, when connected and aligned with national health sector goals and plans, can increase the visibility of MRA activities within a country's national agenda. Strategic plans describe the action that an organization must take to reach its short-, medium-, and long-term goals. Strategic plans also help MRAs fulfill their organization's mission and value statements. PQM assists MRAs to develop strategic plans and incorporates MRA development priorities identified during the gap analysis (see box 10).

The gap analysis report highlights the areas that need to be strengthened and identifies the areas to be prioritized in the implementation of activities. This forms the basis for the strategic plan. The MRA should identify key strategic priorities for a course of 5 years and should plan for their effective implementation, including necessary human and financial resource requirements. A strengths, weaknesses, opportunities, and threats (SWOT) analysis of the MRA should be carried out as part of the development of the strategy plan. The purpose of this SWOT analysis is to clearly identify the internal strengths that can be built upon, weaknesses that need to be addressed, opportunities for improvement, and external threats that may influence the implementation of the strategic plan.

The MRA should appoint a committee composed of competent individuals in regulatory practices to help develop and vet the content of the strategic plan. The appointed committee would be responsible for developing and implementing the agreed-upon activities in the strategic plan. This will help to build capacity and sustainability within the MRA.

An MRA strategic plan typically covers a period of 5 years and should have several critical components, including the MRA's institutional background, role in protecting public health, strategic priorities, sustainability plan, communication strategy, and monitoring and evaluation framework. The strategic plan should enumerate expected costs; have short-, medium-, and long-term milestones and deliverables; and be implemented through an annual operational plan.

Box 10. Shaping regulatory advancements in Bangladesh, the Philippines, and Senegal through strategic planning

PQM assisted regulatory authorities in Bangladesh, the Philippines, and Senegal to establish, define, redefine, and execute their regulatory mandate to competently regulate pharmaceutical products from pre- to post-market. PQM began its first in-country activity in Bangladesh by conducting a gap analysis to determine the country's medicines regulatory capacity-strengthening needs. The findings of the gap assessment, as described in a technical report, formed the basis for the Directorate's Annual Strategic Plan and the National Health Sector Plan (2016–2020). PQM provided technical assistance to the Philippine Food and Drug Administration to develop its 5-year strategic plan (2017–2021) through the creation of terms of reference with specific competencies. The strategic priorities for strengthening the administration include reducing the time for processing registration applications and attaining a zero backlog, as well as strengthening administrative and regulatory actions. PQM worked with the Senegalese Directorate of Pharmacy and Drugs to incorporate critical elements into a draft 5-year strategic plan, recommending the creation of an inspection department, the recruitment of qualified personnel, a list of training needs (GMP, dossier evaluation), and the creation of an efficient medicines registration system.

Monitoring and evaluation

As part of its efforts to strengthen regulatory systems, PQM works to collect and measure indicators associated with medicines quality and regulation. Regular monitoring helps to incorporate continuous quality improvement into the processes and interventions developed by regulatory authorities and laboratories. Monitoring and evaluation also help to generate data to understand the progress and outcomes of PQM assistance, make decisions for adaptive management purposes, and understand where gaps remain.

Lessons Learned and Future Directions

Despite the tremendous strides that have been made to strengthen regulatory and quality assurance systems in recent years, significant challenges that are inimical to public health persist. Additionally, as the regulatory environment grows more complex, PQM is working to capture lessons from its years of implementation while also looking toward activities and areas that should be prioritized in the future. Going forward, emphasis should be placed on helping countries to adopt good regulatory practices involving harmonization or convergence, reliance, work sharing, information sharing, transparency, and risk-based approaches to medicines regulation.

Risk-based approaches to medicines regulation should be used to protect the public while making the most of limited resources

PQM's extensive experience in conducting medicines quality monitoring exercises in partnership with MRAs led PQM to develop guidance and subsequently assist several countries in establishing or strengthening institutionalized and regular risk-based post-marketing surveillance programs. By establishing post-marketing surveillance as a regulatory function and by using risk-based approaches to sampling and testing, MRAs can use data to inform and drive their post-marketing surveillance activities. This also places the MRA at the center of post-marketing activities, solidifying its role as leader and coordinator, thus reducing ad hoc, non-strategic, or unsound medicines quality surveys. This ensures that resources and data are better utilized to protect the public. Coordination among medicines quality and safety surveillance teams is also critical to ensure the data gathered can be fully interpreted and utilized. Risk-based approaches are not only useful for post-marketing surveillance but can also be applied to a range of regulatory activities, including dossier review, facility inspections, quality control testing, and regulatory actions.

