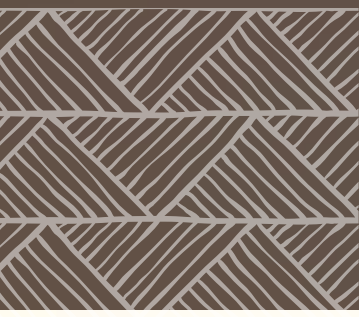


Final Report

2009-2020

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Promoting the
QUALITY of
MEDICINES



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Note from the **DIRECTOR**



Nearly 2 billion people worldwide lack access to essential medicines. At the same time, for those living in low- and middle-income countries who have access to medicines, it is estimated that at least 10 percent of products available are substandard or falsified.¹ In the countries and communities with the weakest health systems, the proliferation of poor-quality products is likely far greater. For the past 10 years, the U.S. Agency for International Development (USAID) and the U.S. Pharmacopeia (USP) partnered through the Promoting the Quality of Medicines (PQM) program with countries to develop sustainable quality assurance systems that can both increase patients' access to quality-assured, safe and effective priority products and decrease the prevalence of falsified and substandard medicines. These urgent public health goals are two sides of one coin.

Poor-quality medicines undermine the treatment of priority diseases such as tuberculosis, malaria and HIV/AIDS, and can contribute to antimicrobial resistance by incompletely treating disease. Funded by USAID and implemented by USP, PQM dedicated itself to protecting public health by strengthening the quality assurance systems that are the foundation of medicines regulation and manufacturing. These systems are the only safeguard patients have from the silent threat of poor-quality medicines; patients are not able to tell whether the medicines they receive are of poor quality and may cause them harm.

It is extremely satisfying for me to see the many accomplishments of PQM and its partner countries described in this report, but it is essential for us to also use this opportunity to take an extensive look at what we have discovered during 10 years of implementation. Our lessons

learned will inform and improve future programming to strengthen country medicines quality assurance systems. Above all, PQM's experiences across Africa, Asia, Central Asia, and Central and South America have shown us that quality assurance systems for medicines regulation and medicines manufacturing are interdependent. Interventions to strengthen both must occur in parallel, especially in countries with local manufacturing capacity.

Being a part of the PQM program and seeing the progress that our in-country partners have made to improve their medicines quality systems and ensure the availability of quality-assured products for their populations has been one of the most fulfilling and enlightening experiences of my career. It has been a great honor to share this journey with committed stakeholders at the global, regional and country levels.

Please join me in continuing to advocate for progress toward ensuring that quality-assured medicines are always available to patients, no matter who they are or where or when they need them.

Jude I. Nwokike
Director,
PQM Program

Nearly **two billion** people worldwide **lack access** to essential medicines

About the PQM Program

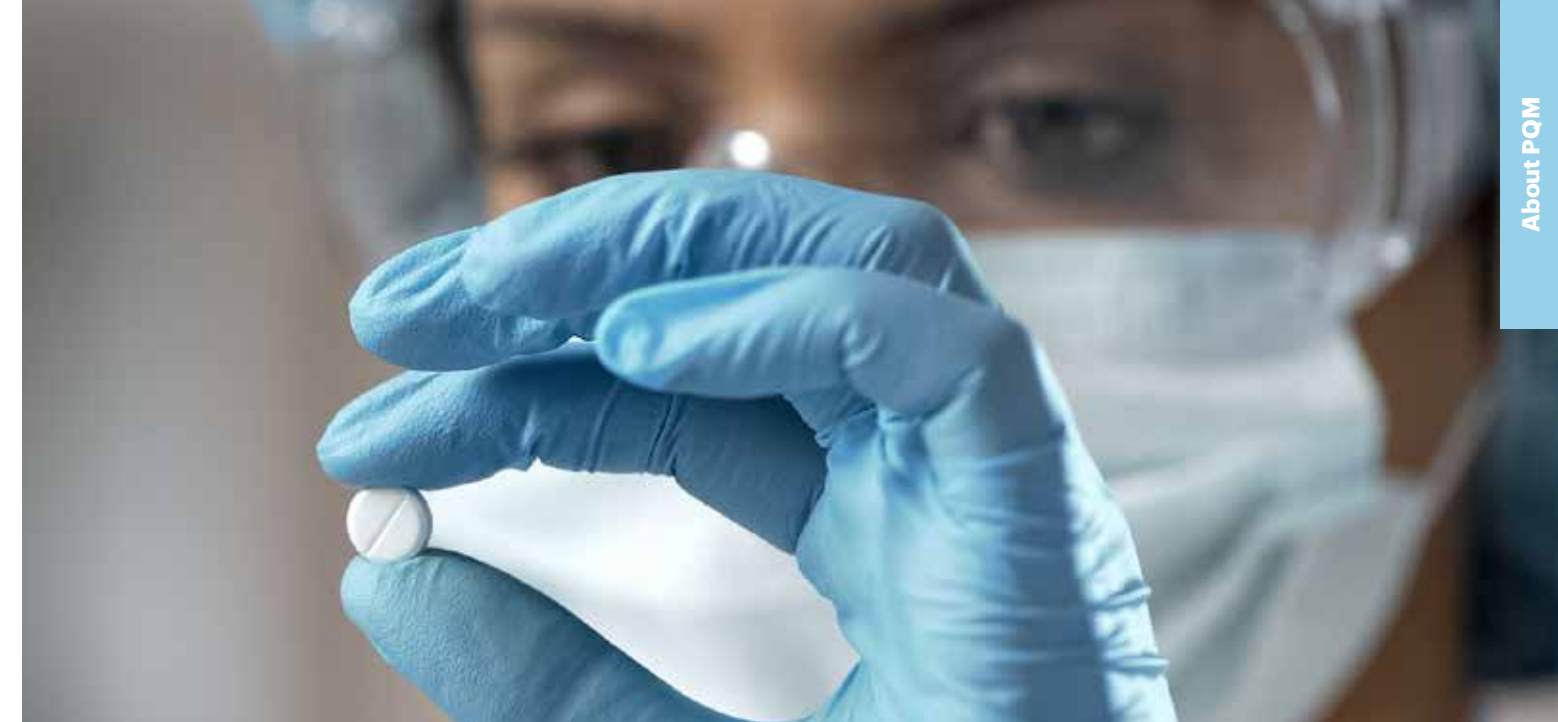
USAID Funding Sources	Bureau for Global Health, Office of Health Systems, Office of Infectious Disease, Office of Maternal/Child Health and Nutrition, USAID Country Missions
Name of Implementing Partner	Promoting the Quality of Medicines Implemented by the U.S. Pharmacopeial Convention
Cooperative Agreement Number	GHS-A-00-09-00003-00
Period of Performance	September 18, 2009, to September 17, 2020
Agreement Officer's Representative Team	Alison Collins, Health Systems Advisor Elisabeth Ludeman, Senior Pharmaceutical Management Advisor Tobey Busch, Senior Pharmaceutical Management Advisor
PQM Responsible Staff	Mr. Jude Nwokike, Director

The Promoting the Quality of Medicines (PQM) program was a Cooperative Agreement between the U.S. Agency for International Development (USAID) and the U.S. Pharmacopeial Convention (USP). Beginning in 1992, USP worked with USAID to address critical medicines information and quality challenges in low- and middle-income countries. The earliest program, the Rational Pharmaceutical Management Project, implemented and evaluated country-specific drug information resource programs in selected developing countries. Subsequently, the Drug Quality and Information program focused on medicines quality control and quality assurance systems. The PQM program (2009–2019) provided technical assistance to strengthen medicines regulatory authorities and quality assurance systems and support manufacturing of quality-assured priority medicines for malaria, HIV/AIDS, tuberculosis, neglected tropical diseases, and maternal and child health.

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Promoting the Quality of Medicines. 2018. Promoting the Quality of Medicines Program Annual Performance Report: Fiscal Year 2018, October 1, 2017–September 30, 2018. Submitted to the U.S. Agency for International Development by the Promoting the Quality of Medicines Program. Rockville, MD: U.S. Pharmacopeial Convention (USP).

This document is made possible by the generous support of the American people through the U.S. Agency for International Development. The contents are the responsibility of the Promoting the Quality of Medicines program and do not necessarily reflect the views of USAID or the U.S. Government.



Acronyms

API	active pharmaceutical ingredient	NOMCoL-SSA	Network of Official Medicines Control Laboratories–Sub-Saharan Africa
CEP	Certificate of Suitability of Monographs of the European Pharmacopoeia	NQCL	national quality control laboratory
CHX	chlorhexidine	NTD	neglected tropical disease
CRO	clinical research organization	PIR	Product Information Report
EFMHACA	Ethiopian Food, Medicine and Health Care Administration and Control Authority	PMS	post-marketing surveillance
ERP	expert review panel	PPH	postpartum hemorrhage
FPP	finished pharmaceutical product	PQ	prequalification
GDF	Global Drug Facility	PQM	Promoting the Quality of Medicines (program)
GMP	good manufacturing practices	QMS	quality management systems
IEC	International Electrotechnical Commission	SOP	standard operating procedure
IGAD	Intergovernmental Authority on Development	SRA	stringent regulatory authority
IR	intermediate result	TB	tuberculosis
ISO	International Organization for Standardization	UN	United Nations
LMIC	low- and middle-income country	UNICEF	United Nations Children's Fund
MDR-TB	multidrug-resistant tuberculosis	U.S. FDA	U.S. Food and Drug Administration
MNCH	maternal, newborn and child health	USAID	U.S. Agency for International Development
MQDB	Medicines Quality Database	USP	U.S. Pharmacopeia
MRA	medicines regulatory authority	WHO	World Health Organization
NAFDAC	National Agency for Food and Drug Administration and Control (Nigeria)		



Medical Product Quality:

A Critical Component of Health Systems Strengthening

Making sustainable and long-term progress against global health threats such as tuberculosis (TB), malaria, HIV/AIDS, neglected tropical diseases (NTDs) and antimicrobial resistance, as well as improving the health of women, children and communities, requires sustained and coordinated investment in strengthening health systems. Strong and resilient health systems help improve universal access to quality-assured, safe, effective and affordable essential medical products and health services.

A foundational requirement for strong health systems and gains against global health threats is the continuous availability of quality-assured medical products. Yet, in many parts of the world, the systems that help ensure the quality of medical products are not strong enough to keep poor-quality medical products from reaching patients. These systems are also the least equipped to deal with the repercussions: prolonged disease that is more complicated and costly to treat, the emergence and spread of drug resistance, and loss of confidence in the health system, to name a few.

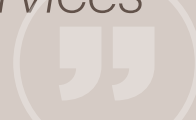
Therefore, strengthening medical product quality assurance systems must go hand in hand with health systems strengthening efforts, particularly

as countries endeavor to achieve universal health coverage through expanded coverage of health products and services. To do good and not harm, those products and services must be of assured quality.

From 2009 to 2020, the Promoting the Quality of Medicines (PQM) program, funded by the U.S. Agency for International Development (USAID) and implemented by the U.S. Pharmacopeia (USP), worked to strengthen medical product quality assurance systems and support manufacturing of quality-assured essential medicines for malaria; HIV/AIDS; TB; NTDs; and maternal, newborn and child health (MNCH).

PQM was USAID's first centrally managed program aimed at improving and diversifying the sources of quality-assured priority products critical to USAID's initiatives to combat infectious diseases such as TB, malaria and HIV/AIDS, as well as conditions related to MNCH. The program worked through a systems strengthening approach in alignment with USAID's Vision for Health Systems Strengthening and efforts to advance priority countries on the path to self-reliance.

Strong and resilient health systems help improve universal access to affordable, essential medical products and health services



PQM's Systems Strengthening Approach

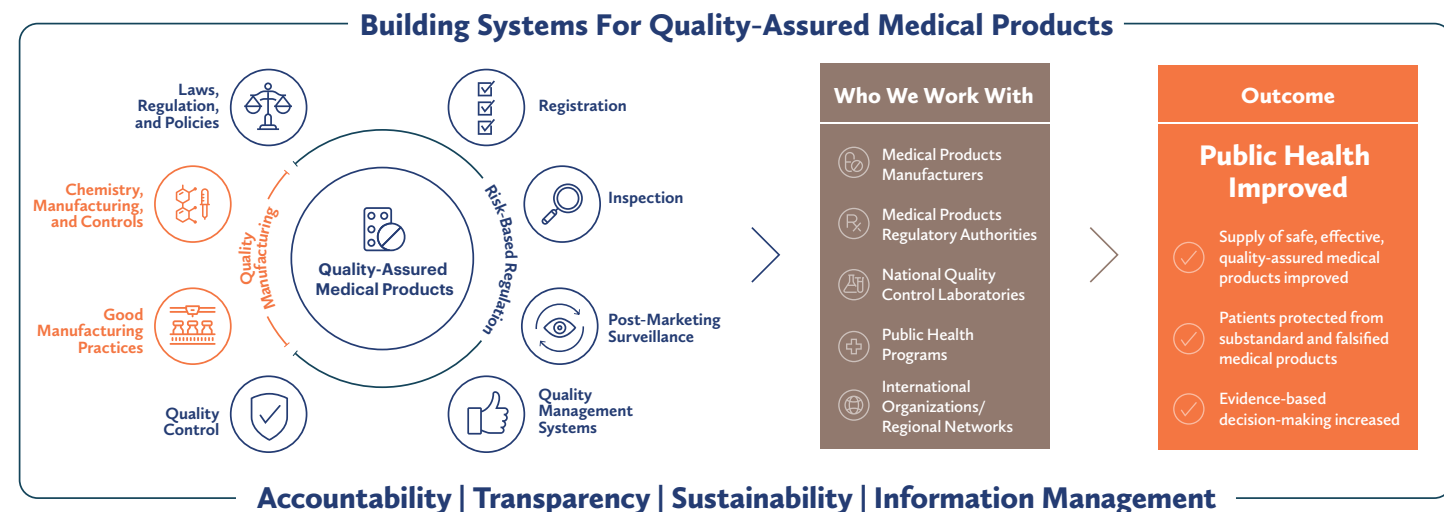
Our Approach

The PQM approach reflected a holistic view of medicines quality assurance—seeking to address quality-related aspects of medicines production, medicines regulation, patient use and everything in between—to sustainably strengthen and improve the systems, structures and processes that promote product quality. This approach recognized the dynamic and cross-cutting relationships among different components of the health system and therefore aimed to address product quality issues in a sustainable manner using systems-based thinking and solutions. The framework below serves as a visual guide for how PQM helped countries build quality assurance systems for medicines by working with key stakeholders in the areas of quality manufacturing and risk-based regulation to safeguard public health and achieve critical global health outcomes.

As the implementing partner for PQM, USP worked with a multitude of stakeholders to advance medical product quality assurance systems:

- National regulatory authorities and regional regulatory bodies to strengthen the governance and legal frameworks for medical product quality assurance
- Medicines quality control laboratories to improve the ability of countries to reliably test the quality of products on the market
- Academic and training institutions to ensure new graduates in pharmacy and regulatory sciences are ready to tackle quality assurance challenges in the workforce
- Manufacturers in the private sector in low- and middle-income countries (LMICs) to elevate medical product production practices to be in line with international standards
- Research organizations to conduct rigorous bioequivalence studies that help improve access to generic products
- Multinational pharmaceutical companies to facilitate technology transfer for essential medical products to local manufacturers

PQM Technical Framework



PQM Principles

The PQM program was implemented in accordance with the following principles:

- **Regional harmonization:** Harmonization at the regional level helps leverage resources to address regulatory needs across multiple countries and encourages South-to-South collaboration.
- **Risk-based and pragmatic solutions:** Assessing local risks to public health helps prioritize interventions and direct human and financial resources where they are most needed.
- **Complementarity and partnership:** PQM works with other implementing partners, multilateral organizations, government agencies, and academic institutions to coordinate efforts and maximize results.
- **Internationally recognized standards and best practices:** PQM assists countries to build on existing systems to achieve international standards such as WHO prequalification and ISO/IEC 17025.
- **Resilience and sustainability:** We seek to improve the quality of medicines by addressing cross-cutting quality assurance issues that influence quality through systems-based approaches and solutions.

Progress on the Path to Self-Reliance

The PQM approach to implementation and partnership enabled the program to make progress in its three intermediate results (IRs) and the overall program goal. Through its technical assistance efforts, PQM worked with medical product regulators in USAID priority countries at varied levels of regulatory maturity through incremental and sustainable steps to help them advance on the path to self-reliance and protect populations from poor-quality medicines.






The program's approach was tailored and adapted to provide state-of-the-art support to countries across the regulatory maturity spectrum, including countries that worked to strengthen nascent regulatory systems, as in the case of Liberia, and those with institutionalized advanced regulatory capabilities, as in the cases of Ethiopia and Nigeria. This report highlights the major advances in medical product quality assurance systems in the countries in which PQM worked and highlights progress made in the key health areas of malaria, TB, HIV/AIDS, NTDs and MNCH.

The program's approach was tailored and adapted to provide state-of-the-art support to countries ”


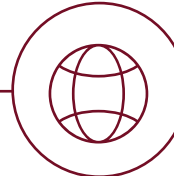
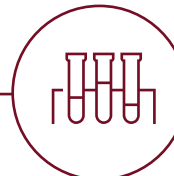
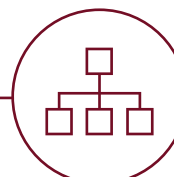


Quality assurance systems strengthened to sustainably ensure quality and safety of medical products and protect public health




IR1 Medical products quality assurance systems strengthened

-  **IR1.1**
Quality assurance policies, legislation, guidelines and procedures improved
-  **IR1.2**
Registration, inspection, and licensing functions of medicine regulatory agencies sustainably improved (pre-market)
-  **IR1.3**
Standard of practices at national quality control laboratories sustainably improved
-  **IR1.4**
Institutional capacity for regulatory workforce sustainably improved
-  **IR1.5**
Capacity for post-marketing surveillance of medical products sustainably improved

IR2 Supply of quality-assured priority medicines increased

-  **IR2.1**
Quality-assured priority medicines produced locally increased
-  **IR2.2**
Quality-assured priority medicines produced globally increased
-  **IR2.3**
CROs' compliance with good clinical practices and good laboratory practices increased
-  **IR2.4**
Sources of quality-assured API and FPP diversified and supply secured

IR3 Utilization of medical product quality information for decision-making increased

-  **IR3.1**
Availability of information related to quality of medical products increased
-  **IR3.2**
Enforcement actions against falsified, substandard and unapproved medical products increased
-  **IR3.3**
Information on quality assurance of medical products used for advocacy increased





IR1

Medical products quality assurance systems strengthened

Medical products are instrumental to any health system, but only if they are safe, effective and affordable, and if processes are in place to ensure their quality. Quality is paramount to ensuring the safety and efficacy of medicines and medical products are maintained, from the moment a product—including its raw materials—is manufactured, across the entire supply chain, until it reaches the patient.

By strengthening systems that help ensure quality—from developing effective and enforceable legislation, policies and workforce capacity to helping implement regulations, guidelines and operational procedures—the PQM program aimed to address the end-to-end challenges that affect medicines quality. The ultimate goal was to reduce and eliminate substandard and falsified products that pose serious risks to patients' health and undermine health and development efforts.

Quality assurance policies, regulations, and legislation

National medicines policies define the requirements that help ensure medicine access, quality and rational use. A medicines policy also serves as the framework for developing sound pharmaceutical law, which provides the legal mandate for the creation of a national medicines regulatory authority (MRA).

Working with in-country stakeholders, PQM provided technical assistance to 12 MRAs to develop or revise 25 national policies and regulations, as well as legislation to ensure quality assurance topics were adequately covered and that the overarching regulatory framework was appropriate to their context and met internationally accepted standards.

As a notable example, PQM's earliest days included an assessment of Liberia's quality assurance capacity following several years of conflict. The assessment revealed significant gaps, including the absence of a regulatory agency for medical products and of a laboratory that could reliably test medicines quality. These findings informed advocacy efforts that led to the development of a pharmaceutical law in 2010. The law established the Liberia Medicines and Health

Product Regulatory Authority as an MRA with the mandate of assuring the safety, efficacy and quality of medical products in the country. The legislation also allowed for the establishment of a national quality control laboratory (NQCL), a registration department and an inspectorate to focus on post-marketing surveillance (PMS) for product quality. Subsequently, PQM helped establish key guidelines and policies, introduce standard operating procedures (SOPs), build staff capacity and skills, and procure laboratory equipment; today, the regulatory authority carries out its main functions according to its mandate.

Similarly, in Guinea and Mozambique, PQM supported the revision and enactment of pharmaceutical laws that gave MRAs the authority to improve regulation of medical products in order to ensure their quality, safety and efficacy at the national level. See figure 1.

At a more granular level, guidelines, SOPs and quality manuals are regulatory tools meant to guide MRA practices and provide instructions for performing operations. During its 10 years, PQM supported 16 country MRAs and two regional initiatives to develop or update more than 2,100 of these documents to improve quality systems.

