

Promoting the Quality of Medicines (PQM) Program

FY 2018 Fourth Quarter Report
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About the Promoting the Quality of Medicines (PQM) Program

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The Promoting the Quality of Medicines (PQM) program is a Cooperative Agreement between the U.S. Agency for International Development (USAID) and the U.S. Pharmacopeial Convention (USP). Since 1992, USP has worked with USAID to 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) provides technical assistance to strengthen medicines regulatory authorities and quality assurance systems and supports manufacturing of quality-assured priority medicines for malaria, HIV/AIDS, tuberculosis, neglected tropical diseases, and maternal and child health.

As of September 2018, USAID supports PQM's work in 18 countries, 1 regional mission, 1 Cross Bureau program, and 3 core health programs.

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Acronyms

ACT	artemisinin-based combination therapy
API	active pharmaceutical ingredient
CAPA	corrective and preventive action
CHX	chlorhexidine
CRO	clinical research organization
CTD	common technical document
DFDA	Department of Food and Drug Administration [Burma]
DGDA	Directorate General of Drug Administration [Bangladesh]
DRAP	Drug Regulatory Authority of Pakistan
EFMHACA	Ethiopian Food, Medicine and Health Care Administration and Control Authority
FPP	finished pharmaceutical product
GFDA	Ghana Food and Drug Administration
GLP	good laboratory practices
GMP	good manufacturing practices
HPLC	high-performance liquid chromatography
IGAD	Intergovernmental Authority on Development
IR	Intermediate Result
LMHRA	Liberia Medicines and Health Products Regulatory Authority
M&E	monitoring and evaluation
MDR-TB	multidrug-resistant tuberculosis
MNCH	maternal, newborn, and child health
MOH	Ministry of Health
MQDB	Medicines Quality Database
MQM	medicines quality monitoring
MRA	medicines regulatory authority
NAFDAC	National Agency for Food and Drug Administration and Control [Nigeria]
NMCP	National Malaria Control Program
NQCL	national quality control laboratory
NTD	neglected tropical disease
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PMI	U.S. President's Malaria Initiative
PMS	post-marketing surveillance
PQ	prequalification
PQM	Promoting the Quality of Medicines
QA	quality assurance
QC	quality control
QMS	quality management systems
SOP	standard operating procedure
SRA	stringent regulatory authority
TB	tuberculosis
TOT	training of trainers
UNICEF	United Nations Children's Fund
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
UV-Vis	ultraviolet-visible
WHO	World Health Organization

Executive Summary

The Promoting the Quality of Medicines (PQM) program provides technical assistance in partnering countries to strengthen quality assurance (QA) systems to sustainably ensure medical products quality and safety and to protect public health. PQM's assistance helps to build the capacity of medicines regulatory authorities (MRAs) and QA systems. PQM supports the manufacture of quality-assured priority essential medicines for malaria; HIV/AIDS; tuberculosis (TB); neglected tropical diseases (NTDs); and maternal, newborn, and child health (MNCH). PQM also provides support to increase the utilization of medical product quality information for decision-making. This report summarizes results achieved during the fourth quarter (Q4) of FY 2018, from July 1 to September 30, 2018.

By strengthening systems that help ensure quality, PQM aims to reduce and eliminate substandard and falsified products that pose serious risks to patients' health and undermine global health and development efforts. In Q4, as a result of PQM's support, Ethiopia's National Metrology Institute (NMI) issued official confirmation that it would be providing the Ethiopian Food, Medicine and Health Care Administration and Control Authority's (EFMHACA) laboratory equipment calibration support services going forward. As PQM is approaching closeout of the program, this achievement showcases a huge success and demonstrates a major milestone toward ensuring sustainability and country ownership. In Guinea, Q4 was marked by the promulgation of a revised law; this law, which requires the establishment of priority medicines regulations that take into account pivotal functions such as registration and post-marketing surveillance (PMS) activities, will now be enacted for effective regulation of the pharmaceutical market of Guinea. In Bangladesh, it had been necessary to modernize legislation to respond to new challenges and to meet the new and growing need for regulation to ensure medicines quality, safety, and efficacy; in Q4, PQM worked to review proposed legislation and recommended a number of new provisions, including one for the recall of substandard and falsified medicines. On September 3–5, Bangladesh's National Control Laboratory (NCL) successfully completed the ANAB audit toward ISO 17025:2017 accreditation for its physio-chemical laboratory. NCL subsequently developed a corrective and preventive action (CAPA) plan and submitted it to the assessor for review. NCL also conducted a customer satisfaction survey toward assessing its service quality.

A continuous supply of quality-assured products—particularly for essential priority medicines for TB, NTDs, and MNCH—is necessary to address national health priorities and plans. PQM works with manufacturers to improve compliance with international quality standards to meet local and global demand for quality-assured medicines. In Q4, two dossiers from manufacturers of priority essential medicines were accepted for review for World Health Organization (WHO) prequalification. One manufacturer's dossier for magnesium sulfate injection, a maternal health product key for preeclampsia/eclampsia, was accepted for review in July 2018, and PQM's technical assistance contributed significantly to achieving this important milestone. The other manufacturer's dossier for clofazimine was accepted by WHO for prequalification review in August 2018; this is particularly significant because WHO now considers clofazimine one of the essential medicines for treatment of multidrug-resistant TB. With an additional source of the product eventually approved by WHO, the market for quality-assured clofazimine will be more secure. Also in Q4, PQM supported Indonesia's Kalbe Farma to complete its CAPA implementation and successfully submit full documentation and evidence of this achievement to WHO.

PQM also facilitated a meeting organized by Bangladesh's Directorate General of Drug Administration for selecting potential in-country manufacturers of first-line anti-TB medicines. The Bangladesh Association of Pharmaceutical Industry took the lead in bringing manufacturers interested in producing these medicines, and four private and one government-owned company attended the meeting. As Bangladesh looks toward local production of first-line anti-TB medicines, it is key for manufacturers to ensure these products are quality assured.

As Uzbekistan is graduating from Global Fund support for procurement of anti-TB medicines, its strategy is to develop local manufacturing capacity to ensure that locally produced quality-assured anti-TB medicines are available. PQM provides important technical assistance to anti-TB medicines manufacturers to improve their good manufacturing compliance standards and to the MRA to improve its capacity to ensure medicines quality on the local market. In Q4, PQM continued to provide support to Nobel Pharmsanoat with its anti-TB product, levofloxacin. PQM provided technical assistance to assess a cross-contamination risk between products manufactured at a new site and products manufactured at an adjacent facility, as well as to develop risk mitigation measures. The 4-day risk assessment audit included a plant walkthrough and review of the building design plans and technical site drawings. PQM also provided hands-on training to Nobel Pharmsanoat staff for risk assessment and mitigation of cross-contamination. A CAPA list of risk mitigation strategies for each of the risks identified was recommended and discussed with Nobel Pharmsanoat staff. PQM will continue to assist the manufacturer in developing and implementing the CAPA plan, which will help prepare its product for potential submission for WHO prequalification.

More than a billion (one-sixth) of the world's most vulnerable people—almost exclusively those living in impoverished rural areas and urban slums of low-income countries—suffer from one or more NTDs. A major constraint to the

effective scale-up of NTD control and elimination programs is the scarcity of quality-assured active pharmaceutical ingredient (API) suppliers that can fulfill the WHO requirements of finished pharmaceutical product (FPP) manufacturers. To overcome these challenges, it is necessary to provide technical assistance to API and FPP manufacturers. One of the manufacturers that PQM is providing technical assistance to for praziquantel FPP has obtained approval for the bioequivalence protocol from the local regulatory authority. The manufacturer and clinical research organization can now prepare for and initiate the enrollment of subjects. The manufacturer is continuing to complete the CAPAs and submitting the evidence to PQM for review. PQM is also working with the manufacturer to source and procure the comparator product for the in vitro dissolution study and bioequivalence study.

The collection, analysis, and use of data on medical products' evaluation, inspection, and post-approval surveillance support evidence-based decision-making that is critical for promoting access to quality-assured products and reducing and eliminating substandard and falsified products. In Ethiopia, the first draft report from the audit inspection of the retail outlets in Addis Ababa and the Southern Nations Nationalities and People Region was completed; a total of 298 medicine outlets were covered, and the storage practices observed showed several deficiencies, including that 188 (63.5%) of the retail outlets stored medicines in compromised conditions (e.g., exposed to moisture, temperature, and light) that affect medicine quality, safety, and effectiveness, posing risks to the population at large.

The Intergovernmental Authority on Development (IGAD) region, which comprises eight countries in the horn of Africa, experiences migration and cross-border mobility due to economic uncertainty and political conflicts. Because the cross-border mobile populations face major barriers to access of basic healthcare, IGAD has sought to implement medicines regulatory harmonization (MRH) for the horn of Africa in line with the vision and goals of the African Medicines Regulatory Harmonization initiative. PQM's work plan activities in the region were adopted from the proposed IGAD health program activities, which are aligned to two of the three Development Objectives of USAID's Regional Development Cooperation Strategy, 2016–2021. In line with the activity to implement PMS on the quality of oxytocin injections available in selected cross-border areas, PQM continues to liaise with IGAD-MRH to prepare for the next Expert Working Group workshop aimed to train sample collectors and initiate the sample collection. After incorporating feedback received from IGAD-MRH and USAID in the first round of review, PQM has provided an updated draft protocol for a PMS survey of oxytocin at the cross-border, and it is currently under review. At the next workshop, the protocol will be shared with member states for review and endorsement.

Program Background

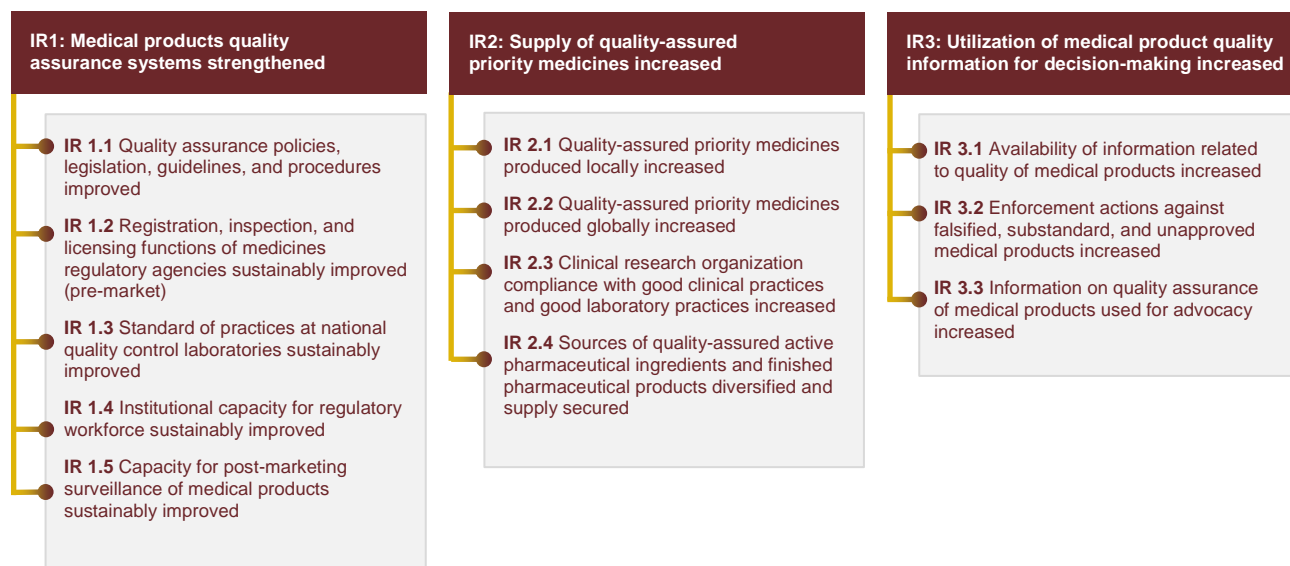
The Promoting the Quality of Medicines (PQM) program is a cooperative agreement between the U.S. Agency for International Development (USAID) and the U.S. Pharmacopeial Convention (USP). Since 1992, USP has worked with USAID to support low- and middle-income countries in addressing critical issues related to medicines information and quality. The PQM program provides technical assistance to build the capacity of medicines regulatory authorities (MRAs) and quality assurance (QA) systems in countries with weak health systems. PQM also provides technical support to manufacturers of quality-assured priority medicines for malaria, HIV/AIDS, tuberculosis (TB), neglected tropical diseases (NTDs), and maternal, newborn, and child health (MNCH).

This quarter, PQM implemented projects for 18 USAID country missions, 1 regional mission, 1 Cross Bureau program, and 3 core health programs.

Results Framework

PQM's Results Framework is organized according to three result areas. These complementary areas contribute to PQM's approach of affecting a country's health system as a whole. The globally designed systems-based approach is tailored to fit the needs of individual countries or regions and includes key stakeholders throughout the health system.

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



This report highlights the results achieved by PQM, organized by result area representing multiple countries where the program works, as well as by country and Core portfolio for the July–September 2018 period.

Result Highlights



Intermediate Result (IR) 1: Medical Products Quality Assurance Systems Strengthened

Description of Sub-IRs

Medical products are instrumental to any health system, but only if they are safe, effective, and quality assured. Quality, in particular, is paramount to ensuring that the safety and efficacy of medicines and medical products are maintained from the moment a product 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 aims to address the end-to-end challenges that affect medicines quality. The ultimate goal is to reduce and eliminate substandard and falsified products that pose serious risks to the health of patients and undermine global health and development efforts.

Sub-IR 1.1 Quality assurance policies, legislation, guidelines, and procedures improved

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 MRA. Working with in-country stakeholders at all levels, PQM helps to develop or revise policies, legislation and regulations, and guidelines by providing technical assistance to MRAs to ensure QA topics are adequately covered and that the overarching regulatory framework is appropriate to their context and meets internationally accepted standards.

Sub-IR 1.2 Registration, inspection, and licensing functions of medicines regulatory agencies sustainably improved (pre-market)

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 enter the market. PQM works with MRAs to build strong institutional capacity and support registration and licensing through hands-on training and technical assistance. By helping MRAs prioritize key issues through risk-based approaches, PQM guides regulatory agencies to focus their premarket resources toward solutions that add value and will result in high-impact and sustainable health outcomes.

Sub-IR 1.3 Standard of practices at national quality control laboratories sustainably improved

MRAs, national procurement agencies, and international donors require reliable and accurate data from quality control laboratories during the medicines registration process, when implementing corrective actions for poor-quality medicines identified following post-marketing surveillance (PMS), and to ensure that procured and donated products meet quality requirements. To help guarantee consistently reliable and accurate data, PQM builds the capacity of national quality control laboratories (NQCLs) to improve laboratory standards through assessments, hands-on training, and technical assistance. PQM places particular emphasis on strengthening quality management systems (QMS) to help laboratories attain certifications of compliance with internationally recognized standards, such as ISO/IEC 17025:2005 and/or World Health Organization (WHO) prequalification (PQ).

Sub-IR 1.4 Institutional capacity for regulatory workforce sustainably improved

Building workforce capacity at central and decentralized institutions and facilities involved in maintaining operationally effective QA systems is a core component of PQM's approach. PQM experts work in collaboration with WHO's global, regional, and national offices to provide hands-on trainings focused on a wide range of good practice guidelines, particularly bioequivalence aspects of good clinical practices, good manufacturing practices (GMP), and good laboratory practices (GLP), including quality control (QC) testing procedures and laboratory equipment maintenance.

PQM's in-service training programs, application of the Collaborative Learning Model, train-the-trainers approach, and hands-on support facilitate the turning of knowledge into practice. PQM supports the strengthening of QA topics in preservice programs in academic institutions as a critical part of the long-term solution for workforce development. Adopting a Collaborative Learning Model, PQM first gathers staff from multiple laboratories within each country and provides consolidated trainings to them. This ensures that the material delivered is consistent, reduces costs typically incurred from decentralized training operations, and promotes country ownership and collaboration among laboratory staff. In addition, if one laboratory experiences a high rate of attrition, new staff can be mentored by previously trained, tenured colleagues from neighboring laboratories, rather than relying on foreign assistance again. By combining preservice and in-service training interventions and the development of structures and processes necessary for effective QMS, PQM builds a sustainable in-country regulatory and QA workforce.

Sub-IR 1.5 Capacity for post-marketing surveillance of medical products sustainably improved

Ensuring the quality of medical products throughout the supply chain presents challenges that extend beyond the registration and procurement processes. Substandard medicines may occur due to poor manufacturing practices or as a result of poor storage conditions or practices. In addition, weak regulatory systems leading to unregulated distribution and sale of medicines and porous country borders facilitate the introduction of substandard, falsified, and unapproved medicines. To help address these challenges, PQM collaborates with MRAs to establish and strengthen PMS programs that regularly examine the quality of medicines throughout the supply chain.

PQM's support to MRAs includes implementation of risk-based approaches that help prioritize scarce human and financial resources, assistance in strategic planning, and targeted sampling for products and locations where surveillance is most needed. PQM also provides training to field staff in sampling procedures, use of field screening tools and technologies (such as the GPHF Minilab™), data management, and reporting. Field testing with screening methods and laboratory testing with complex and comprehensive compendial methodologies are integrated within the implementation of a risk-based framework for PMS.

Overview of FY 2018 Fourth Quarter IR1 Achievements

Key Results and Highlights

In this quarter, confirmation was received from Ethiopia's National Metrology Institute (NMI) on its capability to calibrate all of the Ethiopian Food, Medicine and Health Care Administration and Control Authority's (EFMHACA) laboratory equipment. Going forward, EFMHACA will no longer need to contract a foreign institute to calibrate any of its equipment. PQM has long been supporting EFMHACA in equipment maintenance and calibration as part of building capacity of the QC laboratory and attaining/maintaining its international accreditation. While equipment maintenance was transferred to EFMHACA about 2 years ago, providing technical assistance on equipment calibration continued as part of PQM's support. PQM explored various options to build local capacity of third-party providers to EFMHACA to promote sustainability. Equipment calibration was identified as one of the more important areas to support because it is a mandatory requirement for maintaining EFMHACA's current ISO accreditation. Technical support to NMI began in FY 2017 when PQM identified the institute as a key partner and initiated building its capacity. As PQM is approaching the end of the program's period of performance, this is a huge success and major milestone in terms of ensuring sustainability and transitioning long years of technical assistance in a highly technical area.

In Q3, the revised pharmaceutical law was adopted by the national assembly of Guinea. This quarter was marked by the promulgation of the revised law by the president of Guinea. The revised law will now be enacted by the National Directorate of Pharmacy and Medicine (DNPM) for effective regulation of the pharmaceutical market of Guinea. The enactment of the law requires the establishment of priority medicines regulations that take into account the pivotal functions of DNPM, such as registration and PMS activities, which needed to be strengthened to reduce the public's exposure to the falsified and poor-quality medicines circulating in the market.

Bangladesh's medicines regulatory system was developed through several pieces of legislation, beginning with enactment in the 1940s and subsequent amendments. Relative to current standards, there is a necessity to modernize the legislation to respond to changes and new challenges, as well as to build capacity to meet the new and growing need for regulation to ensure medicines quality, safety, and efficacy. This quarter, PQM worked to review the proposed legislation and recommended a number of new provisions, including one for the recall of substandard and falsified medicines.

Key IR1 Indicators for FY 2018 Q4

Number of national medicines QA policies, regulations, and legislations developed or updated and submitted for adoption	1 – Bangladesh
Number of quality control laboratories reaccredited	2 – Ghana FDA, NAFDAC Kaduna
Number of quality control laboratories with expanded scope of accreditation	1 – NAFDAC Kaduna
Number of instances PQM-supported local institutions or organizations provided training services or technical assistance in QA/QC systems strengthening	4 – Benin (2), Ghana (2)

IR2: Supply of Quality-Assured Priority Medicines Increased

Description of Sub-IRs

A continuous supply of quality-assured products—particularly for essential priority medicines for TB, NTDs, and MNCH—are necessary to address national health priorities and plans. However, the limited number of manufacturers weakens supply security and increases the vulnerability of supply chains to shortages, stock-outs, and poor-quality medicines. Supply challenges are further exacerbated by the lack of economic incentives for manufacturers to produce essential medicines. PQM works with manufacturers to improve compliance with international quality standards to meet local and global demand for quality-assured medicines. PQM's assistance ensures a steady supply of essential medicines of assured quality, safety, and efficacy, thus strengthening countries' health systems to improve health outcomes.

Sub-IR 2.1 Quality-assured priority medicines produced locally increased

In support of key USAID priority health programs, PQM provides technical assistance and guidance to manufacturers for the local production of priority essential medicines, including those used to treat newborn infections and MNCH products. Local production 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.

Sub-IR 2.2 Quality-assured priority medicines produced globally increased

To address global needs for essential medicines, PQM works with manufacturers to help them develop and submit dossiers for certification by the WHO PQ of Medicines Program for medicines to treat TB, malaria, maternal and child health, and NTDs. Both WHO PQ and stringent regulatory authority (SRA) approval confirm that these medicines meet acceptable international standards for quality, safety, and efficacy, and can be purchased by international procurement agencies. In addition, by increasing the number of suppliers and creating a competitive environment, PQM helps shape the market for essential medicines and contributes to reducing the price of these essential medical products.

Sub-IR 2.3 CROs' compliance with good clinical practices and good laboratory practices increased

In the process of submitting an application to the WHO PQ of Medicines Program or other SRA, manufacturers require access to clinical research organizations (CRO) to conduct bioequivalence studies when indicated. PQM engagement with CROs helps them to address compliance issues and timeliness and improve the cost-effectiveness of the services they provide in the approval process for priority medicines. PQM engagement aims to decrease the time needed for product approval as well as the actual cost of bioequivalence studies. PQM prioritizes support to CROs that can provide reliable data for timely approval of priority essential medicines.

Sub-IR 2.4 Sources of quality-assured API and FPP diversified and supply secured

In some instances, there is only one source of quality-assured essential medicine 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. PQM has witnessed companies that manufacture both the active pharmaceutical ingredient (API) and the finished pharmaceutical product (FPP) become the sole source of a quality-assured product on the market. Interrupting the supply of APIs to other FPP manufacturers allows for price increases in a monopolized FPP market. To prevent this, PQM works to identify API manufacturers that can supply APIs to multiple FPP manufacturers. This increases sources and competition within the market and helps reduce the prices of essential medicines. Additionally, by developing multiple sources of quality-assured FPPs, the risk of price gouging is averted and the vulnerability of the global supply chain to shortages is greatly reduced.

Overview of FY 2018 Fourth Quarter IR2 Achievements

Key Results and Highlights

Two manufacturers of priority essential medicines saw their dossiers accepted for review for WHO PQ. One manufacturer's dossier for magnesium sulfate injection was accepted for review in July 2018. This maternal health product is key for preeclampsia/eclampsia, and PQM's technical assistance contributed significantly to achieving this important milestone.

The other manufacturer's dossier for clofazimine was accepted by WHO for PQ review in August 2018. This is particularly significant since, according to WHO's recent "Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB)," clofazimine's importance has been upgraded, and it became one of the essential medicines for treatment of multidrug-resistant tuberculosis (MDR-TB). Currently there is only one quality-assured source on the market. With an additional source of the product eventually approved by WHO, the market for quality-assured clofazimine will be more secure.

Also in Q4, PQM supported Indonesia's Kalbe Farma to complete its corrective and preventive action (CAPA) implementation following the WHO inspection in Q3. With the aim of being listed as prequalified by WHO. Kalbe Farma successfully submitted full documentation and evidence of its CAPAs to WHO on July 24, 2018. As of September 2018, the PQ product has been included in WHO Public Inspection Reports (PIRs).

Key IR2 Indicators for FY 2018 Q4

Number of dossiers accepted for review by WHO PQ	2 – magnesium sulfate injection, clofazimine
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Number of Manufacturers Provided with Technical Assistance in FY 2018 Q4

Countries/ Core Programs	Number of Manufacturers	Product Types
Core MNCH	1	magnesium sulfate injection
Core TB	13	clofazimine FPP, cycloserine API, rifapentine API, rifapentine FPP, gatifloxacin API, gatifloxacin FPP, kanamycin API, kanamycin FPP, rifampicin/isoniazid/ethambutol/pyrazinamide tablets
Core NTD	7	praziquantel API, praziquantel FPP, albendazole API, albendazole FPP
Bangladesh	1	chlorhexidine solution
Ghana	1	artemether–lumefantrine tablets
Nigeria	10	sulfadoxine-pyrimethamine tablets, chlorhexidine gel, zinc sulfate dispersible tablets, artemether–lumefantrine tablets, oxytocin injection, magnesium sulfate injection, ready-to-use therapeutic foods
Indonesia	2	levofloxacin
Kazakhstan	1	levofloxacin
Pakistan	6	amoxicillin dispersible tablets, chlorhexidine gel, zinc sulfate dispersible tablets
Uzbekistan	1	levofloxacin

IR3: Utilization of Medical Product Quality Information for Decision-Making Increased

Description of Sub-IRs

The collection, analysis, and use of data on medical products' evaluation, inspection, and post-approval surveillance support evidence-based decision-making that is critical for promoting access to quality-assured products and reducing and eliminating substandard and falsified products. PQM supports the adoption of data standards and integrated regulatory information management 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 helps bring

awareness to the use of 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.

Sub-IR 3.1 Availability of information related to quality of medical products increased

PQM assists national stakeholders with implementing medicines quality monitoring (MQM) to generate data on the quality of pharmaceuticals circulating in country. To sustain such a critically protective public health activity, PQM supports countries to develop or strengthen PMS as a regulatory function. PQM also supports countries to increase the body of knowledge generated on the quality of priority essential medicines used in public health programs, particularly medicines used for MNCH, HIV/AIDS, and TB.

The Medicines Quality Database (MQDB), developed and actively managed by PQM, is the largest freely available, web-based, and internationally referenced database of QC test results. The MQDB has information on approximately 15,000 medicines sampled and tested in PQM-assisted countries in Africa, Asia, and Latin America. With the information available in the MQDB, PQM recently created the Poor-Quality Medicines ALERT feature. The ALERT provides rapid access to the most recent information on poor-quality medicines identified from PMS activities in PQM countries, including those performed independently of PQM assistance. Through collaborations with the World Wide Antimalarial Resistance Network and the newly formed Infectious Diseases Data Observatory, PQM is exploring ways to integrate information among these databases and expand the scope of medicines included.

PQM is undertaking a series of additional initiatives to increase the availability of data related to the quality of medical products, including working across regulatory functional areas; registration, licensing, and inspection; and PMS to harness opportunities for data capture and sharing.

Sub-IR 3.2 Enforcement actions against falsified, substandard, and unapproved medical products increased

PQM works with in-country partners to detect and support actions against cases of substandard and falsified medicines. When poor-quality medicines are detected, PQM collaborates with MRAs to facilitate compliance and enforcement actions and remove these medicines from the market. PQM also shares information to alert stakeholders and the public about the issue. By creating and supporting regional networks for sharing information, PQM also facilitates implementation of corrective actions in neighboring countries on poor-quality medical products sourced from the same manufacturers.

Sub-IR 3.3 Information on quality assurance of medical products used for advocacy increased

PQM raises awareness about the dangers of substandard and falsified medicines, providing information to the public and government stakeholders by supporting local, regional, and global initiatives on medicines quality. Activities often include hosting and attending partner meetings, developing regional databases and alert systems, advocating for the allocation of resources to improve pharmaceutical quality systems, and encouraging collaboration among stakeholders. PQM develops e-learning courses on medicines QA, participates in educational courses organized by international partners, collaborates with local universities to develop QA-related content for pharmaceutical curricula, and supports studies and operational research on QA and regulatory systems strengthening.

At the local level, PQM works with authorities and civil society to develop awareness campaigns and public service announcements. To share information globally, PQM participates in regional and international meetings and develops printed and digital media materials to increase advocacy on matters related to medical products quality.

Overview of FY 2018 Fourth Quarter IR3 Achievements

Key Results and Highlights

In Q4, PQM facilitated a meeting organized by Bangladesh’s Directorate General of Drug Administration (DGDA) for selecting potential in-country manufacturers of first-line anti-TB medicines. The Bangladesh Association of Pharmaceutical Industry (BAPI) took the lead in bringing manufacturers interested in producing these medicines, and four private and one government-owned company attended the meeting. As Bangladesh looks toward local production of first-line anti-TB medicines, it is key for manufacturers to ensure these products are quality assured.