Regulatory convergence, harmonization, and reliance efforts build collective capacity

LMICs stand to benefit immensely from regulatory convergence, harmonization, and reliance efforts, particularly if those efforts are implemented in transparent, accountable, and participatory ways that encourage capacity building of MRAs in key areas. For instance, countries that have moved to adopt the standardized CTD format for dossier applications are reducing their regulatory burden while also facilitating an easier submission process for manufacturers that no longer have to submit dossiers in multiple different formats.

In addition, joint dossier review sessions, such as those supported by PQM in the East African Community, allow countries to participate in the dossier review process and make approval decisions based on the joint reviews. This helps to expedite the time required to bring a product to market, as a manufacturer does not have to submit individual applications to each regulatory authority within the region. Regional workshops are also helping to advance regional regulatory capacity and support implementation of ICH and WHO guidelines. A 2017 workshop led by PQM for EAC regulators helped to enhance regional capacity for implementing good clinical practices and assessing bioequivalence data for market authorization in support of the AMRH initiative.[28] These types of regional capacity-building efforts, which also strengthen national-level competencies in quality assurance, will continue to be critical in making advances in regulatory convergence and harmonization initiatives.

Strengthening networks of quality control laboratories starts with sustainability

The important and central role of NQCLs in ensuring product quality means that any effort to strengthen quality control laboratories must start with a thorough consideration of how advances can be made sustainably. PQM learned that only through a multifaceted approach rooted in systems thinking could sustainable progress be achieved. This includes addressing cross-cutting laboratory challenges, such as staffing, skill building, and laboratory management in several different ways:

- Using the Collaborative Learning Model, PQM worked to strengthen the capacity of several laboratories concurrently and foster connections among laboratories so that each laboratory could serve as a resource to the others. This work also served to standardize laboratory functions, documents, and processes across laboratories, making it easier for information exchange and learning to occur.
- Reviewing cost and fee structures for several laboratories led PQM to make recommendations for revised fee structures that would help ensure laboratories charge appropriate fees that cover the costs of laboratory testing and help move them toward more sustainable business models.
- Supporting laboratories in attaining method-based accreditation rather than seeking accreditation for testing of single products widened the number of products that a newly accredited laboratory could test and thus increased their potential client pool and number of products being submitted for testing.

Looking ahead: future priority areas

Efforts to strengthen regional bodies and national regulatory authorities in LMICs must remain relevant and responsive to a rapidly changing pharmaceutical sector. The challenge of regulating the production and distribution of complex products, such as biologics, combined with a growing number of national and international stakeholders involved in regulating product quality and increasingly complex supply chains, means that MRAs in LMICs need to keep pace with an ever-evolving field. This is critically important as some middle-income countries are transitioning or graduating from donor-led procurement and becoming locally responsible for sourcing medicines with relatively weak or vulnerable supply chains and regulatory systems. Key areas that may warrant increased focus in the future include:

- Conducting **multi-country/regional cross-border post-marketing surveillance activities** to assess the quality of medicines in key regions.
- Assisting countries in using data to identify and implement **appropriate screening technologies** into post-marketing surveillance programs.
- Supporting the adoption of **traceability and serialization standards** to support medicines quality and improve the ability of MRAs to issue recalls.
- Strengthening the **regulation of medical devices, including diagnostics,** which are increasing in complexity and are often poorly regulated in most LMICs.
- Developing and implementing **guidelines for bioequivalence** to ensure that manufacturers are able to prove that generics are absorbed and act in a way that can be considered equivalent to the innovator product.

- Strengthening support for **analytical instrumentation maintenance and calibration** to reduce reliance on contract service providers.
- Supporting **preservice curriculum review and revision** at additional universities and training centers in LMICs.
- Using **data standards and integrated regulatory information systems** to improve information sharing, data mining, risk modeling, and analytics to support medicines quality research objectives.
- Reducing regulatory barriers to support **local and regional pharmaceutical production and manufacturing,** including introducing preferential policies and implementing harmonization standards and reliance mechanisms.
- Strengthening **coordination and harmonization** efforts conducted under the African Medicines Agency and other harmonization initiatives.

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