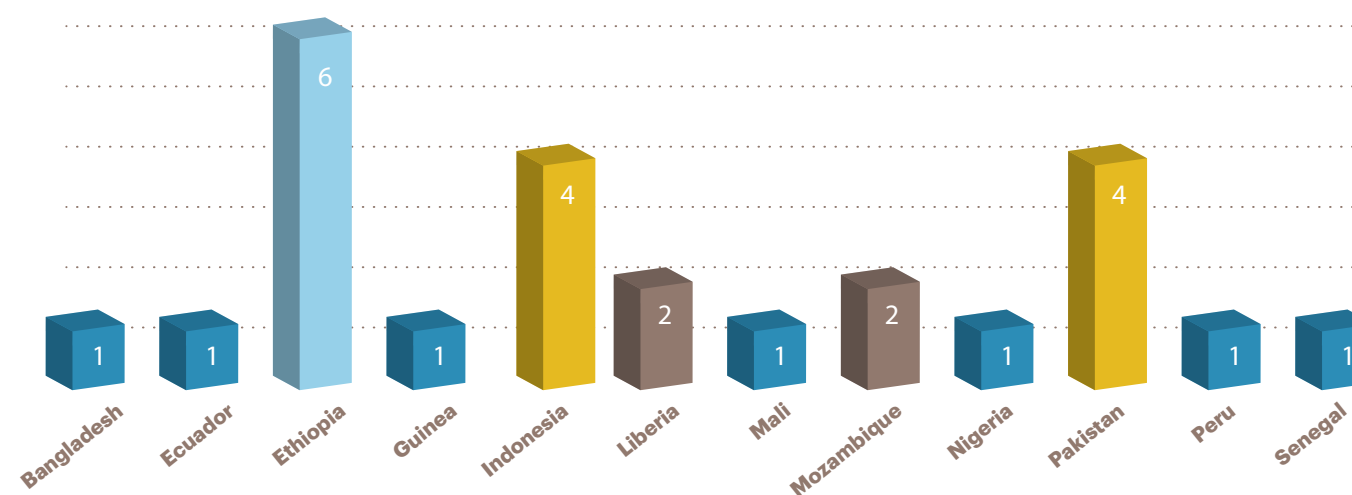
Pre-market regulatory functions

Among the key functions of an MRA, the registration or approval of medical products and the inspection and licensing of manufacturing facilities are crucial processes designed to ensure that only quality-assured products are allowed to enter the market.

PQM worked with MRAs to build strong institutional capacity and support registration and licensing through hands-on training of regulatory staff, as well as establishment and institutionalization of quality management systems (QMS) according to international standards to strengthen country regulatory functions. By helping MRAs prioritize key issues through risk-based approaches, PQM guided regulatory agencies to focus their pre-market resources toward solutions that add value and result in high-impact and sustainable health outcomes.

In Ethiopia, for example, improved processes and the capacity to review dossiers for new medicines resulted in increased efficiency and a 25 to 40 percent reduction in registration times while ensuring the integrity of reviews following good regulatory review practices, facilitating timely access to essential medicines in the country.

Figure 1: National medicines quality assurance policies, regulations and legislation developed or updated and submitted for adoption 2009-2019



Standard of practices at national quality control laboratories

MRAs, national medical product procurement agencies and international donors require reliable and accurate data from quality control testing laboratories during the medicines registration process, to confirm poor product quality and enable enforcement action (whether punitive and/or corrective) following PMS, as well as to ensure that procured and donated products meet quality requirements.

At the inception of PQM, many LMICs, even those with large pharmaceutical industries, lacked national drug quality control laboratories to reliably test drug quality following international standards. This represented a serious deficiency and vulnerability in the health system. To help ensure consistently reliable and accurate data, PQM provided support to build the capacity of 91 quality control laboratories in 33 countries to improve laboratory standards through specialized assessments and technical assistance to reform processes and procedures and improve staff skills. Importantly, PQM emphasized strengthening and institutionalizing laboratories' QMS to attain

certifications of compliance with internationally recognized standards, such as ISO/IEC accreditation or WHO PQ. As a result, 21 laboratories in 14 countries achieved 28 instances of initial ISO/IEC 17025 accreditation or WHO PQ during the following years, as seen in Table 1.

On a scheduled basis, accrediting bodies will reassess laboratories to ensure they continue to comply with international standards. During the life of the program, *PQM-supported laboratories attained 37 instances of reaccreditation or requalification, reaffirming their ability to produce reliable and accurate data.*

In addition, several laboratories expanded the scope of their testing capabilities beyond their initial accreditation for additional test methods. As laboratories increase their testing capabilities, they can expand their capacity from testing only pharmaceuticals to more advanced microbiology and biologic testing methods and medical devices, including condoms. This has been the case in Nigeria, with multiple laboratories now able to test more complex medical products, and in Ethiopia, which added the capability to test condoms.

Table 1: International recognition for laboratory competency

Country	ISO/IEC 17025 (Pharmaceuticals)	ISO/IEC 17025 (Microbiology)	ISO/IEC 17025 (Biologics)	ISO/IEC 4074 (Medical Devices)	WHO PQ (Pharmaceuticals)	WHO PQ (Microbiology)
Bolivia					2010	
Ethiopia	2011			2014		
Ghana	2014	2017		2017		
Guatemala	2015					
Indonesia (Jakarta)					2019	
Kenya	2015				2018	2018
Laos	2014					
Myanmar	2016					
Nigeria (Agulu)	2016	2017				
Nigeria (Kaduna)	2017	2018				
Nigeria (*NIPRID)	2018					
Nigeria (Vaccines and Biologics)	2019		2019			
Nigeria (Yaba)	2014	2017				
Pakistan (*PDRTC)					2019	
Peru					2010	2010
Russia (Khabarovsk)	2016					
Russia (Krasnoyarsk)	2014					
Russia (Rostov-on-Don)	2014					
Russia (Yekaterinburg)	2016					
Thailand	2014				2012	2012

The dates presented in the table represent initial attainment of international laboratory quality standard certification.

*NIPRID - National Institute for Pharmaceutical Research and Development

*PDRTC - Pakistan Drug Testing and Research Center



Spotlight: Nigeria

As part of its efforts to expand access to quality-assured medicines, the government of Nigeria is working to ensure its ability to efficiently test medical products. Nigeria's partnership with PQM helped five Nigerian public-sector quality control laboratories achieve and maintain ISO/IEC 17025 accreditation, adhering to internationally recognized standards for medicines testing.

With expansive geographic coverage, 100 percent of quality tests for pharmaceuticals performed in the National Agency for Food and Drug Administration and Control's (NAFDAC's) three NQCLs (Yaba, *2014; Agulu, *2016; and Kaduna, *2017) are now performed in ISO/IEC-accredited facilities, providing reliable results for post-marketing surveillance.

Also managed by NAFDAC, the National Control Laboratory for Vaccines and other Biologics (NCLVB) provides the same type of testing for health product regulation as the NQCLs but does so for vaccines, biologics and medical devices. Improvements in NCLVB have enhanced Nigeria's

ability to ensure the quality of vaccines, including the Bacille Calmette-Guérin vaccine, a mandatory immunization for newborns against TB and a key public health asset in the effort to address the country's high infant mortality rates. NCLVB also works to ensure that test kits used at service delivery points for malaria, HIV and TB are quality assured.

Similarly, Nigeria's National Institute for Pharmaceutical Research and Development (NIPRD) mandate includes conducting quality assurance tests for locally manufactured medicines. As part of meeting the requirements for permission to market new or generic products in Nigeria, local pharmaceutical manufacturers rely on the NIPRD quality control laboratory to test their products pre-market.

In 2017 alone, tests performed by these five accredited laboratories informed NAFDAC's approval of 11,240 new or generic medical products for the Nigerian market.

*Year first ISO/IEC 17025 was attained.

Regulatory workforce institutional capacity

A skilled workforce for pharmaceutical quality assurance is a critical piece of the overall health system. Building workforce capacity at both central and decentralized institutions and facilities was a core component of PQM's approach.

To support in-service skills development programs, PQM adopted a collaborative learning model (CLM), in which PQM first gathered staff from multiple laboratories within each country and provided consolidated trainings to them. This ensured the material delivered was consistent, reduced costs incurred from decentralized training operations, and promoted country ownership and collaboration among laboratory staff. In cases in which one laboratory experienced a high rate of attrition, new staff were mentored by previously trained, tenured colleagues from neighboring laboratories rather than relying on foreign assistance again, promoting full organizational ownership of the process. Similarly, PQM's train-the-trainers approach ensured that countries had sustained capacity to internally train staff in certain technical areas without relying on outside support.

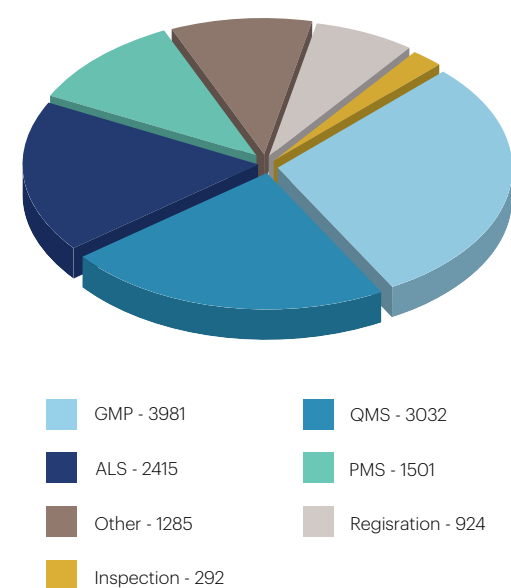
PQM experts also worked in collaboration with WHO's global, regional and national offices to provide hands-on trainings focused on a wide range of good practice guidelines (e.g., good manufacturing practices [GMP], good laboratory practices, good clinical practices) for the benefit of staff from MRAs and manufacturing facilities. In total, more than 13,000 individuals completed training in key quality assurance/quality control-related technical areas as a result of PQM support. See more details in figure 2.

PQM also supported preservice programs in academic institutions as a critical part of the long-term solution for workforce development. Curricula for both undergraduate and graduate programs were developed or reformed to address pharmaceutical quality assurance/quality control with universities

in Bangladesh, Cambodia, Ethiopia and Nigeria. The curricula aimed to address existing challenges and respond to the emerging needs of professionals in specific pharmaceutical sectors.

In Nigeria, for example, a series of stakeholder meetings identified gaps within the existing curriculum of Nigerian university programs, and a new curriculum on pharmaceutical quality system was developed for undergraduate and graduate pharmacy students. PQM supported pilot implementation of the revised curriculum at Nnamdi Azikiwe University. Instructors were trained on the new materials, were invited to observe manufacturer audits and participated in training of MRA staff on dossier evaluation. PQM also directly engaged students by delivering lectures while their

Figure 2: Number of individuals completing training in key quality assurance/quality control related technical areas 2009-2019



professors observed. After the pilot, a workshop was organized to share experiences with representatives from 22 schools of pharmacy throughout the country to enable scale-up.

By combining preservice and in-service training interventions and the development of structures and processes necessary for effective QMS, PQM worked with in-country stakeholders to build a sustainable regulatory and quality assurance workforce in Nigeria. Reform processes and procedures are equally important as—if not more important than—providing ad hoc trainings. PQM considers this fundamental to achieving sustainability.

Post-marketing surveillance

Ensuring the quality of medical products throughout the supply chain is a common challenge in LMICs. PMS, the practice of monitoring the quality and safety of pharmaceutical products after they are approved for sale in the market, is the main mechanism through which regulatory authorities detect substandard and falsified medical products in the public and private supply chains in countries.

It is unrealistic and unaffordable for countries to test the quality of every product on the market, but regulators lack tools to help them know where to look and what to test to make the best use of limited resources. PQM collaborated with MRAs to establish and strengthen country PMS programs using risk-based approaches that consider various product characteristics (e.g., temperature sensitivity, sterility requirements) and disease characteristics (e.g., burden, severity) to best direct efforts. Risk can be considered in both the sampling strategy and the plan for testing medical products. Risk-based PMS helps prioritize scarce human and financial resources through targeted sampling for the types of products for which and in locations where surveillance is most needed. In support of this, PQM developed a web-based tool, MedRS, that facilitates the design of sampling plans based on risk considerations. The

tool helps countries answer important questions they encounter when planning and implementing PMS, including which medicines, geographical locations and outlets should be sampled; how many locations and outlets should be sampled; and how many samples should be collected to have a statistically representative sample.

Risk-based PMS involves a tiered approach to monitoring the quality of medical products in the market. Compensial testing in a laboratory setting provides the most extensive and definitive information on product quality but is also the most complex, expensive and time-consuming type of testing. Costs are incurred both for sampling medical products (e.g., logistics costs) and for testing the products (e.g., some are more expensive to test than others). Using a tiered approach, countries first use screening methods such as visual inspection and field-based screening technologies to quickly examine a large, statistically representative number of samples across many geographic areas at limited cost and then determine the samples suspected of being of poor quality that should undergo more extensive compendial testing in a fully qualified quality control laboratory.

Toward this end, PQM supported MRAs to establish and institutionalize PMS procedural documents and standards to ensure the process is consistent at all levels. PQM trained field staff in sampling procedures, use of field screening tools and technologies, data management and reporting. PQM also supported MRAs to add 230 additional sampling sites for medicines quality surveillance. By building in-country capacity and skills, over 20 percent of these additional sampling sites that were originally financially supported by PQM transitioned to become fully government-funded, -owned and -sustained programs.

During the 10 years of the program, PQM supported 16 countries and three regional bodies to generate medicines quality test results for over 35,000 samples of key public health products, including those for malaria, TB, HIV/AIDS and MNCH. These PMS data are crucial for MRAs to identify poor-quality medical products and take regulatory actions when needed.

Spotlight: Indonesia

The National Agency of Food and Drug Authority of the Republic of Indonesia or Badan POM (BPOM) serves as the country's MRA responsible for medicines registration, post-marketing surveillance and other vital regulatory functions. Prior to 2015, no formal policy or regulation existed that allowed BPOM to sample public-sector medicines from government-run storage facilities, hospitals or health centers. BPOM data were also traditionally kept confidential, and dissemination of results or data sharing for decision making with other government entities, including the Ministry of Health (MOH), was minimal. In some cases, this allowed poor-quality products to circulate in the market even after they were identified.

Recognizing these challenges, PQM helped design a comprehensive

plan of action to strengthen the overall capacity of Indonesia's medical product quality assurance system through a multipronged approach involving communication, collaboration and policy change.

PQM collaborated with WHO to convene a national workshop for BPOM and MOH to discuss the challenges in collecting medicines samples for quality testing from public sector-owned facilities. The joint MOH-BPOM recommendations resulted in a national regulation that outlined the roles and responsibilities of both entities in conducting effective post-marketing surveillance, moved to include public-sector medicines in BPOM's annual sampling guidelines, and set requirements for timely data dissemination and regulation enforcement.

PQM subsequently coordinated a joint pilot sampling exercise between BPOM and MOH in which representatives from both agencies traveled to health department storage facilities in 11 provinces across the country to collect medicines samples side by side. This was the first time BPOM inspectors joined forces with provincial and district health offices in collaborative sampling and testing efforts specifically to assess the quality of public-sector medicines. The government of Indonesia plans to replicate and expand the sampling and testing of medicines from the public sector annually with the aim of incorporating these activities into the country's long-term routine post-marketing surveillance.



IR2

Supply of quality-assured priority medicines increased

A continuous supply of quality-assured products—particularly for essential medicines for TB, malaria, HIV, NTDs and MNCH—is necessary to address national health priorities and plans. Having only a limited number of manufacturers produce quality-assured active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs) weakens supply security and increases the vulnerability of supply chains to shortages, stockouts and poor-quality medicines. Further exacerbating supply challenges is the lack of economic incentives for manufacturers to produce quality-assured essential medicines, many of which have very limited markets and profit margins.

PQM worked with manufacturers to improve compliance with international quality standards to meet local and global demand for quality-assured medicines. PQM’s assistance helped increase the number of producers of essential medicines of assured quality, safety and efficacy, thus strengthening countries’ health systems to improve health outcomes and make the best use of limited financial resources.

Local production of quality-assured medicines

Many USAID-supported countries have ambitious goals to expand their pharmaceutical manufacturing industries as part of larger economic growth agendas. Local production of essential medicines of assured quality may decrease reliance on international donations and help establish a sustainable local supply. In addition, developing local manufacturing capacity where feasible and appropriate, and enhancing regulatory oversight, can improve both national and regional capabilities for sustainable sourcing of quality-assured medicines.

In support of USAID priority health programs, PQM provided technical assistance to 45 manufacturers in 12 countries for the production of 23 essential medicines (see table 2) approved by the country regulatory authorities for local market sale and global export.

A notable achievement was attained in Nigeria when its MRA, NAFDAC, issued market authorization approval to Juhel Pharmaceuticals Ltd. for quality-assured oxytocin and magnesium sulfate injections, two lifesaving maternal health products used to prevent postpartum hemorrhage and treat preeclampsia/eclampsia, respectively. PQM provided technical assistance to the manufacturer to improve its production processes (i.e., GMP) and prepare the regulatory dossier submission. For both medicines, which require sterile production, this marked the first approval granted to a local manufacturer in West Africa. Having a local supply closer to the end of the supply chain in Nigeria helps reduce supply issues and lessen opportunities for product degradation along the supply chain to impact product quality and efficacy.

PQM also worked with the Nigerian manufacturer Drugfield Pharmaceuticals Ltd. to produce quality-assured chlorhexidine gel, an antiseptic used to prevent umbilical cord infections in newborns. The product was approved and registered in Nigeria in 2014. When a tragic incidence of blindness in children occurred in 2015 after chlorhexidine liquid packaged in an eyedrop-like container was mistaken by caregivers for an eyedrop, Drugfield’s chlorhexidine gel was a ready and available substitute. The company became the first African manufacturer to supply the NAFDAC-approved chlorhexidine gel to other African countries, including Benin, Ghana, Mali, Mozambique, Niger and Zambia.

*Developing local manufacturing capacity... and enhancing regulatory oversight can **improve both national and regional capabilities for sustainable sourcing of quality-assured medicines.***

Table 2: Quality-assured medicines recognized by country MRAs

Country	Products Locally Approved
Bangladesh	Chlorhexidine
Ethiopia	Chlorhexidine, chloroquine, cotrimoxazole, sulfamethoxazole-trimethoprim, amoxicillin dispersible tablet, mebendazole
Indonesia	Oxytocin, levofloxacin
Kenya	Chlorhexidine
Nigeria	Chlorhexidine, zinc sulfate, amoxicillin dispersible tablet, oxytocin, magnesium sulfate
Pakistan	Chlorhexidine



Spotlight: Pakistan



Globally, 2.7 million babies die during their first month of life—16 percent of these deaths are from sepsis, meningitis or tetanus.²

Despite this dire statistic, use of preventive medicine, when it is affordable and available, can significantly reduce newborn mortality. Chlorhexidine, an antiseptic used to clean umbilical cords, can reduce the risk of newborn death by 23 percent.³ Quality-assured chlorhexidine, when produced locally, costs pennies per patient—but without a local supply, countries are vulnerable to fluctuations in foreign pricing and timely availability from outside the country.

Pakistan has a sizable pharmaceutical industry. For years, global health workers and government officials in Pakistan advocated for a local source of chlorhexidine, with little success. Recognizing the high rate of newborn mortality in Pakistan, USAID engaged PQM to begin work in 2015 to identify Pakistan-based manufacturers that could produce quality-assured chlorhexidine gel. This was achieved through a general call for interested manufacturers, detailed discussion on chlorhexidine and requirements, and an audit of selected manufacturing facilities to shortlist three manufacturers to work with. Of the potential companies identified, many felt that producing quality-assured chlorhexidine gel was neither technically feasible nor commercially viable.

To respond to these concerns, PQM helped conduct gap analyses of manufacturers' capacity to produce the gel, instituted corrective and preventive actions of the findings, trained local manufacturing staff, standardized testing techniques and protocols, and helped the manufacturers apply for government approval to produce chlorhexidine. PQM also built the capacity of the Drug Regulatory Authority of Pakistan and the Ministry of National Health Services, Regulations & Coordination—efforts intended to help expedite the medicines registration process and establish a fair price for medicines like chlorhexidine.

In March 2017, two manufacturers, ATCO Laboratories Ltd. and Aspin Pharma Ltd., became the first in Pakistan to receive government authorization to produce chlorhexidine gel. With this authorization, a dose of chlorhexidine now costs just 14 cents—one-third the price of chlorhexidine gel in neighboring Nepal.

Two additional manufacturers, Zafa Pharmaceutical Laboratories Ltd. and Akhai Pharmaceuticals Ltd., followed suit, and in a matter of months, locally produced, affordable, quality-assured chlorhexidine reached health facilities across the country.



By developing multiple sources of quality-assured products... **the risk of price gouging is averted and the vulnerability of the global supply chain to shortages is greatly reduced.**



API and FPP supply security

In some instances, only one source of a quality-assured essential medicine exists to supply the global public health market. This makes the medicine vulnerable to substantial price increases for both procurement agencies and countries purchasing the product. It also increases the risk for potential disruptions in supply if the manufacturer sustains any operational setbacks during production.

To prevent price increases that could result from a monopolized market, PQM worked to increase the number of sources and competition within the market and helped reduce the prices of essential medicines. By developing multiple sources of quality-assured products, including their active ingredients, the risk of price gouging is averted and the vulnerability of the global supply chain to shortages is greatly reduced.

PQM's work helped bring new suppliers and new quality-assured products to the market, including the first quality-assured sources of five APIs and three FPPs and additional quality-assured sources of nine APIs and eight FPPs (see Table 3).

PQM contributed to ensuring the availability and avoiding the global shortage of quality-assured medicines. For example, clofazimine is one of the highest-priority products for USAID/TB, as it became a key medicine for the shortened regimen for multidrug-resistant TB (MDR-TB) treatment, as recommended by WHO's treatment guidelines updated in 2018. When a PQM-supported manufacturer of clofazimine FPP became the second

generic source for the Global Fund's Expert Review Panel (ERP), it helped ensure that increased demand for the product due to updated WHO MDR-TB treatment guidelines could be met.

Finally, significant price reductions through the Global Drug Facility (GDF) were seen for cycloserine in 2013, kanamycin in 2016, capreomycin in 2014 and clofazimine in 2019 (see Table 3).

Global supply of quality-assured medical products

Both WHO PQ and stringent regulatory authority (SRA) approval confirm that medical products meet acceptable international standards for quality, safety and efficacy and that they can be purchased by international procurement agencies.