Key IR3 Indicators for FY 2018 Q4

Number of PQM-supported awareness raising or advocacy events promoting quality of medical products	6 – Bangladesh, AMI, Mali, Mozambique
Number of publications issued and presentations made on medical products quality assurance at national or international level that are presented or authored by PQM	3 – Ethiopia, Nigeria, Cross Bureau

Africa



Benin

I. Quarter 4 Highlights

In this quarter, PQM facilitated sampling and testing of antimalarial medicines in four Benin departments (Borgou, Collines, Donga, and Zou). A total of 141 samples were collected and underwent visual inspection. A set of samples underwent further screening using Raman spectroscopy and thin-layer chromatography (TLC). Although final testing and results are expected next quarter, preliminary results indicated that one sample of quinine sulfate lacked the API.

PQM also trained staff of the national quality control laboratory (LNCQ) this quarter on dissolution testing with a focus on performance verification of the dissolution tester.

II. Country Context

Malaria is the leading cause of morbidity in Benin, which is a high malaria transmission country according to WHO. In 2016, there were 1,324,576 reported and confirmed cases of malaria and 1,646 reported deaths. Benin adopted artemisinin-based combination therapy (ACT) in 2004 and began large-scale implementation of artemether–lumefantrine combination as a first-line treatment in 2007.

PQM was selected by PMI and USAID/Benin to strengthen the QA/QC systems of antimalarial medicines in Benin, and activities focused on strengthening LNCQ's capacity. Technical assistance in these areas supports PMI's Strategy for 2015–2020 Core Operating Principle #6 to ensure that all commodities provided to countries are of high quality and that systems are in place to continually improve the quality of services provided. It is also part of PQM's efforts to mitigate risk against current gains in malaria control and limit the spread of ACT resistance. ACTs from the central medical store must be tested prior to release into the market. However, LNCQ does not have the capacity to test these products in accordance with international standards.

III. Quarter 4 Progress by Objective

Objective 1 – Strengthen the capacity of the NQCL

To continue strengthening LNCQ's capacity, PQM trained five laboratory staff members on performance verification of the dissolution apparatus. Dissolution testing characterizes the release of API from solid dosage form, a process required for medicines to be absorbed. It can indicate the efficiency of in vivo dissolution. The training included mechanical and chemical calibration of the equipment. Performance verification allows the laboratory to use the dissolution apparatus in future testing. The trained laboratory staff are now able to schedule and perform future performance verification of the equipment.

PQM also conducted a rapid assessment of the laboratory and informed the laboratory management that the QA manager's responsibilities should be delegated to other staff as necessary during absences. Ideally, the laboratory should have more than one QA staff member. Laboratory staff should also have access to standard operating procedures (SOPs) at any time. PQM provided a recommendation to improve the laboratory's samples storage and to increase efficiency of space usage.

Objective 2 – Support sustainable local capacity to monitor the quality of medicines in the country

PQM facilitated sampling and testing of antimalarial medicines in four departments (Borgou, Collines, Donga, and Zou) that were not covered in previous PMS activities. Two LNCQ teams collected 141 samples. LNCQ provided a brief summary of the findings, however, the final report is expected in the next quarter. After extensive visual inspection, 71 samples were selected for further screening with Raman spectroscopy and TLC (Minilab™). One sample of quinine sulfate from a 1,000-tablet package lacked quinine sulfate API but contained a different API. The same sample had a 10-year shelf life indicated on the packaging, which is unusual. Further investigations are needed by the Directorate of Pharmacy, Medicines and Diagnostics (DPMED).

Burkina Faso

I. Quarter 4 Highlights

The Directorate of Medicine Control laboratory is aiming at attaining ISO 17025 accreditation by the end of 2019. To assist the laboratory in its preparedness for the accreditation, PQM focused its efforts during this quarter on strengthening its QMS by reviewing and helping laboratory staff and management finalize several QMS documents, including SOPs and related forms. PQM also actively participated in a workshop sponsored by the Sahel Women's Empowerment and Demographic Dividend (SWEDD) project for Burkina Faso to assist the laboratory in preparing an application dossier for accreditation that was submitted to the French accreditation body French Committee for Accreditation (COFRAC).

PQM had discussions with the newly established National Pharmaceutical Regulatory Agency (ANRP) about remaining activities. They came to an agreement to reduce the scope of PMS activities to allow more resources for developing the agency's PMS strategy and establishment of a mechanism for collaboration and coordination with the National Laboratory of Public Health in the implementation of PMS activities. Budgets and terms of reference for these activities have been developed.

II. Country Context

In Burkina Faso, USAID's primary health sector focus is to expand the prevention and treatment of malaria. Working closely with the Burkinabe government, USAID aims to reduce morbidity and mortality due to malaria, primarily targeting children under 5 and pregnant women (the populations most vulnerable to this disease).

PQM was selected by USAID/Burkina Faso to strengthen the capacity of the country's national MRA (Direction Générale de la Pharmacie, du Médicament et des Laboratoires (DGPML)), NQCL (Laboratoire National de Santé Publique (LNSP)), and other major pharmaceutical systems with the primary goal of improving its QA/QC of medicines.

In February 2015, in response to the USAID Mission's request, PQM conducted a rapid assessment of Burkina Faso's QA/QC capabilities and met with key stakeholders involved in the regulation, control, management, and distribution of medicines. The results of the assessment showed that traditional medicines were widely used by patients in Burkina Faso and are included in MOH's National Strategic Plan. The assessment also revealed an immediate need to strengthen DGPML's capacity and build LNSP's. Strengthening these two pillars of medicines QA is essential to advancing the country from use of unregulated medicines to use of regulated, quality-assured medicines based on international standards. To achieve this goal, it is critical to address the challenges that health programs are facing and to work closely with the Central Medical Store, DGPML, and LNSP to ensure that all medicines procured by USAID and the government are of good quality prior to release into the market and that their quality is maintained throughout the supply chain to distribution.

III. Quarter 4 Progress by Objective

Objective 1 – Strengthen the capacity of the NQCL

PQM is actively involved in the review of the laboratory QMS documents as a member of a team tasked to review and approve the documents. In this quarter, the laboratory developed the following QMS documents:

1. Methods of analysis management SOP and associated forms (method verification sheet).
2. Equipment management SOP and associated forms (equipment inventory, list of persons authorized to use a given equipment, and maintenance schedule).
3. Change control SOP and related forms (main changes in the quality plan, change request form, change control form, and change assessment form).

PQM also participated in a workshop sponsored by the SWEDD project to prepare ISO 17025 accreditation application dossier for submission to the accreditation body COFRAC. The participants in the workshop identified the gaps in the laboratory QMS. PQM worked with the QA manager and developed a corrective action plan to address the gaps. The corrective action plan will be executed by October 2018. The laboratory aims at attaining ISO 17025 accreditation by the end of 2019.

Objective 2 – Support sustainable local capacity to monitor the quality of medicine

PQM discussed with the National Pharmaceutical Regulatory Agency (ANRP) the limited budget available and proposed to change an activity for routine sampling and testing of antimalarials to the development of a PMS strategy for ANRP. Since ANRP was just established, PQM suggested it would be more beneficial for the agency to develop a longer term strategy than to perform another round of antimalarial PMS. However, ANRP decided to maintain the activity because it is part of the indicators that the agency set for this year.

Given the funding constraints, PQM proposed to facilitate the PMS activities with limited scope and separately organize a workshop as a starting place for the development of the agency's PMS strategy and establishment of a mechanism for collaboration between ANRP and the national laboratory. These activities are planned for October 2018.

Objective 3 – Support the creation of the National Pharmaceutical Authority

In addition to facilitating the development of the ANRP PMS strategy, PQM will facilitate drafting of a regulatory provision aimed at sustainability of PMS activities, as well as establishing a mechanism for coordination between the agency and the National Laboratory of Public Health in the implementation of PMS.

Ethiopia

I. Quarter 4 Highlights

In Q4, PQM provided technical assistance in the development of a medicines and medical devices registration directive; completed report writing of the audit-based inspection conducted in Addis Ababa and the Southern Nations Nationalities and People Region (SNNPR); and completed draft report of the FY 2017 PMS. Technical support was provided in the facilitation of panel discussions at the Ethiopian Pharmaceutical Association (EPA) 38th Annual Conference. PQM also participated in the annual conference convened by EFMHACA in collaboration with regional regulatory bodies and other stakeholders. Overall, the following achievements are highlights from Q4.

1. Official confirmation was issued by NMI of Ethiopia through a letter stating that EFMHACA's laboratory equipment calibration support services will be provided by NMI going forward. As a result of PQM's technical support, NMI can now provide calibration support services for 100 percent of EFMHACA's existing laboratory equipment. As PQM is approaching closeout of the program, this achievement showcases a huge success and demonstrates a major milestone toward ensuring sustainability and country ownership. Successful transition of this mandatory service requirement for reaccreditation to a local affiliate at a cost affordable to EFMHACA was achieved through the direct support of PQM.
2. The first draft report from the audit inspection of the retail outlets in Addis Ababa and SNNPR was completed. In this audit inspection, a total of 298 medicine outlets were covered: 78.2 percent were from Addis Ababa city administration, and the rest were from SNNPR, while 65 percent of the retail outlets were pharmacies, and the remaining were drug stores. Of the total audited medicine retail outlets, 158 (53.4%) were found to stock illegal medicines that included medicines without invoices, medicines stocked above standard, program medicines diverted from public institutes/unknown sources, and medicines not registered in the country. The storage practices observed showed several deficiencies, including that 188 (63.5%) of the retail outlets stored medicines in compromised conditions (e.g., exposed to moisture, temperature, and light) that affect medicine quality, safety, and effectiveness, posing risks to the population at large.
3. EFMHACA has officially applied to the Ethiopian National Accreditation Office (ENAO) to transition its laboratory ISO 17025 accreditation from ANSI-ASQ National Accreditation Board (ANAB), an international body, to ENAO. ENAO conducted a preliminary review of EFMHACA's QMS documents, and a plan has been developed with PQM support to ensure smooth transition. PQM provided support to the EPA 38th Annual Conference, which convened on July 27–28. The event, which was attended by key stakeholders and professionals in the pharmaceuticals sector, is an important platform to discuss issues related to medicines quality. PQM, represented by the Chief of Party as a moderator, contributed to the discussion on "Ensuring the quality of medicines to contain antimicrobial resistance" during the panel discussion, where invited government officials, EPA members, and other invited guests participated. The discussion addressed the key findings from results of the PMS conducted in the previous nine rounds (since 2009) with PQM's support and the implications on preventing and containing antimicrobial resistance in Ethiopia. PQM presented on "The National Pharmacovigilance System" as part of the continuing education program.

II. Country Context

Ethiopia aspires to achieve elimination of malaria from its mid- and lowlands in the eastern part of the country. While malaria control measures will be scaled up and sustained, the country has planned to implement several other strategies to pave the way for a malaria-free Ethiopia by 2030.

The impact-level targets included under the Health Sector Transformation Plan indicate that, by 2020, the country plans to reduce measles, mumps, and rubella to 199 per 100,000 live births; reduce under-5, infant, and neonatal mortality rates by 30, 20, and 10 per 1,000 live births, respectively; reduce stunting, wasting, and underweight in under-5 to 26 percent, 4.9 percent, and 13 percent, respectively; and reduce HIV incidence by at least 60 percent compared with 2010 and achieve zero new infections among children.

Ethiopia has achieved Maternal and Neonatal Tetanus Elimination (MNTE) status and became the 42nd country validated for MNTE. The joint mission from UNICEF and the WHO Africa Regional Office made the final validation assessment and noted the remarkable achievement.

PQM contributes to the achievement of Ethiopian national health targets and goals through ensuring the availability of quality-assured, safe, and efficacious medicines that address the priority health needs of the people of Ethiopia.

III. Quarter 4 Progress by Objective

Objective 1 – Support to strengthen the medical products quality assurance systems of Ethiopia

Sub-IR 1.1 Quality assurance policy, legislation, guidelines, and procedures improved

In Q3, three guidelines on specialized areas of medicines registration were completed: a recall directive was reviewed and approved by EFMHACA management; an inspection manual and good clinical practice guidelines were also approved and posted on EFMHACA's website.

In Q4, PQM continued provision of technical assistance in the development of a medicines and medical devices registration directive. A 5-day workshop was conducted and included participants from the medicine and licensing directorate, medico-legal directorate, and PQM. The first draft of the directive was completed. This directive will be applicable for the marketing authorization of medicines and medical devices manufactured locally or imported from abroad. The directive is in line with international best practices and is based on guidelines developed for medicines and medical devices registration in Ethiopia with technical support from PQM. The presence of such a directive will help enhance enforcement of the guidelines, as it establishes a legally binding framework.

Sub-IR 1.2 Registration, inspection, and licensing functions of medicine regulatory agencies sustainably improved (pre-market)

In Q3, PQM provided technical assistance to conduct audit-based inspections in Addis Ababa, Amhara, and Tigray regions to assess regulatory compliance by medicine retail facilities in Addis Ababa and other regions.

In Q4, a report on the inspection of retail outlets in Addis Ababa and SNNPR was completed. In this audit inspection, 298 medicine retail outlets were covered (78.2% were from Addis Ababa city administration, and the others were from SNNPR; 65% were pharmacies, and the remaining were drug stores). Of these, 158 (53.4%) possessed illegal medicines, including medicines without invoices, medicines stocked above standard, program medicines diverted from public institutes/unknown sources, and medicines not registered in the country. The source of the illegal medicines was unknown in 148 (98.4%) medicines retail outlets. Examples from known sources included contraband antimalarial medicine from Uganda. Moreover, 135 (46.2%) of the retail outlets stocked medicines without invoices, and 30 (28.8%) stocked medicines above standards during the time of inspection. As stipulated in EFMHACA's medicine retail outlets model directives (2013), each level of medicine retail outlets (pharmacy, drug stores, and rural drug vendors) are expected to fulfill certain requirements to handle a defined list of medicines. The inspection checklist is developed considering these requirements and the medicines list defined for each level. Accordingly, the results from the inspection showed some deviations from EFMHACA's requirement. The deviations as stated above included stocking medicines out of scope defined for drug stores and medicines without invoices. These challenges exemplify the multitude of issues around the integrity of the supply chain system, which complicates efforts toward ensuring the quality and safety of medicines. Among the 298 audited medicine retail outlets, 9 (3%) possessed medicines supplied by the government for free as part of priority public health programs, including antimalarial, MNCH, antiretroviral (ARV), and opportunistic infection medicines (program medicines), which were not allowed to be handled by 8 (88.9%) of the retail outlets. Among the illegal medicines, contraband antimalarial medicines from Uganda were found. In addition, storage practices reflected several deficiencies: 188 (63.5%) of the retail outlets were found to store medicines inappropriately, exposing them to moisture, temperature, and direct light. They were

not also recording and monitoring temperature and humidity. Temperature monitoring devices were not available at 167 (65.7%) of the medicine outlets, and there were no suitable refrigerator thermometers in 155 (67.4%).

PQM also provided technical assistance to improve the medicine registration information system. New updates on the system include incorporation of online attachment features. Other related technical assistance provided in the medicine registration directorate includes:

- Development of terms of reference that define the roles, responsibility, accountability, and scope of the task force for developing a medical device registration information system (MDIS).
- Development of a pharmaceutical traceability directive by the traceability technical working group (of which PQM is technical assistance member).

Sub-IR 1.3 Standard of practices at national quality control laboratories sustainably improved

During Q2 and Q3, the EFMHACA QC laboratory's accreditation was renewed, and the scope was expanded to 3 additional test methods, bringing the total number of accredited test methods to 16.

In Q4, NMI confirmed its capability to calibrate all of EFMHACA's equipment. Going forward, EFMHACA will no longer need to contract a foreign institute to calibrate any of its equipment. PQM has long been supporting EFMHACA in equipment maintenance and calibration as part of building capacity of the QC laboratory and attaining/maintaining its international accreditation. While equipment maintenance was transferred to EFMHACA about 2 years ago, providing technical assistance on equipment calibration continued as part of PQM's support. PQM explored various options to build local capacity of third-party providers to EFMHACA to promote sustainability. Equipment calibration was identified as one of the more important areas to support because it is a mandatory requirement for maintaining EFMHACA's current ISO accreditation.

The inception of technical support to NMI began in FY 2017 when PQM identified the institute as a key partner and initiated building its capacity through the use of USP supplemental funds. PQM identified key gaps that could help NMI expand the scope of its calibration services to include equipment at EFMHACA. This strategy started bearing fruit in FY 2018, when NMI was able to calibrate more than 70 percent of EFMHACA's laboratory equipment, which not only resulted in a substantial reduction to USAID's investments but also meant EFMHACA was able to cover all the local costs (paid to NMI). PQM continued working with NMI in FY 2018 to fill the few remaining gaps. Lastly, in Q4, as per a request from PQM on NMI's capacity with regard to covering calibration of existing equipment, NMI reassured that it would be able to cover all of EFMHACA's needs in FY 2019 (100% coverage). As PQM is approaching closeout, this is a huge success and major milestone in terms of ensuring sustainability and transitioning long years of support (on a very technical and sensitive area). EFMHACA has begun working with NMI to have a contract in calibrating its equipment.

In addition, a transition plan for laboratory accreditation from ANAB to ENAO was prepared, and its respective implementation has been started. EFMHACA has officially applied to ENAO to transition its accreditation from ANAB to ENAO, and preliminary review of EFMHACA's QMS documents was conducted by ENAO. EFMHACA is also responding to comments received from ENAO. The main reason PQM had been recruiting the accreditation body from the United States is that ENAO had not been a full member of the International Laboratory Accreditation Cooperation (ILAC) and hence the accreditation service it provides was not traceable. However, ENAO became a full member of ILAC in January 2018. This paves the way to transit the accreditation process from ANAB to ENAO.

ENAO was established as an autonomous federal government office having its own legal personality. The mandate of ENAO includes provision of accreditation services to laboratories (test and calibration), certification bodies, and inspection bodies.

Sub-IR 1.4 Institutional capacity for regulatory workforce sustainably improved

Planned activities are accomplished under this activity during previous quarters, and there is no update for this quarter.

Sub-IR 1.5 Capacity for post-marketing surveillance of medical products sustainably improved

During previous quarters, preliminary results from FY 2017 PMS were reported, and on-time regulatory measures were also taken on products that did not meet quality requirements.

In Q4, the FY 2017 PMS draft report was prepared and shared with EFMHACA for comments. Once the report is finalized, it will be shared with relevant stakeholders.

Objective 2 – Support increased supply of quality-assured priority medicines

PQM continued to participate in the technical working group for implementation of the National Strategy and Plan of Action for Pharmaceuticals Manufacturing Development in Ethiopia (NSPA-pharma) by participating at the regular regulatory working group meetings. The technical working group identified the activities to be performed in 2018/2019. A few highlighted planned activities are outlined below:

- Support development/update and implementation of law, policies, legal framework, standards, and guidelines for control of good manufacturing of medicines.
- Strengthen/expand use of appropriate software for the major regulatory functions: market authorization, GMP and supply chain inspection, and e-regulation of the supply chain.
- Track and trace the e-regulation of the supply chain related to local industry.
- Support EFMHACA to achieve a minimum of maturity level III in at least three priority regulatory functions:(market authorization, GMP bioequivalence inspection, and QC laboratory),

PQM has provided technical assistance to Blue Nile Pharmaceuticals, which is in the project development phase. The technical assistance requested by the manufacturer was to review a concept design and layout of the plant according to GMP requirements. Accordingly, PQM attended a 3-day workshop (July 25–27) organized by Blue Nile to provide the needed support in line with the NSPA-pharma initiatives. Blue Nile’s plan is to focus and fill gaps on shortages of priority medicines in the country, including amoxicillin dispersible tablets (DT), family planning products, and essential medicines. The technical support provided by PQM in this regard will help address one of the NSPA-pharma objectives to ensure GMP compliance by the new manufacturing facility during set-up of the plant and prior to starting production, which ultimately will help ensure the quality and safety of medicines during manufacturing.

In collaboration with the Food, Beverage and Pharmaceutical Industries Development institute (FBPIDI), PQM provided training on GMP for FBPIDI staff, industry bureaus, and local manufacturers on July 2–6. A total of 30 staff attended the training. PQM participated as a trainer, and FBPIDI exclusively covered training expenses.

Similarly, as part of implementation of NSPA –pharma specifically aimed at creating a pool of experts, training of trainers (TOT) on GMP was conducted by EFMHACA in collaboration with WHO, Jhpiego, and UNFPA to staff from different institutes. The TOT consisted of 2 days focused training on teaching methodologies and 5 days of technical training on GMP. A total of 24 experts (all male) were trained from 4 universities, 2 local manufacturers, FBPIDI, EFMHACA, and the Quality and Standards Authority of Ethiopia. Preparations for rollout of a basic GMP training continue. The training (financed by EFMHACA) will be provided for 300 experts of regional regulatory bodies, MOH, FBPIDI, and universities. The rollout of training on GMP will help fill the anticipated demand to cover inspection of local and foreign manufactures on a large scale by a pool of inspectors with basic knowledge of GMP.

Objective 3 – Strengthen utilization of medical product quality information for decision-making

Sub-IR 3.1 Availability of information related to quality of medical products increased

PQM provided support for the annual health regulatory sector workshop conducted by EFMHACA and regional regulatory bodies in Dire-Dewa (July 20–25). The main objective was to evaluate the annual performance of EFMHACA and the different regional regulatory bodies, discuss ways to enhance linkages, and highlight future directions for strengthening the regulatory system. The workshop was attended by 115 participants from EFMHACA, regional regulatory bodies, PQM, the House of Peoples, plan commission, the Prime Minister’s office, and Dire-Dewa city administration. The annual performance of EFMHACA and 11 regional regulatory bodies was presented and evaluated with respect to the 5-year health regulatory sector strategic plan. Some of the action items agreed upon during the workshop included enhancing collaboration to combat illegal medicines, strengthening risk-based regulation in all aspects, scaling up audit inspections, strengthening country pharmacovigilance systems, and strengthening alignment among federal and regional regulatory bodies.

PQM provided technical support to the EPA 38th Annual Conference on July 27–28. Attended by key stakeholders and professionals in the pharmaceuticals sector, the event is an important platform for discussing medicines quality. PQM contributed to the presentation on “Ensuring the quality of medicines to contain antimicrobial resistance” during the panel discussion, where invited government officials, EPA members, and other guests participated. The discussion addressed key findings from the PMS conducted in the previous nine rounds (since 2009) with PQM’s support and the implications for preventing and containing antimicrobial resistance in Ethiopia.



Annual health regulatory workshop between EFMHACA and regional regulatory bodies

PQM continued providing technical assistance to EFMHACA to strengthen its pharmacovigilance/medicine safety monitoring system. In relation to the public health programs safety monitoring/pharmacovigilance system, PQM participated on supportive supervisions of the Armauer Hansen Research Institute on cohort event monitoring of ARV medicines. In addition, technical assistance was provided on preparing checklists to assess the safety monitoring system of TB and leprosy programs. The checklists will be used to assess safety monitoring systems at different levels, ranging from the regional level to the health facility level.

Accordingly, data on 140 adverse drug events were recorded into the pharmacovigilance data recording system; of these, 8 product defects had been received by EFMHACA. Also, 32 adverse drug reaction reports were shared with the WHO UMC drug safety monitoring center. Further investigation on product quality defects was started by the Inspection directorate on 2 medicines (acetylsalicylic acid 81 mg tablet and ciprofloxacin 500 mg tablet).

Other activities carried out during Q4 related to strengthening the pharmacovigilance systems of Ethiopia included:

- PQM presented on findings of tramadol abuse by students to the National Drug Advisory Committee. Based on discussion with the committee, plans of action were prepared and shared with the Ministry of Education and medico-legal directorate of EFMHACA to minimize such. Circular letters were sent to responsible stakeholders, including 11 regional health bureaus, to inform them to be vigilant about such abuses.
- PQM provided technical assistance for the revision of the National Pharmacovigilance Guideline, which was last revised in 2014. Development of draft zero is underway.
- PQM provided technical assistance on data collection, using the WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems to assess the pharmacovigilance system level and gaps.
- PQM presented at the annual EPA conference on the national pharmacovigilance system. The presentation covered mandates of EFMHACA, current interventions, policy requirement, challenges, and opportunities related to the country's pharmacovigilance system. As workshop participants are key players in implementation of the pharmacovigilance system, this was a unique opportunity to raise awareness.

Objective 4 – Support office management and strengthen integration of M&E activities within regulatory authority

Activities under this objective were completed in previous quarters. No additional update for Q4.

IV. Key Challenges

Challenges involved delay of some planned activities, including PMS, due to continually changing priorities of the regulatory authority and its branch laboratories.

V. Lessons Learned

Building local capacity of third-party laboratory service providers is a feasible solution to promote self-reliance, ownership, and sustainability of laboratory activities and achieve accreditation. This was revealed by the success achieved through the technical support PQM provided to NMI to help EFMHACA get its laboratory accredited. Similarly, ENAO becoming a full member of ILAC is another example that provided an opportunity to transition EFMHACA's ISO accreditation from ANAB to a local organization.

Ghana

I. Quarter 4 Highlights

PQM activities this quarter focused on the ongoing technical assistance to Entrance Pharmaceuticals Limited (EPL) to address the gaps identified during an assessment in Q1. The manufacturer has continued to take positive strides toward the goal of improving its GMP compliance and submitting its artemether–lumefantrine product dossier for WHO PQ. Although there were challenges with the initial sourcing of its starting raw material and identification of a CRO for the bioequivalence study, significant progress has been made. The needed API has been obtained and a new CRO identified. The manufacturer has also completed significant intermediate steps, such as the manufacture of trial batches and initiation of stability studies (real time and accelerated) in Q4. Due to the delayed start in the stability studies, the timelines for the project and the expected timeline for submission of the product dossier for WHO PQ are now revised to sometime in March 2019. Although this changes the original aggressive timeline of January 2019, the new timeline is still considered an aggressive timeline and is attributable to the commitment of the management and technical staff at EPL.

Previous survey on the quality of oxytocin injections in Ghana, conducted in 2015, had indicated that as much as 55 percent (69 of 124) of samples collected did not meet acceptable quality specifications when tested. The Ghana FDA (GFDA) has continued to monitor the quality of this product and plans to conduct another round of PMS this year. In line with the work plan activity, the sample collection for the PMS of uterotonic medicines (oxytocin and ergometrine injections) started in Q4.

II. Country Context

Malaria is a leading cause of morbidity and mortality in Ghana. The goal of PMI in Ghana is to reduce malaria deaths and substantially decrease malaria morbidity, toward the long-term goal of elimination. Through PQM, since 2009 USAID has been assisting GFDA to strengthen the medicines QA and QC systems. Activities have focused on strengthening GFDA's capacity in drug registration, medicines QC, and PMS. PQM has also recently provided technical assistance to ensure locally manufactured ACTs meet internationally acceptable quality standards.

The objectives of PQM interventions in Ghana are in line with PMI's strategic approach in the area of building capacity and health systems, as described in the PMI 2015–2020 strategic plan. PQM-proposed activities in Ghana fall under PMI's core operating principles that "ensure that all commodities provided to countries are of high quality and that systems are in place to continually improve the quality of services delivered."

There are several local manufacturers of pharmaceutical products in Ghana. GFDA continues to build capacity for its GMP inspectors to ensure it can adequately inspect facilities and provide guidance to industry to address GMP gaps. This will help to ensure locally produced medicines meet internationally acceptable GMP standards.

III. Quarter 4 Progress by Objective

Objective 1 – Facilitate sustainable implementation of a risk-based approach for PMS of antimalarial and MCH medicines

Facilitate PMS of MCH products

Implementation of activities for the surveillance of the quality of oxytocin and ergometrine injections started this quarter. Sample collection will be implemented in all 10 regions in the country, and testing of the collected samples is

expected to be completed in October 2018. This survey allows GFDA to monitor the quality of oxytocin injections and ergometrine injections available to patients in Ghana.

Objective 2 – Strengthen Ghana FDA QA/QC system through sustainable laboratory accreditation

Activities under this objective were completed in Q3.

