Promoting the Quality of Medicines

Strengthening National Quality Control Laboratories in Low- and Middle-Income Countries to Improve the Quality of Medicines

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About PQM

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

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Acronyms

CLM	Collaborative Learning Model
CSP	contract service provider
GFATM	Global Fund for AIDS, TB, and Malaria
GMP	Good Manufacturing Practices
ILAC	International Laboratory Accreditation Corporation
ISO	International Organization for Standardization
LMIC	low- and middle-income country
MOH	ministry of health
NQCL	national quality control laboratory
PQM	Promoting the Quality of Medicines [program]
QA	quality assurance
QC	quality control
QMS	quality management system
SATTA	Stepwise Assessment Tool Toward Accreditation
SOP	standard operating procedure
USAID	U.S. Agency for International Development
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization
WHO PQ	World Health Organization Prequalification [program]

Program Background

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

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

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

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

Executive Summary

Strengthening the medicines quality assurance systems of national quality control laboratories (NQCLs) is critical for assuring the quality of medicines to safeguard public health. Most NQCLs experience challenges in assuring the quality of medical products, in part due to their limited technical capacity. As part of its mandate, PQM strengthens the capacity of NQCLs in low- and middle-income countries to detect falsified and substandard medicines using science-based, cost-effective, customized, sustainable technical interventions that enable accurate and reliable testing of medicines.

This document highlights PQM's technical approach to strengthening medicines laboratory systems in developing countries. Using carefully created targeted interventions, PQM focuses on supporting NQCLs to strengthen their laboratory capacity by providing state-of-the-art analytical instruments, compendial training, and trainings on internationally recognized best practices.

PQM's technical approach to strengthening NQCLs is centered along three processes as follows:

1. **Laboratory system assessment**. PQM conducts a targeted assessment of the quality assurance system and the NQCLs to establish baseline data on the functionality of existing laboratory activities and the level of technical skills. The assessment highlights existing opportunities for improvement and helps to customize practical and feasible laboratory interventions.
2. **Implementation**. After the assessment, recommendations for specific interventions and/or continuous improvement are developed to address identified gaps in capacity and other areas for improvement. Interventions may include the following: supporting the development of legal frameworks to enhance medicines quality testing (e.g., the adoption of pharmacopeial standards as legal documents); training and capacity building of technical personnel on quality management systems and best practices in analytical testing; post-marketing surveillance of medicines; collecting and using quality control data for public health decisions; procuring state-of-the-art analytical instruments; and implementing long-term preventive maintenance plans for the continuous provision of quality-control activities to prevent substandard medicines from reaching the population.
3. **Monitoring and evaluation**. Quality improvement of interventions through effective monitoring and evaluation is a key component of PQM's laboratory system strengthening. PQM incorporates risk identification and mitigation as well as measurement indicators in all of its interventions. Performance indicators (e.g., compliance with pharmacopeial requirements, standard operating procedures developed and implemented, staff adequately trained to perform tests, z-score for inter-laboratory comparison, etc.) are measured continuously throughout the implementation lifecycle, and revised where necessary, in order to align PQM technical support with national and international medicines laboratory technical standards.

As a result of PQM's work, NQCLs in 40 countries have stronger quality assurance systems, leading to improved detection of poor quality medicines and subsequently stronger public health systems.

1. Introduction

Pharmaceutical supply chains in low- and middle-income countries are vulnerable to the introduction and proliferation of substandard and falsified medicines and medical products. Therefore, continuous monitoring of medicines quality across all levels of the supply chain is critical to ensure the safety and efficacy of medicines being made available to the public.

Effective laboratory testing is the cornerstone of assuring the efficacy, quality, and safety of medicines on the market. Along with analytical testing, data generated from national laboratories are used to take regulatory actions and to inform public health interventions associated with substandard and falsified medicines. However, only a small number of laboratories in LMICs have met the internationally recognized standards and best practices set forth by ISO 17025:2005 or the WHO Prequalification (PQ) program, which helps to ensure that laboratories can consistently produce reliable and accurate laboratory results. Therefore, additional efforts to strengthen quality control laboratories in LMICs are necessary to respond to the global need for quality-assured medicines.

NQCLs play an active role in assuring medicines quality and detecting substandard and falsified medicines. Most LMICs have NQCLs that are mandated to conduct routine testing of medicines quality to support market authorization and for post-marketing surveillance. However, insufficient technical capacity, lack of required technology, extensive instrument maintenance breakdown, lack of reference materials, and limited resources hinder the ability of NQCLs to effectively carry out their mandates.

To help address these challenges, PQM uses a comprehensive collaborative technical approach to build the managerial and technical capabilities of NQCLs to strengthen their ability to detect substandard and falsified medicines and maximize the use of existing resources in their country.

Since 2009, PQM has worked in 40 countries to conduct laboratory assessments, implement effective quality management systems, build capacity for proper analytical testing, and continuously refine interventions that support NQCLs to assure the quality of medicines. This document outlines PQM's technical approach, including the processes, procedures, and tools used to successfully strengthen the quality control and quality assurance capabilities of laboratories in developing countries.