To address global needs for essential medicines, PQM worked with manufacturers to help them comply with international GMP standards and develop and submit dossiers for WHO PQ, SRA (e.g., U.S. Food and Drug Administration [FDA]) and/or Global Fund ERP approval for priority medical products—both for FPPs and APIs. For most products, optimal value in terms of price for a quality product is achieved when there are more quality-assured sources to drive the market price down (according to United Nations Commission Recommendation 4, there should be at least three manufacturers of both the API and the FPP). As a result of PQM's assistance, 36 products were approved and became available for international procurement.

Table 3: Quality-assured medical products (API and FPP) recognized by international organizations

Medicine	Indication	Manufacturer	Regulatory Approval/ Year	Public Health Impact
Amikacin FPP	Tuberculosis	Qilu Pharmaceutical	WHO PQ/2018	First and only WHO-prequalified source
Capreomycin API	Tuberculosis	NCPC Pharmaceutical	WHO PQ/2014	First WHO-prequalified source for public health market
Capreomycin API	Tuberculosis	Hisun Pharmaceuticals	WHO PQ/2014	Second WHO-prequalified source for public health market
Capreomycin FPP	Tuberculosis	Hisun Pharmaceuticals	WHO PQ/2014	Additional quality-assured source of FPP
Capreomycin FPP	Tuberculosis	NCPC Pharmaceutical	WHO PQ/2017	Additional quality-assured source of FPP
Clofazimine FPP	Tuberculosis	Dong-A ST Pharmaceutical	ERP/2019	Second generic source for ERP. Ensures that increased demand for the product due to the updated WHO MDR-TB treatment guidelines is met.
Cycloserine API	Tuberculosis	Dong-A ST Pharmaceutical	WHO PQ/2016	Additional quality-assured source of API
Cycloserine API	Tuberculosis	Hisun Pharmaceuticals	WHO PQ/2016	Additional quality-assured source of API
Cycloserine FPP	Tuberculosis	Dong-A Pharmaceutical	WHO PQ/2012	Led to price decrease of 30% for GDF supply
Isoniazid API	Tuberculosis	Second Pharma	WHO PQ/2013	WHO PQ achieved in time to address global shortage in 2013
Kanamycin API (non-sterile)	Tuberculosis	Fuzhou Fuxin	U.S. FDA/2014	Currently the only quality-assured source registered in the United States
Kanamycin API (non-sterile)	Tuberculosis	Fuzhou Fuxin	WHO PQ/2015	First API source to receive WHO PQ
Kanamycin API (sterile)	Tuberculosis	Fuzhou Fuxin	WHO PQ/2016	First API (sterile) source to receive WHO PQ
Kanamycin FPP	Tuberculosis	Interpharma/Shanghai Harvest Pharmaceutical	Global Fund ERP/2015	Led to 30% price decrease for GDF supply
Levofloxacin API	Tuberculosis	Langhua Pharma	WHO PQ/2014	First API source to receive WHO PQ
Levofloxacin API	Tuberculosis	Shangyu Jingxin Pharmaceutical	WHO PQ/2016	Additional source of API
Levofloxacin FPP	Tuberculosis	PT Kalbe Farma	WHO PQ/2019	First local source of the product for treatment of TB in Indonesia to receive WHO PQ
Linezolid FPP	Tuberculosis	Celltrion Pharm	WHO PQ and U.S. FDA/2019	First company to achieve both US FDA and WHO PQ for TB medicine
Moxifloxacin API	Tuberculosis	Hisun Pharmaceuticals	WHO PQ/2015	Additional quality-assured source of API
Moxifloxacin API	Tuberculosis	HEC Pharm	CEP/2015	Additional quality-assured source of API
Rifampicin API	Tuberculosis	Shenyang Antibiotic Manufacturer	WHO PQ/2016	Addressed shortage of the product on the public health market
Streptomycin API	Tuberculosis	Shengxue Pharma	Spanish RA/2013	Additional quality-assured source of API
Streptomycin API	Tuberculosis	NCPC Huasheng Pharma	WHO PQ/2016	First API source to receive WHO PQ
Streptomycin FPP	Tuberculosis	NCPC Pharmaceutical	WHO PQ/2017	First FPP source to receive WHO PQ

Medicine	Indication	Manufacturer	Regulatory Approval/ Year	Public Health Impact
Chlorhexidine FPP	Neonatal sepsis	Universal Corporation	UNICEF/XXXX	Additional quality-assured source of FPP
Oxytocin FPP	Postpartum hemorrhage	Sanbe/Caprifarmindo	WHO PQ/2017	First local source for treatment of PPH in Indonesia to receive WHO PQ
Oxytocin API	Postpartum hemorrhage	Shanghai Soho-Yiming Pharmaceuticals	CEP/2017	Additional quality-assured source of API
Zinc sulfate FPP	Diarrhea	Laboratoire Pharmaceutique Rodael	WHO PQ/2012	First WHO-prequalified source for public health market
Zinc sulfate FPP	Diarrhea	CHI Pharmaceuticals	UNICEF/2015	Additional quality-assured source of FPP
Mebendazole API	Neglected tropical disease	Yabang Pharma	CEP/2014	First EU approval (eligible for WHO PQ of FPP)
Mebendazole API	Neglected tropical disease	Changzhou Yabang Pharmaceutical	WHO PQ/2016	First API source to receive WHO PQ
Praziquantel API	Neglected tropical disease	Shanghai Jiayi Pharma	CEP/2016	Additional quality-assured source of API
Praziquantel API	Neglected tropical disease	Hisun Pharmaceuticals (Nantong)	WHO PQ/2017	Additional quality-assured source of API
Praziquantel – micronized API	Neglected tropical disease	Jiangsu Chengxin Pharmaceutical	WHO PQ/2018	Additional quality-assured source of API
Praziquantel – non-micronized API	Neglected tropical disease	Jiangsu Chengxin Pharmaceutical	WHO PQ/2018	Additional quality-assured source of API
Azithromycin FPP	HIV/AIDS	HEC Pharma	WHO PQ/2014	First FPP source to receive WHO PQ

* API = active pharmaceutical ingredient; CEP = Certificate of Suitability of Monographs of the European Pharmacopoeia; EU = European Union; FPP = finished pharmaceutical product; GDF = Global Drug Facility; MDR-TB = multidrug-resistant tuberculosis; NTD = neglected tropical disease; PPH = postpartum hemorrhage; TB = tuberculosis.



CROs' compliance with good practices

As part of the market authorization application for generic medicines products required by some regulatory authorities and the WHO Prequalification of Medicines Programme, manufacturers must present clinical data from bioequivalence studies that demonstrate the equivalence of their product to the originator product (i.e., the same effect). Often, the manufacturer contracts clinical research organizations (CROs) to conduct bioequivalence studies on its behalf. PQM engaged with CROs to improve their compliance, timeliness and cost-effectiveness of services.

In Ethiopia, for example, PQM collaborated with partners in supporting the Regional Bioequivalence Center (RBEC) to build the capacity and expertise of its staff on advanced bioequivalence studies methods and clinical trial principles. PQM also strengthened the RBEC's laboratory's compliance with good laboratory practice standards. The presence of a strong RBEC, serving manufacturers in the region to conduct bioequivalence studies, represents a key step forward to ensure the quality and safety of medicines manufactured in the region, including medicines for priority health programs such as malaria, MNCH, HIV/AIDS and TB. Having a CRO capable of performing bioequivalence studies in compliance with good clinical practice standards means that regulators will be able to confirm the safety and efficacy of generic medicines supplied to patients in the region.

Similarly, in Indonesia, PQM collaborated with universities and centers of excellence that provide bioequivalence expertise to develop a sustainable mechanism for high-quality technical assistance. This included supporting the Bioavailability/Bioequivalence Forum, a communication forum for CROs working in bioequivalence in both the academic and private sectors that builds capacity in Indonesia and regularly conducts training workshops for members. Using a train-the-trainers approach, PQM helped establish a pool of experts for providing bioavailability/bioequivalence trainings for CROs in the country.

*PQM engaged with CROs to **improve their compliance, timeliness and cost-effectiveness of services***





IR3

Utilization of medical product quality information for decision-making increased

The collection, analysis and use of data on medical products' evaluation, inspection and PMS supports evidence-based decision making critical for promoting access to quality-assured products and for reducing and preventing substandard and falsified products from entering the market. PQM supported the adoption of data standards and an integrated regulatory information management system to ensure that accurate, up-to-date and reliable data inform regulatory actions and are disseminated to all stakeholders. By working with local, national and international partners, PQM helped bring awareness to using data to improve transparency and accountability in the pharmaceutical sector, inform decision making, shape public policies on pharmaceuticals and support the attainment of public health objectives.

Enforcement actions against poor-quality products

When substandard, falsified or unapproved medical products are detected in a country, it is the MRA's duty to take enforcement actions to remove the products from the market and prevent harm. Enforcement actions can include recalls, product confiscation or incineration, written notices or fines, policy revisions or development of action plans, and even criminal prosecution.

PQM supported MRAs in this critical function for regulatory actions, first to create systems to identify poor-quality products through PMS and then to take compliance and enforcement actions. Over the course of the program, 1,396 enforcement actions were made by MRAs in 11 countries to reduce the presence of poor-quality medical products posing public health risks to the population.

PQM also collaborated with in-country partners to share information to alert stakeholders and the public about potential quality issues with medical products. In Senegal, for example, PQM supported the country to establish an Inter-Ministerial Committee with the main objective of collaboration among the MRA and enforcement agencies to combat the sale and import of poor-quality medicines. In 2017, this joint effort in Senegal led to the confiscation of poor-quality medicines, including antimalarials, worth approximately \$2.4 million USD.

Information on the quality of medical products

Raising awareness about the dangers of substandard and falsified medicines is critical to ensuring appropriate and timely action to protect the health of populations. PQM supported countries to increase the body of knowledge generated on the quality of essential medicines used in public health programs. The program also aimed to increase the availability of data related to the quality of medical products by working across regulatory functional areas to harness opportunities for data capture and sharing.

Additionally, PQM encouraged countries to engage in regional networks for information sharing to help facilitate implementation of enforcement actions across neighboring countries, when poor-quality medical products were sourced from the same manufacturer. One example is the Network of Official Medicines Control Laboratories in Sub-Saharan Africa (NOMCoL-SSA), founded in 2009 with USAID's financial and technical resources through PQM. NOMCoL-SSA was a network of 18 member countries in Africa with three main objectives: Enhance and strengthen the performance and technical skills of laboratory staff; promote information exchange on work activities to optimize technical expertise and laboratory resources among members; and promote implementation of good laboratory and documentation practices. NOMCoL-SSA was renamed the African Medicines Quality Forum in 2017. It became an Africa-led network protecting consumers

from poor-quality medicines under the management of the African Union's development agency, the New Partnership for Africa's Development, and is on its way toward self-reliance.

PQM also developed the Medicines Quality Database (MQDB)⁴, a free, web-based internationally referenced database of results for over 17,000 medicines quality tests conducted by PQM and country counterparts in 16 countries in Africa, Central and South America, and Southeast Asia. The MQDB ALERT feature allows rapid access to the most recent information on poor-quality medicines identified from PMS activities in PQM-supported countries, including those performed independently of PQM assistance.

Various approaches were used by PQM to raise awareness among local partners and civil society about the potential dangers of poor-quality medical products and strategies to combat them, each tailored to best reach the individual audience. To support information sharing with the public, government officials and stakeholders at local, regional and international levels, PQM hosted and attended partner meetings, advocating for continued strengthening of pharmaceutical quality assurance systems and encouraging collaboration among partners. During the program's 10 years, 128 publications were issued and 272 presentations were made on medical product quality assurance at national or international levels.

PQM also developed the e-learning course *Strengthening Quality Assurance Systems for Medical Products*, which was published on the USAID Global Health eLearning Center platform⁵ to increase stakeholders' awareness and knowledge about the importance of quality assurance systems. Since this course was launched in September 2019, more than 1,000 visitors from 17 countries have visited the course site and over 250 have completed the course. Throughout the program, PQM has provided in-person training to manufacturers on GMP. To reach a wider audience beyond those manufacturers directly supported by PQM, the program published an online modular training course on GMP. These lasting resources will stay available beyond the life of the PQM program.

\$2.4 million

The amount of poor-quality medicines, including antimalarials, confiscated in Senegal in 2017 with the help of PQM supported Inter-Ministerial Committee.

Spotlight: Nigeria

During PMS activities for MNCH products in Nigeria from May 2016 to February 2017, an alarming test result revealed that 74 percent of oxytocin injection samples failed quality testing. Oxytocin is a critical medicine used to treat postpartum hemorrhage and save mothers' lives during childbirth, but it is temperature sensitive and requires cold-chain storage from the time the medicine is produced until it reaches the patient to be effective.

Based on the test results, batch collection commenced from all affected health facilities and markets to ensure that the ineffective products could not be accessed and used. In a testament to NAFDAC's successful regulatory action, 1,183 ampoules of poor-quality oxytocin were removed from the market.

Following the incident, NAFDAC, with PQM's technical assistance, held a workshop on good storage and distribution practices for marketing authorization holders or approved pharmaceutical suppliers of the product. Key outcomes of the workshop included that prospective market authorization holders without suitable storage facilities would not be given marketing authorization of oxytocin in Nigeria, and that temperature tracking and

trending would be performed for sensitive products to ensure they are maintained at the recommended temperature for optimal efficacy. NAFDAC also increased collaboration with the Nigeria customs service to ensure that customs clearance of temperature-sensitive pharmaceutical products requiring cold-chain storage were fast-tracked, including speedy clearance from ports, different storage processes for sensitive and non-sensitive products, and adoption of direct marketing of sensitive products.

In an effort to share the findings with healthcare workers in a way that would be useful to them, PQM collaborated with researchers at the Lagos University Teaching Hospital to study whether any link existed between the PMS results and clinical experiences of healthcare providers in the use of oxytocin for treating postpartum hemorrhage. Findings suggested a high level of substandard oxytocin injections and poor knowledge of proper oxytocin storage. Findings also indicated excessive, inappropriate and inconsistent use, including varying dosage administration, which likely led to the spuriously high perception of drug effectiveness among respondents.

“In Nigeria from May 2016 to February 2017 an alarming test result showed that **74 percent of oxytocin injection samples failed quality testing**”



Health Element Summaries



Tuberculosis

Despite progress in the global fight against the TB epidemic, TB was one of the 10 top causes of death worldwide in 2018, according to the 2019 WHO global TB report.⁶ The report also related that, in 2018 alone, there were an estimated 10 million new TB cases and 1.5 million deaths worldwide.

Consistent themes within WHO's End TB Strategy and the U.S. government's strategy for the global fight against TB include safeguarding treatment for all people with TB, including drug-resistant TB, preventive treatment for individuals at high risk of contracting the disease, regulatory frameworks for quality and rational use of medicines. These strategies rely on uninterrupted availability of affordable, quality-assured anti-TB medicines to achieve the desired treatment outcomes for people with TB as well as to prevent drug-resistant TB.

Increased supply of quality-assured TB products for global and local markets

PQM contributed to global efforts to increase the supply of quality-assured anti-TB products by providing technical assistance to manufacturers of first-line and second-line anti-TB products to help ensure that sufficient sources of quality-assured medical products were available on the market. PQM also worked with donors and stakeholders to identify countries transitioning from donor-funded procurement to local procurement to ensure that manufacturers in the local market could provide first-line anti-TB medicines that were quality assured through attaining WHO PQ, SRA or ERP approval.

PQM provided technical assistance to manufacturers of anti-TB products, including helping manufacturing sites become compliant with international GMP standards.

Gap assessments of manufacturers' quality systems were conducted, followed by the development and implementation of corrective and preventive action plans. PQM then supported these manufacturers to respond to inspections queries from WHO or SRAs. In addition, PQM also provided technical assistance to manufacturers to compile, review and submit product dossiers in accordance with WHO PQ, SRA or ERP requirements. Once products are approved by WHO PQ, SRA or ERP, they become eligible for supply through GDF, enabling countries to access quality-assured anti-TB medicines.

PQM support brought new suppliers of quality-assured priority anti-TB products to market, increasing the availability of quality-assured APIs and FPPs and reducing prices of anti-TB medicines. Between 2012 and 2019, 15 APIs and 9 FPPs received WHO PQ, SRA or ERP approval. See table 4.

Table 4: Quality-assured anti-TB medical products (API and FPP) recognized by international organizations

Medicine	Manufacturer	Regulatory Approval/Year	Public Health Impact
Amikacin FPP	Qilu Pharmaceutical	WHO PQ/2018	First and only WHO-prequalified source
Capreomycin API	NCPC Pharmaceutical	WHO PQ/2014	First WHO-prequalified source for public health market
Capreomycin API	Hisun Pharmaceuticals	WHO PQ/2014	Second WHO-prequalified source for public health market
Capreomycin FPP	Hisun Pharmaceuticals	WHO PQ/2014	Additional quality-assured source of FPP
Capreomycin FPP	NCPC Pharmaceutical	WHO PQ/2017	Additional quality-assured source of FPP
Clofazimine FPP	Dong-A ST Pharmaceutical	ERP/2019	Second generic source for ERP. Ensures that increased demand for the product due to the updated WHO MDR-TB treatment guidelines is met.
Cycloserine API	Dong-A ST Pharmaceutical	WHO PQ/2016	Additional quality-assured source of API
Cycloserine API	Hisun Pharmaceuticals	WHO PQ/2016	Additional quality-assured source of API
Cycloserine FPP	Dong-A Pharmaceutical	WHO PQ/2012	Led to price decrease of 30% for GDF supply
Isoniazid API	Second Pharma	WHO PQ/2013	WHO PQ achieved in time to address global shortage in 2013
Kanamycin API (non-sterile)	Fuzhou Fuxin	U.S. FDA/2014	Currently the only quality-assured source registered in the United States
Kanamycin API (non-sterile)	Fuzhou Fuxin	WHO PQ/2015	First API source to receive WHO PQ
Kanamycin API (sterile)	Fuzhou Fuxin	WHO PQ/2016	First API (sterile) source to receive WHO PQ
Kanamycin FPP	Interpharma/Shanghai Harvest Pharmaceutical	Global Fund ERP/2015	Led to 30% price decrease for GDF supply
Levofloxacin API	Langhua Pharma	WHO PQ/2014	First API source to receive WHO PQ
Levofloxacin API	Shangyu Jingxin Pharmaceutical	WHO PQ/2016	Additional source of API
Levofloxacin FPP	PT Kalbe Farma	WHO PQ/2019	First local source of the product for treatment of TB in Indonesia to receive WHO PQ
Linezolid FPP	Celltrion Pharm	WHO PQ and U.S. FDA/2019	First company to achieve both US FDA and WHO PQ for TB medicine
Moxifloxacin API	Hisun Pharmaceuticals	WHO PQ/2015	Additional quality-assured source of API
Moxifloxacin API	HEC Pharm	*CEP/2015	Additional quality-assured source of API
Rifampicin API	Shenyang Antibiotic Manufacturer	WHO PQ/2016	Addressed shortage of the product on the public health market
Streptomycin API	Shengxue Pharma	Spanish RA/2013	Additional quality-assured source of API
Streptomycin API	NCPC Huasheng Pharma	WHO PQ/2016	First API source to receive WHO PQ
Streptomycin FPP	NCPC Pharmaceutical	WHO PQ/2017	First FPP source to receive WHO PQ

* CEP = Certificate of Suitability of Monographs of the European Pharmacopoeia

Tuberculosis (cont.)

Global technical leadership

PQM actively worked to share its unique expertise and experience in the area of medicines quality assurance with the global TB community through participation and contribution to working group meetings, stakeholder meetings, workshops and conferences organized by WHO, GDF and others. PQM organized two regional workshops held in Dubai (31 participants) and Bangkok (90 participants; co-funded with USAID NTD core funds) to engage manufacturers interested in strengthening their quality systems. The workshops brought manufacturers and regulators together to identify the challenges of registering quality-assured anti-TB medicines in different countries and offer possible solutions.

PQM also communicated its experiences through publications and presentations. For example, posters were presented at the Union World Conference on Lung Health, and product information reports (PIRs) for rifapentine, clofazimine and isoniazid/rifapentine were developed to provide critical information and guidance to manufacturers and stakeholders concerned with access to and supply of these essential medicines.

Co-funded by USAID NTD core funds, PQM developed a series of online learning modules related to GMP. The modules were designed to be accessed by regulators and

pharmaceutical industry personnel working in LMICs to strengthen their capacity in current GMP, which will help ensure the quality of essential medicines, including those for TB.

Country level accomplishments

Working with local manufacturers

With support from USAID Missions, PQM worked to build the capacity of local manufacturers. In Indonesia, for example, PQM supported six manufacturers for anti-TB products. After years of PQM technical assistance in GMP compliance and dossier preparation, PT Kalbe Farma successfully had its levofloxacin FPP product WHO prequalified in 2019, making it the first Indonesian manufacturer to have an anti-TB medicine prequalified by WHO. PQM also worked with three manufacturers in Kazakhstan and Uzbekistan to improve quality assurance systems for their levofloxacin FPP products.

Improving laboratory practices

To help countries accurately and reliably test the quality of anti-TB medicines in their markets, PQM provided technical assistance to quality control laboratories in several countries. PQM supported one laboratory in Indonesia and four in Russia to improve their standards of practices in order to attain WHO PQ and ISO/IEC 17025 accreditation, respectively.