Objective 3 – Strengthen facility inspection capacity of Ghana FDA

Provide training to strengthen capacity of Ghana FDA to perform inspection of local manufacturing facilities for cGMP compliance and in response to gaps identified through GMP roadmap

GFDA's Industrial Support Department continues to receive hands-on training by working closely with PQM GMP experts as technical assistance is provided to EPL. PQM GMP experts opted for this hands-on approach as it allows GFDA inspectors to learn from PQM experts while concurrently providing technical assistance to the manufacturer with PQM guidance. The GFDA inspector (head of department) provides in-country visits to the facility and helps to address some GMP gaps. With this arrangement, GFDA is gaining more experience while learning from the routine interactions with PQM GMP experts.

With PQM's oversight, the FDA inspectors of the Industrial Support Department have been involved in providing support in the following GMP improvement activities:

- Review of CAPA and providing guidance for updates.
- Review of product development protocol with reference to the WHO model dossier.
- Review of temperature mapping protocol and provision of further guidance for update of the protocol.

Objective 4 – Increase supply of quality-assured antimalarial products (ACTs) by providing technical assistance to local manufacturers

Facilitate multiple technical assistance visits to manufacturing facilities

In Q1, in collaboration with GFDA inspectors, PQM GMP experts assessed four local manufacturers (EPL, Amponsah Efah Pharmaceuticals, Phyto-Riker Pharmaceuticals, and Ernest Chemist) for their GMP compliance toward WHO PQ for the manufacture of ACTs. Following the assessment, EPL was selected to continue receiving technical assistance from PQM to help EPL improve GMP compliance and submit a dossier for WHO PQ of artemether-lumefantrine, a first-line ACT in Ghana.

In Q3, PQM GMP experts working in collaboration with the GFDA Industrial Support department provided technical assistance to EPL to address some key GMP gaps. PQM supported by providing API source review and product development protocol review, contact information for comparator tablet sources, technical criteria for CRO selection, and CRO contact information. PQM facilitated discussions with multiple CROs to enable EPL management to select a CRO for the required bioequivalence study. EPL obtained the comparator tablets and expects to receive the API from a WHO-approved supplier so that it can manufacture the bio-batch that is required for the study. The manufacturer is also expecting the draft bioequivalence study protocol from the CRO it selected.

In Q4, PQM continued to provide technical support as EPL progresses toward the formulation and production of its trial batches. Progress recorded includes product development documentation and production of trial batches, which have also been utilized for the required stability studies. As a result of PQM's technical assistance, EPL recognized that the CRO initially selected may not meet the stipulated project timeline. Recognizing that this could affect the project goal, EPL management immediately took steps to seek the services of another CRO. PQM supported this initiative by providing guidance on the selection. A new CRO with more experience in bioequivalence studies was therefore selected, and EPL is finalizing the contract arrangements.

The project has experienced delays with the supply of the API, which was addressed in Q3 but resulted in the late production of the trial batch and subsequently impacted the timelines for initiation of stability studies. In Q4, the trial batches were successfully produced and stability studies initiated. Based on the current timeline for the stability studies, the submission of the product dossier is now expected to occur sometime in March or April 2019, as the earlier planned January 2019 date is no longer feasible. Despite the delay, PQM considers this a successful response to the challenges encountered, due to the commendable commitment of EPL management.

Guinea

I. Quarter 4 Highlights

In Q3, the revised pharmaceutical law was adopted by the national assembly of Guinea. Q4 was marked by the promulgation of the revised law by the president of Guinea. The revised law will now be enacted by DNPM for effective regulation of the pharmaceutical market of Guinea. The enactment of the law requires the establishment of priority medicine regulations. These must take into account the pivotal functions of DNPM such as registration and PMS activities that needed to be strengthened to reduce exposure to falsified and poor-quality medicines circulating in the market.

As part of supporting the QC of the laboratory, LNCQM has received funds from the European Union to procure laboratory equipment and renovate the existing laboratory. To leverage this activity with EU, PQM assisted providing the list of required equipment for QC testing and their specifications. The majority of laboratory equipment (including high-performance liquid chromatography (HPLC), ultraviolet-visible (UV-Vis), and dissolution tester) was procured with EU funds.

To assist the laboratory during the renovation phase, PQM last quarter met with MOH and EU representatives. PQM provided amendments on the existing renovation plan and submitted a new layout and partition renovation plan to the laboratory. This support was welcomed by the laboratory director and MOH engineers involved in this activity. The revised PQM renovation plan included some security measures that were missing in the previous plan and provided a better remodeling plan that complies with international standards. The revised renovation plan will enable LNCQM to expand and include other QC activities, such as testing for endotoxins.

The last quarter was also marked by a new organizational structure of the MOH departments, including DNPM. Within DNPM, a new director and new staff were appointed, and other personnel familiar with PQM's work transitioned to other MOH departments. This organizational change has pushed the validation of the PMS protocol and the implementation of the registration activities. PQM has made plans to address this delay by conducting several activities in FY 2019 Q1.

II. Country Context

Together with other donors and USAID partners, PQM supports efforts to strengthen the pharmaceutical system. Like other African countries, Guinea is often disproportionately affected by the burden of poor-quality medicines. PQM can play a key role in strengthening the pharmaceutical system and the capacity of the national drug regulatory authority to assure the quality of medicines in the supply chain through registration, inspection, and QC activities. Malaria is the primary cause of consultations, hospitalizations, and deaths in Guinea—it especially affects children under 5 years of age. In 2011, Guinea was included in PMI; USAID and partners in Guinea are not only procuring malaria commodities but also helping to strengthen the country's health and pharmaceutical systems.

Guinea and other countries in sub-Saharan Africa are often hurt by falsified medicines. One way to combat this public health challenge is to ensure that medicines are registered and tested according to international quality standards. Guinea does not have local pharmaceutical manufacturers and depends on importation for all required essential medicines. Proper registration of medicines is a necessary step to ensure that only quality-assured medicines are licensed and available in the market; in addition, registration fees generate revenues to sustain MRA activities.

To reduce the disease burden, there is an immediate need to ensure reliable access to quality-assured, safe, and efficacious essential medicines and to build up the country's QA/QC systems. USAID/Guinea selected PQM to assume this task. PQM received funds from Maternal and Child Health and Family Planning funding streams to conduct a rapid assessment of Guinea's QA/QC systems and subsequently proposed activities to address the major gaps and challenges identified.

III. Quarter 4 Progress by Objective

Objective 1 – Strengthen the legal and regulatory framework to enable DNPL to implement a comprehensive QC/QA mandate

After more than 2 years of PQM and other stakeholders' support, the revised pharmaceutical law was promulgated in September 2018 by the president of Guinea. The numerous amendments of the law will help DNPM to ensure effective control of the medicines and health products in Guinea.

To help DNPM during the enactment of the law, PQM proposed to work with DNPM on priority regulations and policies specifically in the areas of PMS and registration. The DNPM director thanked PQM for its support and preferred to have DNPM support for inspection and PMS. To this end, PQM will make changes to the FY 2018 work after consultation with the USAID Mission and replace registration activities with inspection, which is a new function under the DNPM mandate.

Objective 2 – Continue strengthening DNPL capacity in product registration

PQM was informed by DNPM and the Mission that registration activities would be carried out by GHSC-PSM. PQM will work in collaboration with GHSC-PSM and will focus on supporting inspection activities as requested by the new DNPM Director. Communication on this matter was sent to the AOR and to the Mission.

Objective 3 – Enable DNPL to assume MQM responsibilities

During the revision of the pharmaceutical law, PQM assisted DNPM in drafting the PMS protocol and provided guidance on sampling and testing. The draft protocol was reviewed in Q2 by the former director and his staff as well members from various health programs. Last quarter PQM planned to validate the protocol and to plan for the first official round of PMS program. Unfortunately, the new DNPM director pushed back this activity. The new director suggests that a new committee should review the PMS protocol again before its submission to MOH for institutionalization. To respond to the new DNPM director's request, PQM plans to have a workshop in FY 2019 Q1 to validate the protocol and to conduct the first round of MQM in two selected sentinel sites.

Objective 4 – Strengthen QC capacity of LNCQM

Last quarter PQM shared with LNCQM the revised demolition plan and the revised renovation plan. In Q4, PQM followed up with the laboratory on implementation of these plans and the safety measures recommended by the PQM consultant. PQM also shipped the necessary reagents and laboratory supplies to conduct analytical training as part of the FY 2018 work plan. Due to the delay in completion of the laboratory, the training was postponed to FY 2019 Q1.

IGAD

I. Quarter 4 Highlights

In Q4, follow-up activities to the June 25–29 kickoff workshop conducted in Addis Ababa were carried out. The PMS protocol was further reviewed to address comments from the Intergovernmental Authority on Development (IGAD) medicines regulatory harmonization (MRH) and USAID. Plans for implementation of the survey to determine the prevalence of substandard and falsified medicines within selected cross-border regions are ongoing. The training for the sample collectors is scheduled to take place in Entebbe, Uganda, on October 1–5. In addition to oxytocin injections, amoxicillin DT, a first-line antibiotic for pneumonia and other infections, was recommended. Member states' MRAs have nominated sample collectors from their respective MRAs, and preparatory works were conducted for the training. Sudan and South Sudan are not expected to participate in the quality surveillance activity. In line with capacity-building efforts for adoption of risk-based PMS principles, PQM also provided technical assistance to the Uganda National Drug Authority (NDA) on August 3–10. A hands-on training was provided on using the medicine risk assessment tool to determine sample size and representative facilities based on an assessment of certain relevant risk factors. Following the training, the Uganda NDA adopted this risk-based PMS approach in the development of the national 2018 PMS plan.

II. IGAD Context

The IGAD region comprises eight countries in the horn of Africa region: Djibouti, Eritrea, Ethiopia, Kenya, Somalia, South Sudan, Sudan, and Uganda. The region experiences migration and cross-border mobility due to economic uncertainty and political conflicts. The cross-border mobile populations face major barriers to access of basic healthcare due to the complex sociopolitical dynamics of the public health system in the context of migration and cross-border mobility. IGAD hopes to reduce regional health disparities and risks associated with cross-border mobility of people through interventions to reduce maternal and child morbidities, improve unmet demand for family planning among women and girls, prevent outbreaks of communicable diseases, prevent and control TB and HIV, monitor the safety and quality of medicines, and reduce and control the movement of substandard and falsified medical products.

The IGAD Health and Social Development division has sought to implement an MRH for the horn of Africa in line with the vision and goals of the African Medicines Regulatory Harmonization (AMRH) initiative. With funding from USAID/East Africa, the PQM program will implement targeted interventions, including establishment of an expert working group (EWG) to identify pharmacovigilance/PMS document gaps, provide recommendations for implementation of pharmacovigilance/PMS activities in the region, and facilitate a survey to determine the prevalence of substandard and falsified medicines at selected cross-border sites to inform future interventions. Details of the planned activities are delineated in the approved PQM work plan.

The activities of the PQM work plan were adopted from the proposed IGAD health program activities and align with IGAD's strategic interventions #1 and #3: (#1) institutionalize a system for monitoring safety and quality of medicines used at IGAD cross border points, and (#3) develop and institutionalize IGAD regional cross-border health policies and sector-specific strategies on MNCH, MRH, TB, and HIV/AIDS. These IGAD strategic interventions are aligned to two of the three Development Objectives (DOs) of USAID's Regional Development Cooperation Strategy, 2016–2021: Improved management of risks that transcend borders (DO2) and East African institutions' leadership and learning strengthened (DO3).

III. Quarter 4 Progress by Objective

Objective 1 – Establish a Regional Expert Working Group (PV/PMS-EWG) on Pharmacovigilance and Post Market Surveillance

EWG to conduct and PQM to facilitate the assessment of current PV/PMS manuals/guidelines, technical requirements and standards, tools, standard operating procedures for monitoring of safety and quality of registered medical products in IGAD member states

In the previous quarter, working with the EWG, PQM facilitated a gap assessment of pharmacovigilance/PMS documents and practices at the workshop on June 25–30. During the workshop, member states were asked to complete checklists to assess their respective authority's pharmacovigilance systems. Report from the member countries is still pending and were expected to be received this quarter. However, the reports have been delayed and PQM plans to follow up at the next workshop in October. Once the checklists are completed and received from the member states, PQM will compile the report, and the EWG will make recommendations.

Objective 2 – implement a survey to determine the prevalence of Substandard and Falsified (SF) medical products used in the MCH-FP/TB/HIV-AIDS at selected IGAD cross-border areas

Facilitate a survey to determine prevalence of SF used in the MCH-FP/TB/HIV; PQM will work with the EWG to implement this survey

In Q3, a survey protocol to determine the prevalence of substandard and falsified MNCH-FP/TB/HIV medicines was prepared at the workshop held in Addis Ababa.

In Q4, as per assignments provided to member states, information needed for samples size estimation, selection of sampling outlets was received from Somalia, Djibouti, Ethiopia, Uganda, and Kenya. PQM used this information to estimate a statistically representative sample size and randomize sampling outlets from the selected cross-border sites. This information will be shared with the member state MRA experts at the upcoming October workshop.

In addition and as a follow-up activity from Q3, further revision of the protocol was made to address stakeholders' queries from USAID/KEA and IGAD-MRH. Based on suggestions to include another MNCH/FP related product, PQM, an IGAD-MRH consultant, and a USAID activity manager discussed medicines included in the UN Commission on Life-Saving Commodities that could be included in this survey, in addition to oxytocin. Amoxicillin DT was suggested. Options to be considered are the dispersible tablets (a newer formulation for children and currently widely recommended) or suspension (older and more widely available). A final decision will be made when the options are shared with the IGAD-MRH EWG during the next workshop.

PQM met with USAID and the IGAD-MRH consultant in September to discuss preparedness for the forthcoming EWG workshop. The group discussed how best to engage AMRH partners and manage relationships to ensure that all the USAID work fits within the broader AMRH initiatives and that USAID-supported activities are included in the broader calendar. Accordingly, the importance of strengthening linkages with the New Partnership for Africa's Development (NEPAD), which is responsible for leading coordination advocacy across the regional economic communities, was highlighted. With regard to the process of engaging IGAD with national government, it was discussed that IGAD still relies on the Ministry of Foreign Affairs. PQM also indicated that USP is a recognized member of the AMRH partnership platform. This platform can be used for aligning USAID-funded PQM activities with the regional and continental MRH initiatives.

In line with the work plan activity to implement PMS on the quality of oxytocin injections available in selected cross-border areas, PQM continues to liaise with IGAD-MRH in preparation for the next EWG workshop aimed to train sample collectors and initiate the sample collection. The following preparatory steps were accomplished this quarter:

- A draft agenda for the workshop to be conducted in Entebbe, Uganda, on October 1–5 was shared with the EWG. The team is waiting for a response.
- IGAD wrote to agencies to request nomination of sample collectors, and member states provided their lists
- An updated draft protocol for a PMS survey of oxytocin at the cross-border is in review. PQM incorporated feedback received from the first round of review. At the next workshop, the protocol will be shared with member states for review and endorsement. Procurement of essential supplies to be used for the collection of samples has begun. Supplies under procurement include temperature data logger devices and software for data transfer from the logger.
- PQM has requested quotes from the testing laboratory on the sample collection.

Provide TA to enable uptake of risk-based PMS approach and facilitate development of selected member state PMS guidance and/or protocol that applies risk-based approach to PMS of pharmaceutical products quality; selected member states will be based on MRA interest in risk-based PMS

In line with the IGAD-MRH work plan activity, PQM efforts focus on capacity-building and provision of technical assistance to help member states adopt risk-based PMS principles for their national PMS program. The Uganda MRA continues to demonstrate interest in adopting risk-based PMS principles following an earlier introduction of risk-based PMS principles during an African Medicine Quality Forum (AMQF) in Tanzania (February 2018) and during the Q3 IGAD MRH work plan kickoff workshop in Addis Ababa (June 25–29, 2018). In Q4, PQM provided hands-on training to NDA staff on the use of the medicine risk assessment tool. This tool is a complement to the PQM risk-based PMS guidelines. It allows MRAs to assess medicines risk when selecting medicines to be included in the national PMS plan. The tool helps MRAs make a statistically sound decision so the number of samples to be collected is statistically representative, and it allows the MRA to randomize the selection of outlets where the samples are collected from. The tool also helps NQCLs to prioritize analytical test for the samples collected during PMS.

Following the training on August 6–10 at the NDA office in Kampala, the Uganda NDA PMS team was able to adopt elements of the risk-based PMS approach into the development of the 2018 national PMS plan.

Objective 3 – IGAD Cross-border draft health policy developed and shared with stakeholders

No activity to report this quarter.

Kenya

I. Quarter 4 Highlights

Per a directive from USAID, PQM submitted an addendum to the FY 2017 work plan to the Mission. PQM will begin the implementation of the addendum activities after approval from the Mission. PQM anticipates starting implementation of the proposed activities at the county level in FY 2019 Q1.

Liberia

I. Quarter 4 Highlights

With the reappointment of the former head of the Liberia Medicines and Health Products Regulatory Authority (LMHRA), progress has been made in the launch of the implementation of the fixed amount award (FAA) PMS plan and in the application of the recent dossier evaluation guidelines for the common technical document (CTD) format by the by the registration staff.

Q4 witnessed the reprise of laboratory activities at the new temporarily facility and the continuous regulation of the Liberian pharmaceutical market via the confiscation of falsified and poor-quality medicines. As part of the implementation of the Monotherapy Act, LMHRA in collaboration with NMCP is planning to conduct the second exercise of the recall of antimalarial monotherapies from Lofa County.

Despite this progress, LMHRA's QC laboratory is facing challenges in receiving the remaining laboratory equipment and supplies, procured through World Bank, which impeded the laboratory's routine analytical work and delayed the implementation of PQM's planned activities for this fiscal year. Additionally, during this quarter, PQM shared with the Mission information on timelines to complete FY 2018 work plan activities, including closeout event plans.

II. Country Context

Malaria is endemic in Liberia and poses a serious public health threat, accounting for at least 33 percent of all inpatient deaths and 41 percent of deaths among children under 5 (NMCP, 2012). In 2012, the National Malaria Control Program (NMCP) reported that hospital records showed malaria as the leading cause of visits to outpatient facilities. It is also the leading cause of inpatient deaths, making malaria prevention and control a significant concern in Liberia. In collaboration with international partners, NMCP has made significant efforts to scale up malaria prevention interventions as well as improve public-private partnerships to increase access to quality-assured antimalarial medicines.

Since 2011, PQM has provided technical assistance to strengthen PMS in Liberia through MQM for antimalarial medicines and has encouraged LMHRA to take appropriate regulatory actions when poor-quality medicines are identified. As a result of these MQM activities, several antimalarial medicines, including quinine tablets and chloroquine, were removed from circulation. Monotherapies such as quinine tablets and chloroquine were once widely available. They have been subsequently banned through a regulatory action by LMHRA and since then have become less prevalent. Results from various MQM activities and subsequent regulatory actions have been encouraging, but data continue to show that falsified and substandard medicines are still a major concern in Liberia.

PQM activities in Liberia are focused on:

- Building LMHRA's QA/QC capacity.
- Reducing the incidence of falsified medications and increasing awareness about the quality of medicines.

As part of the approved FY 2017 work plan, PQM provides technical assistance toward building the QC capacity of the existing LMHRA QC laboratory and attaining compliance with international standards (ISO 17025), strengthening and expanding quality monitoring of antimalarials, promoting regulatory actions when falsified and substandard medicines are identified, and increasing awareness about the quality of medicines.

III. Quarter 4 Progress by Objective

Objective 1 – Rebuilding capacity of LMHRA QC laboratory

While waiting to get final approval from the Global Fund to build a permanent laboratory, LMHRA has moved to a new temporary laboratory. During the renovation of this facility, PQM provided guidance on the workflow design, including partitioning of the physico-chemistry area, and on safety measures. Last quarter, PQM assisted with the installation of selected laboratory equipment and training on preventive maintenance. In Q4, PQM had planned to conduct refresher training on compendial testing, but this has been postponed due to delays from the local vendor in delivering the remaining laboratory equipment and consumables. Since the laboratory equipment is funded through the World Bank, LMHRA is following up directly with the vendor through the Ministry of Health.

As a next step, PQM is planning to resume QC laboratory training in FY 2019 once the remaining laboratory equipment and laboratory consumables are received at the end of October.

Objective 2 – Continue building the QA/QC capacities of LMHRA in registration and inspection

To strengthen the capacity of LMHRA in medicine registration and inspection, In Q3, PQM provided training in dossier evaluation that will allow LMHRA staff to conduct registration activities effectively and according to international standards. As part of empowering LMHRA's inspection capacity, in Q4 PQM began planning hands-on mentorship and skills-building training on GMP at a pharmaceutical manufacturing company in Ghana. This training will allow inspectors in Liberia to be exposed to GMP principles in a real-world setting. Liberia currently does not have an in-country manufacturing company.

Objective 3 – Build LMHRA capacity to take appropriate regulatory actions

LMHRA has confiscated several consignments of expired, falsified, and banned drugs from various clinics and pharmacies that they had been administering and dispensing to patients. The confiscated products included antimalarial treatments and medicines intended for use by the government hospitals.

The head of LMHRA named and shamed the clinics involved in these practices and shared the outcomes of this raid with the local media.

More information on this regulatory action and the confiscated products can be found in this media report: <https://frontpageafricaonline.com/health/liberia-clinics-in-liberia-administering-and-dispensing-fake-banned-drugs-to-patients/>.



"Recently we visited some clinics and imagine a clinic knowingly and intentionally administering expired drugs or dispensing expired drugs to patients. This is very unacceptable." – Managing Director, Liberia Medicines & Health Regulatory Authority



Objective 4 – Development of integrated PMS in Liberia (via leveraged funding)

As part of the implementation of the FAA, LMHRA held a stakeholders meeting in Monrovia with the county health team, police authority, and health programs at MOH, including the NMCP. LMHRA provided an update on PQM activities aimed at monitoring the quality of medicines in Liberia and encouraged the full participation and engagement of all stakeholders in the implementation of PMS.

Due to the delay in implementing the FAA, LMHRA provided a revised schedule for the remaining milestones. PQM will work closely with LMHRA to ensure effective implementation of the PMS activities and on-time achievement of the deliverables according to the approved FAA.

Objective 5 – Expand and improve dissemination efforts to raise awareness about poor-quality medicines

For this objective, dissemination meetings will take place after implementation of PMS under the FAA.

IV. Key Challenges

- Slow progress in getting approval from the Global Fund to build the permanent laboratory. For this reason activities under this section may need to be reprogrammed
- Delays in receiving laboratory reagents and consumables, as well as some laboratory equipment not meeting agreed specification delayed planned timelines for PQM laboratory analytical training to FY 2019 Q1. This refresher analytical laboratory training on compendial methods is needed because laboratory staff have not been able to conduct routine analytical testing for over 9 months since last year's fire incident, except for screening tests with Minilabs™.

Mali

I. Quarter 4 Highlights

PQM facilitated PMS of antimalarial medicines activities that started in May 2018. Sampling was completed in July. A total of 615 samples were collected and underwent extensive visual inspection, after which 352 samples underwent further screening using Minilab™ and handheld Raman spectrometer. The testing revealed the presence of falsified artemether–lumefantrine and quinine sulfate. The proportion of failed samples was 5 percent. LNS submitted certificates of analysis of the failed samples to the Directorate of Pharmacy and Medicine and the Inspectorate of Health and also informed the Ministry of Health and Public Hygiene. The results of these activities were shared with stakeholders at a dissemination workshop. The Minister of Health headed the opening ceremony of the workshop.

PQM assisted the DPM in developing internal documents relating to governance including code of conduct, confidentiality, and declaration of conflict of interest. PQM trained seven DPM staff members on SOP writing. PQM coordinated the review of required QMS documents.

II. Country Context

Malaria is the primary cause of morbidity and mortality in Mali. The goal of PMI in Mali is to reduce malaria deaths and substantially decrease malaria morbidity, toward the long-term goal of elimination. Through PQM, since 2008 USAID has been assisting Mali's MOH to strengthen the medicines QA systems. Activities have focused on strengthening DPM and LNS capacity in pharmacovigilance, drug registration, medicines QC, and PMS.

The objectives of PQM interventions in Mali are in line with PMI's strategic approach in the area of building capacity and health systems, as described in the PMI 2015–2020 strategic plan. PQM-proposed activities in Mali fall under PMI's core operating principles that "ensure that all commodities provided to countries are of high quality and that systems are in place to continually improve the quality of services delivered."

III. Quarter 4 Progress by Objective

Objective 1 – Strengthen the capacity of the Directorate of Pharmacy and Medicine

To support strengthening DPM governance, PQM organized a training workshop to finalize good governance documents and initiate SOP development. Seven DPM staff attended the workshop. The documents discussed included:

- Confidentiality
- Declaration of conflict of interest
- Staff code of conduct

Confidentiality and declaration of conflict of interest documents were discussed in detail before adoption and submission to the DPM Director. The staff code of conduct document elicited more discussions that highlighted the challenge for its implementation. The document was adopted after revision.

DPM has recently appointed a QA manager. PQM presented the elements relating to the organization of a QMS and highlighted needs for the following:

- Commitment of the DPM leadership to mobilize necessary means for the implementation of this system
- Creation of a QA unit
- Development and update of QMS documents
- Implementation of procedures
- Establishment and implementation of internal audit

At the end of the workshop, PQM assigned DPM staff to draft the following SOPs:

1. Management of pharmacovigilance reports issued by manufacturers
2. Licensing of pharmaceutical establishment
3. Medical products recall management
4. Development and dissemination of QMS documents within DPM
5. Mail Management within the DPM
6. Records archiving

So far, DPM has drafted documents number 2, 3, 5, and 6. PQM will finalize draft documents with DPM staff.

Objective 2 – Strengthen the capacity of the National Laboratory of Health (LNS) to meet international standards

PQM facilitated the participation of LNS in the inter-laboratory testing (ILT) organized by USP. The laboratory received samples of albendazole tablet and its reference standard. LNS has not completed the test yet. ILT allows evaluating the performance of the laboratory compared to other laboratories participating in the testing. Participation of a laboratory in ILT or performance testing (PT) scheme is an ISO 17025 requirement.

Objective 3 – Strengthen sustainable local capacity to monitor the quality of medicines in the country

PMS workshop for dissemination of FY 2018 PMS activities was held on September 28, 2018. Pr. Samba O. Sow, the Minister of Health and Public Hygiene, presided over the opening ceremony of the workshop. The participants included stakeholders from the central and regional level.

In collaboration with DPM and the Regional Directorate of Health, LNS completed the sampling of antimalarials by collecting 28 additional samples. All 615 samples underwent extensive visual inspection; 59 were non-registered medicines. Some of these products were procured by the central medical store and others by private wholesalers. A total of 352 samples were selected and submitted for further screening using TLC and Raman spectroscopy, and 11 of these failed. The results were verified using TLC. The laboratory conducted confirmatory testing on 5 samples of artemether–lumefantrine. All 11 samples (7 quinine sulfate tablet and 3 artemether–lumefantrine tablet) were confirmed as failed. LNS sent certificates of analysis of failed samples to DPM and the Health Inspectorate, and a short report to MOH regarding these products. PQM has not received copy of the documents yet.

Objective 4 – Facilitate studies on resistance of antimalarial medicines

The new FAA packet was prepared and will be submitted to the AOR team for approval by early October 2018.

Mozambique

I. Quarter 4 Highlights

In Q4, the PQM program continued providing technical support to the National Directorate of Pharmacy (DNF) and the national quality control laboratory for medicines (LNCQM) to strengthen the medicine regulatory system of the country by empowering DNF and LNCQM to carry out their statutory responsibilities. To achieve this goal, PQM carried out the following key activities this quarter:

- Hands-on QMS training, which entailed review, development, or update of SOPs and a quality manual. The first complete quality manual was developed.
- Hands-on-training on compendial testing methods, including the application of analytical equipment currently in the laboratory.
- Received the results of 14 samples of oxytocin and 5 samples of magnesium sulfate injections sent for confirmatory test from the ISO accredited Vietnam Institute of Drug Quality Control. The results showed that 10 samples of oxytocin failed the assay test, 1 failed both the assay and pH tests, and 3 passed. All samples of magnesium sulfate injection passed the tests.
- Trained DNF, LNCQM, and key program and supply chain management partner on PQM's risk-based approach to PMS.
- With support from PQM, DNF conveyed a stakeholder meeting to evaluate the quality of medicine: post market review. This meeting was used to share the results of the of the post marketing quality surveillance activity from the previous round of quality surveillance of oxytocin and magnesium sulfate injections in Maputo city, Maputo province, and other provinces in Mozambique.
- Continued to provide technical inputs to DNF and LNCQM on medicines regulation development. PQM received and made valuable technical inputs to the current law vis-à-vis the Africa Union model law on

medical products regulations, internal regulation for DNF (structure and functions), and internal regulation for LNCQM (structure and functions).