In Kazakhstan, PQM's CLM was used to strengthen the capacities of three laboratories rapidly and simultaneously in their efforts to attain compliance with international standards for medicines quality control for testing anti-TB and other products. Using the CLM approach, PQM trained staff from all three laboratories and encouraged open communication and learning, to share lessons learned and best practices and to harmonize information. This approach helped ensure that the materials delivered were standardized and consistent, that costs typically incurred from decentralized training operations were reduced, and that country ownership and collaboration among laboratory staff were promoted. The CLM approach is also an effective solution for

staff attrition, in that new staff are mentored by previously trained, tenured colleagues from sister laboratories, rather than relying on foreign assistance again. After PQM conducted an initial gap assessment of the three laboratories in 2016, the laboratories used the CLM approach to perform their own cross-audits of their QMS and worked together to revise appropriate documents based on the findings. A quality team was established, comprising members from each of the laboratories, to oversee revisions to and standardization of QMS documents and share their progress with quality control laboratories nationwide.

Strengthening post-marketing surveillance

In Indonesia, Myanmar and the Philippines, PQM worked to build in-country systems to conduct PMS as a mechanism for regulatory authorities to detect substandard and falsified anti-TB products.

- Indonesia:** PQM supported the country to change a national regulation to clarify roles and responsibilities for the Ministry of Health and regulatory authority in conducting PMS, include public-sector medicines in annual sampling guidelines, and set requirements for timely data dissemination and enforcement actions.
- Philippines:** With strengthened system and capacity to conduct PMS, the Philippines tested more than 1,600 anti-TB medicines from 2009 to 2017. The data generated by the Food and Drug Administration of the Philippines were shared with stakeholders, including the National TB Program, and enabled the regulatory authority to take enforcement actions, including national recalls to remove poor-quality anti-TB medicines from the market.
- Myanmar:** Building on years of progress made to improve the country's PMS system for antimalarial medicines, PQM supported the regulatory authority to expand its PMS capacity to include testing of anti-TB medicines in 2019.



Neglected Tropical Diseases

NTDs have been a global concern for decades and are a major cause of morbidity and mortality worldwide. More than a billion people—one-seventh of the world's population—suffer from one or more NTDs. These diseases affect the world's most vulnerable populations, almost exclusively affecting impoverished populations living in rural areas and urban slums of low-income countries. The impact of NTDs on individuals and communities is devastating. Many of them cause severe disfigurement and disabilities.

Major constraints to the effective scale-up of NTD control and elimination programs are the scarcity of quality-assured medicines

suppliers and the limited number of products. WHO invited manufacturers to submit expressions of interest for NTD product analysis to support national and global efforts to increase access to and affordability of treatments. Of the treatments listed in the WHO expression of interest, the priority products for the USAID NTD team were albendazole, mebendazole and praziquantel.

Increased supply of quality-assured NTD products for the global market

Given USAID's priorities, PQM identified and provided technical assistance to manufacturers of APIs and FPPs for albendazole, mebendazole and praziquantel for the treatment of lymphatic Filariasis, soil-transmitted helminths and schistosomiasis diseases, respectively. Having a quality-

ssured API source is vital for the production of quality finished products. Along with WHO-prequalified APIs, Certificate of Suitability (CEP)-approved APIs in the monograph of the European Pharmacopoeia may be used by FPP manufacturers interested in WHO PQ or other SRA approval. PQM supported the manufacturers to comply with international GMP standards and develop dossiers.

Of the six APIs for NTD products that WHO has prequalified, four were supported by PQM. Two additional API products were also CEP approved. See table 5.

With the NTD products receiving WHO PQ and CEP approval, there are now more sources of quality-assured mebendazole and praziquantel APIs that can be used for production of quality-assured FPPs for both products, potentially increasing the supply of needed quality-assured FPPs on the global market.

Table 5: Quality-assured API sources for NTD recognized by international organizations

Medicine	Manufacturer	Regulatory Approval/Year	Public Health Impact
Mebendazole API	Yabang Pharma	CEP/2014	First European Union (EU) approval (eligible for WHO prequalification of FPP)
Mebendazole API	Changzhou Yabang Pharmaceutical	WHO PQ/2016	First API source to receive WHO PQ
Praziquantel API	Shanghai Jiayi Pharma	CEP/2016	Additional quality-assured source of API
Praziquantel API	Hisun Pharmaceuticals (Nantong)	WHO PQ/2017	Additional quality-assured source of API
Praziquantel – micronized API	Jiangsu Chengxin Pharmaceutical	WHO PQ/2018	Additional quality-assured source of API
Praziquantel – non-micronized API	Jiangsu Chengxin Pharmaceutical	WHO PQ/2018	Additional quality-assured source of API

1,600

The number of TB medicines tested in the Philippines from 2009-2017.

Neglected Tropical Diseases (cont.)

In addition, PQM supported two manufacturers of FPPs for albendazole and praziquantel to conduct bioequivalence studies. Bioequivalence studies are a necessary step in the WHO PQ process to demonstrate a generic product's equivalence in the body (or "bioequivalence") relative to the referenced original "innovator" drug. However, these studies can be challenging and costly for pharmaceutical manufacturers, including those that produce NTD products, particularly given the low price point of NTD medicines. PQM also provided financial support to offset the cost for conducting the bioequivalence studies, which helped interest the manufacturers in undertaking the bioequivalence studies and other efforts necessary to submit applications to the WHO PQ program for approval. Both manufacturers submitted applications for

WHO PQ; if the products are successfully accepted, they would become the first WHO-prequalified sources of albendazole FPP and one additional source of praziquantel FPP.

Global technical leadership

To raise awareness about the dangers of substandard and falsified NTD medicines and the need to increase the supply of quality-assured products, PQM regularly supported local, regional and global information-sharing and awareness-raising initiatives on medicines quality. In 2017, for example, PQM organized a regional meeting for 90 representatives from MRAs, manufacturers and national disease programs from 14 countries to identify the challenges of registering quality-assured NTD medicines in different countries and possible solutions. One-on-one meetings were held with manufacturers that wished to receive PQM's technical assistance to discuss their product pipeline, facility and dossier status; interest in producing products at international

standards such as required by WHO PQ; and areas that would require technical support to do so.

PQM also developed PIRs for albendazole and praziquantel. These documents provide critical information and guidance to manufacturers and other stakeholders concerned with manufacturing of essential medicines to increase global supply. The PIRs offer expert scientific analysis of physicochemical, pharmacokinetic, toxicological and other information about the product and analyze key manufacturing challenges.

Co-funded by USAID's TB and NTD core portfolios, PQM produced a series of online learning modules related to GMP. The modules are intended to be accessed by regulators and pharmaceutical industry personnel working in LMICs who are interested in building their capacity in current GMP. The purpose of the series is to help ensure the quality of essential medicines, including those for NTDs.

Maternal, Newborn, and Child Health

Since 2008, the lives of 4.6 million children and 200,000 mothers in USAID priority countries have been saved through USAID-supported interventions.⁷ USAID's goal of preventing child and maternal deaths includes a target of saving the lives of 15 million children and nearly 600,000 women by 2020 and continuing this pace through 2035, as set out in the Acting on the Call reports.^{8,9}

The 2012 UN Commission on Life-Saving Commodities for Women's and Children's Health identifies that maternal, newborn and child deaths can be avoided if 13 essential, lifesaving and quality-assured medical products are available to women and children. Through PQM, USAID has worked to increase the supply of quality-assured medical products for MNCH. PQM provided technical assistance to manufacturers of quality-assured MNCH medicines, assessed the quality of MNCH medicines available in select countries, and advanced technical leadership and expertise in quality assurance of MNCH products. By using a systems

strengthening approach to build institutional and individual capacity and developing strategic partnerships, PQM helped spur manufacturing of quality-assured MNCH products (at both local and global markets), defined product testing protocols and monographs, and contributed to a greater

Since 2008, the lives of 4.6 million children and 200,000 mothers... have been saved through USAID-supported interventions.



understanding of the challenge of poor-quality MNCH products through periodic medicines quality surveys and routine PMS.

Monograph and screening procedure development

NQCLs test medical products for quality according to their pharmacopeial monographs. However, for many priority essential medicines, no monograph exists in any internationally recognized pharmacopeia, impeding the assessment of product quality. Through USAID support, five monographs for medicines used to treat MNCH conditions were developed and included in the U.S. Pharmacopeia (USP). These monographs are needed to evaluate product quality for medicines used in newborns and children. Since July 2018, these monographs have been accessed online more than 600 times.

MNCH products in official USP monographs include the following:

- Chlorhexidine topical gel
- Zinc sulfate tablets
- Zinc sulfate oral solution
- Zinc gluconate tablets
- Vitamin A oral liquid preparation

Table 6: MNCH products for which PQM provided technical support

Maternal Health	Newborn Health	Child Health
Magnesium sulfate injection	Benzathine benzylpenicillin injection	Amoxicillin dispersible tablet
Oxytocin injection	Benzylpenicillin sodium or potassium injection	Zinc dispersible tablet
	Procaine benzylpenicillin injection	Oral rehydration salts
	Gentamicin injection	
	Chlorhexidine gel and liquid	



Maternal, Newborn, and Child Health

(cont.)

Increased supply of quality-assured MCH products for the global market

PQM improved the manufacturing capacity of 29 pharmaceutical companies toward production of quality-assured MNCH products for both local markets and global procurement agencies. These efforts directly contributed to achieving UN Commission Recommendation 4 (at least three manufacturers per commodity by 2015 producing quality and affordable medicines) and resulted in the first WHO PQ of a medical product with production facilities in an LMIC (oxytocin injection produced by a manufacturer in Indonesia and procured by United Nations Children's Fund [UNICEF]). Table 7 presents products that received WHO PQ, CEP or UNICEF procurement approvals. These approvals contribute to increasing the number of quality-assured sources of MNCH products that can save the lives of vulnerable mothers and children globally.

Averting shortages of a critical antiseptic for newborns

PQM helped expand availability for chlorhexidine—an essential, lifesaving

antiseptic used to prevent umbilical cord infections in newborns—in Africa and Asia. In total, PQM supported nine manufacturers to improve GMP for chlorhexidine production. These efforts resulted in new chlorhexidine products receiving regulatory approval to go to market in Pakistan (four chlorhexidine gel products), Nigeria (three chlorhexidine gel products), Ethiopia (one chlorhexidine gel product), Kenya (one chlorhexidine gel product) and Bangladesh (one chlorhexidine solution product). PQM also facilitated submission of a chlorhexidine gel dossier to the East African Community for joint regulatory review to expand registration approvals and the market for chlorhexidine in Africa.

PQM engaged key private-sector partners to further address chlorhexidine supply challenges. PQM collaborated with GlaxoSmithKline to transfer manufacturing technology and “know-how” pertaining to the production of chlorhexidine gel to PQM and subsequently for PQM to build the capacity of several local manufacturers to stimulate local production and sustainable access to this critically needed product in LMICs. PQM conducted a workshop during which information was disseminated to interested manufacturers for the technology transfer.

Together, these efforts have not only averted potentially life-threatening shortages of quality-assured chlorhexidine in PQM-supported countries but have also drastically expanded the availability of this

critical antiseptic in countries and regions where the product is needed most.

Improved capacity to detect poor-quality MCH products

PQM supported the establishment and strengthening of PMS programs in several countries to improve systems for monitoring the quality of critical medical products, including those used to support MNCH.

To demonstrate the need and generate the support required to improve the overall PMS system in a country, PQM supported ad hoc surveys of medicines quality, including for MNCH products. This exposed the presence of poor-quality medicines and elucidated the importance of investing in systems to ensure medical product quality as part of efforts to strengthen the health system and prevent maternal and child deaths. In selected sites in Nigeria, for example, one survey showed that 74 percent of oxytocin samples failed quality control tests. While the sampling strategy was not meant to be representative of the overall burden of poor-quality oxytocin in the country, the results indicated potential challenges in maintaining the quality of oxytocin in Nigeria. As a result, NAFDAC embarked on several measures, including conducting a root cause analysis, issuing a warning to marking authorization holders to adhere to strict storage conditions (i.e., cold-chain storage) or risk losing marketing license, and training oxytocin injection suppliers and



distributors on good distribution practices. PQM also provided technical assistance to a local manufacturer that achieved NAFDAC approval for oxytocin injection in January 2018. The manufacturer partnered with a company to ensure cold-chain storage and distribution of the injection nationwide. This multipronged approach helped improve the substandard storage practices responsible for the poor-quality PMS results from 2016. Subsequent PMS for oxytocin carried out in selected regions and facilities, although not statistically comparable, showed improvements for the samples collected (only 40 percent failed quality tests).

In a major step forward for regional collaboration, PQM supported a first-of-its kind survey on the quality of oxytocin injection and amoxicillin dispersible tablet/suspension circulating in selected cross-border areas of six countries (Djibouti, Ethiopia, Kenya, Somalia, Sudan and Uganda) in the Intergovernmental Authority on Development (IGAD) region. The results were reviewed and validated by the IGAD Post-Marketing Surveillance Expert Working Group and accepted by all IGAD member state regulatory authorities. Overall, the survey showed that 21 percent of oxytocin injection samples tested did not meet quality specifications and 72 percent of oxytocin injection products, 30 percent of amoxicillin dispersible tablet products and 26 percent of amoxicillin suspension

products collected were not registered by the relevant national MRA. Based on these and other findings, the Expert Working Group on Pharmacovigilance/PMS made several recommendations to member state MRAs to address medicines quality in the countries.

Global technical leadership

PQM provided expertise and thought leadership in several ways, including serving as the medicines quality technical lead on several UN Commission Technical Reference Teams and Working Groups; supporting regional harmonization; and publishing testing protocols, monographs and other key reference materials.

PQM supported the East African Community-Medicine Registration Harmonization initiative to strengthen the capacity of MRAs to perform key regulatory functions and register medicines through joint dossier evaluations to achieve harmonized and functioning medicines registration and other quality assurance related regulation system functions in accordance with international standards. In collaboration with WHO and Swiss Medic, PQM helped build local capacity for adopting and operationalizing harmonized registration standards. As a result, a series of 12 SOPs were developed to help guide future practices related to regional medicine evaluation registration.

Examples of PQM's work in thought leadership and key publications include the following:

- UNCoLSC-related publications
 - Chlorhexidine for Umbilical Cord Care: A New, Low-Cost Intervention to Reduce Newborn Mortality. Chlorhexidine working group, Nov. 2017
 - Production Strategy: 7.1% Chlorhexidine Digluconate for Umbilical Cord Care. Chlorhexidine working group, Nov. 2015
- Manufacturing-related publications
 - Product Information Report: Amoxicillin
 - Chlorhexidine Digluconate (7.1%) Technology Transfer Report
- Quality surveillance-related
 - Revisiting the Stability and Storage Specifications of Oxytocin Injection: A Literature Review
 - Quality medicines in maternal health: results of oxytocin, misoprostol, magnesium sulfate and calcium gluconate quality audits (Anyakora C, Oni Y, Ezedinachi U, Adekoya A, Ali I, Nwachukwu C, Esimone C, Abiola V, and Nwokike J, BMC Pregnancy Childbirth. 2018; 18: 44 doi: 10.1186/s12884-018-1671-y)
 - Quality of Oxytocin Injections: A Case Study in Indonesia
 - Clinical Experiences With the Use of Oxytocin Injection by Healthcare Providers in a South-Western State Nigeria: A Cross Sectional Study

Table 7: Quality-assured medical products (API and FPP) recognized by International organizations

Medicine	Manufacturer	Regulatory Approval/Year	Public Health Impact
Chlorhexidine FPP	Universal Corporation	UNICEF/XXXX	Additional quality-assured source of FPP
Oxytocin FPP	Sanbe/Caprifarmindo	WHO PQ/2017	First local source for treatment of PPH in Indonesia to receive WHO PQ
Oxytocin API	Shanghai Soho-Yiming Pharmaceuticals	CEP/2017	Additional quality-assured source of API
Zinc sulfate FPP	Laboratoire Pharmaceutique Rodael	WHO PQ/2012	First WHO-prequalified source for public health market
Zinc sulfate FPP	CHI Pharmaceuticals	UNICEF/2015	Additional quality-assured source of FPP

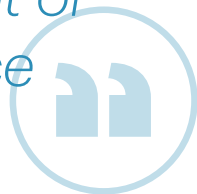


Malaria

Although tremendous progress has been made in the fight against malaria, the disease continues to affect the health and economy of endemic countries globally.

Sustaining the progress made in the fight against malaria, including combating the emergence and spread of resistance, relies on continued efforts to ensure the availability and appropriate use of quality-assured antimalarial medicines. Furthermore, current treatments may be rendered ineffective if proper measures are not taken to ward off the threat of resistance. The mainstay for malaria control recommended by WHO is artemisinin-based combination therapies; however, the emergence of antimicrobial resistance poses a threat to the progress made to date. PQM supported the U.S. President's Malaria Initiative in the fight against malaria by working to increase the availability of quality-assured antimalarial medicines, institutionalizing stronger procedures to assess quality, training quality assurance/quality control personnel to reliably and accurately test the quality of antimalarials using globally recognized standards, and improving the availability of antimalarial medicines quality data for decision making. To ensure countries have the tools necessary to assess the quality of antimalarial medicines, PQM facilitated the development of standardized test procedures (e.g., monographs) and screening methods for use in the laboratory and field.

Current treatments may be rendered ineffective if proper measures are not taken to ward off the threat of resistance



Improving access to quality-assured antimalarial medicines

PQM made notable progress in ensuring that quality-assured antimalarial medicines were available in LMICs. Using its systems strengthening approach, PQM worked with countries to address the availability of poor-quality antimalarials while also working to strengthen systems that ensure the production and distribution of quality-assured medical products.

As a result of PQM's technical support to countries such as Benin, Liberia and Senegal, the regulatory capacity was strengthened such that each country is now able to take swift and decisive regulatory actions based on PMS findings. In 2018, the Benin Customs Authority seized and destroyed several suspicious medicines parcels at the Cotonou Cadjehoun Airport after mobile screening technologies (i.e., handheld Raman and Minilab™) were used to screen medicines quality.

Another critical contribution of the PQM program was extensive collaboration with Global Pharma Health Fund (GPHF), the manufacturer of Minilab™ field test kits, which contain simple test methods to verify medicines quality. PQM worked with GPHF to develop numerous thin-layer chromatography methods, including methods to test two key antimalarial fixed-dose artemisinin-based combination therapies: artemether-lumefantrine and dihydroartemisinin-piperaquine. These methods are still in use and included in current GPHF manuals.

In Nigeria, PQM worked with a manufacturer to develop a new nationally approved quality-assured source for the antimalarial medicine sulfadoxine-pyrimethamine 500+25mg tablet. With PQM support, the manufacturer made significant progress in addressing the observations from PQM's initial technical assistance assessment, so much so that it has since received procurement requests for over 7.5 million doses of sulfadoxine-pyrimethamine procured by the Medical Exports Group for delivery to different states in Nigeria.

Strengthening Systems for Quality-Assured Antimalarials in Ethiopia: Progress on the Path to Self-Reliance

Since 2009, PQM's partnership with the government of Ethiopia has yielded major improvements in the country's medical product quality assurance systems and enabled the Ethiopian Food and Drug Authority (formerly the Ethiopian Food, Medicine and Health Care Administration and Control Authority [EFMHACA]) to better protect Ethiopians from poor-quality antimalarials.

Following multipronged support from PQM to strengthen the regulatory workforce, improve the standard of testing at the nation's network of medicines quality control laboratories, and institutionalize and strengthen PMS activities, Ethiopia is emerging as a regional regulatory leader in the fight to keep poor-quality essential medicines—including antimalarials—off its market and out of the hands of patients.

Between 2009 and 2019, 10 rounds of PMS were conducted and 3,455 medical product samples, including antimalarials, were tested in Ethiopia. According to the annual PMS reports, from 2009 to 2019, the typical annual failure rate of antimalarial medicines samples collected was as high as 17.2 percent. Based on quality surveillance results, EFMHACA took 114 regulatory actions, almost all (92 percent) of which involved recalling or withdrawing medical products from the market—actions that directly protected the public from potentially harmful poor-quality products.

The impact of EFMHACA's PMS capacity extends beyond the borders of Ethiopia. One aspect of PQM's approach to data sharing was functional information-sharing platforms such as the WHO Medical Product Alerts System, which ensures timely, proportionate and accurate response to health events from substandard and falsified medical products that present a threat to public health. For example, in 2013, information

about a falsified quinine product identified by EFMHACA was shared with WHO and disseminated through the WHO Medical Product Alerts System; this limited the product's distribution in other countries.

Launching a Locally Led Network of National Quality Control Laboratories

At the inception of the PQM program, recognizing the need for robust quality control laboratory capacity as a foundational component of stronger health systems, USAID funded PQM to provide the necessary financial and technical resources to establish NOMCoL-SSA. The network was established to provide a platform for countries to share technical expertise and information, strengthen the technical capacity of participating laboratories and promote South-South collaboration, with an initial focus on quality control of common antimalarials. Following additional support and investment from USP, NOMCoL-SSA was integrated into and managed by the New Partnership for Africa's Development agency as a technical working group and renamed the African Medicines Quality Forum (AMQF). With USAID's initial investment and technical support, AMQF is now supporting several countries to sustainably improve their medicines quality control laboratory capacity, an essential part of protecting the continent from poor-quality medicines.

Global technical leadership

PQM's work to support countries in testing the quality of antimalarial medicines has been integral to improving the understanding of the size and scale of the problem of poor-quality antimalarials among decision makers, the global health community and the general public. The program also raised awareness of the potential role that poor-quality antimicrobial medicines may have in contributing to the emergence of antimicrobial resistance.