II. Country Context

USAID and USP have been providing technical assistance to Mozambique through PQM since 2010. Activities have focused on strengthening the QA/QC capabilities of Mozambique's MRA, the pharmacy department (PD). PD and MOH updated the pharmaceutical law of Mozambique in 2016. The law was approved by the Parliament in early 2017 and signed by the President in September 2017. This law transitioned the MRA from PD to DNF.

PQM conducted a rapid assessment of PD's QA/QC capabilities in December 2010, which revealed that LNCQM's infrastructure, equipment, and staff were inadequate to provide the necessary QC services. The assessment also identified a lack of PMS of medicines quality. In 2011, PQM and PD partnered to establish an MQM program that included training on screening medicines quality.

In 2012, PQM facilitated significant investments in a variety of laboratory equipment, supplies, and reagents necessary for a QC laboratory to adequately test medicines. These investments also included training in equipment operation and in testing procedures required to analyze antimalarial and anti-HIV medicines.

Throughout 2013 and 2014, PQM developed and trained LNCQM technical staff and provided them with day-to-day laboratory consumables, equipment, supplies, and reagents to run the QC laboratory. To date, LNCQM has improved its technical capacity in analytical testing, proficiency, and use of key equipment. Through PQM training, LNCQM is better able to collaborate with other Portuguese-speaking countries.

With more than 90 percent of medicines circulating in Mozambique being imported, the authorities are aware of the country's vulnerability and exposure to poor-quality medicines. This new legislature, including Article 4 that addresses quality, offers a great opportunity for PQM and other supporting partners to make long-lasting contributions to the country's efforts to strengthen medicines regulation and work toward eliminating substandard and falsified products.

III. Quarter 4 Progress by Objective

Objective 1 – Continue to strengthen the capacity of Mozambique National Laboratory, LNCQM

LNCQM needs appropriate QMS in place that cover the scope of its activities for attainment of GLP and ISO accreditation. In view of this, over the years PQM has supported LNCQM to establish, implement, and maintain appropriate QMS suitable for its activities despite existing challenges. In Q4, PQM built capacity of three staff (two females and one male) for the first four days, and eight (four females and four males) staff on the fifth day via interactive lectures, demonstration, and hands-on-training on QMS. In the second week, seven staff (four females and three males) were trained on compendial testing methods as part of the continuous capacity-building strides on analytical laboratory testing. Some of the sessions covered included, but were not limited to, the topics below:

- Development and approval of a Quality Manual
- Conducting an internal audit
- Implementing CAPAs
- Determination of impurity in drug products using HPLC method
- Use and application of UV-Vis spectrophotometer
- Use and application of Fourier transformed infrared (FTIR) spectrophotometer
- Practical implementation of equipment management and personnel training SOPs:
 - Equipment history file was created for one of the HPLCs.
 - Individual personnel history file was created for one of the staff.
 - All equipment was identified with a unique ID number as per the new equipment management SOP and labeled accordingly.

At the end of the training and July trip, PQM outlined the following next steps for LNCQM to implement as part of the drive to strengthen QMS and attain ISO accreditation/GLP:

- Appoint a substantive QA Manager with a letter of authorization.
- Train on all developed SOPs and finalize the remaining SOPs which were drafted and shared by PQM.
- Approve the management meeting SOP and start its implementation.
- Participate in proficiency testing for 13 test methods.
- Conduct and complete internal audit.
- Implement GLP.
- Cascade the sample SOP implementations conducted by PQM to other SOPs.

- Appoint deputies for each critical position in the laboratory.
- Provide an authorization letter to staff for operating laboratory equipment, based on competency.



Photos taken during QMS and compendium methods training at LNCQM in Q4

PQM has continued to provide remote support to LNCQM to ensure implementation of activities outlined after the training held in Q3 on Instrument Calibration & Qualification (AIQ) and preventive maintenance.

Objective 2 – Support and strengthen post-marketing surveillance

In Q4, the results for 19 samples (14 oxytocin and 5 magnesium sulfate injections) were received from the external laboratory, Vietnam Institute of Drug Quality Control (IDQC). These samples were randomly selected to conduct confirmatory testing of failed and passed samples previously collected from public and private health facilities and drug outlets. Of the 14 oxytocin injection samples, 12 failed and 2 passed preliminary tests conducted by LNCQM. The results from the external laboratory showed that 11 failed and 3 passed confirmatory tests. This meant that one of the failed oxytocin samples passed the confirmatory assay test. Of the three failed samples, two failed assay tests, while one oxytocin injection sample failed both the pH and assay tests. All samples tested passed sterility and Bacterial Endotoxin Test (BET). The four samples of magnesium sulfate that failed the pH test and one sample that passed were sent for confirmatory test. The results showed that all five samples passed pH, assay, sterility, and BET. The table below summarizes the results obtained at LNCQM, Mozambique and IDQC, Vietnam.

Test level	Product	# samples tested	# samples passed	# samples failed (nonconformance)
Preliminary	Oxytocin injection	135	114	21
Confirmatory		14	3	11
Preliminary	Magnesium sulfate injection	39	35	4
Confirmatory		5	5	0

Possible reasons for the inconsistency of test results of pH measurements are listed below:

- Immaturity of the QMS in the laboratory.
- The buffer solutions used to verify the pH meters at that time were not traceable, and the pH meters were not calibrated.
- No SOP for the pH meter and training record assessment.

The last two issues were identified during the rapid assessment conducted during the testing period in Q2. This has since been addressed as the staff have been trained and SOPs were developed for pH.

PQM has continued to strategically push for implementation of the recommended next steps outlined to DNF/LNCQM after the PMS. PQM and DNF are working toward holding the dissemination meeting in September 2018.

In Q4, PQM built capacity of DNF, LNCQM, and key stakeholders in the supply chain management systems of medicines on the concept, methodology and implementation of risk-based approaches to PMS. This approach would help Mozambique to prioritize scarce human and financial resources, assist DNF and other partners in strategic planning, and select products and sampling sites. PQM also provided training on protocol development. The workshop was conducted using interactive lectures, hands-on-training, and case studies. Development of the draft protocol for the FY 2018 PMS activity was started during the workshop. Workshop attendees were drawn from MOH; DNF; LNCQM; Central Medical Stores (CMAM): national HIV, TB, and malaria programs; WHO; and Quntrol Laboratories India (the company responsible for conducting pre-shipment inspection, testing, and certification of pharmaceuticals sourced from India). A total of 18 (15 females and 3 males) people participated in the workshop.



Interactive lectures, hands-on training, and case studies presented during the risk-based approaches to PMS workshop

Additionally in Q4, PQM supported DNF to convey a medicines quality post-marketing review meeting, which was conducted to disseminate and discuss the results of the oxytocin PMS conducted in 2017 and oxytocin and magnesium sulfate PMS conducted in 2018. Several presentations were made during this meeting to increase awareness on the work of DNF, LNCQM, and PQM in delivery of quality health services. With PQM's support, the results of the PMS activities were combined and presented by the Head of LNCQM. During the question and answer session, many interesting questions were asked, including the following:

- What regulatory actions have been taken?
- What mechanisms are in place to monitor quality of medicines?
- Where was the country of origin of the failed drugs?
- What are the ideal storage conditions for oxytocin injection and other products?

PQM and other stakeholders encouraged DNF to take regulatory actions as a deterrent to importing poor-quality medicines. The meeting was attended by 41 individuals (28 females and 13 males) drawn from WHO, DNF, LNCQM, CMAM, provinces (Maputo, Sofala and Nampula), MOH, National Programs (of HIV, TB, and Malaria), health facilities (public and private), the USAID local Mission, and PQM.

Objective 3 – Provide technical assistance to the Pharmaceutical Department

In Q4, PQM continued providing technical support to DNF to support the transition to an MRA according to the newly approved national pharmaceutical law. PQM has consistently motivated DNF to develop robust regulations that would empower the directorate to deliver quality-assured medicines to Mozambicans.

PQM received and made valuable technical inputs to the current law vis-à-vis the Africa Union model law on medical products regulations, internal regulation for DNF (structure and functions), and internal regulation for LNCQM (structure and functions). The comments and recommendations on the law and regulations were summarized and shared with DNF and LNCQM in addition to resource materials. The DNF inspectorate department shared its draft regulation with PQM for technical inputs and review.

Though the pharmaceutical law has been passed, PQM technical team reviewed the law against the recently published African Union law on medical products regulation. They identified gaps, errors, and additions that needed to be adjusted to make their law compliant with the AU law.

Objective 4 – South–South collaboration with SADC countries and PALOP countries

No updates this quarter.

Nigeria

I. Quarter 4 Highlights

As a result of PQM's technical assistance, the NAFDAC Kaduna Area Laboratory received the ISO 17025:2005 accreditation certificate for 13 scopes by a third-party audit accreditation body, ANAB, having resolved minor nonconformances identified during the audit.

Through the PQM Nigeria program, USP donated laboratory equipment to Nnamdi Azikwe University to help build a pipeline of professionals who will advance the country's capacity to support the manufacture of quality-assured priority medicines.

II. Country Context

Through PMI funding, USAID/Nigeria is focused on strengthening NAFDAC's regulatory capacity and increasing the availability of locally manufactured quality-assured antimalarial medicines. This supports PMI's overarching goal to reduce malaria-associated mortality by 50 percent in Nigeria.

Through Maternal and Child Health funding, USAID/Nigeria is also working to increase the availability of medicines for MNCH in support of the UN Commission on Life-Saving Commodities for Women and Children. The Commission was established in April 2012 to improve access to affordable medicines and supplies essential to the health and welfare of women, newborns, and children under the age of 5—populations who most often die of preventable causes. The Commission recommended 13 essential health commodities for women and children that it considered will have the greatest impact on achieving health-related UN Sustainable Development Goals.

The overall goal of PQM in Nigeria is to strengthen NAFDAC's regulatory capacity and increasing the supply of locally manufactured quality-assured priority medicines. To accomplish this, PQM will continue to provide technical assistance to NAFDAC, the Federal Ministry of Health, the Pharmacists Council of Nigeria, the National Institute for Pharmaceutical Research and Development (NIPRD), and the National Malaria Elimination Program. In addition, the activities of pharmaceutical and nutraceutical manufacturers and other stakeholders directly impact system strengthening of NAFDAC and PQM-supported local manufacturers.

III. Quarter 4 Progress by Objective

Objective 1 – Increase support to NIPRD laboratory toward attaining international standards of quality and practices

In Q4, USAID/Nigeria Deputy Mission Director Dr. Erin Holleran presented Minister of State for Health Dr. Osagie Ehanire a certificate of ISO 17025 accreditation for six test methods on behalf of the (NIPRD) laboratory. The laboratory is responsible for pharmaceutical research and development of local phytomedicines (the use of plants, parts of plants, and isolated phytochemicals for the prevention and treatment of various health concerns) in Nigeria. It is the first non-regulatory and the fourth laboratory to be ISO accredited as a result of PQM's technical assistance in Nigeria. "USAID has long supported the Nigerian pharmaceutical manufacturing sector to ensure it meets international best practices," Dr. Holleran said at the ceremony. This accreditation should open up new opportunities for research into quality medicines and increase public confidence in the medicines manufactured, prescribed, and sold in the country.

Two NIPRD staff participated in a PQM-planned advanced training on instrument maintenance during the quarter. The trained staff will constitute the agency's meteorology team that will help sustain PQM's efforts at NIPRD. This capacity is critical for maintenance of equipment and will lead to cost savings for the agency as it takes over this necessary prerequisite for maintaining its laboratory accreditation status.

Objective 2 – Strengthen the national quality assurance and regulatory system

NAFDAC's National Control Laboratory for Vaccines and other Biologicals (NCLVB) is the only regulatory laboratory in the country responsible for the QC of vaccines and biologicals in Nigeria. When accredited, the laboratory will provide quality testing for vaccines that are locally manufactured and imported into the country. Following the gap assessment conducted last quarter, PQM provided technical assistance toward establishing a QMS and in preparation for ISO/IEC 17025 accreditation of the laboratory this quarter. Technical assistance included:

- The nonconformances identified during the gap assessment conducted in Q3 were addressed.
- Training was provided for 21 staff (11 females, 10 males) on QMS toward ISO/IEC 17025 accreditation. Topics covered included writing and implementing effective SOPs, good documentation practices, GLP, root cause analysis, CAPA, handling out-of-specification (OOS) test results, proficiency test/inter-laboratory comparison scheme, internal Q checks, QMS, and roadmap toward 17025 accreditations. Pre- and post-tests showed knowledge improvement on the subject matter with an increase from 73 percent to 86 percent.
- Another training on compendial techniques was provided for 17 staff (8 females, 9 males). Topics covered laboratory safety, proper use of pharmacopoeia, UV-Vis absorption spectrophotometry, volumetric titration, pH measurement, measurement uncertainty. Pre- and post-tests showed knowledge improvement on the subject matter with an increase from 67 percent to 93 percent.
- PQM commenced equipment calibration and procurement of reagents and equipment in preparation for ISO 17025 accreditation. PQM facilitated the procurement of an ultra-low freezer (-80°C) for the laboratory. This cooling device is crucial for conducting QC tests in the laboratory
- PQM reviewed technical and QA documents, including SOPs for measurement uncertainty, document control, review of request, subcontracting of tests, purchase of service and supplies, handling of laboratory service to customers, handling complaints, handling of test items, and quality manuals. Next steps include preparation of the laboratory to participate in proficiency tests and a mock audit scheduled for next quarter.

As part of PQM's sustainability of efforts made in laboratories, training on performance verification of equipment was conducted for 12 (all males) instrumental maintenance staff from 6 laboratories, including NAFDAC Agulu, Yaba, Oshodi, Kaduna, Biologics, and NIPRD. In line with building a pipeline of professionals, a staff member from the laboratory unit, faculty of pharmacy, Nnamdi Azikiwe University participated in the training. Topics covered included balance performance verification, HPLC/UPLC performance verification, UV-Vis spectrophotometer performance verification, and timer performance verification. The training was a hands-on demonstration and will be crucial for equipment maintenance in the laboratories.

Last quarter, an activity startup meeting with NAFDAC monitoring and evaluation (M&E) champions was held to develop a roadmap for the pharmaceutical M&E plan. A detailed assessment of NAFDAC's M&E system was conducted, and results revealed an ambiguous reporting system, untimely reporting of data, and a poor data storage system. PQM conducted a Pharmaceutical M&E Plan workshop to develop performance monitoring indicators and clearly articulate goals, targets, and methods of data collection and management to help improve the use of data for evidence-based decision-making in the regulatory agency. The workshop was attended by 49 NAFDAC staff from all pharmaceutical-related directorates. The next steps are to provide technical assistance to the NAFDAC M&E team, design and adopt an improved data reporting system, and conclude the draft plan and share it with the NAFDAC Director General by FY 2019 Q2.

Objective 3 – Provide technical assistance to selected manufacturers with strong interest and commitments to locally manufacture products of interest (zinc sulfate tablet, oral rehydration salts, chlorhexidine, amoxicillin dispersible tablet, artemether-lumefantrine, oxytocin injection, magnesium sulfate injection, and ready-to-use therapeutic food) to successfully register their products at NAFDAC

PQM continued to provide technical assistance to 10 local manufacturers, including Emzor Pharmaceuticals, to improve quality that will yield increased interest in local procurement for sulfadoxine 500 mg and pyrimethamine 25 mg by Medicins Sans Frontieres (MSF) and the Medical Export Group (MEG). PQM's tailored assistance has continued to impact positively on the overhaul of Emzor's QMS to comply with WHO GMP standards. MSF has indicated it would conduct a GMP assessment of Emzor's Richfield plant as part of its intention to procure sulfadoxine 500 mg and pyrimethamine 25 mg. Emzor received an additional procurement order from MEG for clotrimoxazole 120 mg and 960 mg for treatment of opportunistic infection in HIV. It will be distributed to health programs implemented in Nigeria.

Other activities carried out in Q4 included:

- PQM presented on systems strengthening of Nigeria's pharmaceutical sector at a regional workshop on scale-up of chlorhexidine gel 7.1% in Nigeria organized by Drug Field Pharmaceuticals. In attendance were representatives from USAID/Nigeria, FMOH, pharmaceutical distributors from Francophone West Africa (Benin, Burkina Faso, Niger, Togo, Ivory Coast, Senegal, Mali, and Guinea), and other implementing partners, including the Maternal Child Survival Program, PATH, and Bill & Melinda Gates Foundation.
- PQM collaborated with NAFDAC to conduct a workshop on current best practices for MRAs. It covered topics such as regulatory reliance, data standards in CTD submission, and models for inspection and approval. The PQM team made recommendations to NAFDAC to adapt the concepts discussed at the workshop, as they will position NAFDAC greatly among contemporaries in the continent.
- In the last 2 years of implementation, PQM provided continuous technical assistance to Juhel Pharmaceuticals for production of oxytocin and magnesium sulfate injection, which has increased procurement interest by MEG for the products. PQM also met with the management of Juhel Pharmaceuticals to provide guidance on their application to WHO for the PQ of USAID priority MNCH medicines (oxytocin injection and magnesium sulfate injection). PQM highlighted the guidelines and critical steps involved in the preparation of the product dossier for submission to WHO for PQ of oxytocin injection. The management of Juhel Pharmaceuticals confirmed their commitment to this project. The PQM GMP team developed a roadmap with timelines for WHO PQ of oxytocin, which was shared with the management for their commitment and buy-in of the process.
- PQM provided guidance to Swipha on WHO PQ requirements for artemether–lumefantrine, zinc DT, ARVs, and anti-TB medicines.
- PQM conducted a 4-day workshop on dossier compilation for professionals from a cross-section of the pharmaceutical industry and academia. Participants included staff from Juhel Nigeria Ltd, Drug field Pharma Ltd, Daily Need Industries Ltd, Dana Pharmaceuticals Ltd, Neros Pharmaceuticals Ltd, Swiss Pharma Nigeria Ltd, Ranbaxy Nigeria Ltd, Fidson Health Care Plc, May and Baker Plc, SKG Pharma Nigeria Ltd, Emzor Pharmaceutical Industries Ltd, AfrabChem Nigeria Ltd, Phamatex Industries Ltd, Tuyil Pharma Nigeria Ltd, Nemel Pharma Nigeria Ltd, Department of Pharmaceutics and Pharmaceutical Technology and Department Clinical Pharmacy of the Faculty of Pharmacy University of Lagos Nigeria.
- The Chairman of the Pharmaceutical Manufacturers Group of the Manufacturers Association of Nigeria (PMGMAN) acknowledged and appreciated the support of the PQM program to local manufacturers during his opening remarks. The 4-day workshop covered the overview of CTD structure modules 1 to 5, the architecture of each module, the sub-modules and how they are interrelated, data on APIs, FPP data, patient information leaflets, requirements for bioequivalence and the bio-waiver using the biopharmaceutical classification system (classes 1 to 4). Next steps after the workshop include compilation of dossiers for products by PQM-supported local manufacturers.

Objective 4 – Strengthen human capacity of academia

In the last three quarters, PQM maintained a partnership with the Faculty of Pharmacy of Nnamdi Azikwe University in Awka to provide technical leadership, experience sharing, and professional networking to both lecturers and students. The partnership has contributed to capacity-building of professionals in the country. PQM participated in a 2-day workshop on current GMP organized by the Faculty of Pharmacy for local manufacturers in the southeast geopolitical zone of the country. The workshop was attended by participants from Alben Pharmaceuticals, Nemel Pharmaceuticals, and the drug compounding unit of the Nnamdi Azikwe University Teaching Hospital. Topics covered included good documentation practice, data integrity, managing nonconformance, GMP in production and QC, and experiences from WHO PQ inspection of manufacturers.

Through the PQM Nigeria program, USP donated laboratory equipment to Nnamdi Azikwe University as part of its contributions to building a pipeline of professionals who will advance the country's capacity to support the manufacture of quality-assured priority medicines.

Equipment donated included:

Quantity	Equipment
1	Mettler Toledo Analytical Balance AT201 with Power supply, reference manual and declaration of conformity and operation instruction

1	Mettler Toledo MT5 analytical Micro Balance with power supply
1	Mettler Toledo DL38 Karl Fischer
1	Fisher scientific stirrer hotplate

The PQM Nigeria Chief of Party, USP Global Public Health Senior Vice President, and PQM Senior Director made a courtesy visit to the Pharmacists Council of Nigeria (PCN). PCN is responsible for regulating and controlling the education, training, and practice of pharmacy in Nigeria. The aim of the visit was to identify areas of partnership to strengthen implementation of the Pharmaceutical Quality Assurance (PQA) curriculum in Nigerian universities. Identified areas of partnership include the provision of technical assistance to improve training curriculum used by PCN for continuing professional development courses for pharmacists in line with the PQA curriculum. The PCN registrar commended PQM for its interest in enhancing the quality of professionals in the supply chain sector of the country. He further described the area of collaboration as part of his administration's four-point agenda, which included regulation of education, training, and practice of pharmacists and non-pharmacists in the pharmaceutical landscape of the country to ensure better service delivery.

Next steps include implementation of the PQA curriculum in two Nigerian universities and technical assistance to review PCN's curriculum, which are scheduled for next quarter.

Senegal

I. Quarter 4 Highlights

As part of strengthening LNCM's toward ISO 17025 accreditation, in Q3, PQM provided technical assistance for the qualification of selected laboratory equipment under the scope of ISO accreditations. Having qualified equipment ensures reliable QC testing results. In Q4, PQM provided preventive maintenance technical assistance to assist the laboratory in addressing the recent PQM audits, as well as calibration of the metrology laboratory equipment. This has been helpful to move the agenda of the laboratory toward accreditation, but it was not sufficient to get the laboratory assessed by the accrediting body TUNAC. PQM alerted the LNCM director about this issue and requested that the laboratory address PQM findings by November 2018.

PQM provided technical support to DPM's registration department to harmonize importation data with registered products data to enable DPM to better monitor imported medicines in the country.

For PMS activities, the FAA was approved and its implementation by LNCM is underway.

II. Country Context

Since the beginning of its involvement in Senegal in 1979, USAID has supported development of the health system to help improve maternal and child health, fight infectious diseases, and make health services accessible to the Senegalese population at large. Malaria remains a major cause of morbidity and mortality and is a high priority for government programming. Malaria is endemic throughout Senegal, and the entire population is at risk. The country has made significant progress against malaria and remains a leader in piloting and scaling up new recommendations and innovative strategies. In this context, USAID is expanding integrated health services countrywide through PMI.

In collaboration with DPM, the regulatory authority, in August 2015 PQM organized an Inter-Ministerial Workshop on Reinforcing Regulatory Actions against Counterfeit and Substandard Medicines that included illicit markets. The main objective of the workshop was to develop a roadmap with an enforceable action plan detailing how to join efforts among DPM and other enforcing entities. One recommendation included the organization of an operation called "Coup de Point" to eradicate at least one illicit market in Senegal in addition to the one in Dakar that had been removed in 2012. As of April 2016, PQM has participated in strategic planning on how to execute this activity jointly with IMC members. Delays in receiving PMI funds pushed PQM to execute this activity in late 2016.

As part of strengthening LNCM's QC capacity, in 2014 PQM performed an audit of the laboratory that revealed the following problems: inadequate QMS; inability of skilled laboratory staff to maintain their roles and responsibilities in the laboratory due to university work commitments; lack of motivation that led staff members not to fulfill their assigned duties; insufficient laboratory staff with the technical capacity to conduct QC testing of medicines according to compendial methods; delays in procuring laboratory equipment; lack of equipment maintenance and services leading to non-calibrated analytical balances and improper use of verification and calibration tools; lack of fully employed personnel, as opposed to contractual staff, which led to high turnover; periodic turnover and restructuring; hindered progress toward ISO 17025; and the need for five additional full-time, trained, qualified staff in the physical chemistry group.

Under the new LNCM leadership, some of the deficiencies listed above have already been addressed. The LNCM Director restructured the organization and defined new roles and responsibilities for staff. Following the interventions of the PMI advisor, LNCM Director, and MOH Director of Health, the status of two laboratory staff members was changed from contractual to full-time employees.

Presently, the laboratory management seeks to pursue compliance with international standards and attain WHO PQ or ISO 17025:2005 accreditation.

III. Quarter 4 Progress by Objective

Objective 1 – To support the LNCM in building its capacity toward ISO 17025 Accreditation

PQM provided a series of technical support to LNCM with the goal of preparing the laboratory for the official audit by the accrediting body TUNAC. PQM first reviewed the CAPAs implemented to resolve the previous PQM audit findings. PQM also provided technical assistance to address some of the findings, witnessed analytical testing under the scope of LNCM accreditation, and assessed the capability of the QMS updates implemented to fulfill the revised ISO/IEC 17025:2017 standard requirements. In the second intervention, PQM assessed the status of the laboratory equipment under the scope of ISO accreditation, provided advanced maintenance training to selected LNCM staff, and performed troubleshooting on HPLC, UV-Vis, and dissolution tester. In the last intervention, PQM conducted calibration of the LNCM metrology equipment and provide hands-on training on:

- Balances performance verification
- UV-Vis spectrophotometer performance verification
- HPLC performance verification
- Dissolution performance verification testing
- USP Analytical Instruments and Qualification <1058>

The calibration of the above laboratory equipment is intended to eliminate or reduce bias in an instrument's readings over a range for all continuous values. Calibrated equipment will help the laboratory analyst to get accurate and precise results in QC testing.

PQM has helped LNCM to improve its technical and managerial capacities, but this progress is insufficient to have the laboratory audited by TUNAC next quarter. PQM raised this issue with the laboratory director and PQM internal management. PQM shared the technical report that include critical, major, and minor technical and managerial findings that the laboratory needs to address by the end of November 2018.

Objective 2 – Adoption of the risk-based PMS system by the LNCM

To ensure direct implementation and sustainability of the PMS activities, USAID granted LNCM its first FAA. Following the FAA approval process, LNCM, with the guidance of PQM, is working to implement the first milestones of the FAA, which include meeting with key stakeholders to identify the samples to be tested and discuss the sampling strategy and QC testing using a risk-based PMS protocol.

Objective 3 – Support DPM in improving its regulatory function

To continue building the capacity of DPM to perform its main functions, PQM provided technical assistance to the registration staff in addressing the identified gaps on the use of SIAMED software and updated the directory of the registered products. PQM also provided assistance to effectively harmonize the importation data with the registered products, which will enable DPM to better monitor imported medicines and allow entry of only registered medical products into the Senegalese market. To maintain the effectiveness of registration activities, PQM also trained the DPM IT department to understand the required data fields and processes for the tools deployed to support registration and importation of medicines activities.

West Bank and Gaza

I. Quarter 4 Highlights

To build the capacities of the regulatory authority, General Directorate of Pharmacy (GDP), and pharmaceutical control laboratory (CPHL), PQM conducted a 2-week assessment of the QA/QC of these government entities in Q2.

These assessments provided a clearer picture of the strengths and gaps in the legal framework and regulatory functions of the GDP and the technical capacities of CPHL toward ISO 17025 accreditation. In Q3, PQM shared the outcomes of the assessments with the Mission and key stakeholders, including GDP and CPHL directors, and provided recommendations on how to address the identified gaps. Based on the assessment outcomes, PQM provided a series of instructional and hands-on training to the pharmaceutical laboratory staff and initiated the launch of the PMS program by providing training and guidance on the establishment of a risk-based PMS. PQM also worked with both entities to streamline sampling and testing processes for medicines, encouraging both entities to meet regularly and to have GDP QA staff work closely with CPHL during the validation process for medicines registration.

In Q4, PQM followed up with the laboratory to be part of NOMCoL activities and to procure the needed laboratory equipment and supplies for the upcoming training. Based on internal recommendations, a local vendor was selected, and due diligence was completed by PQM. For NOMCoL activities, the WHO office in Jerusalem was instrumental in facilitating the shipment of medicines for testing as part of the ILT.

Next steps include providing technical assistance support to strengthen GDP's legal framework and policies, and to improve the registration unit activities to align with international standards. PQM also plans to commence preparations for GDP's inspectorate and clinical departments' trainings.

II. Country Context

PQM has provided technical assistance in the areas of QA and QC, regulatory systems support, and current GMP. In 2015, the PQM program conducted an assessment of manufacturing services in the Palestinian Territory of West Bank and Nablus. However, due to continuous uncertainty in the region, after that visit the PQM program could not undertake additional activities in the area for more than 2 years. In FY 2017, the USAID Mission in Israel, with responsibility for West Bank programming, provided funding for PQM to initiate activities in the West Bank. The focus builds on past PQM efforts to provide a comprehensive systemic approach in building the capacity of the regulatory agency to protect people's health by ensuring the availability of quality-assured medicines.

III. Quarter 4 Progress by Objective

Objective 1 – Strengthening the General Directorate of Pharmacy's organizational structure and regulatory functions

This quarter, PQM shared with the Mission and the stakeholders the reports on outcomes of the QC/QA assessments of CPHL and GDP. The main outcomes of the assessment of GDP included the gaps identified in the legal framework and policies that required either revisions and/or development. For LNCM, the technical and managerial findings were shared with laboratory director and his staff, along with an action plan on the technical assistance that PQM would provide that will help move forward the agenda of laboratory accreditation and WHO PQ.

In FY 2019 Q1, PQM plans to carry out activities geared toward revisions of the pharmaceutical policies and regulations based on the outcome of the GBT assessment.

Objective 2 – Strengthen the regulatory capacity of the General Directorate of Pharmacy, MOH Palestinian Authority (PA) for improved control and management of pharmaceuticals including but not limited to registration and inspection

As part of strengthening GDP's capacities, PQM is planning to provide technical assistance for the registration department. One of the limiting steps to carry out this assistance is the installation of the SIAMED for GDP by WHO. Currently, communication is in progress between GDP and a local WHO representative to facilitate the visa application and other travel logistics of a WHO expert to the country.

After its installation, PQM will provide the necessary technical support to optimize its proper use for data harmonization and accessibility by end users from different GDP units, including QA, registration, and inspection.

In FY 2019 Q1, PQM plans to strengthen the capacity and skills of the registration team. This support will include technical assistance to develop guidelines and the SOPs for registration/marketing authorization, renewal and variation/amendments and to provide training in good review practices based on the WHO recommendations. This technical assistance will help address some of the identified assessment gaps and improve the registration processes to meet international standards.

Objective 3 – Raise the technical capacity of the General Directorate of Pharmacy, MOH PA to apply to become a member of the regional pharmaceuticals schemes such as the PIC/S and/or to WHO regional initiatives

Nothing to report this quarter.

Objective 4 – Provide direct support to national quality control laboratory (CPHL) toward achieving QMS leading to international ISO/IEC 17025:2005 accreditation and/or WHO PQ of the laboratory

CPHL is a member of USP's NOMCoL-MENA. One of the activities of the network is ILT. This test is important and helpful in evaluating the performance and/or competence of CPHL staff for testing against other laboratories of the NOMCoL Network and to assure that analytical test results generated by CPHL are accurate, precise, and reliable. Participation in NOMCoL-MENA ILT is a platform to prepare and help CPHL become cognizant of its competencies and support preparation in achieving international standard such as ISO/IEC 17025 and/or WHO prequalification. Toward this goal, PQM, with help of the WHO office in Jerusalem, was able to ship the needed medicines and laboratory supplies to support the NOMCoL ILT activity.

Also, to support the CPHL for the upcoming compendial trainings, PQM procured the needed laboratory supplies and consumables and is expected to be delivered to CPHL by the local vendor Technoline next month.

Objective 5 – Provide support to local pharmaceutical manufacturers by supporting compliance with PIC/S

Nothing to report this quarter.

IV. Key Challenges

- Limited direct communications with the key stakeholders.
- Procurement process is tedious and requires several layers of communications and clearance.
- Travel logistics requires a lengthy process to get travel visa to West Bank.

Asia



Bangladesh

I. Quarter 4 Highlights

PQM's activities in FY 2018 Q4 were focused on the implementation of objectives 1, 3, and 4 in the approved work plan and remaining activities from last quarter. On September 3–5, the National Control Laboratory (NCL) successfully completed the ANAB audit toward ISO 17025:2017 accreditation for its physio-chemical laboratory. NCL subsequently developed a CAPA plan and submitted it to the assessor for review. NCL also conducted a customer satisfaction survey toward assessing its service quality. Q4 highlights include the following:

- On July 1–4, NCL analysts attended a training on uncertainty measurement facilitated by PQM to comply with ISO 17025:2017 requirements; the training was held at a third-party accredited laboratory, Plasma Plus. The 16 participants (8 males and 8 females) were trained on how to calculate uncertainty measurement on results generated during testing. They were trained on six scope tests: HPLC, pH meter, loss on drying (LOD), UV-Vis, balance, and dissolution. After completing the training, they performed uncertainty measurement by themselves at their laboratory, toward increasing reliance of test result for customers' satisfaction.
- In April 2018, it was identified that NCL had a critical need of a vacuum oven to perform LOD testing, as this is 1 of the 10 tests included in the scope for ISO accreditation. As per NCL's request, PQM provided a vacuum oven that was received in July 2018. PQM Bangladesh staff trained the principal analysts to perform the LOD test. PQM also provided a balance to support another test included in the scope, Karl Fischer titrator for water content measurement.
- In July 2018, PQM Bangladesh conducted a practical demonstration on the 10 tests included in the scope of ISO 17025:2017 accreditation (HPLC, UV-Vis, dissolution, pH, LOD, DT, TLC, uniformity of dosage units, infrared, and Karl Fischer) for the analyst at NCL associated with each test. Their testing competency and standard practices toward compliance with ISO 17025:2017 was checked. NCL documented all the gaps and suggestions provided by PQM during the demonstration and staff skill assessment and took the necessary actions for readiness toward the ISO 17025:2017 audit by ANAB planned for September 3–5.
- In August 2018, NCL conducted a customer satisfaction survey. Fifty-six customers took part in the survey, made comments, and indicated areas for improvements. PQM supported NCL on how to address and prepare the response to the clients, including the actions taken by NCL as a part of its continual improvement process. The mean score against the customer comments to NCL was over 4, which indicates "satisfied, needs minor improvement of NCL."
- On September 3–5, NCL successfully completed the ANAB audit toward ISO 17025:2017 accreditation for its physio-chemical laboratory. NCL subsequently developed a CAPA plan and submitted it to the assessor for review.
- On July 19, DGDA organized a meeting facilitated by PQM toward selecting potential manufacturers for first-line anti-TB medicines in the country. The Bangladesh Association of Pharmaceutical Industry (BAPI) agreed to take the lead in bringing the manufacturers interested in producing first-line anti-TB medicines. Four private and one government-owned company were present at the meeting.
- Jude I. Nwokike, PQM Senior Director, visited Bangladesh on September 13–14 to provide guidance to the Bangladesh program team about program implementation, strategy formulation, and government relations, and also to meet high-level officials from different stakeholders. During his visit, Mr. Nwokike met with the DGDA Director General, Directorate General of Health Services Director General, Nutrition Director General, and Pharmacy Council Bangladesh (PCB) Vice President to enhance relations with the government and update them on PQM activities in Bangladesh. He also met with Mohamed Ramzy Ismail, WHO Technical Officer, and Dr. Samina Choudhury, USAID Activities Manager. Mr. Nwokike joined a staff meeting and provided guidance to PQM Bangladesh for the PQM closeout and implementation of FY 2019 work plan activities, particularly objective 2, which focuses on technical assistance to local manufacturers.
- PQM's Asia Regional Manager and PQM Bangladesh staff attended the WHO Coalition of Interested Partners (CIP) meeting on September 23–24 in Dhaka. PQM provided a programmatic progress update and detailed how PQM activities impact NCL and DGDA functions toward achieving international standards such as ISO 17025:2017 and WHO PQ.

- PQM staff assisted in developing SOPs, key documents, and CAPA implementation. In Q4, 9 new SOPs were developed and implemented, and 21 CAPA were closed toward achieving compliance with the internationally recognized standard ISO 17025:2017.
- In Q4, NCL staff were trained on key operation areas of the laboratory by local experts, through hands-on and theoretical trainings.

II. Country Context

PQM's goal in Bangladesh is to strengthen the institutional capacity for sustainable regulatory and QA/QC systems to operate in compliance with international standards. To achieve this goal, PQM has developed strategic objectives based on a PQM gap analysis conducted in April–May 2016, as well as discussions and consultations with the USAID Bangladesh Mission, DGDA, SIAPS, and other relevant partners/stakeholders.

III. Quarter 4 Progress by Objective

Objective 1 – Continue to provide technical assistance to the DGDA laboratory – NCL in Dhaka and DTL in Chittagong toward achieving international ISO/IEC 17025:2017 accreditation or WHO PQ

In terms of laboratory capacity-building, PQM has been providing technical guidance/input to NCL to strengthen its QMS toward attaining compliance with ISO 17025:2017 and accreditation.

PQM worked alongside NCL management and technical staff to follow up on its progress in the CAPA plan developed based on the findings from an internal audit and a PQM audit. In Q4, CAPAs were addressed, and ongoing support was provided to close some of them.

With the assistance of PQM technical staff in Bangladesh, NCL developed SOPs to improve internal processes toward achieving compliance with international standards. PQM also provided support to review OOS, deviation, and change control reports around investigation, root cause analysis, risk assessment, and an action plan. Logbooks were reviewed accordingly. The following are some key accomplishments during this quarter:

- On July 1–4, NCL analysts attended a training on uncertainty measurement facilitated by PQM to comply with ISO 17025:2017 requirements; the training was held at a third-party accredited laboratory, Plasma Plus. The 16 participants (8 males and 8 females) were trained on calculating uncertainty measurement on the generated result during testing. They were trained on six scope tests: HPLC, pH meter, LOD, UV-Vis, balance, and dissolution. After completing the training, they performed uncertainty measurement by themselves at their laboratory, toward increasing reliance of test result for customers' satisfaction.
- In July, PQM Bangladesh conducted practical demonstrations on 10 tests included in the accreditation scope (HPLC, UV-Vis, dissolution, pH, LOD, DT, TLC, uniformity of dosage units, infrared, and Karl Fischer) for the NCL analyst associated with each test, to check their testing competency and standard practices toward compliance with the ISO 17025:2017 standard. During the hands-on demonstration sessions, the analysts performed their routine tests following compendia (USP or British Pharmacopeia). PQM staff observed the analytical activities, recordkeeping, personal protective equipment use, and quality of documents (e.g., SOPs, logbooks, daily calibration/verification, calibration reports, labelling, qualification documents). After the demonstration, the identified gaps in practice and documentation were shared with the respective analysts and management. The NCL authority documented



PQM Bangladesh staff demonstrating on analytical techniques on July 2018 at NCL Lab. Photo credit: Tabassum Munira



NCL staff with assessor after successful completion of ISO 17025:2017 inspection on September 3–5 at NCL Lab

all the gaps and suggestions and took the necessary actions toward readiness for the ISO 17025:2017 ANAB audit that was planned for September 3–5.

- In Q4, PQM Bangladesh conducted refresher trainings as an immediate response to NCL’s request, focusing on the upcoming ISO 17025:2017 assessment. The summary of quarterly progress and training lists are included below.
- On September 3–5, NCL successfully completed the ANAB audit toward ISO 17025:2017 accreditation for its physio-chemical laboratory and subsequently developed a CAPA plan, which was submitted to the assessor for review.

Summary of Laboratory Progress from July 1 to September 14, 2018

PQM staff assisted in developing SOPs, reviewing key documents, following up on CAPAs implementation, and equipment calibration

Items	Number of Items completed
Approved and implemented SOP through PQM review	08
CAPA status in FY 2018 Q4:	
CAPA generated during Q4 (Jul to Sep-2018) based on the observations by an internal audit done on Jun 2018 (18) (CAPA No.: CAPA/MB/034/JUL/18 – CAPA/MB/051/JUL/18)	Completed: 10 (10 in Q4). Remaining 08 CAPA under follow up
Total remaining CAPA up to July 2018:	
CAPA from PQM audit (2017) (24) (CAPA No.: CAPA/CD/004/17)	Completed: 24 (03 in Q4).
CAPA from NCL Internal Audit – March 2017 (28) (CAPA No.: CAPA/MB/003/17)	Completed: 26 (01 in Q4); Under follow up: 02
CAPA from NCL Internal Audit - June 2017 (26) (CAPA No.: CAPA/CD/005/17)	Completed: 26 (03 in Q4).
CAPA from NCL Internal Audit on November 2017 (09) (CAPA No.: CAPA/NCL/009/17)	Completed: 09 (01 in Q4).
CAPA from PQM assessment on November 2017 (13) (CAPA No.: CAPA/CD/(008,010)/FEB/18)	Completed: 11 (02 in Q4) Pending: 02 to be followed up
CAPA from NCL Internal Audit on March 2018 (04) (CAPA No.: CAPA/DW/014/MAR/18)	Completed: 04 (01 in Q4).
Deviation Report review from Jul to Sep-2018	06
Out of Specification report review from Jul to Sep-2018	06
Discontinuation report of analysis review from Jul to Sep-2018	06
Change Control report review from Jul to Sep-2018	03
Calibration performed by NCL staff	1. Electronic balance (03 balances) 2. pH Meter (2 pH Meters) 3. DT (2) 4. KF Titrator 5. Vacuum Oven
Support to develop documents	1. Standard Testing Procedure for Doxophylline method validation 2. Standard Testing Procedure for Ranitidine method validation 3. Analytical Method Validation Protocol- Doxophylline

Summary of Trainings conducted in FY 2018 Q4

SL/ No.	Training	Date	Laboratory Designation	Gender	Total Trained	Technical Areas	Training conducted by
01	Measurement of Uncertainty Training	July 1–4	16 NCL	8M, 8F	16	ALS	Third-party laboratory Plasma Plus
02	Refresher training on analytical method validation and verification	July 15	04 NCL	2 M, 2F	04	ALS	Local staff
03	Refresher training on preparation and management of mobile phase and solvent	July 31	12 NCL	8M, 4F	12	ALS	Local staff
04	Refresher training on analytical method transfer/ Training on General Testing Procedure (GTP) and column management	August 5 and 9	12 NCL	9M, 3F	12	ALS	Local staff
05	Refresher training on preparing for external audit/ Refresher training on waste management	August 28 and 31	17 NCL	11M, 6F	17	QMS	Local staff
	Total in Q4			M=38 F= 23	61	ALS= 44 QMS=17	

Objective 2 – Provide technical assistance to local pharmaceutical manufacturers toward WHO PQ for priority MCH/FP and TB products

Based on the inspection conducted on December 26–27, 2017, ACI Limited submitted for review its CAPA plan against the observations. The evidence and completion statement from ACI were reviewed by HQ GMP staff and PQM Bangladesh staff. Subsequently, a final CAPA assessment report was submitted to ACI Limited on August 18, 2018.

On July 19, DGDA organized a meeting facilitated by PQM toward selecting potential manufacturers for first-line anti-TB medicines. BAPI agreed to take the lead in bringing the manufacturer interested in producing first-line anti-TB medicines. Square, Eskayef, Beximco, Delta, ACI and EDCL were present at the meeting. It was decided that NTP and DGDA would work together to identify ways to incentivize the industry to invest in PQ, and PQM would provide technical assistance to the selected manufacturer toward attaining compliance with international standards. BAPI assured it would call a meeting in September 2018 to make a decision regarding the selection of manufacturers.

Objective 3 – In collaboration with WHO, provide technical assistance to strengthen DGDA's regulatory functions

Several activities were implemented to enhance DGDA's regulatory capacity. These include strategic planning, human resources, international standards, and improved PMS.

- PQM Bangladesh continues to support DGDA functions, providing guidance and review of developed SOPs and guidelines. PQM provided support in five (of nine) functions: regulatory inspection, clinical trial, laboratory access, lot release, and marketing authorization. Support for marketing authorization as an extended scope started began in March 2018. Also, a risk-based PMS guideline is now under review by DGDA's PMS unit.

- In August 2018, PQM proposed two provisions to the proposed Drug Act 2018 based on the technical report provided by PQM Law Consultant Dr. Sauwakon Ratanawijitrasin in April 2018: (1) to use “good practices (GxP)” instead of “good manufacturing practices”/“(GMP)” to cover all good practices that will more accurately reflect the content and the intent of the law to mandate good practices that are critical to regulate activities throughout the supply chain under Chapter-IV, Section 20(1), and (2) to include product recall provision for the products distributed in the market for being substandard and/or falsified or for any adverse drug reaction occurred that included under Chapter-xii, Section 12(7). This proposed Drug Act is now under review by the Ministry of Law and Parliamentary Affairs.
- On September 16–20, a WHO assessor conducted the WHO interim benchmarking assessment, which aimed to assess and document the status of the Bangladesh vaccine and medicine regulatory system against the WHO GBT and measure the maturity level of the system. PQM Bangladesh staff actively participated in the five of nine functions for supporting the DGDA functional team. The assessment was successfully completed with good impression; i.e., adequate documents (SOPs, guidelines, training records) were found to be in place. The feedback of this assessment was presented by the lead assessor at the Coalition of Interested Partners (CIP) meeting on September 23–24. PQM Asia Program Manager Cheng Tiang Ng, along with the PQM Bangladesh team, attended this meeting and provided PQM programmatic progress update and detailed how PQM activities impact on NCL and DGDA functions toward achieving international standard i.e. ISO 17025:2017 and WHO PQ.



DGDA staff and stakeholders with Mohammad Nasim, Member of Parliament, Ministry of Health & Family Welfare, Bangladesh, after successful completion of CIP meeting on September 23–24 at DGDA, Dhaka

Objective 4 – Increase visibility and relevance of QA/QC in support to National Health Programs with the primary focus on MNCH, TB and FP programs

On August 30, PQM facilitated the first meeting of the Core Committee to support development of a National Quality Assurance Policy (NQAP) for quality-assured medical products at DGDA. Members from DGDA, PCB, Directorate General of Family Planning, BCDS, EDCL, USAID, and WHO were present in the meeting. Two key decisions were taken at the meeting. The first is that the document should be developed as a guideline and not as policy, because a policy needs Cabinet approval, which takes a very long time. Second, a small working committee will be formed to develop the draft of the guideline, and this committee will submit the draft to the core committee for review.

IV. Key Challenges

- Safety and security remain a concern in Bangladesh. Since June 2018, 1.2 million Rohingya refugees have arrived in the southeast region, near the border with Myanmar. The current Rohingya refugee crisis is a global concern. The PQM country focal person is working closely with the global security director to monitor the security situation.
- The upcoming Parliament election in December 2018 may affect implementation of PQM activities and meeting project goals and objectives (e.g. ISO accreditation, WHO PQ).
- Custom clearance of items donated by the donor organizations remains a challenge for DGDA to support the program in Bangladesh.
- The organizational registration process is taking longer than anticipated, hence limiting the visibility of operating the PQM office.
- Frequent changes in key positions in the government departments that collaborate with the PQM program remain a challenge for program implementation.
- Utilization of Government of Bangladesh resources, along with USAID support, is important. If government resources do not materialize as anticipated, achievement of overall program objectives is hampered.

V. Lessons Learned

Motivated leadership in key positions is critical for decision making and for sustaining organizational environment for good performance. Availability of motivated and skilled personnel is also key for success. Motivation of existing NCL and Chittagong Drug Testing Laboratory (cDTL) staff emerged as a concern in different observations. Special attention needs to be provided in identifying and resolving demotivation factors especially in NCL.

VI. Sustainability, Partner Contributions, and Ownership

DGDA, NCL, national priority health programs, Pharmacy Council, and the pharmaceutical industries are the prime stakeholders of the PQM program in Bangladesh, and PQM has been working closely with these partners. In the process, PQM is providing technical assistance to the MRA, NCL, and manufacturers to build institutional sustainability toward achieving compliance with international standards and ensure long-term public health benefits.

Indonesia

I. Quarter 4 Highlights

As of FY 2018 Q4, the BAST January–June 2018 (activity and equipment handover document with the government of Indonesia, as required by the Ministry of Finance) was requested and the draft completed, pending signature by USAID and the country's MRA, the National Agency for Drug and Food Control (Badan POM; (BPOM)). In Q4, PQM supported Kalbe Farma to complete its CAPA implementation following the WHO inspection in Q3, submitting full documentation and evidence to WHO with the aim of being listed as prequalified by WHO, Kalbe Farma successfully submitted evidence of its CAPAs to WHO on July 24. As of September, the PQ product has been included in WHO Public Inspection Reports. PQM also continued to support Sanbe Farma in its bid to have its levofloxacin 500 mg tablet prequalified by WHO. The product dossier will be submitted at the end of December 2018 (FY 2019 Q1). PQM conducted a mock audit of Sanbe Farma at the end of Q4, with audit findings pending as of submission of this report. In Q4, PQM embarked on an initiative to develop the external QA and QMS for the rapid diagnostic tests used by the HIV program in Indonesia under the authority of the Directorate Pengawasan Alkes DG Farmalkes and in collaboration with WHO and Chemonics' PSM program. PQM also continued to finalize the technical assistance plan for the Global Fund with the MOH HIV and TB programs.

II. Country Context

The PQM Indonesia program has conducted activities to strengthen the QA/QC systems of medicines to treat TB and HIV/AIDS in Indonesia since 2011 (with funding from the U.S. President's Emergency Plan for AIDS Relief (PEPFAR)/HIV starting in FY 2014). PQM Indonesia focused first on supporting selected local manufacturers of anti-TB medicines to strengthen their QA/QC systems and GMP toward achieving WHO PQ status. Beginning in 2013, the PQM program expanded its activities to support building the capacity of BPOM, additional private manufacturers of medicines to treat TB and HIV, and select local CROs for bioequivalence studies to improve their QA systems.

PQM has initiated WHO PQ projects with two government QC laboratories in Indonesia with the goal of achieving global recognition for its national QA system. BPOM's PTBB national QC laboratory is the first laboratory in Indonesia targeting WHO PQ, followed by the provincial BBPOM laboratory in Denpasar. Indonesia is well-positioned to provide regional leadership in ASEAN as a PIC/S country, with a large manufacturing sector and the largest pharmaceutical market in Southeast Asia. PQM initiated and has provided ongoing technical assistance to the BPOM laboratory with the goal of achieving WHO PQ, a status that demonstrates technical and operational excellence for regulatory QC activities.

PQM Indonesia's overall vision and strategic engagement with Indonesia is to support all aspects of medicines QA, from the point of manufacture or import, through the supply chain, down to the service delivery point. To this end, PQM Indonesia has designed a comprehensive approach to engage directly with manufacturers, regulators, government disease programs, supply chain specialists and warehouses, CROs, and official medicines QC laboratories across the country. This holistic approach ensures that quality is considered at all stages of the medicines life cycle, with the long-term aim of systematically developing robust and reliable QA/QC systems for promoting the quality of medicines in Indonesia, based on international standards. PQM is also working with the national Pharmacists' Association and other networks/associations to promote sustainable solutions for technical knowledge transfer, public awareness, and advocacy.

PQM receives field support funding through TB and PEPFAR funding streams from the USAID Indonesia Mission Office of Health.

Since 2011, PQM has conducted activities to strengthen the QA/QC systems of medicines to treat TB and HIV/AIDS in Indonesia (with PEPFAR/HIV funding starting in FY 2014). PQM focused first on supporting selected local anti-TB medicines manufacturers to strengthen their QA/QC systems and GMP toward achieving WHO PQ status. Beginning in 2013, PQM expanded its activities to build the capacity of BPOM, additional private manufacturers of anti-TB and anti-HIV medicines, and select local CROs for bioequivalence studies to improve their QA/QC systems.

PQM's overall vision and strategic engagement with Indonesia are to support all aspects of medicines QA from the point of manufacture or import, through the supply chain, down to the service delivery point. To this end, PQM has designed a comprehensive approach for engaging directly with manufacturers, regulators, government disease programs, supply chain specialists and warehouses, CROs, and official medicines QC laboratories across the country. This holistic approach ensures that all aspects of medicines quality are addressed, with the long-term aim to systematically develop robust and reliable QA/QC systems, based on international standards, for medicines in Indonesia.

III. Quarter 4 Progress by Objective

Objective 1 – To strengthen Indonesia’s medicines quality assurance system by supporting the MOH and BPOM regulatory, inspection, post-marketing surveillance, anti-counterfeiting investigations, and quality control (of national and provincial laboratories) functions with a focus on TB and essential medicines to achieve international standards of practice

Activity 1.1: Conduct an extensive onsite, preparatory mock audit of the PTBB National QC laboratory (POMN/BPOM) following submission of LIF to WHO for Prequalification

The PTBB national QC laboratory of BPOM is the first laboratory in Indonesia to target WHO PQ. Indonesia is well-positioned to provide regional leadership in ASEAN as a PIC/S country, with a large manufacturing sector and the largest pharmaceutical market in Southeast Asia. PQM initiated and has provided ongoing technical assistance to the BPOM laboratory with the goal of achieving WHO prequalification, a status which demonstrates technical and operational excellence for their regulatory QC activities.

In Q4, the BPOM national QC laboratory completed its CAPA implementation following the WHO inspection during Q3, with plans to submit CAPA completion evidence to WHO by mid-October 2018 (FY 2019 Q1). WHO informed the laboratory of its plans to conduct a follow-up inspection in December 2018. In preparation for this event, NQCL scheduled an internal mock audit for the end of September (findings pending as of the submission of this report) conducted by two BPOM staff (from the Registration Directorate and the Distribution Directorate). PQM will be onsite to assist, oversee, and help prepare the CAPA plan for the mock audit. In Q4, PQM conducted a training at the NQCL on Good Data and Record Management Practices referring to WHO TRS 996, Annex 1, 2016. This was one requirement assigned by WHO in support of addressing deficiencies in data integrity.

Activity 1.4: Continue to build capacity of Pool of Experts at PTBB as trainers for provincial BBPOM laboratories [FY 2018 topic “Deviation Handling”] to build QMS capacity

As part of PQM's support to strengthen the capacity of BPOM laboratories, on September 3–7, NQCL conducted a technical training for 16 provinces on HPLC, with a focus on testing impurities in AIDS, TB, and malaria medicines. This is an annual training, divided into 2 rounds of 16 provincial laboratory participants each. The second round will be conducted on October 1–5 (FY 2019). In addition to the impurities training, NQCL also shared good procedures on how to perform investigations for OOS testing results and deviation handling. The objective of sharing this procedure was to ensure that the provincial QC Laboratories can confirm their testing results when an OOS is found. Based on recent structural changes in the BPOM organization, the provincial QC laboratories are now responsible for OOS final test results, as there will no longer be confirmatory testing at NQCL.

Activity 1.10: Provide intensive training and technical assistance for WHO PQ Implementation Plan of the BBPOM Denpasar QC laboratory, including training on adopting procedures & compilation of LIF

In Q4, PQM helped the laboratory to review and revise key quality documents such as the quality manual and 42 other quality procedures. The quality manual and several quality procedures were produced bilingually (Bahasa and English) in preparation for submission to WHO. As part of the Denpasar implementation plan, PQM provided training on Good Data and Records Management Practices in reference to WHO TRS 996, Annex 1, 2016, which was conducted on September 12 with Therapeutic Laboratory personnel. The aim was to train laboratory personnel on data integrity in their laboratory activities. In addition to the data integrity training requirements for WHO, PQM facilitated the qualification and hands-on training on laboratory software (for primary equipment such as HPLC, gas chromatography, UV-Vis spectrophotometer, and FTIR). The training and qualification was conducted on September

3–7. On September 19–21, BBPOM Denpasar will conduct an internal audit program and PQM will act as auditor along with BBPOM staff. This internal audit program refers to ISO/IEC 17025:2017 and to WHO GPQCL TRS 957, Annex 1, 2010. PQM will make sure that all elements in WHO TRS 957 are in the internal audit check list and all WHO requirements are addressed and implemented accordingly.