Key Publications

- Journal articles and commentaries
 - Medicines quality assurance to fight antimicrobial resistance. *Bulletin of the World Health Organization*. 2018;96:135-137. doi: <http://dx.doi.org/10.2471/BLT.17.199562>.
 - Were medicine quality and pharmaceutical management contributing factors in diminishing artemisinin efficacy in Guyana and Suriname? (Pribluda VS, Evans L, Barillas E, Marmion J, Lukulay P, Chang J. *Malaria J*. 2014 Mar 3;13(77). doi: 10.1186/1475-2875-13-77.)
 - Assessment of the effectiveness of the CD3+ tool to detect counterfeit and substandard antimalarials. (Batson JB, Bempong, DK, Lukulay PH, Ranieri N, Satzger RD, Verbois, L. *Malaria J*. 2016 Feb 25;15(119). doi: <https://doi.org/10.1186/s12936-016-1180-2>.)
 - The quality of antimalarial medicines in western Cambodia: a case study along the Thai-Cambodian border (Phanouvong S, Raymond C, Krech L, Dijiba Y, Boravann M, Lukulay P, Socheat D, Sovannarith T, Sokhan C. *Southeast Asian J Trop Med Public Health*. 2013 May;44(3):349-62.)
 - Quality of anti-malarials collected in the private and informal sectors in Guyana and Suriname (Evans L, Coignez V, Barojas A, Bempong D, Bradby S, Dijiba Y, James M, Bretas G, Adhin M, Ceron N, Hinds-Semple A, Chibwe K, Lukulay L, Pribluda V. *Malaria J*. 2012 Jun 15;11(203). doi: <https://doi.org/10.1186/1475-2875-11-203>.)
 - Implementation of basic quality control tests for malaria medicines in Amazon Basin countries: results for the 2005–2010 period (Pribluda VS, Barojas A, Añez A, López CG, Figueroa R, Herrera R, Nakao G, Nogueira FHA, Pianetti GA, Povoá MM, Viana GMR, Mendonça Gomes MS, Escobar JP, Muñoz Sierra OL, Rendon Norena SP, Veloz R, Silva Bravo M, Aldás MR, Hinds-Semple A, Collins M, Ceron N, Krishnalall K, Adhin M, Bretas G, Hernandez N, Mendoza M, Smine A, Chibwe K, Lukulay P, Evans L. *Malaria J*. 2012 Jun 15;11(202). doi: <https://doi.org/10.1186/1475-2875-11-202>.)
- Reports and technical briefs
 - Strengthening Medical Product Quality Assurance Systems in Ethiopia: Progress on the Path to Self-Reliance*
 - Baseline Survey on the Quality, Presence and Source of Priority Antimalarial Medicines in Select Geographical Areas of Burma/Myanmar*



HIV/AIDS

94 million

The number of condoms recalled and/or prevented from distribution into the market as a result of substandard samples detected through quality testing between 2015-2016.

Ensuring that medical products to treat and prevent HIV/AIDS are quality assured is vital to responding to the global HIV/AIDS crisis. With support from the U.S. President's Emergency Plan for AIDS Relief, PQM worked to help countries improve regulatory and laboratory capacity to test antiretrovirals and condoms for quality.

In Indonesia, PQM supported HIV/TB control by strengthening the medical product quality assurance system, including the national PMS program of BPOM (the National Agency of Drug and Food Control) to detect and remove substandard and falsified medicines from the local market. Since 2017, Indonesia's National AIDS Program has conducted quality testing of antiretroviral samples from 16 provincial sites throughout the supply chain at BPOM's NQCL. Prior to 2019, when the NQCL in Jakarta attained WHO PQ, Indonesia had to use a WHO-prequalified

laboratory outside of the country to perform reliable quality testing, which required additional time and cost. With a lower cost per sample using a quality control laboratory certified to international standards, Indonesia's National AIDS Program increased the number of antiretroviral samples tested with the same budget, maximizing value for money.

In Ethiopia, to combat the circulation of potentially defective male condoms, PQM supported the NQCL to achieve ISO/IEC 4074 accreditation for medical devices in 2014. With this, the laboratory was able to produce accurate and reliable test results for the quality of condoms, including those used to prevent HIV infection. A total of 25 million condoms in 2015 and 69 million condoms in 2016 were recalled and/or prevented from distribution into the market as a result of substandard samples detected through quality testing.



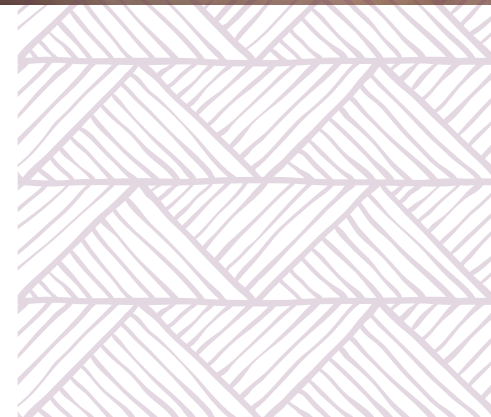
Sustainability

Enabling countries to make sustainable improvements in their medicines quality assurance systems was the guiding principle of the PQM program. PQM's emphasis on sustainability was an essential consideration to implementing projects and interventions to successfully meet the systemic challenges shared by key country counterparts and partners.

Sustainability must be inherent to quality-assured medicines programming. Technical assistance planning with stakeholders must not look at only how to introduce international standards to health product manufacturing and regulation but also how to maintain those standards over the long term. International accreditations such as ISO/IEC 17025 or WHO PQ that validate adherence to international norms are not static; they require recipients' regular renewal, and the accreditation standards themselves are periodically updated to keep pace with evolution in global health programming and pharmaceutical markets.

In LMICs, limited resources and competing priorities present the most obvious challenge to investing in and achieving sustainability of medical product quality assurance systems, despite the overwhelming public health benefit of doing so. In this context, PQM developed a risk-based approach to streamlined PMS, which allows government regulators responsible for sampling and testing products to use statistically valid risk analysis to focus their efforts and budget on the products and locations most likely to be affected by poor quality and cause the greatest harm to public health.

*Sustainability is inherent to **quality-assured medicines programming***



Sustainability planning

At the country level, defining sustainability plans was integral to many of the technical assistance strategies PQM developed in collaboration with its country counterparts. For example, strategic planning to achieve ISO/IEC 17025 accreditation in five public-sector medicines quality control laboratories in Nigeria included defining how the

budgetary responsibility for meeting technical and financial needs would be assumed by the government of Nigeria. PQM covered approximately 85 percent of spending on operational reform and product testing in the five laboratories from 2015 to 2018 and then roughly 20 percent in 2019.

However, as numerous other examples from PQM's experience show, sustainability

planning requires more than just addressing financial autonomy. A self-reliant quality assurance system is one that is also operationally sufficient: that is ultimately built on a solid legal framework; reliably adheres to cost-efficient, standardized procedures that make the optimal use of scarce resources; functions in a timely manner; effectively uses human resources; and is responsive to demand and change.



A solid legal framework

Ensuring legal standing for medicines regulation is essential to allow regulators to take swift action when substandard medicines are found in the local markets and is especially important in countries where regulatory authorities either do not exist or have been significantly weakened. Yet this legal foundation represents only part of the work involved in building a quality assurance system.

In Guinea, where a significant number of pharmaceuticals on the national market were unregistered, PQM supported the government to update its 24-year-old pharmaceutical regulatory law in 2018. This revision gave authority to the National Directorate of Pharmacies and Medicines over medicines quality assurance and surveillance of medicines in circulation; it also established a new system for regulating the domestic health commodity supply

chain based on international best practices. Guinea's Director General of Health noted that the regulatory legislation that had been enacted stimulated the funding process for the necessary human and financial resources.

In Pakistan, in 2017, as part of supporting medicines regulatory reform, PQM advocated that the Drug Regulatory Authority of Pakistan adopt the Common Technical Document for submission of medical product dossiers for marketing authorization approvals from medicines manufacturers. The Common Technical Document is an internationally accepted standard format for application of medical product dossiers to regulatory authorities for marketing authorization approval.

Cost-efficiency

In Ethiopia, EFMHACA must periodically calibrate its instrumentation in the NQCL to produce reliable results and maintain ISO

17025:2005 accreditation. With no local expertise to turn to for equipment calibration in its NQCL, for example, EFMHACA spent around \$15,000 USD annually on foreign service providers to perform this fundamental task. EFMHACA's limited resources could be more effectively utilized to support laboratory operations and work toward sustainability. EFMHACA and PQM agreed that developing local capacity for instrument calibration would strengthen Ethiopia's medicines quality assurance system, particularly by garnering critical savings. In 2016, they approached the National Metrology Institute (NMI) of Ethiopia, which provided various calibration services but lacked the specific capability for servicing equipment in laboratories such as EFMHACA's. After NMI fell short in attempts to self-fund capacity-building using private-sector expertise, PQM used USP funds to provide technical assistance and training. As a result, NMI received ISO accreditation for calibration of two initial pieces of apparatus in June 2017. By the project's end, EFMHACA

was spending 80 percent less per year on calibration and projects that will continue to reap additional savings as NMI expands the types of equipment it can service.

Timeliness

Having local capacity for equipment calibration does not guarantee that the challenges countries without this capacity face (e.g., timeliness of service) are eliminated. Unlike Ethiopia, the National Control Laboratory in Bangladesh already had a cost-effective local option for equipment calibration. Even so, the wait time for these urgently needed services was too long, causing four to five months of downtime annually across its pool of testing equipment. Through PQM-led technical assistance, the National Control Laboratory's equipment maintenance team added calibration to its list of capacities, improving its processes and turning it into a truly on-demand service. In Ethiopia, through PQM technical assistance,

EFMHACA collaborated with Jimma University to review and clear a backlog of 467 new medicine applications for registration in 2017. In addition, the fast-track review process for critical public health medicines put in place through this technical support reduced the lead time for registration of these products from two years to four-and-a-half months.

Effective use of human resources

In Bangladesh, Ethiopia and Nigeria, in response to the unmet need for specialized professionals tailored for the pharmaceutical sector, PQM worked with academic institutions and key government stakeholders to develop undergraduate and graduate curricula for pharmacy schools in the area of pharmaceutical quality assurance to prepare preservice pharmacists for the workforce. In Nigeria, the curriculum was piloted in one university, and the experience and challenges were then shared with other pharmacy schools in preparation for its adoption.

For in-service training, PQM's CLM approach was utilized for laboratory strengthening to consolidate and standardize the training of multiple laboratories within a country. This approach promotes ownership and collaboration among the laboratory staff in the country and reduces costs typically associated with decentralized training. PQM utilized this model in Nigeria to build the capacity and skills of five medicine laboratories to attain ISO 17025 accreditation. Through this model, PQM-trained technicians at laboratories that were certified earlier in the process supported their peers at the remaining facilities. The CLM reduced the role of PQM over time and will be instrumental in enabling the effective orientation of new staff joining any one of the laboratories, as well as extending locally led training further into the sector.

Responsiveness

WHO PQ issues expression of interest calls for new manufacturers to increase quality-

assured sources of priority public health products. Responding to these calls quickly is critical to shaping the product market and to preventing delays in supply. With technical assistance from PQM, in 2019, Indonesian manufacturer PT Kalbe Farma achieved WHO PQ for levofloxacin, a key medication for treating MDR-TB. High-impact commodities like levofloxacin often provide a minimal profit margin and require significant investment to launch production of a WHO-prequalified product. However, they can be a springboard for overall improvement of a pharmaceutical manufacturer's quality assurance system, benefiting the manufacturer's full range of current and future products and even serving as a model for other manufacturers. Following its success with levofloxacin, Kalbe worked with PQM to hold a workshop to share knowledge and experience from the WHO PQ audit and committed to developing a quality manual that will be adopted by all sister manufacturers under Kalbe's corporate structure. This is expected to boost implementation of international GMP standards across Kalbe's vast international network of production sites.

80%

The annual decrease in spending by the National Metrology Institute of Ethiopia on calibration, with technical assistance and training from PQM.

Lessons Learned

One of the most valuable parts of reflecting on a 10-year program is not necessarily the achievements and progress made, but the lessons learned that can inform and improve the future. PQM's experiences across Africa, Asia, and Central and South America have generated many lessons learned in medical product quality assurance.

Strengthening the regulatory framework underpins advances in medical product quality assurance

Major advances have been made in strengthening medical product quality assurance systems and mechanisms have been put in place to ensure the quality of donor-related procurements. However, poor-quality medical products will continue to be a major public health threat until national regulatory authorities and regional bodies can be strengthened such that they are capable of effectively regulating all medical products circulating in the market.

For regulatory functions to be effective, they must be rooted in appropriate and enforceable legislation and policies. However, these regulatory legal frameworks are not always appropriately implemented or enforced, for reasons including a lack of clarity regarding roles and responsibilities. This may be due, at least in part, to fragmentation of functions and responsibilities, which makes coordination and information exchange difficult.

Tackling these challenges requires systems strengthening approaches that can address interconnected health system functions and factors that can influence medical

product quality. Improving the regulatory legal frameworks for medical product quality assurance can help countries align their policies with other countries, making it easier to share resources and information and to take coordinated action. Enacting stronger regulatory legal frameworks also improves the ability of the MRA to work with enforcement agencies to remove poor-quality products from the market and take appropriate action against those that produce and distribute them.

Integrated regulatory information supports effective medical product quality reporting, decision making and accountability to the public

The lack of integrated mechanisms for collecting, analyzing, managing and sharing regulatory information impairs many MRAs in LMICs from effectively carrying out their mandate. Taking feasible and practical steps toward centralized systems to integrate regulatory information can improve coordination and efficiency within departments and support the MRA's coordination with various external stakeholders.

One way this can be supported is through the adoption of data standards to improve the interoperability of regulatory information systems and facilitate information exchange, work sharing and reliance among regulatory authorities. Additionally, developing clear procedures for sharing key information with enforcement agencies (e.g., a list of products with marketing approval to identify unregistered products circulating in the

market), practitioners (e.g., list of products with safety concerns and why) and the public (e.g., a list of products recalled and why) based on centralized and validated data sources helps foster trust in the regulatory authority's competence and decisions.

Medical product quality surveys can generate signals that reveal weaknesses in the broader quality assurance system

Medicines quality monitoring (MQM) surveys help reveal systemic weaknesses in quality assurance and procurement systems, providing valuable information and acting as a catalyst for interventions to strengthen quality assurance systems. For example, in Nigeria, routine quality surveillance identified a major challenge with ensuring the effectiveness of temperature-sensitive products, particularly oxytocin, throughout the supply chain. The information about this shortcoming prompted regulatory action and changes to the management of pharmaceuticals requiring cold-chain storage in the country.

Utilizing a risk-based approach to medicines quality monitoring can promote sustainability of PMS activities in resource-limited settings

Medicines quality surveillance is a key quality assurance activity undertaken by countries to identify and prevent the circulation of substandard and falsified medicines that can harm the population. PQM adopted the MQM approach, collaborating with public health disease programs to identify substandard and falsified medicines. While the MQM program was successful, there was a general perception among the ministry of health counterparts that MQM was a PQM intervention being implemented in parallel and not necessarily as part of a country's PMS program. As experience and support progressed, a



PQM realized that the MQM approach was not sustainable; the main purpose of MQM to identify substandard and falsified medicines and remove these products from causing harm to the population was defeated. The MQM counterparts did not have the official mandate to withdraw poor-quality medicines from the market.

Over the years, PQM helped transition the MQM function to the PMS department of the MRAs to institutionalize the process and ensure country ownership and continuity of activities. This approach worked well to support overall health systems strengthening to ensure the quality of medicines circulating in a country. However, one major limitation to successful implementation was insufficient human and financial resources to survey all essential medicines or even a subset of selected products. PQM worked with global and country counterparts to develop a

framework and guidelines for implementing a risk-based approach for medicines quality sampling and testing, providing detailed criteria to consider for interventions to stay focused and effective with limited resources. Over the years, 14 countries implemented elements of the risk-based PMS approach during the PQM implementation period. As countries transition from donor-supported to locally funded PMS, having this process integrated and implemented as a core regulatory function will be important for PMS success and sustainability.

Access to a quality control laboratory that generates reliable results is integral to effective medicines regulation

As MRAs begin to implement more routine and institutionalized PMS programs, it is

important that they also have ready access to an NQCL that can reliably and accurately test the quality of medical products. PQM's expertise in strengthening NQCLs and laboratory networks has yielded several insights that can inform future efforts.

The capacity-building that takes place while a laboratory works to achieve international accreditation is as important as the accreditation itself. Achieving ISO/IEC accreditation or WHO PQ can be a long road. Incremental progress is critical, as capacity is built gradually, well before accreditation or WHO PQ is achieved. This capacity is built, for example, through development and use of quality manuals and SOPs as part of robust QMS. Therefore, it is important that accreditation or WHO PQ not be seen as the only measure of an NQCL's capacity.

A need also exists to strengthen local and

regional capacity in laboratory equipment calibration and maintenance. In several countries (e.g., Ethiopia), building in-house capacity for maintenance and calibration of laboratory equipment helped NQCLs minimize equipment downtime and quickly realize cost savings, as laboratories no longer relied on an expensive third-party entity to provide this needed service.

Strengthening pharmaceutical production should go in tandem with strengthening systems for quality assurance

To ensure the continued supply of essential medical products, efforts must continue to assess the global supply and available producers of these medicines. Where necessary, a sufficient number of manufacturers must be supported to produce medicines in compliance with internationally accepted practices, such as GMP, to increase the number of quality-assured sources of the FPP and API and ensure continuous supply. Increasingly, LMICs are looking to invest and support manufacturers of these medicines locally.

As efforts to increase quality-assured product sources are undertaken, increasing and strengthening the capacity for local manufacturing should be strategic, market based and carried out with cross-sectoral support. Development and implementation of GMP roadmaps—a stepwise approach for the pharmaceutical industry to attain WHO GMP standards in line with national priorities—can help guide these efforts. For example, in Ethiopia and Nigeria, PQM collaborated with country government counterparts and other stakeholders in the pharmaceutical sector to develop a GMP roadmap for the countries to reform the pharmaceutical sector and increase their capability to compete in the global market.

Strengthening manufacturers' GMP compliance should be accompanied by improving regulatory inspection capabilities, so that manufacturers adhering to GMP

benefit from an enabling regulatory environment while those that do not maintain GMP are appropriately penalized. Continued efforts should be made to ensure regulatory processes are streamlined (e.g., use of the Common Technical Document, reliance on information and decisions across countries), accountable (e.g., regulatory authorities held to dossier review timelines) and transparent (e.g., clear industry guidelines for dossier submission and adherence to other regulatory requirements) to support pharmaceutical manufacturers in the decision to bring a product to market and continue to manufacture it.

Value of collaboration with medicines quality assurance partners cannot be overemphasized to achieve successful outcomes

No MRA has the capacity to fully regulate all aspects of medical products. Thus, there is increasing recognition among regulatory authorities, of the value and necessity of collaboration to effectively address essential regulatory challenges related to medical product quality.

Coordination among implementing partners and other stakeholders can prevent duplication of efforts and improve the effectiveness of technical assistance. In some countries and regions, PQM worked through the WHO-led Coalition of Interested Partners, which brought together partners and donors to review information from the Global Benchmarking Tool and other assessments to support MRAs in developing strong institutional development plans and clarifying the specific areas donors and partners were supporting. This and other similar coordination mechanisms are critical in maximizing the use of both donor and local resources, as well as the impact of development assistance.

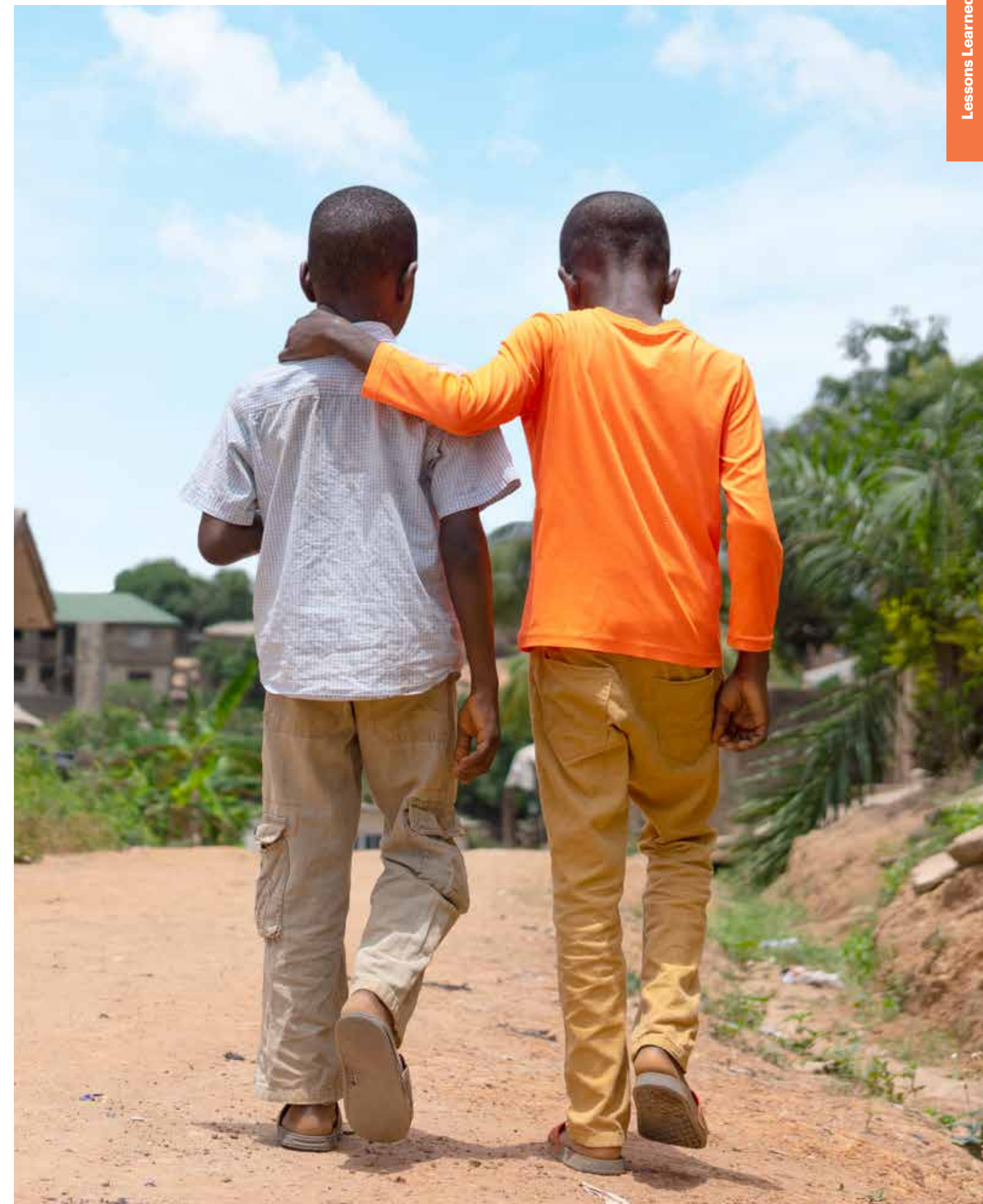
Also, participation in regional initiatives and networks strengthens national capacity and encourages information sharing and

South-South collaborations. Local and regional collaboration may take many forms, many of which not only help extend the capacity of national regulatory authorities in terms of scope but also strengthen existing MRA capacity by providing opportunities for joint review, learning and information exchange. PQM found this valuable through its experience in assisting the East African Community with joint dossier review, a process that reduced duplication by enabling products approved by the regional body to be approved across member states' regulatory authorities. Similarly, the establishment of regional laboratory networks in Africa, Asia and other regions helped establish a culture of cross-institutional learning and process improvement.



It's about time we tackle this issue [of poor-quality medicines], and we can only do it when everyone is trained to appreciate the need for quality assurance and [has] the skills to perform all these tests and help maintain purity."

**Dr. Isaac Asiedu-Gyekye,
Dean of the University of
Ghana's Pharmacy School**



Remaining Challenges



2 Billion

The number of people globally who still lack access to essential medicines

Despite the tremendous progress the PQM program achieved over the past 10 years, significant challenges persist. Globally, 2 billion people still lack access to essential medicines and millions are at risk of harm from poor-quality medicines.³⁰

Quality assurance systems are not yet fully developed

A recent review of the preliminary results of the WHO assessment of regulatory systems using the Global Benchmarking Tool indicated that none of the countries where PQM worked have achieved the status of “functional regulatory system,” described by WHO as maturity level 3. However, most of those countries are pushing toward

achieving that status, building on the basic systems and infrastructure put in place with support from the PQM program.

Most countries lack stable, well-functioning and integrated regulatory quality assurance systems

Having centralized, well-coordinated regulatory functions executed through a regulatory system with a legally enforceable mandate for responsible entities, namely the regulatory authority, is fundamental to assuring the quality of medical products. Siloed or parallel operations, fragmentation or duplication of roles and responsibilities, and uncoordinated

regulatory activities only serve to increase opportunities for the entry of substandard and poor-quality medical products.

Data analytics and informatics also have a major role in transforming the pharmaceutical quality assurance space. Data collection, analysis and use for product evaluation, inspection and PMS can support evidence-based decision making critical for promoting access to quality-assured products and for reducing and eliminating substandard and falsified products. As identified in the Lessons Learned above, there is an overwhelming need among countries to define data standards and set user specifications that match their regulatory processes.

Pharmaceutical regimens for global health programs are increasingly complex

The products available and of interest to the public health community continue to evolve. The Lancet Commission recommended that WHO improve the WHO PQ program to develop a more flexible focus, including on new essential medicines. WHO is already doing so, having launched a pilot program in May 2017 for biosimilars (i.e., rituximab for non-Hodgkin’s lymphoma/chronic lymphocytic leukemia and trastuzumab for breast cancer) to help make select high-priced cancer treatments available in LMICs.³¹ WHO is also making plans for the PQ of insulins. As the complexity of products and regimens for global health programs

increases and as they are introduced more rapidly into LMICs with less-mature regulatory systems, the public health pharmaceutical landscape will continue to change, requiring more advanced technical assistance to manufacturers that can produce the products and to the regulatory authorities in LMICs that can review them and ensure their quality, safety and efficacy.

Local production capacity required to ensure sustainable supply

Even as the global burden of disease shifts, in many LMICs the top five causes of death remain infectious diseases and MNCH conditions. The demand for

products to prevent these deaths is high, but manufacturing capacity to produce quality-assured medicines in many LMICs is not able to meet that demand. Bringing manufacturing closer to the burden of disease when it is feasible and appropriate can help ensure the supply of quality-assured medicines where they are needed most. However, challenges still exist in this space from both a technical and economic perspective. Some of the priority products have fragmented supply sources and are of small volume and small value. Technical assistance to local manufacturers and technology transfer projects can facilitate efforts to address public health issues related to the availability of these quality-assured essential medicines.

Country and Regional **SUMMARIES**



You cannot rely on another country for something that is a lifesaving commodity for your country. **It's better to source locally, so that you can be sure of availability and assure affordability**

*Dr. Adebimpe Olugbeminiyi Adebisi,
Nigeria's Ministry of Health Director of Family Health*



Bangladesh



Background

In October 2016, USP began implementing the USAID-funded PQM program in Bangladesh. PQM conducted a gap analysis to determine the capacity-strengthening needs of the medicines regulatory system, including quality assurance and quality control functions. The gap analysis informed specific pragmatic recommendations for system capacity strengthening at the Directorate General of Drug Administration (DGDA), the national medicines quality control laboratory (NCL) and pharmaceutical manufacturers. PQM's key strategic objectives in Bangladesh were to support NCL sites in Dhaka and in Chittagong to attain international standards, strengthen DGDA and its systems toward internationally accepted standard practices, and improve local priority product manufacturers' compliance with current national and international GMP standards.

Key accomplishments

International recognition for competency achieved by NCL. In March 2020, DGDA's NCL achieved WHO PQ. This success was realized with PQM's technical support to NCL to improve its capabilities to meet the WHO PQ requirements. Prior to achieving WHO PQ, NCL achieved ISO 17025:2017 accreditation, first in 2018 through PQM's technical support. ISO/IEC 17025 is an internationally recognized standard for testing and calibration laboratories, demonstrating competence in operations and generation of valid results. PQM provided technical assistance to strengthen NCL's QMS; improve its appropriate use of instruments for accurate testing; and develop its staff skills, including establishing an in-house metrology team to maintain laboratory instruments. These accreditations affirm that NCL can provide a conduit for regulators and industries to find reliable products and services to meet their specific needs. Achieving ISO 17025 accreditation can also promote resource generation for laboratory operations. For example, NCL once ISO 17025 accredited is eligible to access funds from the Global Fund for testing medicines to treat TB, HIV and malaria.

Medicines quality monitoring system strengthened by implementing risk-based postmarketing surveillance (RB-PMS).

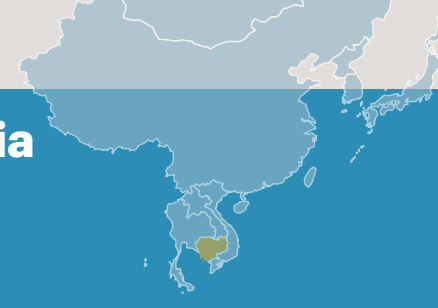
Each national regulatory authority has the responsibility to ensure the quality of medical products available on the market. However, none is resourced to test all products wherever they are sold. Prioritization decisions must be made, and the RB-PMS approach developed by PQM allows those making product sampling and testing decisions to take into account relevant risk factors associated with product quality. DGDA developed the Guidelines on RB-PMS of Finished Medicinal

Products, which cover risk-based prioritization of PMS implementation, including field-based screening and confirmatory laboratory testing. For field-based screening, the guidelines include a visual inspection checklist, field-based sampling SOPs and the Minilab™ screening SOP. In 2018, PQM visited five sentinel sites (Barisal, Chittagong, Khulna, Rajshahi and Rangpur) where DGDA was sampling medicines and using Minilab™ test kits to screen for their quality. DGDA inspectors received both hands-on and theoretical training on the RB-PMS approach. Implementation of RB-PMS helped triage only those screened products suspected of quality problems for confirmatory testing, thereby reducing NCL's medicines samples testing burden. PQM's technical assistance to DGDA capacitated NCL staff to conduct risk-based testing for public health products and provided DGDA with evidence-based information to carry out regulatory enforcement actions for non-quality compliant products.

Supply of quality-assured priority medicines increased. PQM provided technical assistance in good manufacturing practices to a local manufacturer of chlorhexidine gluconate 7.1% solution, used for newborn umbilical cord care. Advanced Chemical Industries (ACI) Ltd achieved national GMP standards, and DGDA approved registration of the product. ACI now manufactures this product for domestic and international markets, increasing the regional source of quality-assured chlorhexidine in the country and region.



Cambodia



Background

Cambodia is a resource-limited country that lacks effective medicines regulations and a robust MRA. As a result, substandard, falsified and expired medicines circulate in both public and private markets. Previous investigations in the region had revealed the production and circulation of falsified antibiotics, anti-TB medicines and antimalarials in the country. This major public health threat and the country's weak quality assurance/quality control systems are challenges that national stakeholders such as the MRA, National Health Product Quality Control Center (NHQC) and disease programs need to address. From 2009 through 2016, PQM supported Cambodia in strengthening its medical product quality assurance systems and improving the availability and use of information on product quality for evidence-based decision making. PQM also worked to build the capacity of the Department of Drugs and Food (DDF) - the Cambodian MRA, and the NHQC - the national medicines quality control laboratory, to make effective and data-driven regulatory decisions.

Key accomplishments

Regulatory foundational framework strengthened. PQM technical assistance helped strengthen the DDF regulatory framework. PQM provided technical support to develop the Cambodian national medicines policy that the Ministry of Health adopted in 2013. PQM also provided technical support for the revision and implementation of the good pharmacy practice guidelines.

NHQC institutionally strengthened toward self-reliance. PQM's support to NHQC significantly improved its QMS and technical capabilities (e.g., testing, equipment calibration, maintenance). PQM's advocacy led to the government of Cambodia obtaining a loan from the World Bank to build a state-of-the-art facility to house NHQC. Striving towards attaining good laboratory practices, PQM's technical support included review of the facility blueprints and hands-on support for analytical methods and procedures. NHQC's capability to appropriately test and detect substandard and falsified medicinal products helped generate more funding for its operations. Between 2008 (during PQM's predecessor program, Drug Quality and Information -DQI) and 2013, NHQC retained 30 to 50 percent of the revenue it generated; by 2014, it retained 100 percent of generated revenue for its operations and maintenance. PQM's technical assistance was instrumental in advocating for this change to increase sustainability and self-reliance.

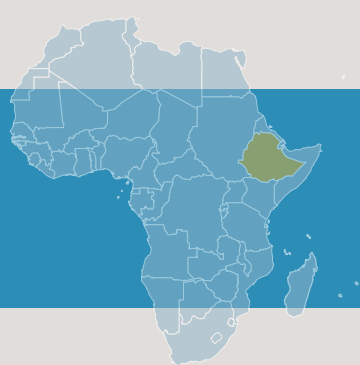
PMS data used to save lives. PQM supported DDF to develop tools to monitor medicines quality as part of Cambodia's PMS to identify substandard, falsified and unapproved medicines, and subsequently to undertake MQM activities in 12 sentinel sites and cross-border areas with Laos, Thailand and Vietnam. Due to the increased availability of quality data, DDF's response went from no action in the early years of PQM support to shutting down 100 percent of illegal pharmacies by the end of 2011 and banning substandard, falsified and unregistered medicines and pharmaceutical products, as well as illegal manufacturers, between 2012 and 2014. With support from the Inter-Ministerial Committee Against the Counterfeit and Substandard Medicines and Illegal Health Services and an official Ministry of Health declaration to act, DDF's PMS data facilitated the closing of 1,420 facilities found to be part of an illegal medicines scheme.



PQM's technical assistance was instrumental in advocating for this change to increase sustainability and self-reliance.



Ethiopia



Background

Ethiopia is the second-most-populous nation in Africa, with about 102 million people (2016 estimates), and has the fastest-growing economy in the region. However, Ethiopia also has one of the lowest per capita incomes and aims to reach lower-middle-income status by 2025. New reforms introduced by the Federal Ministry of Health have led to many changes, including the approval of legislation (Proclamation No. 661/2009) that led to the creation of a new regulatory body: EFMHACA. With USAID funding, in 2009 USP began implementing the PQM program in Ethiopia. PQM's focus was to build capacity and strengthen overall medicines quality assurance systems, key regulatory functions and local production of high-quality priority medicines. PQM's work supported USAID's and Ethiopia's common goals of an AIDS-free generation, reducing malaria-related morbidity and mortality, and ending preventable maternal and childhood deaths.

Key accomplishments

Regulatory tools developed and implemented. At the start of PQM's engagement in Ethiopia, medicines regulation had been characterized by suboptimal processes and outdated regulatory norms. With USAID's technical assistance through PQM, six national medicines quality assurance regulations/directives, 22 guidelines and 345 SOPs were developed and/or updated, approved and implemented. International best practices were introduced, leading to substantial improvements in regulatory practices to ensure medicines quality, including medicines registration, inspection of manufacturers and regulatory enforcement. The lead time for registration was reduced for both fast track (two years to four-and-a-half months) and new medicines, registration increased threefold in two years (from 285 to 805) and the quality of dossier review was maintained, which helped improve access to essential medical products.

Regulatory workforce developed. The lack of adequately trained regulatory staff posed a major challenge to ensuring the quality of medical products in Ethiopia. PQM worked with Addis Ababa University in 2018 to develop two new modules— (1) regulatory science and compliance and (2) pharmaceutical product registration and inspection—for inclusion in the curriculum for a new master's program in regulatory affairs that had launched in 2016. PQM also supported training for 1,606 (253 female) experts in key quality assurance/quality control-related technical areas. PQM's support in regulatory workforce development will contribute to substantial improvements in institutional performance and enhance capacity for regulatory enforcement as new graduates join the workforce.

Drug quality control laboratory ISO accredited. The 2009 rapid assessment of EFMHACA's quality control laboratory, responsible for rigorously testing the quality of medical products, identified several challenges that contributed to lack of confidence in its tests results, which hindered implementing regulatory enforcement actions to safeguard the population. With PQM's assistance, EFMHACA's laboratory attained ISO 17025:2005 accreditation in 2011, and the scope of the laboratory's testing capability was expanded from medicines to include a medical device (condoms) in 2014. Since then, EFMHACA has recalled or prevented the distribution of 94 million poor-quality condoms and taken 114 regulatory actions on poor-quality medicines.

GMP roadmap developed and implemented. The national demand for pharmaceuticals in Ethiopia was met mainly through importation, with limited local manufacturing capacity and questionable medicines quality due to inadequate compliance with international current GMP requirements. The government of Ethiopia wanted to change this and invest more to improve the quality of local manufacturers. To support this effort, in 2012 PQM helped EFMHACA conduct baseline assessments of eight of 10 local manufacturers to identify bottlenecks hindering progress toward current GMP compliance and rank them according to their maturity levels. PQM later helped EFMHACA develop and implement a five-year GMP roadmap, which informed the development of the National Strategy and Plan of Action for Pharmaceutical Manufacturing in Ethiopia (2015–2025). PQM's efforts led to the establishment of a pharmaceutical industrial park to support implementation of the strategy. PQM also supported building the capacity of four individual manufacturers in the country for priority health products; five of these manufacturers' products were subsequently approved by EFMHACA. One of the manufacturers became the first to market quality-assured chlorhexidine gel (for newborn cord care to prevent infection) in the country. This low-cost, lifesaving product is simple to manufacture, but quality-assured sources can be in short supply when needed to save vulnerable newborns. Having a local manufacturer will help ensure a reliable supply of this product for Ethiopia's population. Another manufacturer, for first-line anti-TB medicine, is currently undergoing inspection for WHO PQ.

EFMHACA has recalled or prevented the distribution of 94 million poor-quality condoms and taken 114 regulatory actions on poor-quality medicines.



Ghana



Background

Malaria is endemic in Ghana and a major cause of illness and death in the country, particularly among children and pregnant women. Maternal mortality is also a concern in Ghana, with postpartum hemorrhage as the leading cause of maternal death. With USAID funding, from 2009 to 2019 the PQM program provided technical assistance to strengthen medical products quality assurance and quality control systems in Ghana. Key objectives included strengthening the Ghana Food and Drug Authority's (GFDA's) capacity to monitor the quality of priority medicines, strengthening the NQCL's capacity for medicines quality control and improving GMP compliance by local antimalarial medicines manufacturers toward submission of ACT medicine dossiers for WHO PQ.

Key accomplishments

2015 Ghana's medicines quality assurance/quality control systems strengthened through improved capability for PMS. Through PQM's technical assistance, GFDA established and implemented a system for PMS of antimalarial and other medicines to detect and remove substandard and falsified medicines in the local market. This system improvement led to the establishment of a separate Drug Marketing Surveillance Department within GFDA responsible for conducting PMS. Since 2018, GFDA has collected 3,120 medicines samples and effectively assessed their quality after analytical testing in a medicines quality laboratory. Besides detection of poor-quality medicines, PMS helped GFDA identify other problems in the system, including circulation of unregistered products with unknown safety and quality profiles. Over the years, GFDA has consistently removed poor-quality medicines whenever they are found through PMS or adverse drug event reporting. In 2016, GFDA removed 60 substandard and falsified drugs from the market. GFDA continues to work with the Ministry of Health to address the recurring incidence of unregistered oxytocin injection found in the country during a routine quality survey of uterotonics in 2018. The main purpose of conducting regular quality surveys is to safeguard the population and make available quality-assured oxytocin injection for treatment of postpartum hemorrhage.

GFDA's capacity to test for medicines quality improved through better laboratory QMS. In 2014, GFDA's NQCL attained the ISO 17025:2005 accreditation after an assessment visit from a third-party international assessor for its physicochemical laboratory. The NQCL plays a critical role in GFDA's capability to assess medicines quality in line with its mandate to ensure the safety, quality and efficacy of medicines. The NQCL provides the analytical test data necessary

to evaluate medical product dossiers for registration purposes as well as analytical testing of samples collected during quality surveillance activities and during product quality investigations related to a reported adverse drug event. PQM provided technical assistance to procure necessary laboratory instruments and supplies, built staff capacity to conduct appropriate analytical method tests, and strengthened the laboratory's QMS through development of guidelines and SOPs to standardize processes in line with international good laboratory practices. In 2018, the NQCL demonstrated the sustainability of its QMS by successfully transitioning from ISO/IEC17025:2005 to the current ISO/IEC 17025:2017 standard with no support from PQM; this is a testament to its sustainability and country ownership. GFDA, drawing on its expertise and experience from implementing QMS in NQCL, also implemented QMS at the organizational level, resulting in GFDA achieving ISO 9001:2015 certification in 2017, a major accomplishment for an MRA in Sub-Saharan Africa.

GMP compliance for local production of quality-assured antimalarials improved. Seven local pharmaceutical manufacturers have a GFDA-approved artemether-lumefantrine product on the market but none of them have attained internationally recognized GMP compliance or WHO PQ for the product. PQM identified and provided technical support to Entrance Pharmaceutical Ltd., a local manufacturer of artemether-lumefantrine (20/120 mg), to improve GMP compliance and attain WHO PQ standards. Prior to the end of the PQM program, the company had attained key milestones toward this goal.





Background

The population of Guinea is among the poorest in Western Africa. While health indicators have improved over the past two decades, maternal and child mortality remain high, the country faces a generalized HIV epidemic, and malaria is endemic and a leading cause of medical consultations and death. TB is also a leading cause of death. From 2014 to 2015, Guinea faced an Ebola crisis that exposed significant weaknesses within the health system.¹³

With funding from the U.S. President's Malaria Initiative and USAID, the PQM program supported efforts to strengthen medicines quality assurance systems in Guinea from 2014 to 2019. PQM worked with the government to address major challenges in medicines regulation and the medical product quality control systems. Program activities focused on strengthening the capacity of the National Directorate of Pharmacy and Medicine (DNPM) and the National Medicines Quality Control Laboratory (LNCQM).

Key accomplishments

Pharmaceutical regulatory framework improved. The pharmaceutical sector in Guinea had major gaps in its medical product quality assurance regulations, practices and pharmaceutical institutions. The pharmaceutical law of 1994 was outdated and not aligned with current international and African Union recommendations for strong regulatory systems. The Ebola epidemic of 2016 prompted Guinean authorities to review the health system, including regulations to ensure the quality and safety of medical products. In collaboration with USAID's Systems for Improved Access to Pharmaceutical Services program, PQM provided technical expertise for the revision of Guinea's pharmaceutical law to incorporate missing provisions required for alignment with international and African regional requirements to establish an MRA. An MRA is necessary to appropriately regulate the manufacture, sale and use of medicines in a country to safeguard public health. The new legislation was enacted by Guinean Parliament in June 2018 and signed into law by the president in July 2018. The revision of the law marks an important step toward building a strong regulatory framework for medicines and other medical products. To effectively implement this law, more support is needed to develop key regulations and provisions to ensure that individual products meet the criteria of quality, safety and efficacy.

LNCQM strengthened. When USAID engaged PQM to work in Guinea in 2014, LNCQM had inadequate capacity to conduct quality control testing of medicines. The laboratory lacked basic equipment,

the facility was not adequate for conducting laboratory work and laboratory personnel had limited technical know-how in different quality control disciplines. PQM provided technical support to LNCQM through technical training, addressing laboratory infrastructure and equipment gaps and strengthening the laboratory's QMS. Although PQM provided comprehensive support to LNCQM, it lacked financial resources to run its laboratory operations, making it very challenging to sustain its activities. It is anticipated that, with the adoption of the new regulatory provision from the recently enacted law that requires medicines be tested prior to their release into the market, this situation will improve. However, LNCQM still needs to build its capacity and processes in order to be able to provide reliable testing results.