Objective 2 – To increase the local supply of quality-assured TB medicines in Indonesia by providing technical assistance to selected pharmaceutical manufacturers and contract research organizations to achieve international standards, including GMP and WHO prequalification

Activity 2.1: Provide technical assistance to selected local manufacturers and the NTP for first- and second-line TB medicines focusing on government coordination, product development, and fast-track registration

Following on requests from MOH and the Global Fund, PQM conducted an initial audit on GMP implementation at the Indonesian pharmaceutical manufacturer Imedco in West Java, which is developing products to meet the needs of the national TB program for the 2 FDC (INH150/RIF75) daily dosage regimen for adults and children (DT). These products are currently imported by MOH, but under government regulations preference is given for locally sourced products. Imedco has made an expression of interest (EOI) to the government to supply the public sector through the e-catalog procurement system and intends to compile the product dossier for eventual submission to WHO for PQ. Based on the initial audit conducted at Imedco in Q4 with WHO GMP guidance (especially TRS 986 Annex 2), Imedco is currently not operating in full compliance with WHO GMP. A number of major observations were made, and Imedco will be developing a CAPA plan in FY 2019 Q1 to address deficiencies.

Activity 2.2: Provide TA to Sanbe Farma/ Caprifarmindo to finalize levofloxacin 500 mg product dossier to submit to WHO for PQ, and conduct final PD assessment & facility/documentation/practices mock audit by PQM

In Q4, PQM provided onsite assistance to Sanbe Farma in the product dossier compilation in CTD format and performed the dossier assessment. Sanbe Farma is in the process of making the requested changes based on the assessment, with plans to submit the dossier to WHO by the end of the 2018 calendar year. In August, PQM also provided an onsite 2-day training on data integrity and computer systems validation at Sanbe Farma. A mock audit was conducted at the end of Q4, with results still pending as of the submission of this report.

Activity 2.3: Provide TA to Kalbe Farma to finalize levofloxacin 500 mg product dossier to submit to WHO for PQ, and conduct final PD assessment & facility/documentation/practices mock audit by PQM

Kalbe Farma finalized its CAPA implementation plan and submitted all evidence to WHO for PQ. PQM assisted in implementing CAPAs, including supervision on GLP training and data integrity. As of the end of Q4, Kalbe Farma's levofloxacin 500 mg tablet was listed on the WHO PIR and is awaiting final publication of the WHO PAR.

Activity 2.6: Initiate collaboration with key Centers of Excellence universities in Indonesia providing bioequivalence expertise to BPOM on developing a sustainable mechanism for high-quality TA

A national training workshop on data integrity and computer systems validation for bioavailability/bioequivalence studies was held as part of the PQM-initiated training-of-trainers event for the national bioavailability/bioequivalence forum. The workshop was hosted by BPOM's Registration Directorate and facilitated by PQM and Waters Singapore, with over 100 participants from manufacturers, CROs, and BPOM. A final training report and follow-up plan is forthcoming.

Activity 2.8: Conduct training workshop for manufacturers and regulators on “Deviation Handling and Investigation” according to International standards

A 2-day “Training on Deviation Handling and Quality Risk Management” was convened at the end of Q4 for 34 participants from the pharmaceutical industry (local and multinational) and the regulatory agency, including quality control laboratory and inspection staff.

Objective 3 – To enhance the technical capacity of the government of Indonesia to develop and implement inter-agency (MOH, BPOM, donors, professional associations, other stakeholders) policies and procedures for medicines quality assurance (coordination, advocacy, and developing appropriate public awareness tools), and to support the National TB Program, National AIDS Program, and FARMALKES to ensure quality and production is in line with procurement policy/new treatment guidelines

Activity 3.2: Develop Guidelines for Sampling from Government Facilities to implement Permenkes 75/2016 including surveillance of SAS medicines and socialize technical guidelines

PQM facilitated draft guideline development for PMK 75/2016 implementation, which has been reviewed and revised by Directorate KMEI BPOM and Directorate of Public Medicine Farmalkes. The technical guidelines were developed following recommendations from the recent dissemination workshop on the joint MOH–BPOM sampling activity to initiate coordination of the TB and HIV programs and BPOM at the provincial level. The sampling guidelines will likely

be incorporated into a revised version of the PMK 75/2016 regulation; however, due to high-level changes in leadership, PQM is anticipating delays in final approval and incorporation.

Activity 3.8: Raising awareness among professional community through ad hoc participation, facilitation, and representation to raise awareness on GxP standards and technical issues related to implementing good practice for medicines quality

In Q4, PQM coordinated with the University of Indonesia, Faculty of Pharmacy, on a plan to continue to collaborate on education and awareness for professional students. In addition to the technical lecture series, PQM will provide donated laboratory equipment, such as analytical balance, micro balance, HPLC equipment, oven vacuum, and water determination equipment for Karl Fischer titration. This support is part of the partnership with the University of Indonesia aimed at increasing student knowledge on public health and medicines QA. PQM is supporting the laboratory, which is in the process of preparing for an upcoming audit on ISO/IEC 17025 for accreditation by the Indonesian National Accreditation Committee (KAN).

Activity 3.9: Support USAID and USAID health implementing partners (FHI, Chemonics, KNCV) on relevant issues including coordination with BPOM, integrated activities, BAST, agreements, etc.

BPOM requested that the USAID BAST should be submitted for the period of January–June 2018. PQM has compiled all necessary financial and handover data and prepared the corresponding draft BAST document, which is awaiting final signatures from BPOM and USAID. In Q4, PQM discussed with the Australian Therapeutic Goods Administration its upcoming plan to support BPOM in the area of new product registration capacity-building through the Asia-Pacific Regulatory Partnership initiative. PQM and USAID are currently exploring potential areas of mutual support as their project gets underway later in the year.

PQM also convened discussions with the International Pharmaceutical Manufacturers' Group regarding areas of priority for medicines registration and training for regulators. A meeting was held to debrief the MOH Director General and was attended by directors from TB, HIV, and malaria. The purpose of the meeting was to discuss PQM achievements and seek endorsement for the Global Fund 2019–2020 technical assistance plan, which was given. PQM also participated in the BAPPENAS (Indonesian Ministry of National Development Planning) Health Sector Review and provided substantial inputs into the pharmaceutical section of the document. A 2-day SIMS visit for PEPFAR was conducted to examine PQM's work in Jakarta under HIV funding. PQM has also been requested by the national HIV program, WHO, and PSM to help develop the EQA and QMS for the rapid diagnostic tests being used by the HIV program. PQM will explore this further in FY 2019.

Activity 3.5: Follow-up on TB Stakeholder Forum's "Road Map" for NTP transition/new regimens/guidelines—stakeholder engagement in roles/responsibilities

PQM has proposed several times to Farmalkes to conduct the stakeholders meeting, but a fixed schedule agreement has not been made. In the interim, however, PQM has already initiated discussions and engagement with two local manufacturers that have expressed interest in providing the daily dose for 2 FDC anti-TB products required by the national TB program. PQM also participated in Global Fund country team management meetings in Q4, with the GDF team, BPOM Registration Directorate, BPOM, NTP, and Public Medicines of Farmalkes. The meeting resulted in agreement to start the process for registration of imported second-line anti-TB medicines with initial focus on ethionamide and clofazimine, using a local manufacturer as the importer. This mechanism is allowed based on PMK 1010/2008 regarding the use of domestic funds for purchasing pharmaceuticals not currently available via a domestic source. PQM will assist in this process and continued to meet with the Directorate General Farmalkes.

Objective 4 – Monitoring and Evaluation for specific activities

Activity 4.1: Develop tools for evaluating trainees who became trainers based on ToT workshops with BPOM

The tools for evaluating trainees were developed in Bahasa and English, including structured interview, focused group discussion, and observation/documentation. The questionnaire will be used to analyze the effectiveness of using Minilabs™ in a collaborative approach between MOH and BPOM for sampling and testing.

IV. Key Challenges

In support of the MOH national TB and HIV programs, the Global Fund technical assistance plan has been approved, including for the proposed PQM activities (along with other USAID implementing partners). By the end of FY 2018 Q4, PQM had received endorsement from the MOH Director General and from CDC Director General. PQM will continue to finalize the budget and technical assistance plan under the Global Fund reprogramming budget in FY 2019 Q1. However, there will be considerable challenges to scale-up activity implementation once the budget is released.

Myanmar

I. Quarter 4 Highlights

In Q4, PQM coordinated the chemical testing of long-lasting insecticidal nets (LLINs) received at the Department of Food and Drug Administration (DFDA) from USAID/PMI. Testing was completed in early September, with the preliminary report sent to PSI/VectorWorks. The final report will be available by the end of September. This project came about as requested by PMI to help VectorWorks solve a crucial question of how much deltamethrin would still remain in the nets after some washing and especially beyond 2 years. Prior to testing at the DFDA laboratory, VectorWorks sent samples for external testing. However, DFDA was chosen this time due to its recent ISO 17025 accreditation, infrastructure, trust after preliminary testing results, access, and price negotiation.

PQM provided technical assistance in DFDA's preparation for ISO 17025 reaccreditation planned for October 2018. In Q4, the bulk of technical guidance was focused on QMS document review and drafting of DFDA's Impartiality Policy, Confidentiality and No Conflict of Interest Policies as required by the new ISO 17025:2017 standards. PQM also took the lead in conducting the management review meeting and assisted DFDA on document submission to ANAB after the management review meeting.

Because Myanmar has received additional international sanctions, it was not possible for DFDA to obtain proficiency testing services to meet routine ISO 17025 requirements; to this effect, PQM obtained guidance from the accreditation body to institute an intra-laboratory comparison (i-ILC) program as a substitute for the proficiency testing requirement. i-ILC is a process of assessing laboratory performance and competence by comparing the results of different analysts from within the same laboratory. PQM took the lead to provide guidance to DFDA in drafting its first i-ILC SOP, i-ILC reporting format, and a 4-year testing plan. With an appropriate i-ILC SOP on hand and reporting mechanism established, DFDA would be able to adhere to the principle of Good Reporting Practice for its clients; with the 4-year testing plan in place, DFDA would be able to test and report its finding to the clients on time.

PQM participated in a program review of USAID Myanmar Mission conducted by Social Impact in July. The purpose of this evaluation was to document achievements, challenges, and lessons learned from strengthening the MQM capacity of Myanmar DFDA. During the process, the evaluation team interviewed the PQM in-country consultant, DFDA focal persons, and other stakeholders such as WHO and UNOPS. The team also visited DFDA Nay Pyi Taw facilities and DFDA Mandalay facilities, including the laboratories. The evaluation team conducted interviews with PQM staff from the headquarters as well.

II. Country Context

Malaria has been a key public health burden in Myanmar, and the spread of drug-resistant malaria poses a major challenge, especially in the border areas. The combined effort of Myanmar and international donors has led not only to reduction in malaria morbidity and mortality but also to poor-quality medicines in the country that pose a substantial risk to efforts to fight against resistant malaria. Poor-quality medicines not only may contribute to resistance but also lead to treatment failure and waste of scarce resources to fight the disease.

DFDA is responsible for tackling poor-quality medicines in Myanmar. As DFDA is undergoing rapid expansion with field offices and laboratories being opened in every state/division and region of Myanmar, PQM's capacity-building and technical assistance to DFDA are timely and highly useful. DFDA is planning to open four new laboratories in four states and regions to cope with the increasing demand for medicines QC testing. The DFDA laboratory will serve as the reference laboratory in Myanmar and will be the key technical resource to build the capacity of other regional laboratories using its scientists and the knowledge gained from PQM.

To modernize DFDA and develop strong QA systems for Myanmar, alongside with developing laboratory capacity, other key functions—such as medicine product evaluation and registration, licensing, supply chain inspection, and PMS systems—need to be strengthened. Pharmaceutical legislation, such as the National Drug Policy and National Drug Law, needs to be reviewed and revised. In order to use available resources efficiently, PQM is working closely with DFDA to identify gaps in the current regulatory framework and system to tailor technical assistance to specific areas of need. PQM's technical assistance to build DFDA's capacity will result in increased availability of quality-assured medicines in the country. This is expected to contribute toward achieving the NMCP's objectives of malaria elimination by 2030.

III. Quarter 4 Progress by Objective

Objective 1 – Support DFDA Myanmar to revise the current cost structure for quality testing to enable the Nay Pyi Taw laboratory to become self-sustainable

The new testing fees were applied in mid-April 2018, but the Ministry of Health and Sports signed the fees structure later in Q4. It should be noted that prior to establishing the new fees structure, DFDA had a flat fee through which it did not retain anything for the functioning of the laboratory. The new fee structure is higher than the flat fee and enables the laboratory to operate more sustainably.

Objective 2 – Provide technical assistance to Myanmar’s DFDA for ISO re-accreditation and sustainability of the Nay Pyi Taw PC laboratory

LLINs are a key commodity for malaria, and PMI wanted to assure the quality of LLINs in Myanmar after the DFDA laboratory achieves ISO 17025 accreditation. PQM was tasked to build the capacity of the DFDA laboratory to conduct chemical residue testing of deltamethrin in LLINs. The capacity-building efforts coincide with the 24-month LLIN efficacy study conducted by PSI/VectorWorks, a research project funded by PMI. The efficacy studies only included bioassay in the testing; however, after extensive discussion among PMI, PQM and PSI/VectorWorks, the chemical residue testing was sanctioned starting from the 24-month assessment. Chemical residue testing of deltamethrin in LLINs (for 60 samples or nets) was completed in early September. The preliminary report was sent to PSI/VectorWorks.

PQM provided assistance to DFDA Nay Pyi Taw laboratory on developing an impartiality policy, confidentiality agreement, and no conflict of interest agreement, and implementing them in the laboratory. PQM also continued work from FY 2018 Q3: finalizing internal audit reports, risk-management procedures, and risk assessments, as well as reviewing the implementation of corrective actions and improvements.

As part of the preparations toward ISO 17025:2017 reaccreditation of DFDA’s Pharmaceutical Chemistry Laboratory, the annual Management Review Meeting was held on August 8. PQM provided assistance in developing the meeting agenda, facilitating the meeting and discussions, providing input on managing the critical issues, and taking the lead in writing the meeting report. It is noteworthy that the original accreditation was on the 2005 standard and the reaccreditation exercise would be based on the latest ISO standard released in 2017.

The documents required for desk review by ANAB prior to the actual assessment were uploaded to ANAB ShareFile. During the process, PQM and DFDA consulted with ANAB on the PT requirement of ISO 17025 and on the trade embargo imposed by EU that prevented DFDA from acquiring PT samples. ANAB suggested DFDA to perform i-ILC and PQM provided assistance in establishing i-ILC program, writing SOPs, a 4-year plan, i-ILC report and getting ANAB’s approval on the program.

Objective 3 – Provide technical assistance to Myanmar’s DFDA Nay Pyi Taw and Mandalay laboratories on pre-and-post relocations planning and implementation in accordance to ISO 17025 standards

As the construction and thus relocation of the laboratory timeline was delayed due to the DFDA senior leadership change, there has not been any actual relocation activity undertaken by PQM; thus, there nothing to report this quarter. There is a possibility that the relocation exercise, especially the Mandalay laboratory, might only be possible post-PQM closeout. The mitigation plan to be rolled out by PQM is to ensure that the current team of Nay Pyi Taw laboratory staff are fully trained to ISO 17025:2017 requirements, proficient enough to become trainers in their area of work and be empowered to become trainers for other team members in Nay Pyi Taw and Mandalay.

Objective 4 – Provide support to DFDA Nay Pyi Taw laboratory’s technical assistance to Mandalay Pharmaceutical Chemistry laboratory for ISO 17025 accreditation preparation

Nothing to report this quarter.

Objective 5 – Provide technical assistance to DFDA Yangon and Mandalay laboratories on calibration of essential laboratory equipment after the relocation Program Management and Activity Coordination

Nothing to report this quarter.

Objective 6 – Strengthen the pharmaceutical quality surveillance system in the country through the introduction of new detection technologies and effective reporting and data management system at the state/regional levels

Nothing to report in this quarter; activity on hold by DFDA.

IV. Key Challenges

The reaccreditation of the Nay Pyi Taw Pharmaceutical Chemistry laboratory was a key challenge in Q4, as the new ISO 17025:2017 standards are introduced and the laboratory's QA team is newly formed after several key staff members left the posts for further studies and some went searching for new grounds.

Laboratory construction/completion projects in Mandalay, Nay Pyi Taw, and Yangon were delayed, so the capacity for pre- or post-QC testing might be delayed, thereby causing a relative shortage of capacity.

The EU trade embargo against Myanmar posed a serious logistical and technical challenge as the ANAB reaccreditation audit required PT and other items/services from overseas, especially those whose parent companies are headquartered in EU.

Pakistan

I. Quarter 4 Highlights

In FY 2018 Q4, PQM continued to provide technical assistance to strengthen the medicines regulatory system in Pakistan by providing technical assistance to the Drug Regulatory Authority of Pakistan (DRAP) to develop its QMS and achieve WHO Global Benchmarking Maturity Level III. WHO defines Maturity Level III as having a stable, well-functioning, and integrated regulatory system. Attaining this status will enable DRAP to further its efforts to improve access to safe medicines and health products, especially for vulnerable mothers and children, and to protect Pakistanis from substandard and falsified medicines.

PQM continues to support selected manufacturers, including Atco Laboratories and Aspin Pharmaceuticals, which launched CHX 7.1% gel and are currently working toward UNICEF Expert Review Panel (ERP) approval. Support to other two manufacturers (Akhai Pharmaceuticals and Zafa Pharmaceutical Laboratories) ended after the CAPAs were closed and the manufacturers showed no further interest in the global market. CHX 7.1% gel manufactured by all four manufacturers is now available in all provinces and regions of Pakistan as an over-the-counter medicine and is readily accessible by the general public. This product is now also included in the national essential medicines list. In addition, PQM supported a manufacturer of zinc DT, which has been inspected by WHO for PQ.

In Q4, the WHO Prequalification Team (PQT) visited the Pakistan Drug Testing and Research Center (PDTRC) in Lahore to conduct a final audit for WHO PQ. PQM participated as an observer at the request of both WHO and PDTRC management. During the debriefing, WHO PQT expressed its appreciation for PQM's support in preparing the laboratory for WHO PQ. In its closing remarks, WHO PQT expressed satisfaction with the laboratory, and there were no critical observations. The WHO PQT report is expected within the next few weeks.

In Q4, three PQM-supported laboratories—Drug Testing Laboratory (DTL) Lahore, DTL Multan, and DTL Faisalabad—attained ISO 17025 accreditation from the Pakistan National Accreditation Council (PNAC); with this accomplishment, four PQM-supported laboratories have now achieved local ISO certification. PQM completed the gap assessment of two more laboratories, DTL Bahawalpur and DTL Rawalpindi, and provided technical assistance to remove nonconformances toward compliance with ISO 17025 standards. PQM's subsequent support to DTL Lahore, DTL Multan, and DTL Faisalabad continued toward WHO PQ by reviewing their QMS and providing assistance for preparation of the laboratory information file (LIF) for WHO.

II. Country Context

Chlorhexidine is 1 of the 13 life-saving commodities identified by the U.N. Commission on Life-Saving Commodities for Women and Children. PQM is called to work alongside other implementation partners to help USAID achieve the objective of introducing quality-assured CHX in Pakistan. The collective effort would contribute to the Pakistani Government's effort to reduce the mortality (currently at 200,000 deaths/year, about 22 cases/hour) of newborns caused by cord infections that can be prevented by use of quality CHX gels.

PQM is tasked with providing technical assistance to potential manufacturers of CHX gel in improving their manufacturing quality standards. In addition, PQM will help strengthen DRAP's capacity, improving medicines registration processes, PMS, and other key functions, including enabling the QC laboratories work toward international standards and practices. To effectively safeguard the quality of essential medicines, including CHX, a systematic approach to pharmaceutical regulation and management must be implemented throughout the country. PQM's initiative to improving quality standards of medicines covers all key components of medicines QA; it must also be complemented by adequate legislation and a regulatory framework. Such coordinated efforts, encompassing the pre- and post-market activities to render other oversights in monitoring, evaluation, documentation, tracking, and surveillance, are necessary to deliver needed improvements to the quality of medicines for public health.

III. Quarter 4 Progress by Objective

Objective 1 – Continue to provide technical assistance to selected manufacturers with strong interest and commitments to producing CHX products (7.1% chlorhexidine digluconate gel, delivering 4% chlorhexidine) to successfully register their products at DRAP

CHX 7.1% Gel

PQM has been working with four manufacturers of CHX 7.1% gel: Zafa Pharmaceuticals, Akhai Pharmaceuticals, Atco Laboratories, and Aspin Pharmaceuticals. All the manufacturers were able to complete the CAPA implementation plans prepared with PQM's technical assistance. The products of all four manufacturers are in production, were approved for domestic launch, and are freely available on the local market.

Amoxicillin DT

PQM conducted a baseline assessment of Macter International's penicillin manufacturing facility in FY 2018 Q1 and prepared a comprehensive assessment report that was communicated to the company's management. The manufacturer prepared a CAPA plan based on PQM's input. The plan was shared, reviewed, and agreed to by PQM for implementation. PQM provided technical assistance to the manufacturer to close its nonconformances.

Considering the importance of this product and potential demand for it, PQM identified an additional manufacturer, M/s CSH Pharmaceuticals, as another potential manufacturer of amoxicillin DT. A comprehensive GMP assessment of CSH Pharmaceuticals was conducted in Q4. A detailed assessment report is under preparation and will be shared with CSH management. PQM will assist the manufacturer in CAPA development and effectively closing the nonconformances reported during the assessment.

Risks include the following:

- Change in stakeholders' priorities.
- Security situation may affect the visits of international certification bodies (WHO, UNICEF) and expatriates technical experts' visits (USP).
- Change of government/change in tax and duties.
- Limited resources for sustainability of the interventions and progress made so far.

Pneumonia, diarrhea, and malnutrition are leading causes of mortality for children under 5 years old in Pakistan. In consultation with the USAID Mission in Pakistan, in FY 2017 PQM identified the need to provide support for essential MCH medicines, which have high public health impact. The focus was on those products that are not produced in country or are in short supply; have issues of quality, safety, and efficacy; and for which there is a dire need in the country. The products selected included amoxicillin DT, zinc DT, and zinc DT/oral rehydration salts (ORS) co-pack. Amoxicillin is an effective broad-spectrum antibiotic, especially for the treatment of bacterial pneumonia in children.

Diarrheal disease is the second leading cause of death in children under 5 years old, yet it is a known fact that diarrhea is treatable and preventable. Each year diarrhea kills about 248,449 children under 5 in Pakistan. Zinc supplementation has been shown to reduce the duration and severity of diarrhea and to prevent subsequent episodes. In Pakistan, zinc DT (recommended for children under 5 years of age) is not manufactured locally. It is estimated that local production of zinc DT would reduce the treatment cost from 0.4 days' wage to 0.1 days' wage of the lowest paid unskilled worker in Pakistan (Pharmaceutical Situation Assessment Survey 2014–2015 by the Ministry of National Health Services Regulations and Coordination and WHO). Moreover, there would be overall improvement in the quality system that could benefit other products produced by manufacturers and expand the number of overall sources of quality-assured essential medicines.

PQM identified the following manufacturers as potential suppliers of these products and began providing the required technical assistance in FY 2018:

1. **Amoxicillin DT:** In Q4, PQM worked with Macter International to develop a stable formulation of amoxicillin DT. Support was extended to prepare the dossier for WHO PQ. The formulation was developed by the manufacturer and is currently on stability studies that show promising results. The other manufacturer, CSH Pharmaceuticals (Lahore), was audited in September, and the audit report to be shared with the manufacturer is under preparation. PQM will support the manufacturer for CAPA development and will assist in implementing the plan to close nonconformities.
2. **Zinc DT:** One manufacturer receiving technical assistance from PQM, M/s Pharmevo, was inspected by WHO PQT in Q4 for PQ of zinc DT. The audit report is expected within the next few weeks. If the report suggests a need, PQM will continue to provide the necessary technical assistance. Atco Laboratories and Aspin Pharmaceuticals were the two other manufacturers selected for manufacturing of zinc DT. Atco prepared a stable formulation of zinc DT, and the product was tested for stability through a laboratory scale batch. After receiving the raw material, the manufacturer is preparing the pilot scale batches for conducting stability testing, to subsequently confirm the stability of larger batches for commercial production. Aspin Pharma has developed a stable formulation and received support in preparing its registration dossier for DRAP. The application submission to DRAP is expected in November 2018.
3. **Zinc DT/ORS co-pack (diarrhea):** Atco Laboratories has prepared a formulation in accordance with the USP monograph; the stability study is ongoing, and results until now are satisfactory. The manufacturer is preparing its dossier for WHO submission.

Objective 2 – Strengthen Regulatory, Quality Assurance, and Quality Control Systems through building the capacity of DRAP’s quality control systems and laboratories toward attaining international standards of quality and practices

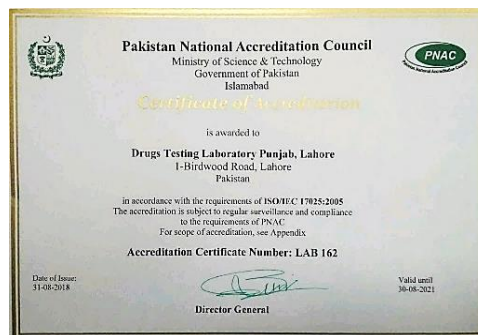
PQM’s substantial laboratory support, with minimal investment, is contributing to system strengthening and industry stability with healthy competition for safe and quality-assured medicines. Reliable quality testing utilizing a risk-based PMS approach is increasing the detection of substandard and falsified medicines. These substandard and falsified medicines cause treatment failure and adverse reactions, increase morbidity and mortality, and contribute to drug resistance development. Poor-quality medicines also increase healthcare costs to both patients and the health system as a whole, wasting resources that could otherwise be used to benefit public health. Through this program, economic support windows are widening by saving the cost to patients and healthcare system due to treatment failure. In addition, the QA infrastructure being strengthened with PQM support can forestall the extensive impact of poor-quality medicines, such as the notorious contaminated cardiac medicines and cough syrup events that took the lives of more than 400 people in Pakistan in 2012. This type of tragedy could have been averted or risk of occurrence reduced through reliable testing facilities, which now exist to support timely investigation.

CDL Karachi

The QMS of the Central Drug Laboratory (CDL) was reviewed by PQM Rockville experts and shared with laboratory management. CDL is preparing the final QMS document, including the LIF to be submitted to WHO PQT. Based on PQM’s advocacy, DRAP invested in CDL infrastructural work and equipment. It is expected that all new pieces of equipment will be received in October; after their qualifications, PQM will review the QMS and remaining operational SOPs and assist CDL in updating its LIF for submission to WHO. Support to this laboratory to meet international standards will support accurate and reliable premarket testing of generics and new medicines applying for market authorization. Further, in Sindh province there is currently no other public sector laboratory available to provide testing facilities for PMS support to provincial health authorities.

DTL Lahore

In Q4, before the visit of the Pakistan National Accreditation Council (PNAC) team, PQM supported DTL Lahore to finalize the QMS review and arrange CAPA closure evidence documents. Through PQM’s support, DTL Lahore attained ISO 17025:2005 accreditation by PNAC (accreditation certificate #LAB 162; granted August 31, 2018, and valid until August 30, 2021.) PQM is now providing subsequent support to DTL Lahore to prepare its LIF for WHO PQ. This will not only help DTL Lahore meet internationally recognized standards but will also ensure the accuracy of results and reliability of the laboratory in surveillance of medicines quality after market authorization.



ISO 17025 Certificate of Accreditation

PDTRC Lahore

PQM has been working with PDTRC toward WHO PQ since last year and has supported the laboratory in preparing its QMS documents and improving its working standards. PQM helped the laboratory develop its LIF for WHO, which

was accepted and followed by the WHO peer audit in December 2017. PQM also supported the laboratory to develop a CAPA plan based on the peer audit report. PQM supported the closure of various observations mentioned in the CAPA and arranged for a final review of PDTRC preparedness before the WHO inspection visit in July 2018. For this, a PQM technical expert conducted a detailed review of the laboratory's readiness, providing valuable input to address other outstanding gaps before the WHO visit. The PQM team cross-checked CAPA points (aligning the documents as per WHO requirements), did a mockup audit for document retrieval and key messages to remember during such audits, and discussed the strategy for addressing the few known deficiencies. Before the visit and to provide a better understanding of the whole process, PQM explained the typical WHO audit and subsequent next steps. Following the WHO audit, PQM prepared the summary of observations and findings discussed during the inspection and closing meetings, identifying observations that could be addressed immediately. Overall, the WHO assessment was positive with no critical observations; the detailed report is expected to be received within the next few weeks. PQM will assist in preparation of the CAPA plan when the WHO formal report is shared and will provide technical assistance through closure of all observations made by WHO PQT.