*From 2014 to 2015, Guinea faced an Ebola crisis that **exposed significant weaknesses within the health system***



DNPM capacity to perform PMS as a regulatory function improved.

PMS of medicines quality is an important regulatory responsibility. At the start of PQM's intervention in Guinea, DNPM lacked the capacity to carry out this function. This meant that Guinea tested very few products on the market to confirm their quality, leaving the public unprotected from poor-quality products. In response, PQM began by establishing processes and building DNPM's capacity to implement these processes to detect poor-quality and falsified medicines in the market. The approach utilized incorporated elements of risk-based PMS, including the three-level testing methodology—visual inspection, handheld Raman and compendial tests. In the three-level approach, less-expensive methods are used first for quality screening and select samples are tested with more-expensive compendial methods. Risk-based sampling strategies were also utilized to help streamline the scope, with more focus on products considered high risk as identified based on set risk criteria. To use limited resources effectively and in such a way that continuity of the process can be sustained by a country to safeguard the population, the risk-based PMS approach is recommended over regular PMS (in the latter, any product, with or without high risk for quality problems, can be sampled and tested). With PQM's support, DNPM carried out its first national-level PMS, which expanded to include areas along the borders with Liberia, Mali and Senegal. This nationwide exercise was completed in fewer than three months, a relatively short time for this type of activity. PQM facilitated the dissemination of PMS results to stakeholders, including national disease programs, as the information gathered will enhance decision making and regulatory action for the delivery of quality-assured medicines to Guinea's population.



Background

According to WHO's Global Tuberculosis Control Report of 2019, Indonesia ranks third of the eight countries that accounted for two-thirds of the global TB burden: Indonesia accounted for 8 percent of the estimated 10 million people who fell ill with TB in 2018. The incidence rate of HIV/AIDS in Indonesia has also become an increasing concern, and Indonesia is experiencing the fastest-growing HIV epidemic in Asia. An estimated 630,000 people were living with HIV and AIDS in 2015, with only 9 percent on antiretroviral (ARV) treatment—a very low figure in Southeast Asia, where the average is 39 percent.¹⁴ The objective of the PQM program in Indonesia (2011–2019) was to build the capacity of the National Agency of Food and Drug Control (BPOM) and its quality control laboratories, improve the regulatory governance environment, and support selected local manufacturers that produce anti-TB medicines and ARVs.

Key accomplishments

2015 Capacity of BPOM's NQCL strengthened to detect poor-quality medicines. PQM provided technical assistance to the NQCL (Chemical Division of Medicines NAPPZA) to achieve WHO PQ status in 2019. This was achieved through PQM's technical assistance to improve the NQCL processes, procedures and staff capacity to accurately test medical products for quality. PQM also leveraged over \$2 million of Global Fund resources for infrastructure upgrades to get the laboratory prepared for WHO PQ. This was the first laboratory in Indonesia to earn global recognition as a trusted quality control

laboratory capable of testing medicines to promote access to quality-assured medicines. This achievement to international recognition and trust in the medicines quality data generated by the laboratory are deemed reliable to trigger a regulatory action. Taking quick regulatory actions when falsified medicines are identified will help the country sustainably ensure the quality of medical products circulating in the local market.

Medicines quality advanced through policy reform. In the policy and regulatory environment, PQM made significant progress in facilitating the development of PMK 75/2016, a regulation that requires sampling and testing of public program medicines and sharing medicines quality data by BPOM with the Ministry of Health. Previously, BPOM had conducted sampling and testing mostly in the private sector and kept the data internally. Many public-sector medicines were supplied by state-owned pharmaceutical companies and were not subject to sampling and testing by law to ascertain quality. PMK 75/2016 allows the government to have more data on medicines quality to support better decision making and acts as a bridge to enhance regular communication and coordination between BPOM and the Ministry of Health.

Steps taken toward self-reliance with local production of quality-assured essential medicines. PQM supported local manufacturers in attaining WHO PQ of their medical products. As a result of PQM's support, PT Kalbe Farma (the largest pharmaceutical manufacturer in Indonesia) attained WHO PQ of its levofloxacin (as hemihydrate) 500 mg film-coated tablets, and PT Sanbe Farma (the fourth-largest pharmaceutical manufacturer in Indonesia) attained WHO PQ of its oxytocin 10 IU/mL solution for injection. Local manufacture of these products directly contributes to an increase in the availability of high-quality medicines in the domestic and global markets. In addition, attaining WHO PQ status can encourage other local manufacturers to adopt international good manufacturing best practices, which in turn may contribute to ensuring that medicines produced in the country are safe, effective and quality assured.



Intergovernmental Agency for Development (IGAD)

Background

Due to economic uncertainties and political conflicts, the Intergovernmental Agency for Development region experiences migration and cross-border mobility, which is often accompanied by movement of diseases. While providing for the healthcare needs of a static population allows for regular follow-up and monitoring, the health outcomes for cross-border mobile populations are often difficult to monitor and implement. Health systems for these marginalized and vulnerable populations in IGAD's arid and semiarid lands are often neglected and not regarded as a priority. In 2018, with funding from USAID's East Africa Mission, the PQM program collaborated with IGAD to strengthen cross-border medicines regulatory capacity across eight member states (Djibouti, Eritrea, Ethiopia, Kenya, Somalia, South Sudan, Sudan, Uganda) in the regional economic community. The purpose of this collaboration was to establish an expert working group (EWG) consisting of representatives from the national MRAs in each of the eight member states, to identify gaps in pharmacovigilance systems and build the capacity of the EWGs to conduct PMS at the cross-border areas to inform future joint regulatory actions.

Key accomplishments

Regulatory EWG for pharmacovigilance and PMS established for IGAD countries to harmonize approaches. Despite efforts since 2015 to harmonize medicines regulation in the IGAD region, little progress had been made in practice. The formation of the EWG to implement activities that involve all countries in the IGAD region was a key

achievement toward this goal. The EWG for pharmacovigilance and PMS was established during a meeting in 2018 jointly organized by the IGAD secretariat and PQM for member countries. At this meeting, members were nominated and terms of reference for the roles were developed and adopted. The EWG platform also emerged as an illustrative model of how to select and implement joint regulatory priorities of common interest to member countries. The first task for the group was to spearhead pharmacovigilance self-assessment of country systems and implement PMS in cross-border regions. This EWG platform and the experience acquired through the activities carried out will help shape the future actions needed to accelerate implementation of the IGAD five year joint work plan for medicines regulatory harmonization to increase access to quality-assured, safe and effective medicines in member countries.

First-of-its-kind regional cross-border PMS implemented in the IGAD region. Although anecdotal information suggested the widespread circulation of substandard and falsified medicines in the region, especially in border areas, quantified data from a credible source had not been available. With technical assistance from PQM, medicines samples were collected from six member states using the protocol developed by the EWG based on a risk-based PMS framework. The samples were all tested by the internationally recognized (ISO 17025 accredited) NQCL of Ethiopia's regulatory authority, previously supported by PQM to attain international standards, to reliably test medicines quality. The analytical test results were validated and disseminated to participating member state national MRAs for appropriate regulatory actions. This was the first-ever joint PMS activity conducted in the IGAD region that included the involvement of MRAs from countries in the economic community. The medicines quality data generated through this survey—relying on prioritized, risk-based selection of medical product samples—will serve as point-in-time reference data for IGAD countries to inform future joint plans to address issues related to the circulation of substandard and falsified medicines. More importantly, member countries gained experience in conducting PMS at the regional level, interpreting medical product surveillance data and prioritizing next steps for strengthening medical product quality assurance systems in the IGAD region.



Kazakhstan

Background

Kazakhstan has made significant progress in recent years in its battle against TB, with TB incidence falling steadily since 2004 and the government ensuring universal treatment coverage for TB. However, the nation still has one of the highest MDR-TB burdens globally, with MDR-TB and rifampicin-resistant TB together making up 27 percent of new TB cases and 64 percent of previously treated cases in the country.¹⁵ To address these challenges, Kazakhstan adopted the Complex Plan for TB Control in Kazakhstan: 2014–2020. In addition, the Ministry of Health issued an order that, beginning in 2018, all local manufacturers need a local GMP certificate for state registration of their medicines. PQM began work in Kazakhstan in 2013, with the goal of supporting the Ministry of Health in improving the quality and capacity of anti-TB medicines manufacturers in country.

Key accomplishments

QMS in three regional medicines quality control laboratories strengthened. PQM built the capacity of three regional quality control laboratories in the cities of Astana, Karaganda and Kostanay to strengthen their QMS and comply with international standards. Instead of working in silos, a team of representatives from the three laboratories participated in the QMS assessments at all three laboratories. Similarly, a quality team was formed with representatives from the three laboratories. The quality team oversaw the revisions and standardization of QMS documents and shared updates with quality control laboratories nationwide. With technical assistance from PQM, the quality team also developed the Karaganda laboratory's LIF (laboratory information file) for submission to the WHO PQ program, and Karaganda submitted its WHO PQ application. The WHO PQ team completed the assessment, no major observations were found and WHO's decision on PQ of the laboratory is pending.

Capacity of local manufacturers to produce quality anti-TB medicines for the local market built. PQM provided technical assistance to Nobel Almaty Pharmaceutical Company, a manufacturer of levofloxacin and moxifloxacin tablets used for treatment of MDR-TB, to improve compliance with internationally acceptable GMP standards. PQM's assistance included GMP assessment of the facility, development and implementation of the corrective and preventive action plan, equipment validation, cross-contamination risk management and capacity development in the different GMP topics. These interventions, along with an investment of \$4.7 million

USD by the manufacturer to construct and equip a new production facility, resulted in significant improvement in line with internationally accepted GMP standards. As a result, the new production site, where the medicines for treatment of MDR-TB are produced, received a local GMP certificate in April 2019. The manufacturer continues preparation work toward submission for WHO PQ of levofloxacin.



Kenya



Background

Malaria remains a major public health problem in Kenya and accounts for an estimated 16 percent of outpatient consultations.¹⁶ The decentralization of healthcare in Kenya to 47 county governments added another layer of complexity to ensuring medicines quality along the supply chain due to the counties' inadequate capacity to determine that quality-assured medicines are procured for their populations. With USAID funding through the U.S. President's Malaria Initiative, the PQM program was implemented in Kenya from 2009 to 2019. PQM's approach was to help Kenya's Pharmacy and Poisons Board (PPB) build its overall medicines quality assurance system. This assistance was tailored to build the capacity of PPB's human resources and operational systems in the most critical components of its regulatory functions: marketing authorization, inspection, quality control and risk-based PMS. By addressing gaps in these vital regulatory functions, PQM intended to reduce the mortality and morbidity resulting from unsafe, ineffective and poor-quality medicines.



Key accomplishments

First-ever PMS program established in Kenya. PQM provided technical assistance to PPB to plan and establish its first PMS. The first PMS protocol—a plan to collect and test samples—that defined the roles of each partner was undertaken in collaboration with the Division of National Malaria Program and other key stakeholders. This approach utilized a risk-based methodology to test the samples: The majority of samples are first screened using visual inspection and a handheld screening tool, Minilab™, with a limited number of samples subjected to the more expensive compendial tests to save resources and time. Prior to this, PMS was conducted in response to either complaints of poor-quality products in the market or surveys conducted in collaboration with partners. There was no consistent and standardized approach for PMS. Since the start of the PMS program, PPB has conducted seven rounds of sampling and testing. Some key findings from PMS activities have included the identification of substandard and falsified, expired and unregistered medicines. Regulatory actions have included recalls and the more severe consequence of jail time for illegal peddling in the local markets.

PPB's registration function strengthened. Medicines registration is a key function of PPB's efforts to safeguard access to quality-assured, safe and effective healthcare products. With PQM's assistance, in 2015 PPB upgraded Kenya's medicines registration system from paper based to online, to facilitate management of a full range of applications for product registration. This transition allowed the pharmaceutical industry to submit online applications in Electronic Common Technical Document format; it also improved PPB's capacity to manage applications for product registration, retention and variations, from receipt to the issuance of a product marketing authorization, thereby allowing the supplier to sell the product in the country. As a result, registration timelines were reduced and suspected poor-quality product alerts were issued more quickly, with improved collaboration between PPB inspectors at ports of entry and at regional PPB offices. Strengthening the registration system sets PPB on the path toward achieving its mandate of safeguarding the population by allowing only quality-assured, safe and effective medicines to be sold in the local markets.

ISO 17025 accreditation achieved and sustained. After three years of intense training, laboratory audits, implementation of an adequate QMS, and equipment calibration and validation, the NQCL in Kenya reached its goal of becoming ISO 17025 accredited in June 2015. The laboratory is now recognized as competent to test medicines quality and generate valid and accurate results in line with internationally accepted standards, promoting confidence and trust by its stakeholders and the population at large. Having an accredited laboratory in Kenya reduces both the cost of quality control testing (as samples otherwise may be sent outside the country) and the turnaround time for results so the regulatory agency can take quicker action. In addition, the laboratory may be able to generate internal funding to support its operations due to its international recognition.

Liberia



Background

According to the National Malaria Control Program in Liberia, malaria accounted for least 33 percent of all inpatient deaths and 41 percent of deaths among children under 5 years of age in 2015. In 2014, an Ebola outbreak exacerbated the burden of malaria in Liberia. A University of Washington survey estimated that Ebola was responsible for 11,000 deaths and that the epidemic resulted in 100,000 untreated malaria cases. In 2009, with funding from USAID through the U.S. President's Malaria Initiative, the PQM program began providing technical assistance to Liberia to strengthen its regulatory system and medicines quality control laboratory. The goal was to build capacity and put in place tools and systems to strengthen medicines quality assurance and key medicines regulatory functions, including registration, inspection, quality control, PMS and local production of quality-assured essential medicines. PQM worked toward achieving USAID's and the government of Liberia's common goals of increasing access to quality-assured health products in Liberia.

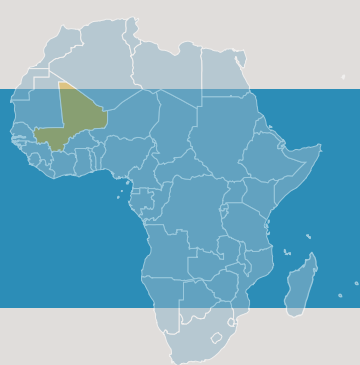
Key accomplishments

Legislation passed to establish the Liberia Medicines and Health Products Regulatory Authority (LMHRA). Prior to 2009, Liberia lacked a system to ensure or control medicines quality. This was mainly due to the absence of a national medicines policy, medicines regulations and medical product quality control capacity. With PQM's support, a new pharmaceutical law was passed. As a result, PQM intensively supported the government of Liberia to establish a regulatory authority, LMHRA. LMHRA is legally mandated to carry out its main functions to ensure the quality, safety and efficacy of medical products, including PMS for product quality, product registration and inspection of manufacturers. LMHRA also regulates the distribution and supply of medicines in Liberia so that only quality-assured medicines are sold and consumed in the country.

LMHRA capacity built to improve its registration and inspection functions. When LMHRA was established, staff lacked practical experience in conducting GMP audits at manufacturing sites and lacked SOPs to guide them in reliably performing their job functions. In 2012 and 2013, PQM, in collaboration with LMHRA, developed a web-based electronic tool for the inspectorate department to allow its staff to conduct inspections without unwieldy paper documents. PQM also developed registration guidelines and tools to introduce an electronic registration system. This increased the efficacy of registration activities, particularly decreasing the time it took to approve marketing authorization for medicines.

Risk-based PMS established. Part IV, Section D of the legislation that created LMHRA calls for continuous PMS of medicines and other health products circulating throughout Liberia. This is designed to ensure that products remain effective and of good quality until they are accessed by patients. Expired, damaged, substandard or falsified medical products are to be collected, removed and appropriately destroyed. To this end, in 2011, PQM supported LMHRA to establish the first joint MQM activities for antimalarials, during which 66 percent of samples that failed quality tests were artemisinin monotherapies. This led to a countrywide ban of artemisinin monotherapies. PQM continued to provide technical assistance to scale up MQM until 2018, when the risk-based PMS approach was introduced. This risk-based PMS considers and includes other medicines (not antimalarials) that pose a high risk for poor product quality based on set criteria. The risk-based PMS approach that also implements a risk-based testing strategy was deemed necessary to reduce the resources (funds and human resources) spent sampling and testing products with low product quality risk when resources could be channeled to focus on the high-risk products. Ultimately, this saves limited resources and creates a sustainable pathway toward continuity of PMS activities in Liberia to safeguard public health.





Background

Malaria is the primary cause of morbidity and mortality in Mali, with 1,918,376 confirmed cases in 2017.¹⁷ Ensuring the availability of quality-assured antimalarial medicines for patients in Mali is an important aspect of making progress toward the government of Mali's goal to primarily target those who are most vulnerable in the population: children under 5 years of age and pregnant women. The focus for the PQM program in Mali was to strengthen the capacity of Ministry of Health institutions involved in medical product quality assurance. PQM aimed to strengthen and support medicines quality control capacity, advocate for the establishment of an MRA, and support studies on the efficacy and resistance of selected antimalarial medicines. This work, which was funded by the U.S. President's Malaria Initiative and USAID, was implemented in Mali during 2009–2012 and 2014–2019.

Key accomplishments

National Laboratory of Health's (LNS) capability toward international good laboratory practices enhanced. PQM built the managerial and technical capacity of the NQCL through building their staff's technical skills for analytical instrumentation methods and instrument maintenance. PQM also addressed laboratory infrastructure and equipment gaps, supported QMS to document and standardize processes, and supported participation of inter-laboratory testing and proficiency testing - to benchmark capabilities to conduct specific tests with other laboratories in the region. More than 90 SOPs and two guidelines were developed in alignment with international standards as part of the laboratory's QMS documentation. One main challenge that still persists is frequent turnover of trained laboratory staff and over-reliance on temporary staff (pharmacy interns) to support laboratory testing and operations.

Collaboration among stakeholders to address medicines quality problems increased. With PQM's support, collaboration improved among LNS, the Directorate of Pharmacy and Medicine (DPM), the National Malaria Control Program and other key stakeholders to conduct and disseminate information from MQM activities. With PQM's facilitation and support, protocols for MQM sampling and testing plans were jointly developed. Results from MQM for noncompliant products were also disseminated widely to all key stakeholders. While regulatory actions were limited for noncompliant products, PQM facilitated joint missions to sites where falsified products were found to investigate the cause of their presence and raise local authorities' awareness about the issue of substandard and falsified medicines circulating in local

markets. In Mali, DPM does not have the mandate by law that other traditional MRAs do to carry out enforcement action for non-quality compliant medicines circulating in the market. DPM also does not have the mandate for regulatory functions such as inspection and PMS. PQM conducted advocacy workshops for further reform of the legal regulatory framework toward African Union and international recommendations for a full-fledged pharmaceutical regulatory authority to safeguard medicines quality, safety and efficacy in the country markets.

National pharmacovigilance center established to safeguard the population. Although medical product safety monitoring was identified as a priority in Mali, attempts to establish a national pharmacovigilance program were unsuccessful. PQM supported efforts to establish a pharmacovigilance program and, to do so, brought together key stakeholders, including national health programs, Ministry of Health directorates and services, pharmacists and doctors' associations, and WHO. A pharmacovigilance center was established within the National Center for Disease Control, which had the technical capability to conduct such activities, and stakeholders developed an action plan to implement pharmacovigilance. One main challenge was the inadequate legal framework to carry out pharmacovigilance activities in Mali. PQM facilitated the revision of the ministerial decree that defined the implementation of pharmacovigilance in Mali, defining roles and responsibilities of the institutions involved. PQM also worked closely with the WHO Collaborative Center in Morocco to build local capacity in Mali for conducting pharmacovigilance activities. Within two years of implementation, Mali became the 105th full member of the WHO Program for International Drug Monitoring in Uppsala, Sweden.

Within two years of implementation, Mali became the 105th full member of the WHO Program for International Drug Monitoring



Background

According to WHO, Mozambique is a low-income country with a population of 27.98 million, approximately 1.6 million of whom have HIV, giving Mozambique 5 percent of the global disease burden. Mozambique also carries 3 percent of the global malaria burden and is one of 22 countries with a high rate of TB. Other diseases (e.g., neonatal disorders, lower respiratory infections, diarrheal disease) are among the leading causes of death among all age groups. In Mozambique, the PQM program, funded by the USAID/Mozambique Mission, provided technical assistance to build the quality control and quality assurance capabilities of the National Directorate of Pharmacy (DNF) to strengthen the country's medicines regulatory system and safeguard access to quality-assured essential medicines. PQM later added activities to improve the legislative framework for establishing a strong, robust and resilient medicines quality regulatory system in Mozambique. During eight years of implementation in the country, PQM's technical assistance helped Mozambique reach several milestones that improved the overall medicines quality assurance systems in the country.

Key accomplishments

Capacity of the National Medicine Quality Control Laboratory (LNCQM) strengthened to comply with international laboratory standards. Due to a fire in 2008, when PQM commenced activities in Mozambique in 2010, LNCQM did not have a physical building to carry out laboratory activities, had no laboratory equipment and had very limited laboratory personnel (three staff) to carry out its statutory functions. PQM developed a long-term plan to support LNCQM, which included identification and advocacy for a dedicated location by the Ministry of Health; procurement of laboratory equipment, reagents and reference standards; and infrastructural outfitting of the space to equip it with everything needed for a functional laboratory. PQM advocated for more staff to be hired, designed training programs on analytical instrumentation methods and testing, and revamped the QMS through development of more than 110 SOPs, seven quality manuals and three quality guidelines. PQM also supported the maintenance of laboratory equipment, including regular calibrations and verifications. In 2019, PQM supported the laboratory to expand the space through procurement of a container office, preparing the laboratory to seek international certification as a capable laboratory with accurate and reliable results. Although LNCQM's capacity to test key essential medicines in Mozambique improved tremendously, challenges (e.g., financing) for LNCQM operations to be sustainable remain.