PQM Team with PDTRC staff discussing WHO audit preparations



PQM Team with WHO and PDTRC Team

This will be the first regulatory laboratory expected to acquire WHO PQ status. Prequalification of the laboratory will provide testing facilities for the prequalification of locally manufactured medicines, especially for integrated disease programs, as well as for testing of medicines to be exported to comply with the requirements of certain importing countries. This laboratory will also be used for pre- and post-marketing of pharmaceuticals as required.

DTL Faisalabad

DTL Faisalabad is a regulatory laboratory that was established under section 15 of the Drugs Act of 1976. It provides services in pharmaceutical testing of medicines samples to the Drug Control Wing, Government of the Punjab, and Primary & Secondary Healthcare Department, through assigned drug inspectors that cover a specific jurisdiction. The Provincial Quality Control Board (internal customer of the laboratory) is the designated body in the Drug Control Wing of the Department that has the technical capabilities and legal function to scrutinize test reports, audit, and suggest improvements in the DTLs. The primary focus of the Q4 visit was to conduct a gap assessment of the level of compliance with WHO Good Practices for pharmaceutical QC laboratories (WHO TRS, No. 957, 2010). The assessment focused on compliance of the laboratory's QMS implementation status to WHO PQ guidelines and to determine areas for improvement. Other WHO guidelines used as references included Guidance on Good Data and Record Management Practices (WHO Technical Report Series, No. 996, 2016, Annex 5) and General Guidelines for the Establishment, Maintenance and Distribution of Chemical Reference Substances (WHO Technical Report Series, No. 943, 2007, Annex 3).

The gap assessment identified deficiencies and areas of improvement that need to be addressed before submitting the EOI and LIF to WHO (e.g., key SOPs, SOPs that require revision, and areas that require improvement and need to be addressed, such as documentation, training on QMS system, and other laboratory trainings). DTL Faisalabad is currently working to address nonconformances and observations. This visit also identified key priority areas for PQM support for capability building in QMS, such as data integrity, risk management, change control, deviation, and validation/verification of methods. Once the identified gaps are addressed, the laboratory will be better prepared to submit the EOI and LIF to WHO in preparation for WHO PQ. PQM will follow up with DTL Faisalabad staff via Skype and physical visits for re-evaluating the QMS status and will assist DTL Faisalabad in preparing and submitting its LIF to WHO.



PQM with DTL Faisalabad staff after QMS assessment

Prequalification of this laboratory will provide reliable testing services for surveillance of medicines quality to three divisions of Punjab (Faisalabad, Gujranwala, and Sargodha), benefiting 38 million people who are more vulnerable to substandard and falsified medicines.

DTL Multan

In Q4, PQM performed an audit of DTL Multan, a provincial DTL established under the Drug Act of 1976/DRAP Act of 2012. The primary focus of the visit was to conduct a gap assessment of the level of compliance with WHO Good Practices for pharmaceutical QC laboratories (WHO TRS, No. 957, 2010). The assessment focused on compliance of the laboratory's QMS implementation status against the requirements of WHO PQ guidelines. The gap assessment identified deficiencies and areas of improvement that must be addressed before submitting the EOI and LIF to WHO. DTL Multan is currently working to remove the nonconformances based on PQM's assessment findings on areas that require improvement, such as documentation, QMS training, and laboratory training and practices, including data integrity, risk management, change control, deviation, and validation/verification of methods. Once the identified gaps are addressed, the laboratory will be better prepared to submit the EOI and LIF to WHO in preparation for WHO PQ. PQM will follow up with DTL Multan staff via Skype and physical visits for re-evaluating the QMS. PQM will assist DTL Multan in preparation and submission of the LIF to WHO. Prequalification of this laboratory will provide reliable testing services for surveillance of medicines quality to 2 divisions of Punjab (Multan and Dera Ghazi Khan), which is less developed and more vulnerable to substandard and falsified medicines, benefiting a population of 15.7 million people. The DTL Multan catchment area (administrative division of cities where laboratories provide testing services) is in the southern part of Punjab, which has the highest vulnerable population due to poverty, poor health facilities, and ongoing conflict and violence.



PQM Team with DTL Multan and Bahaalpur staff after QMS assessment

DTL Bahawalpur

DTL Bahawalpur is a provincial DTL that was established under the Drug Act of 1976/DRAP Act of 2012. In Q4, PQM performed an audit of DTL Bahawalpur to assess its QMS and assist the laboratory in achieving ISO/IEC 17025 accreditation and subsequently WHO PQ. In collaboration with DTL Multan, DTL Bahawalpur will remove nonconformances. PQM will follow up with DTL Bahawalpur staff via Skype and physical visits for re-evaluating the QMS status. PQM will assist DTL Bahawalpur in preparation and submission of the LIF to WHO. The DTL Bahawalpur catchment area is located in the southern part of Punjab, which has the highest vulnerable population.

DTL Rawalpindi

In Q4, PQM performed an audit of DTL Rawalpindi, which was established under the Drug Act of 1976/DRAP Act of 2012. The objective of the visit was to conduct a gap assessment of DTL Rawalpindi with respect to the QMS and assist the laboratory in achieving ISO/IEC 17025 accreditation and subsequently WHO PQ. DTL Rawalpindi will remove nonconformances, and PQM will follow up with staff for re-evaluating the QMS. PQM will assist DTL Rawalpindi in preparing and submitting its LIF to WHO.

Risks include the following:

- Ground conditions may not remain suitable (change in political government, change in management).
- Capital expenditure required for CAPA, including electronic system interfaces, may not be compatible.
- Access to market authorization data and unreliable manufacturers' methods of testing.
- Limited resources for sustainability of the interventions and progress made so far.

Objective 3 – Capacity building of DRAP Pharmaceutical Evaluations and Registration Division (PE&R) to improve its registration system to effectively evaluate all essential medicine products quality

Previously, DRAP's assessment of quality and safety data before product approval was not very robust or well-documented. Pre- and post-registration activities, such as quality testing and inspection, were not conducted according to international standards, and no integration approach was being followed for regulatory decisions.

PQM is supporting DRAP to improve product quality assessment and the registration process, and to build the capacity of dossier evaluators and the inspectorate to perform surveillance of medicines quality for both federal and provincial authorities; this will significantly reduce the backlog of registration applications. In addition, switching to CTD facilitates good review practices for safety, quality, and efficacy data by applicants. Timely and efficient review and approval of essential medicines will ensure that quality-assured medicines are readily available for public health treatment programs in Pakistan. Furthermore, DRAP's international recognition by achieving WHO GBT performance Level III will boost exports and increase Pakistan's share of the global generic market.

Technical Assistance to Drug Regulatory Authority of Pakistan for achieving WHO GBT Level III compliance

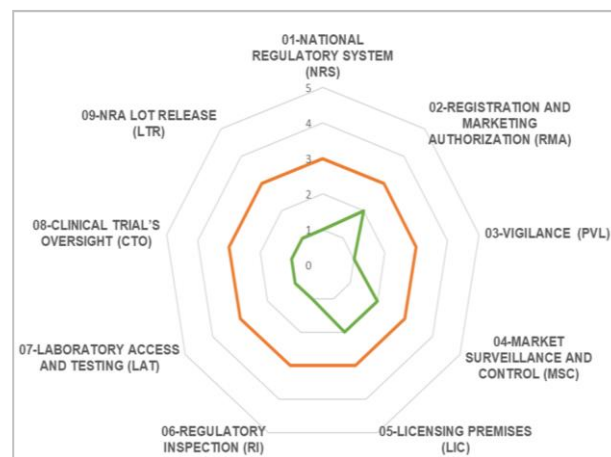
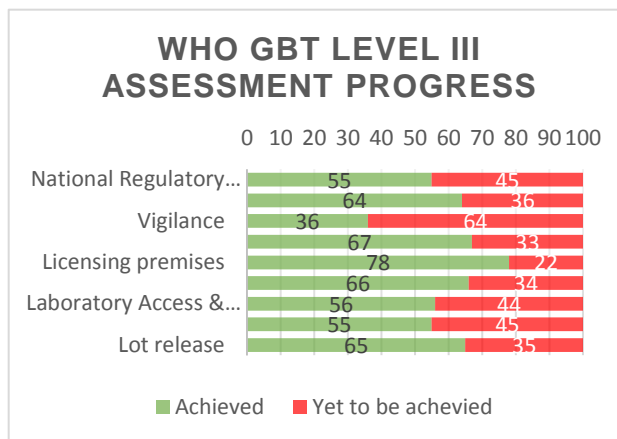
DRAP requested PQM support to achieve WHO Maturity Level III based on GBT. Level III is the minimum acceptable level for a stable, well-functioning, and integrated regulatory system. In Q4, PQM supported DRAP for self-assessment of all nine regulatory functions based on GBT. Based on gaps identified during the self-assessment, PQM is supporting DRAP in developing institutional developmental plans (IDPs). One major gap identified was lack of a QMS. PQM hired a consultant firm to support DRAP in achieving ISO 9001:2005 standards (as per WHO recommendations); a QMS is an integral part of the ISO 9001:2015 standard.

QMS implementation in the national regulatory regime will help to coordinate and direct DRAP's activities to meet customer and regulatory requirements and continually improve its effectiveness and efficiency. This means that all DRAP processes, authorities, and responsibilities are well-defined and documented; performance indicators are developed to achieve targets; performance is monitored and risks are assessed for each critical process; and risk mitigation strategies are in place.

By achieving Maturity Level III, DRAP will attain status as a WHO Listed Authority. This will help DRAP perform functions using systematic regulatory approaches, enabling good quality, safety, and efficacy assessment; safeguarding patients from substandard and falsified medicines; ensuring consistency and transparency in decisions; and achieving worldwide recognition of its regulatory decisions. A fully functional DRAP is a prerequisite for WHO PQ of vaccines, and it is expected this condition will be extended to medicines in near future.

Hands-on Training on CTD for Pharmaceutical Manufacturers in Punjab, KPK, and Islamabad

DRAP adopted the CTD format for registration applications after detailed deliberations and technical assistance from PQM. PQM not only supported DRAP for adoption of the CTD format for registration applications but also collaborated with DRAP for its implementation by training both the DRAP dossier evaluation team and pharmaceutical manufacturers. This will help DRAP to harmonize with international standards and facilitate good review practices for assessment of quality, safety, and efficacy data. To prepare the pharmaceutical industry for submission of registration applications in CTD, PQM collaborated with DRAP and the Pakistan Pharmaceutical Manufacturers Association to conduct a 3-day training course in August



Status of Maturity Levels of Different Regulatory Functions



Hands on Training on CTD in Lahore, August 2018, Additional Secretary (Drugs Control) and Chief Drug Controller, Punjab Health Department

2018 on “Hands on training on ICH common technical document (CTD)” at Lahore. The workshop was attended by 105 participants (37 female and 68 male) from pharmaceutical manufacturers in Punjab, Khyber Pakhtun Khwa, and Islamabad. The objective of the training was to help the industry understand the technical requirements for preparation of the CTD dossier according to DRAP and international requirements. As an outcome of the training, regulatory professionals from industry now understand the recent requirements for developing the registration dossier (CTD), know how to prepare the quality documentation, are familiarized with the information required for submission of CTD, and are enabled to respond to queries if raised by local and international regulatory authorities.

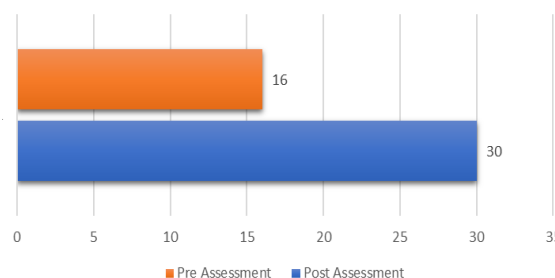
The pre- and post-training knowledge check assessment evaluation (as shown in the graph) indicated that participants’ knowledge about the CTD format and requirements almost doubled. This is a significant improvement, but further training of DRAP dossier evaluators and industry will be conducted to build on this experience and on practical experience to submit applications in the new format. This is an example of how PQM, with USAID assistance, is supporting public–private partnerships to benefit economic growth. This is evident from the increase in exports since PQM began its technical assistance program in Pakistan, from US \$204.4 million in 2015 to US \$212.2 million in 2017.

By supporting the manufacturing and distribution of CHX, zinc, amoxicillin DT, and other products and combating the availability of substandard and falsified medicines, PQM improves access to quality-assured essential medicines for vulnerable populations impacted by violent extremism. Also in Q4, the Chief of Party met with the Vice Chancellor of the University of Baluchistan to organize a PQM training program to support QA and regulatory topics (including support to DTL Quetta for developing a QMS).

Risks include the following:

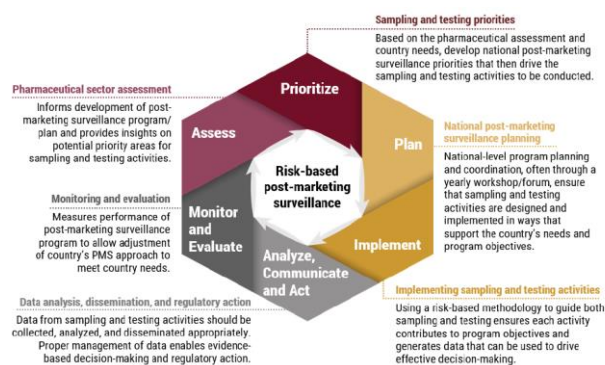
- WHO may change indicators, scoring of GBT.
- Ground conditions may not remain suitable (CEO is not confirmed, change in political government).
- Overly optimistic schedule of IDP implementation by DRAP.
- Lack of a change management process in DRAP.
- Limited funds for capacity-building activities/guidelines development.
- Limited funds to support DRAP for implementation of new mandatory functions required for Level III compliance (pharmacovigilance, clinical trial, risk-based PMS).
- Limited resources for sustainability of the interventions and progress made so far.

Comparison Overall Percentage of Pre & Post Training Assessment



Objective 4 – Capacity Building of Inspectorates at Federal & Provincial levels to perform their role effectively in pharmaceutical establishments licensing, and post-marketing surveillance

In FY 2018 Q4, PQM continued to liaise with stakeholders to finalize a national framework/policy on PMS. The draft guidance document was shared with stakeholders for feedback, and comments are expected within the next few weeks. Using the risk-based approach in monitoring quality is a tool that can facilitate and support a strong management decision-making process. Further adoption of a risk-based approach for market surveillance of medicines quality and related adverse reactions/events would allow DRAP and the provincial inspectorate to concentrate their limited resources on those areas considered most likely to pose a risk to medicines quality. The framework outlined strategies to consider different types of risks, in relation with their impact on patients’ and target populations’ safety and care. Furthermore, this approach will help increase the detection of substandard and falsified products that have a high chance of being



Framework for Risk-Based Post-Marketing Surveillance

missed due to sporadic surveys or collection of medicines samples as part of the routine inspections currently in place. Going forward, PQM will support DRAP and provincial health authorities to formally incorporate risk-based approaches in regulatory inspections. This includes but is not limited to risk classification of manufacturing units and products, a risk-based inspection strategy, and annual plans.

Factors that pose risks to fully realizing the benefits of risk-based PMS in Pakistan include:

- Poor coordination and information sharing among stakeholders (federal and provincial governments); sometimes PMS activities are fragmented, overlapping, or uncoordinated.
- Medicines testing is not performed according to registration specifications or compendial standards, and judicial courts continue to grant stays on compendial testing.
- Limited workforce to implement an integrated, effective, and sustainable post-marketing program, particularly for new chemical entities.
- Change in stakeholders' priorities.
- Project phase-out is approaching, but continuous technical assistance is required for implementation, reprogramming, and monitoring of the draft framework for risk-based PMS.
- Limited resources for sustainability of the interventions and progress made so far.

IV. Key Challenges

The non-availability of multiple-entry visas and the existence of a travel advisory remains a programmatic challenge for PQM. The registration of USP in accordance with Pakistani rules and regulations has been recommended by the scrutiny committee of the Ministry of Interior (MOI); however, with the change of government and appointment of a new secretary, the memorandum of understanding (MOU) was again changed. MOI requested a revised MOU to be signed, and PQM complied with the new requirement. In Q4 the required signature by the Joint Secretary of EAD and MOI was obtained, and USP will be ready to open an office in Pakistan after completion of required formalities. With registration status in the country, the government policy allows for 1-year multiple-entry visas for international nongovernmental organization officials traveling for program-related work.

PQM has been working collaboratively and maintaining open communication with key regulatory stakeholders in Pakistan (e.g., DRAP, Ministry of National Health Services Regulations and Coordination (NHSR&C), provincial governments, WHO). Past experience has shown that provincial governments are less inclined toward strengthening QA and QC systems, which negatively impacts the performance of many QC laboratories. The exception is Punjab, where with PQM support three more laboratories achieved ISO 17025 accreditation in Q4, raising the total number of ISO certified laboratories in the country to four. In a meeting with the new Minister of NHSR&C during the visit of PQM top management in September, PQM emphasized both the improved coordination with provinces and the need for all NQCLs to achieve the same level of competency. The Minister expressed appreciation for PQM's support and assured all possible efforts would be undertaken to achieve the desired objectives as briefed by PQM management.

V. Lessons Learned

PQM works closely with DRAP to strengthen its regulatory capacity. However, a review of provincial health authorities revealed that they require more technical assistance, especially in the smaller provinces. This support in the smaller provinces is necessary to protect public health by promoting the standardization of processes and actions countrywide. The technical assistance that the provinces require is in the area of PMS and strengthening of the provincial QC laboratories. Continued technical assistance is needed to sustain the interventions and progress made so far, as well as to implement new mandatory functions required for attaining Level III compliance based on WHO GBT (pharmacovigilance, clinical trials, risk-based PMS).

Eastern Europe & Central Asia



Kazakhstan

I. Quarter 4 Highlights

In Q4, PQM continued technical assistance to the Karaganda NQCL of the National Center for Expertise of Medicines, Medical Devices, and Medical Equipment of Kazakhstan (NCEM) to strengthen its QMS in preparation for WHO PQ. PQM also continued to work with Nobel Almaty Pharmaceutical Factory, manufacturer of second-line anti-TB medicines.

PQM provided remote technical assistance to the Karaganda NQCL in preparation for WHO PQ and the WHO peer audit. In September, WHO PQT conducted a peer review (pre-assessment visit) of the laboratory. PQM observed the WHO pre-assessment. Follow-up technical assistance will be provided to the laboratory staff to address the observations by WHO PQT. The next step will be a full audit by WHO PQT to assess the laboratory in terms of meeting WHO PQ requirements, which would lead to WHO PQ of the laboratory. As a result of this technical assistance, the laboratory will meet international standards in terms of performing medicines QC. Eventually, this will contribute toward ensuring the quality of medicines in the Kazakhstan market.

As part of PQM's technical assistance to Nobel Almaty Pharmaceutical Factory for its anti-TB product, levofloxacin, PQM organized a site visit for cross-contamination risk assessment and management. Risk of cross-contamination between the products manufactured at the new site and the products manufactured at the adjacent facilities were assessed. Corresponding recommendations were provided to the manufacturer. A CAPA plan is being developed.

II. Country Context

According to WHO, estimated TB incidence in Kazakhstan is 99 per 100,000 people (Global TB Report, 2015). Kazakhstan is also a high MDR-TB burden country; MDR-TB reached 26 percent among new cases and 58 percent among previously treated cases.

In response to these challenges, Kazakhstan adopted a strategic document, "Complex Plan for Tuberculosis Control in Kazakhstan: 2014–2020." One challenge stated in the plan is that anti-TB medicines procured locally are not WHO prequalified. One way to address this is to increase the GMP standards for local manufacturers to apply for WHO PQ.

Kazakhstan has a well-established national medicines regulatory authority, the Kazakhstan FDA. Medicines regulation in Kazakhstan is based on numerous legislative and regulatory documents. However, medicines quality still remains a problem in Kazakhstan. Over a period of 10 years (2004–2014), about 40,000 units of falsified medicines in 40 cases were withdrawn from the market by the Kazakhstan FDA.

In 2009, WHO conducted a survey on the quality of anti-TB medicines in six former Soviet Union countries, including Kazakhstan. The results of the survey, published in 2011, revealed Kazakhstan had the highest overall proportion of substandard samples (23.3%). Although the WHO survey has limitations, including a low number of samples collected and tested and limited scope of medicines targeted, these results indicate that there are quality issues related to noncompliance with GMP, as well as enforcement of medicines regulatory actions.

PQM began receiving funding from USAID/Kazakhstan in FY 2013, with the goal of improving the quality of anti-TB medicines produced by the major medicines manufacturers in the country and enhancing the capacity of these manufacturers to comply with international GMPs. According to Order No. 9 of the Ministry of Health of the Republic of Kazakhstan dated January 14, 2015, Kazakh manufacturers must have a GMP certificate for state registration of their medicines beginning January 2018; thus, the technical assistance provided by PQM is of high importance.

From FY 2013 to FY 2015, PQM worked with two manufacturers of anti-TB medicines in Kazakhstan—Pavlodar Pharmaceutical Factory (Romat Pharmaceutical Company) and Nobel Almaty Pharmaceutical Factory—on the implementation and improvement of their GMP to further participate in the WHO PQ program. Romat Pharmaceutical Company has not invested in the infrastructure of its facility, as it promised to do at the beginning of the project. However, Nobel Almaty Pharmaceutical Factory is committed to continuing cooperation with PQM and improving its GMP standards. Although Nobel already has a national GMP certificate, certain areas require improvement to reach compliance with international GMP requirements.

The Ministry of Health and Social Development of Kazakhstan entrusted the Kazakhstan FDA with the task of strengthening the capacity of NQCLs in the context of entering Kazakhstan in the Eurasian Economic Union and the necessity of mutual recognition of test results by its member countries. The Kazakhstan FDA decided that three NQCLs in its national laboratory network should reach WHO PQ, and it addressed the USAID country mission with a request to provide assistance for WHO PQ through the PQM program, so it could effectively control the quality of medicines in Kazakhstan, including the quality of anti-TB medicines.

III. Quarter 4 Progress by Objective

Objective 1 – Strengthen the medicines quality control system through technical assistance to regional quality control laboratories of the Kazakhstan FDA to achieve WHO prequalification

In Q4, PQM continued remote technical assistance to NCEM NQCLs. This includes advising and providing recommendations on the specific technical topics, as well as facilitating communication with the WHO PQT in preparation of WHO PQT's pre-assessment visit to the laboratory. WHO PQT conducted a peer review (pre-assessment) of the Karaganda laboratory in September. The pre-assessment visit report by WHO PQT is being developed. PQM participated as an observer in WHO PQT's pre-assessment and is working to provide follow-up technical assistance to address the observations and prepare for the PQT audit for prequalification.

Objective 2 – Help increase the supply of quality-assured TB medicines in Kazakhstan through technical assistance to manufacturers of second-line anti-TB-medicines in reaching compliance with international GMP requirements and WHO prequalification

In Q4, PQM continued support to Nobel Almaty Pharmaceutical Factory for its anti-TB product, levofloxacin. When PQM visited the manufacturer for a gap assessment of in FY 2018 Q2, a critical issue was identified with potential cross-contamination between the products manufactured at the new site and the products manufactured at adjacent facilities. In Q4, PQM visited Nobel Almaty Pharmaceutical Factory to provide technical assistance for managing the cross-contamination risk.

The 3-day risk assessment audit included the plant walkthrough and a review of the building design plans and technical drawings of the site where anti-TB medicines would be manufactured and of the sites where the products leading to potential cross-contamination of anti-TB medicines were currently manufactured. The identified risks that may lead to potential cross-contamination must be mitigated before applying for WHO PQ. PQM provided a hands-on training to the staff of Nobel Almaty Pharmaceutical Factory for risk assessment and mitigation of cross-contamination. A CAPA list of risk mitigation strategies for each of the risks identified was recommended and also discussed with the staff. PQM requested that Nobel Almaty Pharmaceutical Factory provide a CAPA plan with timelines for completion of observations made during the assessment.

PQM will continue remote assistance to the manufacturer and will provide further recommendations on mitigation of risks for cross-contamination between the products and preparation of appropriate documentation to comply with international GMP standards.

Uzbekistan

I. Quarter 4 Highlights

As Uzbekistan is graduating from Global Fund support for procurement of anti-TB medicines, the government's strategy is to develop local manufacturing capacity for anti-TB medicines and ensure that locally produced quality-assured anti-TB medicines are available on the local market. To support this strategy, PQM continued technical assistance to manufacturer Nobel Pharmsanoat for its anti-TB product, levofloxacin. With PQM's assistance, the staff were trained on cross-contamination risk assessment and management. A cross-contamination risk assessment was conducted, and corrective actions to mitigate risks were developed. This will help the manufacturer prepare for potential submission for WHO PQ of its product.

Also in Q4, PQM provided a confidential assessment report to the Tashkent QC laboratory resulting from the assessment of the laboratory that was conducted in Q3 for compliance with the international ISO 17025:2017 standard. The laboratory has started work on the relevant corrective and preventive actions.

The Agency for Development of the Pharmaceutical Industry developed a regulation according to which GMP compliance becomes mandatory for all pharmaceutical manufacturers in Uzbekistan starting from 2023.

PQM organized a study tour for GMP inspectors of the Uzbekistan Agency for Development of the Pharmaceutical Industry at a manufacturing facility in Shanghai, China. The inspectors participated in a GMP inspection of the facility conducted by a PQM GMP specialist in compliance with the international GMP standards. This experience will allow the Agency for Development of Pharmaceutical Industry to strengthen its GMP inspection capacity.

II. Country Context

Uzbekistan is classified as a high MDR-TB burden country; MDR-TB reaches 23 percent among new cases and 62 percent among previously treated cases.

To respond to these challenges, Uzbekistan adopted a “Consolidated National Strategic Plan for TB in Uzbekistan 2016–2020.” The plan underlines the importance of the availability of quality-assured anti-TB medicines for patients and supports interventions ensuring the availability of quality-assured medicines supplied through the Global Drug Facility mechanism, as well as those produced and procured locally.

Uzbekistan has an established national MRA, the Directorate of Medicines and Medical Equipment Quality Control (Uzbekistan FDA). Medicines regulation in Uzbekistan is based on numerous legislative and regulatory documents. There is a network of QC laboratories in the country. The central laboratory (State Center of Expert Examination and Standardization of Drugs) is ISO/IEC 17025 certified and seeking WHO PQ. However, regional laboratories are neither ISO 17025 accredited nor WHO prequalified.

Quality of medicines still remains a problem in Uzbekistan. In 2009, WHO conducted a survey on the quality of anti-TB medicines in six former Soviet Union countries, including Uzbekistan. The results of the survey were published in a 2011 report. The study found that 3 of 7 samples of rifampicin capsules and 3 of 11 samples of isoniazid tablets failed quality tests in Uzbekistan. Although the WHO survey has limitations, including the small number of samples collected and tested and the limited scope of medicines targeted, these results indicate that there are quality issues related to noncompliance with GMP, as well as issues with QC of medicines and regulatory enforcement.

The type of GMP technical assistance that PQM provides is highly needed in the country. Uzbekistan graduated from Global Fund support for procurement of first-line anti-TB medicines to procurement with domestic funds. The government’s strategy is to develop local manufacturing capacity for anti-TB medicines and ensure that locally produced quality-assured anti-TB medicines are available on the local market. For this purpose, PQM provides important technical assistance to anti-TB medicines manufacturers to improve their GMP compliance standards and to the MRA to improve its capacity to ensure the quality of medicines on the local market.

III. Quarter 4 Progress by Objective

Objective 1 – Increase availability of locally manufactured quality-assured anti-TB medicines

In Q4, PQM continued to provide support to Nobel Pharmsanoat with its anti-TB product, levofloxacin. The manufacturer is committed to improve its QA system to meet international standards, and PQM provided technical assistance to assess a cross-contamination risk between the products manufactured at the new site and the products manufactured at the adjacent facility, as well as to develop risk mitigation measures. The 4-day risk assessment audit included the plant walkthrough and review of the building design plans and technical drawings of the sites. PQM provided hands-on technical support to Nobel Pharmsanoat staff for risk assessment and mitigation of cross-contamination. A CAPA list of risk mitigation strategies for each of the risks identified was recommended and discussed with Nobel Pharmsanoat staff. PQM will continue to assist the manufacturer in developing and implementing the CAPA plan.

Objective 2 – Strengthen the medicines quality control system

In Q4, PQM developed and provided a report of the assessment of the physical chemical laboratory activities against ISO/IEC 17025:2017 in Tashkent NQCL that was conducted in Q3. The laboratory started work on the corrective actions, and PQM provided assistance in development of the CAPA plan. PQM and the laboratory management had a meeting and discussed the priorities for future PQM technical assistance to the laboratory in FY 2019. PQM will provide several rounds of trainings to the staff of the laboratory and develop an implementation plan, which will allow the laboratory to strengthen its QMS and implement international ISO/IEC 17025:2017 standards in their work.

PQM also completed selection of a vendor for procurement of the equipment for the medicines QC laboratory of the Agency for Development of the Pharmaceutical Industry. The procurement will be executed in FY 2019 Q1.

Objective 3 – Strengthen GMP inspection system

In Q4, PQM arranged a 4-day study tour to a manufacturing facility in Shanghai, China, for three GMP inspectors from the Uzbekistan Agency for Development of the Pharmaceutical Industry. The Uzbekistani GMP inspectors participated in a GMP inspection of the facility, led by a PQM GMP specialist. The participants observed the GMP

inspection and also had an opportunity to be actively engaged by asking questions to the staff of the manufacturer and discussing the audit findings with the PQM staff. This experience will contribute toward strengthening the capacity of the Uzbekistan GMP inspectorate for conducting GMP audits according to international standards.

The Agency for Development of the Pharmaceutical Industry developed a regulation according to which GMP compliance becomes mandatory for all pharmaceutical manufacturers in Uzbekistan beginning in 2023. The new GMP guidelines, which are harmonized with international GMP, are currently under review by the Uzbek government.

The Agency for Development of the Pharmaceutical Industry confirmed its intention to establish a working team responsible for preparation for PIC/S and to work on the self-assessment as trained by PQM. Based on these activities, PQM will develop a roadmap toward PIC/S membership of the Agency for Development of the Pharmaceutical Industry and prepare further recommendations concerning improvements and readiness for the PIC/S membership application.

Latin America & the Caribbean



Amazon Malaria Initiative (AMI)

I. Quarter 4 Highlights

This quarter, MedvigiL1, a tool to assist inspectors in performing visual inspections of registered medicines in the field and send alerts to the MRA, was deployed in Peru.

II. AMI Context

USAID and USP have provided technical assistance to the Amazon Malaria Initiative (AMI) since 2001. AMI offered a multidisciplinary approach whereby international partners and country stakeholders provided support to prevent and control malaria in Brazil, Colombia, Ecuador, Guyana, Peru, and Suriname in South America, and subsequently to selected countries in Central America. In the context of AMI, the PQM program provided assistance to ensure the availability of quality medicines and to QA and QC systems in participating countries.

Although PQM's funding for AMI ended in FY 2015, pipeline funds were committed to complete development and deployment of MedvigiL1, a tool to assist visual inspection of medicines in the field, in selected countries. Visual inspection is the first stage in the evaluation of the quality of medicines. During this process, the package conditions, label, and physical characteristics of the dosage form are assessed and compared with the information existing for the registered product as it appears in the MRA register. A common challenge for visual inspection is that inspectors in the field do not have the registration information at hand and gaining access to it on the MRA's website may not be a straightforward process. Many agencies do not even have this information digitalized or available on the internet. In addition, access to the internet in surveillance areas is frequently deficient or nonexistent. Use of this tool will enable a faster response when suspicious or identified poor-quality medicines are found in the field.

MedvigiL1 also empowers frontline health workers in the inspection of the quality of medicines closest to the point of care of patients, though its use would be beneficial as well at other stages of the supply chain (e.g. customs, central and decentralized warehouses). MedvigiL1 can be accessed through web-based or mobile device-based applications. When poor-quality medicines are suspected or identified, MedvigiL1 allows users to send alerts to the MRA. These alerts can include photos taken within the application in mobile devices or uploaded through the web application. Mapping of the sampling site is also included if GPS is enabled in the device. Importantly, when internet is not available, MedvigiL1 in mobile devices can also be utilized offline to access medicines information.

Although regulatory authorities in Ecuador and Peru originally expressed interest in piloting this tool, due to changes in agency authorities in Ecuador, deployment was performed only in Peru.

III. Quarter 4 Progress by Objective

Objective 1 – Deploy MedvigiL1 in pilot countries

During a workshop held at Peru's MRA (DIGEMID by its Spanish acronym), PQM trained inspectors from DIGEMID and selected regional health offices on the use of MedvigiL1. Subsequently, attendants were assigned to four groups, and MedvigiL1 was tested in the field at several warehouses located in Lima. A summary of the findings were presented, and the benefits and limitations of MedvigiL1 were discussed. The report on this activity will be available within the next couple of weeks.

DIGEMID will assign a limited number of inspectors to continue with the pilot study in the country and committed to providing periodic reports on the suspicious products identified and the alerts sent utilizing MedvigiL1.

Core Portfolio



Core MNCH

I. Quarter 4 Highlights

The PQM-supported Ukrainian manufacturer for magnesium sulfate had its dossier accepted for review by WHO PQT in July 2018. A dossier number was assigned, and it is currently under review.

II. Health Element Context

In 2015, the Sustainable Development Goals were adopted by world leaders to build on the success of the Millennium Development Goals. Goal 3, “Ensure healthy lives and promote well-being for all at all ages,” encompasses targets similar to USAID’s Ending Preventable Child and Maternal Deaths (EPCMD) initiative. The EPCMD initiative focuses resources on 24 priority countries toward life-saving interventions that have the greatest impact on mortality. These 24 countries, primarily in sub-Saharan Africa and South Asia, account for 70 percent of child and maternal deaths.

In the 24 priority countries, 4.6 million children and 200,000 mothers have been saved through interventions supported by USAID. Although much success has been accomplished, a greater collaborative effort is needed to achieve the EPCMD goal of saving the lives of 15 million children and nearly 600,000 women by 2020.

Other recent USAID initiatives, such as “USAID’s Vision for Health Systems Strengthening (2015–2019),” also contribute to the EPCMD goals of saving the lives of women and children. Within the vision, a health system consists of six core functions, one of which is medical products, vaccines, and technologies. This function not only assures an uninterrupted supply of quality-assured medicines, but also strengthens medicines regulatory capacities to protect populations against poor-quality medicines, which is the essence of PQM’s technical expertise.

III. Quarter 4 Progress by Objective

Objective 1 – Increase the availability of quality-assured MNCH products

During Q4, PQM provided technical assistance to manufacturers of the following MNCH products:

- **Magnesium sulfate FPP:** The Ukrainian manufacturer’s dossier for magnesium sulfate was formally accepted for review by WHO PQT in July 2018. PQM continues technical assistance to the manufacturer in preparation for the WHO PQ inspection. This includes training on data integrity that was conducted by PQM in September 2018, at which 25 staff members from different departments were trained. The training will help strengthen and improve the manufacturer’s quality systems.

Another PQM-supported manufacturer has produced 3 pilot batches of 30,000 ampoules of magnesium sulfate and is currently conducting a stability study. The manufacturer will collect 6-month stability data in October, and with PQM’s assistance, will prepare the product dossier for submission for WHO PQ in late November 2018.

- **Oxytocin FPP:** The second manufacturer working on magnesium sulfate is also initiating work on development of oxytocin FPP. PQM will provide technical assistance as needed.
- **Amoxicillin FPP:** PQM has identified a manufacturer that can potentially work toward WHO PQ of its amoxicillin FPP. PQM has engaged in discussions with the manufacturer and is awaiting feedback on a visit date for a GMP assessment and dossier preparation at the manufacturing facility.

PQM is continuing to provide technical assistance to manufacturers of different priority products at various stages to ensure they make progress toward WHO PQ or for global procurement eligibility. This assistance will include providing responses to WHO PQ for dossier queries and a GMP mock audit of the magnesium sulfate FPP manufacturer in preparation for WHO PQ inspection.

Objective 2 – Help to increase access to quality-assured MNCH products

In Q4, PQM participated in the meeting of the East Africa Community (EAC)-MRH Programme. EAC-MRH and PQM discussed potential collaboration to facilitate registration of quality-assured MNCH products in the EAC countries by using the regional harmonized review process. The aim of this effort is increasing access to quality-assured MNCH products in EAC countries. It was agreed that PQM would provide assistance to the EAC in organizing the next

meeting of the Expert Working Group on Medicines Evaluation and Registration. On the other side, PQM will work to engage two to three manufacturers of MNCH products to submit their dossiers for oxytocin and magnesium sulfate for EAC review at the next meeting of the working group.

PQM initiated a kickoff meeting with PQM Pakistan and PQM Indonesia to discuss the engagement of an Indonesian manufacturer to submit its WHO-prequalified oxytocin dossier to Pakistan's DRAP for registration of their product in the country through the WHO Collaborative Registration Procedure mechanism. This activity aims to help DRAP, which recently became a WHO Collaborative Registration Procedure participant, to start effectively using this mechanism for registration of WHO prequalified products in the country.

Objective 3 – Provide technical leadership in support of availability of quality-assured MNCH medicines

PQM initiated a discussion with the pharmaceutical company GlaxoSmithKline (GSK) to transfer the product and manufacturing know-how pertaining to Umbipro (chlorhexidine gel) to PQM, such that PQM could subsequently build the capacity of several local manufacturers in a more hands-on manner. Through this new collaboration, GSK will share manufacturing expertise and specifications for Umbipro to stimulate local production and sustainable access to this critically needed product in low- and middle-income countries. PQM will provide technical assistance in the form of training and technology transfer to local manufacturers interested in producing quality-assured chlorhexidine.

GSK and PQM discussed and agreed upon a detailed implementation plan with timeframes, and the project officially launched in September 2018.

In FY 2019 Q1, PQM will visit the GSK manufacturing site to learn the manufacturing process and review the dossier and technology transfer report.

Core NTD

I. Quarter 4 Highlights

One of the manufacturers that PQM is providing technical assistance to for praziquantel FPP has received approval for the bioequivalence protocol from the local regulatory authority. The manufacturer and CRO can now prepare and initiate the enrollment of subjects for the bioequivalence study to ensure that timelines are not delayed.

II. Health Element Context

NTDs have been a global concern for decades and a major cause of morbidity and mortality worldwide. More than a billion people—one-sixth of the world's population—suffer from one or more NTDs. These diseases affect the world's most vulnerable populations, almost exclusively 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.

A major constraint to the effective scale-up of NTD control and elimination programs is the scarcity of quality-assured medicines suppliers and limited number of products. WHO has invited manufacturers to submit an EOI for NTD product evaluation in an effort to support national and global efforts to increase access to and affordability of treatment. The most recent invitation from WHO focuses on five single-ingredient medicines (albendazole, diethylcarbamazine, ivermectin, mebendazole, and praziquantel) used in the treatment of lymphatic filariasis, soil-transmitted helminthiasis, onchocerciasis, and schistosomiasis. Of the five treatments listed in the WHO EOI, albendazole, mebendazole, and praziquantel have become priority products for WHO and USAID NTD teams.

As PQM continues support for manufacturers to achieve PQ of anti-NTD medicines, some constraints for manufacturers have become evident, including a scarcity of API suppliers that can fulfill the WHO requirements of FPP manufacturers to participate in the PQ of their products. One mechanism available to manufacturers that the WHO NTD team has begun rigorously implementing is the ERP process. This process allows manufacturers to partake in a rapid quality risk assessment of its product dossier and the level of GMP compliance at its manufacturing sites.

Additional constraints toward the submission of an application for WHO PQ include the lack of capital investment for promising FPP manufacturers that would allow them to improve their infrastructure and equipment capabilities to meet GMP requirements, as well as a lack of funding for conducting bioequivalence studies in a CRO that is compliant with good clinical practices. One significant advantage for NTD product manufacturers requiring

bioequivalence studies is that the ERP process allows an FPP manufacturer to go through this rapid assessment prior to investing in costly bioequivalence studies. With only acceptable comparative dissolution studies, a manufacturer may submit an application for the ERP process with a commitment to complete bioequivalence studies at a future date.

To overcome these challenges, it is necessary to provide technical assistance to API and FPP manufacturers in order to increase the pool of GMP-compliant suppliers.

III. Quarter 4 Progress by Objective

Objective 1 – Increase availability to quality-assured NTD medicines

In Q4, PQM provided technical assistance to manufacturers of the following NTD products:

- **Praziquantel API:** PQM continued to provide technical assistance to two manufacturers in their response to WHO PQ dossier queries for praziquantel API. Additional data and responses were submitted in September, and both manufacturers are awaiting further responses from WHO PQT.
- **Praziquantel FPP:** With PQM's assistance, one of the manufacturers obtained approval from the local regulatory agency and the ethics committee on the bioequivalence protocol. By receiving this approval, the manufacturer and CRO can now prepare for the enrollment of subjects. The manufacturer is continuing to complete the CAPAs and submitting the evidence to PQM for review. PQM is also working with the manufacturer to source and procure the comparator product for the in vitro dissolution study and bioequivalence study.

PQM staff made a visit to another manufacturer's facility to assess a potential cross-contamination issue. PQM provided feedback to the manufacturer on corrective actions to implement and will be providing a full report in the coming weeks.

PQM is also working with a third manufacturer whose bioequivalence study is scheduled to start in October. Once the study is complete, PQM will reinitiate technical assistance to help compile the dossier for submission for WHO PQ.

- **Albendazole API:** PQM continued to engage with an API manufacturer in its filing for WHO PQ. The manufacturer agreed to provide API for initial batches to the FPP manufacturer that PQM is currently working with toward WHO PQ.
- **Albendazole FPP:** The manufacturer is continuing to identify a permanent source of API. PQM is provided assistance in implementation of corrective actions.

Objective 2 – Technical support for bioequivalence study

The praziquantel bioequivalence protocol for a praziquantel FPP manufacturer received approval from the local regulatory and ethics bodies. By obtaining this approval, the first milestone of the financial support was met and the bioequivalence study can be initiated.

The EOI for an albendazole bioequivalence study has been finalized and was posted in late September.

PQM will also continue to work with a second praziquantel FPP manufacturer on its bioequivalence protocol review and approval process.

Objective 3 – Provide technical leadership in support of availability of quality-assured NTD medicines

PQM has published a Request for Application in response to the development of online GMP training modules. A total of 12 applications were received. A candidate was selected and notified. The candidate is currently undergoing due diligence, and PQM staff are working on the sub-award packet to submit to USAID for approval. This activity will be cost-shared with Core TB.

Core TB

I. Quarter 4 Highlights

A clofazimine FPP dossier was accepted for review by WHO PQT. This is an important milestone since according to WHO's recent "Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB)" clofazimine's importance has been upgraded and it became as one of the essential medicines for treatment of MDR-TB. Currently there is only one quality-assured source on the market, so if the product is approved by WHO, the supply of quality-assured clofazimine could potentially be more secured.

II. Health Element Context

The mobilization of global efforts to intensify the fight against TB and achieve an end to the global epidemic is demonstrated by the adoption of WHO's End TB Strategy by the World Health Assembly in 2014, its endorsement in several WHO Regional Committee meetings in 2015, and the inclusion of "ending the TB epidemic" as a target within the health-related Sustainable Development Goal 3 by the United Nations General Assembly in September 2015.

The U.S. Government's strategy for the global fight against TB is included in the following documents: "Reach, Cure, Prevent – United States Government Global Tuberculosis Strategy (2015–2019)" and the "National Action Plan for Combating Multidrug-resistant Tuberculosis." Both documents are consistent with the WHO End TB Strategy and outline the U.S. Government's support to ensuring availability of affordable quality-assured anti-TB medicines.

Consistent themes within these publications are safeguarding treatment for all people with TB, including drug-resistant TB, preventive treatment for persons at high risk, regulatory frameworks for quality, and the rational use of medicines, thereby making the uninterrupted availability of affordable quality-assured anti-TB medicines crucial to achieving the desired treatment outcomes for people with TB, as well as for the prevention of drug-resistant TB.

III. Quarter 4 Progress by Objective

Objective 1 – Increase the supply of quality-assured TB medicines and medical products

In Q2, PQM provided technical assistance to manufacturers of the following anti-TB products:

- **Clofazimine FPP:** The dossier was accepted for review in August. This is an important milestone, since WHO's recent "Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB)" upgraded clofazimine's importance to an essential medicine for treatment of MDR-TB. Currently, there is only one quality-assured source on the market. With PQM's technical assistance, the dossier was submitted for WHO PQ in Q3, but WHO PQT had questions and queries on the dossier before accepting it. PQM provided technical assistance to the manufacturer to address those queries and additional data were submitted to WHO before the dossier was accepted in August.
- **Rifapentine API:** One manufacturer completed its API manufacturer's dossier, and PQM is reviewing it.
- **Rifapentine FPP:** PQM conducted an initial GMP assessment of a manufacturer in Q3. In Q4, PQM provided follow-up technical assistance to the manufacturer in development of the CAPA plan and implementation of corrective actions.
- **Linezolid FPP:** A PQM-supported manufacturer received the last round of requests for information from U.S. FDA and responded in May. The manufacturer is awaiting final approval of the application from U.S. FDA (tentatively expected in November 2018).
- **Rifampicin/isoniazid/ethambutol/pyrazinamide (4 FDC):** One manufacturer completed the reformulation and has been conducting stability study of the new formulation. The manufacturer is also working with the CRO to incorporate comments received from PQM and WHO PQT on the protocol for bioequivalence study to file for local regulatory and ethics committee approval. A draft dossier (without the bioequivalence data) has been submitted to PQM, and PQM has been reviewing it.

PQM also reviewed and provided comments on the bioequivalence study protocol to a second manufacturer. The manufacturer will work with the CRO to revise the protocol and send to WHO PQT for its confirmation to continue with the bioequivalence study protocol approval. A draft dossier (without the bioequivalence data) has been submitted to PQM, and PQM has been reviewing it.

Objective 2 – Provide technical leadership in support of availability of quality-assured TB medicines

In response to PQM's Request for Application for development of the online GMP training modules, 12 applications were received. PQM reviewed the applications, and selected and notified a candidate in August 2018. The candidate is currently undergoing due diligence, and PQM staff are working on the sub-award packet to submit to USAID for approval. This activity will be cost-shared with Core NTD.

Cross Bureau

I. Quarter 4 Highlights

Media reports were completed for the year and are posted on the PQM website. Information that PQM gathered for regulatory system country profiles for Bangladesh, Malawi, and Nigeria in a newly developed template is being reviewed and updated in consultation with PQM field personnel and/or countries' agencies. Finalized profiles will be included under resources on PQM's website.

II. Cross Bureau Context

PQM's approach to Cross Bureau priorities focuses assistance on MRAs and advocating for medicines quality. Being a core program, implementing activities at the global and regional levels is a priority. This includes developing tools and approaches for sustainable regulatory functions in various settings and promoting regional harmonization. The approach also includes advocacy for medicines QA systems by raising awareness among key stakeholders about the quality of medicines—specifically for medicines that address the key health goals of EPCMD, AIDS-free Generation, and Protecting Communities against Infectious Diseases.

PQM is increasingly recognized for its international role in the medicines QA arena and is viewed by national institutions, international organizations, and regulatory authorities as a leader in promoting medicines quality. Cross Bureau funds allow PQM to explore new opportunities, develop innovative solutions, and overcome challenges to promoting medicines quality in USAID priority countries around the world.

EPCMD is one of three shared goals of the U.S. Government in global health. To address this goal, PQM focuses on developing tools and approaches that could be piloted or adopted in the 24 priority countries. The USAID Office of Health Systems (OHS) embraces implementation of USAID's strategy to promote effective, sustainable, country-owned health systems. The OHS priority areas within the EPCMD priority countries are the focus for all programming priorities, including pharmaceutical systems strengthening and improving the quality of essential services.

PQM's overall technical assistance contributes to USAID Core Global Health Priorities—Saving Mothers, Child Survival, Fostering an AIDS-free Generation, Fighting Infectious Diseases, Family Planning and Reproductive Health, and Health Systems Strengthening. PQM support for Cross Bureau has been primarily focused on raising awareness of the importance of medicines quality, supporting regional networks, and helping to develop new approaches to strengthen medicine regulatory functions.

Technical assistance provided by PQM will continue to focus on improving MRA capacity, promoting the use of quality-assured and effective pharmaceutical products, and supporting development of new QC testing tools for medicines. PQM will execute on these priorities in close collaboration with partner organizations with the common goal of strengthening medicines QA systems and tools.

The revised version of the FY 2018 Work Plan was approved in August and is reflected in the objectives below.

III. Quarter 4 Progress by Objective

Objective 1 – Increase awareness of the importance of medicines quality

Activity 1.1: Attend and present at international meetings/panel discussions

The International Conference of Drug Regulatory Authorities (ICDRA) brings together WHO member state regulatory authorities and international stakeholders to engage participants in discussions on key regulatory matters. The 18th meeting was held this year in Dublin, Ireland, on September 3–7, and the theme was “Smart Safety Surveillance: A life-cycle approach to promoting safety of medical products.” At the pre-ICDRA workshop, PQM's Senior Director, Jude Nwokike, presented on “Changing procurement models: maintaining safety and quality of medical products.” The presentation focused on challenges and risks faced by countries transitioning from assistance provided by global

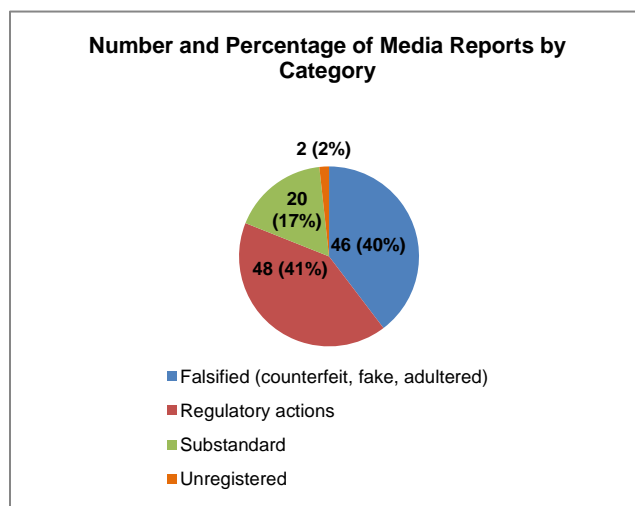
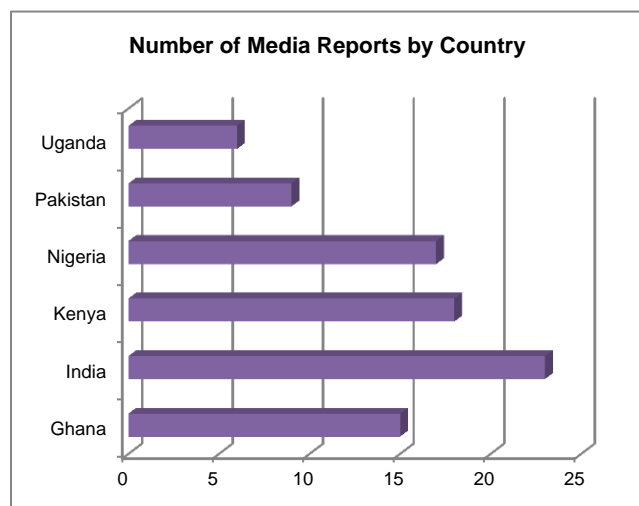
health QA programs. The presentation highlighted options and pathways to sustainability in QA systems, actions required to ensure good procurement practices and medicines quality at the country level, and contributions and lessons learned from PQM interventions in this arena. Mr. Nwokike also held a meeting with leadership from the WHO Regulation of Medicines and other Health Technologies covering several areas of collaboration with PQM.

PQM reviewed and provided suggestions for the development of the concept note for a “Consultation workshop on key enabling factors for successful local production and supply of quality-assured medicines.” PQM will present on key topics at the workshop, whose organization is led by WHO. Objectives of the workshop are to provide training and guidance to African manufacturers on key issues for local production of essential medicines, share experiences and lessons learned in achieving local production of quality-assured products, and understand the gaps and need in capacity-building for pharmaceutical manufacturers and regulators toward local production. The workshop is targeted to take place in November 2018, and the proposed venue is Addis Abba, Ethiopia.

Activity 1.2: Develop customized media reports from EPCMD countries to advocate the need for effective medicine quality assurance systems

Media reports on poor-quality medicines in EPCMD countries were gathered for July–September 2018. The following summary includes the collective data throughout FY 2018, since October 2017. Information will be posted on PQM’s website in FY 2019 Q1.

Mapping of EPCMD countries with media reports for the period October 2017–September 2018



Objective 2 – Provide technical leadership to regional networks of medicines quality assurance professionals

No updates this quarter.

Objective 3 – To improve risk-based quality assurance systems and create models for self-sufficiency and sustainability

No updates this quarter.

Objective 4 – Development of e-Learning course on medicines quality assurance

Following a revision of the scope and module content suggested by the AOR team, new course objectives have been identified and the new draft outline of course modules is being developed. The e-course focus is on the key role quality-assured medicines play in health systems strengthening. In early FY 2019 Q1, the outline will be finalized and the course proposal will be submitted to the Global Health e-Learning Center.

Objective 5 – Establish regulatory system country profiles

Based on overall content of the profiles developed for Bangladesh, Malawi, and Nigeria, a final template was created. The information gathered by PQM for these three countries is currently being verified and completed in consultation with PQM field personnel and countries' agencies. The profiles for the additional proposed countries will be developed using the same template. These profiles provide a snapshot of the legal framework, structures, processes, and overall status of implementation of pharmaceutical regulatory systems in the countries.

Objective 6 – Provide guidance on the importance of medicines quality in Universal Health Coverage (UHC) schemes

No updates this quarter.

Management Overview

The PQM team successfully submitted all new FY 2019 work plans by the USAID deadline of August 31. As PQM enters its final year of implementation, the program drafted new FY 2019 work plans for four country Missions and the Cross Bureau project. These comprehensive documents provide USAID with a considerable amount of information that allows USAID activity managers to clearly understand the plan for the upcoming fiscal year. By submitting the work plans at the end of August, PQM anticipates most will receive USAID approval early in the new fiscal year and be implemented swiftly thereafter. As of the end of October, two of the five work plans had already received full approval.

In Q4, PQM Senior Director Nwokike had a notable trip to Nigeria. In a ceremony held on August 9 in Abuja, Nigeria's NIPRD celebrated attaining ISO/IEC 17025 accreditation, signifying it meets rigorous international standards for testing medicines, food, cosmetics, agricultural products, and herbal products. NIPRD is an essential part of Nigeria's health system. Established as a parastatal under the Federal Ministry of Science and Technology in 1987 and transferred to the Federal Ministry of Health in 2001, NIPRD's primary objective is developing medicines, biological products, and pharmaceutical raw materials. This mandate also includes conducting QA tests as part of its research mandate for locally manufactured medicines, as well as developing specifications for the production of such commodities.



NIPRD Acting Director General, Prof. Kunle Olobayo, stands above as USAID Deputy Mission Director, Dr. Erin Holleran, presents Minister of State for Health, Dr. Osagie Ehanire, with NIPRD's newly-earned certificate of accreditation for quality control from ISO. PQM Senior Director Jude Nwokike applauds in the background.

PQM Senior Director Nwokike also made management support visits to PQM teams in Pakistan and Bangladesh, and made a presentation at the pre-ICDRA workshop on "Changing procurement models: maintaining safety and quality of medical products." The presentation focused on challenges and risks faced by countries transitioning from assistance provided by global health QA programs. The presentation highlighted options and pathways to sustainability in QA systems, actions required to ensure good procurement practices and medicines quality at the country level, and contributions and lessons learned from PQM program interventions in this arena.