Pharmaceutical law and regulations strengthened. A new pharmaceutical law was passed in September 2017 to amend the original law from 1998, which lacked key regulatory provisions. This was achieved through joint technical assistance by PQM and other key stakeholders in the country. PQM's support toward this reform originated from a workshop it conducted in 2015. During the workshop, gaps in the Mozambican legal framework, among other issues, were highlighted. PQM provided technical assistance to revise sections of the pharmaceutical law for quality assurance in line with the African Union model law. PQM also convened stakeholder forums to agree on changes and finalize the revised law for submission. The new approved law created a pathway for an autonomous regulatory authority in the country. PQM provided technical assistance for the development of some key regulations in line with the new law.

PMS system strengthened. As part of the requirements of the newly passed pharmaceutical law, PQM provided technical assistance to DNF to establish a PMS department and structure, which was previously under the mandate of LNCQM. This change was important to institutionalize the PMS process, standardize approaches and have the mandate reside in the appropriate DNF department (since LNCQM's main function is medicines quality testing). In late 2018, a risk-based approach was introduced to prioritize and optimize the use of limited resources and maximize the country's investments while promoting self-reliance rather than continued donor dependence. PQM supported staff capacity and skills building at national and regional levels in this process. A risk-based sampling and testing protocol was also developed. Mozambique still requires technical support to advance this approach and work toward attaining sustainability.



Myanmar

Background

In Myanmar, malaria and TB continue to be serious public health concerns; according to WHO, Myanmar is among the top 30 countries with a high TB burden globally. The PQM program began providing technical assistance to Myanmar's Department of Food and Drug Administration (DFDA) in 2014. PQM's main objective was to strengthen DFDA's medicines quality assurance systems, with a focus on building the analytical testing capacity of DFDA's Nay Pyi Taw Laboratory. These efforts were in support of efforts by the Ministry of Health and Sports (MOHS) and USAID to eliminate malaria and reduce the TB burden. As such, USAID support for PQM activities in Myanmar were financially supported by the U.S. President's Malaria Initiative and the USAID TB program.

Key accomplishments

International accreditation by DFDA's Nay Pyi Taw Pharmaceutical Chemistry Laboratory achieved. In 2016, with PQM's technical assistance, DFDA's Nay Pyi Taw Pharmaceutical Chemistry Laboratory achieved the internationally recognized ISO 17025:2005. This laboratory accreditation certifies competence to carry out tests and calibrations and increases the populations' confidence in the accuracy and reliability of test results from the laboratory. This goal was achieved through intensive support to the laboratory using a multipronged approach to build its capabilities and advance its operations toward complying with international standards. First, PQM assessed the laboratory in 2015 and used the findings to inform the development of a roadmap toward international good laboratory practices and ISO 17025 accreditation. The government implemented major infrastructure renovations, with technical design support from PQM, as part of the assessment recommendation to comply with international standards. PQM conducted a series of capacity- and skills-building workshops for laboratory staff on analytical instrumentation methods, equipment calibration and maintenance, and development of SOPs for the establishment of QMS that were nonexistent at that time. As part of the QMS strengthening, two manuals and 117 SOPs were developed. In 2018, a new standard of ISO 17025:2017 was introduced, and Nay Pyi Taw laboratory became the first laboratory in Myanmar and one of the first in the region to attain the new 2017 standard. DFDA has shown commitment through provision of funding to complement MOHS and USAID support to sustain this achievement and maintain accreditation.

Chemical residue testing for deltamethrin in long-lasting insecticidal nets (LLINs) now performed by DFDA's Nay Pyi Taw laboratory. Myanmar's goal is to achieve malaria elimination by 2030. Use of LLINs by the population to prevent malaria is one of the key strategies implemented for malaria elimination. The projects implementing use of LLINs had concerns about the quality and effectiveness of the LLINs, particularly after washing the nets over periods beyond two years. The national laboratory did not have the capacity to test for the insecticide (deltamethrin) embedded in the nets to prevent mosquito bites. The only option was to send LLIN samples to laboratories outside the country with testing capacity. To save funds and build in-country capacity for testing, PQM developed the skills of DFDA's Nay Pyi Taw laboratory staff to test for deltamethrin quality in LLINs samples. PQM provided technical assistance to conduct chemical residue testing using both high-performance liquid chromatography and gas chromatography. Between 2018 and 2019, the laboratory performed 600 tests (five different tests per sample) from 120 LLINs samples collected after 24 months and 36 months of use. The testing was to determine how effective the LLINs were after prolonged use. Summary results showed that individual net samples still had 45 percent of the loading dose of deltamethrin after 24 months and a predictive threshold of 30 percent after 36 months.¹⁸ Having the capability to test LLINs in the country saves time (tests are conducted in a shorter timeframe than if sent outside the country), saves funds (fewer resources are required to test LLINs in the country) and provides evidence-based data for decision making.



Nigeria

Background

According to the 2017 World Malaria Report, about three out of 10 people with malaria in the world live in Nigeria, and one out of four global deaths due to malaria are in Nigeria.¹⁹ A joint report of the trends in maternal mortality estimated that 58,000 Nigerian women died in 2015 following complications related to pregnancy and childbirth, contributing to 19 percent of global maternal deaths.²⁰ Even though Nigeria has a significant local manufacturing industry, about 70 percent of pharmaceuticals used in the country are imported, further complicating medicines regulation and increasing the prevalence of substandard and falsified medicines in the national market. To address these health challenges, with funding from USAID, the PQM program began working in Nigeria in June 2013. PQM's focus was on strengthening the regulatory capacity of NAFDAC and Nigerian pharmaceutical manufacturers. The main objective of PQM's work was to institutionalize QMS and implement tools and systems that would sustainably improve NAFDAC's regulatory capacity. In addition to supporting essential medicines for national public health programs, PQM focused on the overall improvement of pharmaceutical manufacturing by developing a national GMP roadmap and contributing to workforce development.

Key accomplishments

International recognition and standards attained by five medicines control laboratories. The main goal of the NAFDAC laboratories mandated to test medical products for quality (both before product registration and while medicines circulate the local markets) was to attain international recognition for competency of testing. PQM's technical support to achieve this goal included development of a long-term strategic plan, development and revision of laboratory guidelines and SOPs in line with international QMS requirements, analytical methods training, and equipment calibration and maintenance training. The national laboratory in Yaba was the first to attain ISO 17025 accreditation in 2015. To improve the efficiency of the process, PQM utilized the collaborative training model whereby expert trainers were established and taught to support other laboratories in upgrading their QMS and laboratory services with limited technical assistance from PQM. Using this approach, NAFDAC regional laboratories in Agulu and Kaduna attained ISO 17025 accreditation in 2016 and 2017, respectively. PQM also provided technical support to the National Institute for Pharmaceutical Research and Development to support pharmaceutical manufacturing research and development to attain ISO 17025 certification in 2018. In addition, PQM provided technical

support to the National Control Laboratory for Vaccines and other Biologicals, for testing diagnostic tools and vaccines such as malaria rapid-diagnostic testing and Bacille Calmette-Guerin vaccine for TB, to attain ISO 17025 certification in 2019. With this accreditation, the stakeholders and populations' confidence and trust in the results of medicines quality tests performed by these laboratories increased and was relied on for decision making to safeguard the population and increase access to quality, safe and effective medicines.

Local pharmaceutical manufacturers' capacity enhanced to comply with international standards, and to increase supply of locally produced priority public health medicines. In 2013, no MNCH commodities were produced in Nigeria. USAID/Nigeria engaged with PQM to support manufacturers of chlorhexidine gel, amoxicillin dispersible tablets, magnesium sulfate, oxytocin, zinc sulfate and oral rehydration salts to improve their production practices and submit high-quality applications to NAFDAC for marketing authorization approval. This made locally manufactured quality-assured medicines used to treat a wide range of maternal, neonatal and child health illness easily available for use inside and outside of Nigeria. In addition, production and local approval of sulfadoxine/pyrimethamine (SP), used as an intermittent preventive treatment of malaria during pregnancy, was achieved in Nigeria with PQM's technical assistance. Importation of SP was restricted by the government to promote local manufacturing. PQM's support to upgrade GMP and QMS in the facility manufacturing line for SP provided a local quality-assured option for the population.

Strong PMS system to inform regulatory decisions strengthened. NAFDAC's directorate responsible for PMS for product quality (as well as pharmacovigilance for patient safety related to the use of medicines) was established before PQM started working in the country. However, no structured framework for medicines quality surveillance existed in Nigeria. PQM provided technical support to NAFDAC to develop a robust national PMS program and to conduct several rounds of studies on antimalarials and MNCH medicines across Nigeria. PQM also provided technical assistance for the development of PMS guidelines adoption by NAFDAC to harmonize PMS approaches across all zones and states in the country. Over the years, NAFDAC tested 7,802 samples of medicines (5,291 antimalarials and 2,611 for MNCH) and took regulatory actions to remove poor-quality and falsified medicines from the market. One notable example is oxytocin injection surveillance, which found that more than 70 percent of samples collected from private and public sectors failed the content of the API (assay test). NAFDAC took several actions to address this challenge, including confiscation of poor-quality products, training of the private sector on good distribution practices and implementation of stricter regulation on the import of oxytocin medicines. A local manufacturer supported by PQM was also issued marketing authorization for oxytocin injection. When this study was repeated two years later, the result was shown to have radically improved, to less than 40 percent of the samples collected failing the assay test, reflecting some benefit as a result of interventions by NAFDAC.

Background

UNICEF estimated that Pakistan had one of the highest newborn mortality rates in the world, with an estimated 244,746 newborn deaths in 2015. Sepsis is the third-leading cause of newborn death in Pakistan, accounting for an estimated 18 percent of overall newborn deaths. Pneumonia, diarrhea and malnutrition are other leading causes of mortality for children under 5 years of age in Pakistan. The country also has a high burden of TB cases. With funding from USAID, the PQM program began providing technical assistance to Pakistan in October 2015. PQM worked with the Drug Regulatory Authority of Pakistan (DRAP) and provincial health authorities to reduce neonatal mortality by increasing the availability of safe and quality-assured medicines for MNCH. PQM expanded its focus to strengthen Pakistan's regulatory and medical product quality assurance systems by providing technical support for risk-based PMS, as well as targeted technical support to (1) DRAP to regulate medicines, (2) NQCLs to produce reliable and credible quality testing results, and (3) local manufacturers of quality-assured priority medicines related to MNCH and TB.

Key accomplishments

WHO PQ/ISO accreditation of six NQCLs showing testing and calibration competency in line with international standards.

Pakistan has nine NQCLs at central and provincial levels. To support the pharmaceutical industry in improving the quality of its products by testing existing or newly developed medicines, two other in-country laboratories with nonstatutory functions were established under DRAP: one in Lahore and the other in Islamabad. PQM provided technical assistance to eight of the laboratories to build their capability toward attaining international good laboratory practices. The technical support ranged from advocacy for funds to upgrade infrastructure to overhaul of the QMS and capacity-building for appropriate analytical and instrumentation methods. The Pakistan Drug Testing and Research Center in Lahore attained both WHO PQ and ISO 17025 accreditation. Drug testing laboratories (DTLs) in Lahore, Multan and Faisalabad all attained ISO 17025 accreditation, and all three submitted laboratory information files to WHO for PQ assessment. DTL Bahawalpur and DTL Rawalpindi also attained ISO 10025 accreditation. These achievements will contribute to effective and reliable medicines quality testing for locally produced and imported medicines to promote the sale and use of quality-assured medicines in the country.

DRAP journeying toward WHO Global Benchmarking Tool (GBT) maturity level 3 revamped and reformed. Prior to PQM's support to DRAP, WHO had conducted a GBT assessment of the regulatory

system and found DRAP to be at maturity level 1 (nonfunctional regulatory system). PQM conducted another gap assessment of DRAP in 2016 to dig deeper into the problems and solutions. Jointly with DRAP, a roadmap with a goal of attaining maturity level 3 (stable, well-functioning and integrated regulatory system) was developed. PQM supported advocacy and technical assistance efforts to revamp the pharmaceutical registration system. DRAP transitioned to use of the internationally recognized common technical document (CTD) template, and DRAP evaluators were trained to appropriately evaluate CTD models, including how to appropriately validate analytical methods. DRAP continues to work toward level 3 maturity. PQM conducted a training for DRAP on ISO 9001 international recognition for a functional quality management system, supported DRAP to attain full membership in the WHO Collaborating Center for International Drug Monitoring for pharmacovigilance and helped DRAP apply for Pharmaceutical Inspection Co-operation Scheme (PIC/S) membership. PIC/S is an international membership for authorities with comparable GMP inspection systems aimed at harmonizing inspection procedures worldwide. PQM also advocated for DRAP to participate in the WHO collaborative registration procedure (CRP), developed guidelines and trained staff to appropriately utilize the mechanism by inviting a PQM-supported manufacturer from Indonesia to apply for its WHO-prequalified product registration in Pakistan using CRP. DRAP has progressed with implementing corrective and preventive actions to advance to the next level and has invited WHO to conduct another assessment for maturity level 3.

Local manufacturing of quality-assured priority medicines increased.

USAID/Pakistan and PQM identified the need to support the production of essential MNCH medicines that were in short supply, were not produced locally, or had a history of quality or patient safety concerns. Because pneumonia and diarrhea are leading causes of mortality in children under 5 year of age in Pakistan and the country's main source of anti-TB medicines (the Global Fund) had plans to reduce funding, the products selected included those used to treat pneumonia (amoxicillin), diarrheal diseases in children (zinc) and TB (4Fixed Dose Combination: rifampicin, isoniazid, pyrazinamide and ethambutol). With PQM support, one local manufacturer's zinc dispersible tablet (DT) and zinc oral solution dossiers were accepted for WHO PQ, a second local manufacturer submitted its zinc DT and zinc oral solution dossiers for WHO PQ, and a third local manufacturer is preparing its dossiers for WHO PQ of these products. PQM built the technical skills of more than 1,000 highly technical pharmaceutical manufacturer staff on GMP, the CTD format, quality assurance and quality control. PQM also supported two local manufacturers of amoxicillin DT and two local manufacturers of anti-TB 4FDC formulations in submitting applications for WHO PQ for these products.

Chlorhexidine, an antiseptic used to clean umbilical cords, can significantly reduce the risk of newborn death. In 2015, Pakistan had one of the highest newborn mortality rates in the world, and the supply of chlorhexidine in the country was unreliable. Pakistani health workers and government officials had advocated for a local source of CHX but with little success. To address this urgent public health need, PQM supported four local manufacturers of chlorhexidine gel to improve their practices

and submit applications to DRAP for marketing authorization. DRAP registered their products in January, March, April and May 2018. These products are now widely available in Pakistan for umbilical cord care in neonates.

Philippines

Background

In the Philippines, TB is the sixth-leading cause of death and the country has consistently been placed among the 22 countries with the highest burdens of TB and MDR-TB. Substandard and falsified medicines have proliferated in the country for years because of high prices and weak regulatory and legal enforcement actions against poor-quality medicines. From 2009 to 2017, the PQM program provided technical assistance to the Philippines Food and Drug Administration (FDA) and Department of Health's National TB Control Program, with a focus on strengthening medical products quality assurance and quality control systems. PQM provided support to increase the supply of quality-assured priority medicines and utilize product quality information for decision making.

Key accomplishments

Philippines FDA's PMS program strengthened to safeguard public health. This was achieved through PQM's technical assistance to develop a framework, build capacity and expand sentinel testing sites in the country. PQM conducted trainings for Philippines FDA staff on using a risk-based approach to PMS, including utilization of a three-level testing approach to maximize use of limited resources. The three-level testing approach for PMS includes inspection of physical characteristics of the product as level I, use of a screening tool such as GPHF-Minilabs™ to assess a limited number of product quality attributes for level II and use of compendial laboratory testing for a small subset of failed samples as confirmatory tests in level III. The capacity and skills of eight sentinel sites around the country were built to carry out sampling and testing. Level III tests were referred to the central laboratory for quality control confirmatory tests. From 2009 to 2017, 1,870 anti-TB medicines were tested for quality. Over time, 4.9 percent to 0 percent of samples failed quality control testing requirements. The Philippines FDA disseminates information from PMS to key stakeholders in the country; the information is utilized for decision making and public health advocacy to keep the population informed about risks. The Philippines FDA is committed to continuing PMS using the risk-based approach and to taking appropriate actions to safeguard the population.

Local manufacturer received PQM technical assistance toward the manufacture of quality-assured levofloxacin tablets for TB treatment. To improve access to quality-assured anti-TB medicines, PQM collaborated with the WHO PQ team on a workshop to raise awareness about MRAs and anti-TB medicines manufacturers on medical product quality standard requirements, the WHO PQ process, current GMP, dossier requirements, procurement processes via global mechanisms and WHO's collaborative registration procedure (whereby WHO collaborates with country regulators to accelerate national product registration). PQM provided technical assistance to one manufacturer to help it apply for WHO PQ of its levofloxacin tablets for the treatment of TB. PQM conducted mock audits and developed corrective and preventive actions to be addressed in preparation for the WHO visit. After the WHO PQ team inspection, nonconformances were identified, and PQM supported the manufacturer to develop a corrective and preventive action plan to address findings. PQM's funding was discontinued in the country before this manufacturer could attain WHO PQ for levofloxacin tablets.



Background

Uzbekistan has a high burden of MDR-TB, with MDR-TB occurring in 15 percent and 34 percent of new cases and previously treated cases, respectively.²¹ In response, Uzbekistan adopted a Consolidated National Strategic Plan for TB (2016–2020) that underscores the importance of the availability of quality-assured TB medicines. As Uzbekistan shifts to a locally funded procurement mechanism, there is an increased emphasis on domestically produced quality-assured medicines. Uzbekistan is also graduating from Global Fund–supported procurement of anti-TB medicines to domestically funded procurement. Since 2015, Uzbekistan has allocated domestic funding for the procurement of first-line anti-TB medicines. With funding from USAID, the PQM program supported efforts to strengthen medicines quality assurance systems in Uzbekistan from 2014 to 2019. PQM provided technical assistance to the Agency on Development of Pharmaceutical Industry of the Ministry of Health (Agency) to strengthen the medical products quality assurance system and to increase the supply of quality-assured priority medicines.

Key accomplishments

Availability of locally manufactured quality-assured anti-TB medicines increased. PQM provided technical assistance to local manufacturer Nobel pharmanoat to manufacture GMP-compliant and quality-assured medicines to treat drug-resistant TB (levofloxacin and moxifloxacin tablets). PQM's technical assistance included technical advice during facility construction, as well as staff capacity- and skills-building on GMP, good laboratory practices and fundamental principles of data integrity (a critical element evaluated during WHO PQ inspections). Once the facility was functional, PQM conducted a GMP assessment and document review focused on the manufacturing process, testing, packing and storage of levofloxacin tablets for WHO PQ. PQM developed corresponding corrective and preventive actions and supported implementation to address the gaps. Along with the manufacturer's commitment and financial investment, these efforts adequately paved the way for granting a national product approval to market quality-assured levofloxacin tablets in Uzbekistan. The manufacturer continues to work toward attaining WHO PQ for levofloxacin.

Medicines quality control system strengthened. Robust and effective quality control laboratories form the cornerstone of effective national medicines quality assurance systems, serving as the primary means of detecting poor-quality medicines and supporting national MRAs in taking evidence-based regulatory action. PQM provided technical

assistance to the Agency in strengthening the QMS of the medicine quality control laboratory in Tashkent. As a result of PQM's technical assistance, a quality unit responsible for management of QMS for the Agency's medicines testing operations was created, and the quality unit members' capacity and skills were built. Technical support for laboratory staff capacity included good laboratory practices, data integrity and the new ISO/IEC 17025:2017 standard requirements. PQM worked jointly with key stakeholders to develop a time-based strategy toward attaining international ISO/IEC 17025:2017 accreditation for competency to carry out tests and calibrations. The laboratory is working to implement the plan. As a result of PQM's advocacy, the Agency invested financial resources in expansion and renovation of the Tashkent laboratory. A presidential decree on Measures for Accelerated Development of Pharmaceutical Industry in the Republic of Uzbekistan (2019–2021) was issued in April 2019. According to the decree, a new building for the State Center will be constructed, in which new state-of-the-art laboratory equipment will be installed.

Robust and effective quality control laboratories form the cornerstone of effective national medicines quality assurance systems



GMP inspection system of the national regulatory agency strengthened. One of the key areas identified by Uzbekistan for PQM's support was to strengthen the GMP inspection system with the vision of building a system compliant with the international PIC/S standards. PIC/S is an instrument to improve cooperation between pharmaceutical regulatory inspectorates and the pharmaceutical industry in the area of GMP to foster and maintain mutual confidence in the interest of public health. PQM's advocacy to improve GMP and attain PIC/S was realized through the presidential decree for 2019–2021, which set mandatory compliance with GMP for local manufacturers by January 2022, and the Agency was tasked to work toward PIC/S accession. PQM guided and supported the Agency to strengthen its GMP inspection system to meet the international standards, particularly to lay the foundation for achieving the Agency's long-term goal of ensuring compliance with PIC/S membership requirements. PQM provided technical assistance to build the Agency's institutional and human resources GMP capacity. With PQM's assistance, a working group that developed a detailed roadmap for the PIC/S accession with a detailed action plan was constituted. The Agency is working on implementation of the roadmap.

Appendix

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