The key components involved in providing technical assistance and support to NQCLs are as follows:

1. **Laboratory capacity assessment**, where baseline information on the laboratory's strengths, opportunities, and challenges are identified to inform specific/customized interventions that are aligned with the country's quality assurance needs and essential medicines priorities. PQM believes that no two countries are the same; as such, initial baseline data are important for determining approaches and activities that will successfully strengthen laboratory quality assurance systems.
2. **Implementation**. Following the identification of deficiencies and opportunities for improvement, PQM works collaboratively with country partners and international stakeholders to strengthen the laboratory's quality assurance system. These efforts include capacity building and training of technical staff, and the development of laboratory system manuals, strong quality management systems, effective quality control techniques, instrument maintenance plans, and laboratory information management. These activities enhance the overall proficiency of laboratory practices toward accreditation or prequalification and promote the acceptance of the laboratory's data for regulatory decisions.

3. **Monitoring and evaluation**. Follow-up monitoring helps to incorporate continuous quality improvement into the processes and interventions developed by the laboratories. Continuous improvement and monitoring of laboratory progress toward set goals helps to generate the requisite data reflecting the success of NQCLs. Opportunities are presented to realign interventions to national and international priorities for stronger laboratory services in public health practices. As part of its evaluation, PQM works with monitoring and evaluation experts to collect and measure success indicators associated with medicines quality—compliance to pharmacopeial requirements, standard operating procedures developed and implemented, staff adequately trained to perform tests, z-scores for inter-laboratory comparisons, etc. —are measured continually throughout implementation to assure that PQM's quality interventions address national, regional, and international goals.

Furthermore, PQM collaborates extensively with national and international agencies, technical experts, and implementing partners to leverage resources to build sustainable quality assurance systems. PQM works with accreditation bodies to coordinate mock and final inspections with NQCLs that aim to achieve ISO 17025 accreditation, and works with qualified laboratory instrument calibration providers and vendors to improve the quality of medicines in resource-limited countries. PQM also collaborates closely with the WHO to support national laboratories in gaining WHO PQ, which supports standard testing of essential priority medicines for procurement and distribution by Global Fund, UNICEF, and other international procurement agencies.

2. PQM Technical Approach to Strengthening NQCLs

PQM's approach to strengthening laboratory systems focuses on supporting the use of internationally recognized standards in good laboratory practices (GLP), quality management systems (QMS), instrument maintenance and calibration, proper application of pharmacopeial standards, standard operating procedures, and hands-on analytical testing and quality control. PQM applies science-based, cost-effective, and customized solutions for testing and monitoring the quality of medicines to detect falsified and substandard medicines at the national level. With this approach, PQM has helped NQCLs to develop stronger laboratory quality management systems, comprehensive laboratory quality assurance policies and practices, medium- and long-term instrument maintenance plans, and risk-based sampling and testing activities.

PQM closely collaborates with international public health agencies, including the WHO, USAID, GFATM, Bill and Melinda Gates Foundation, and other implementing partners to strengthen laboratory systems.

PQM's approach to laboratory strengthening has led to the following national, regional, and global advances:

- Strengthened regional regulatory systems for improving the capacity of quality control laboratories through the Network of Official Medicines Control Laboratories (NOMCoL).
- Improved laboratory capacity building through PQM's Collaborative Learning Model (CLM), which strengthens capacity through the exchange of information, collaboration, and inter-laboratory training opportunities.
- Since 2009, thirteen NQCLs have achieved international standards of accreditation for testing and calibration laboratories (ISO 17025), and four others gained WHO prequalification recognitions.

3. Laboratory Systems Assessment

PQM begins technical activities by collecting and analyzing current data on the capacity of laboratories to ensure the quality of medicines. PQM conducts a baseline assessment of the laboratory network within the country and the overall quality assurance practices in the country. Data collected from this assessment is used to inform the country-appropriate response to capacity building.

To support these initial activities, PQM uses standardized and internationally accepted methods of assessment (e.g., international health regulations and health impact assessment tools) and develops project-specific assessment tools as necessary. While many internationally recognized tools provide overarching understanding of health systems, many do not adequately capture medicines quality assurance indicators. Accordingly, PQM has developed additional in-house assessment tools that specifically focus on laboratory quality assurance, laboratory testing capacity, and overall compliance to international standards.

The Stepwise Assessment Tool towards Accreditation (SATTA) and the Laboratory Capacity Maturity Model (LCMM) are among the tools that PQM uses to evaluate the strength of quality assurance of medicines and medical devices in LMICs. SATTA is a tool designed to support the assessment of different aspects of quality management systems of NQCLs. SATTA incorporates the different elements of quality control from ISO 17025 and WHO PQ. PQM has tested this tool in four countries in Asia and Africa. The use of this tool has led to the creation of country QMS profiles as they work toward international accreditation. Data from this tool has led to the development of tailored approaches to strengthen QMS in these countries.

Box 1. **Country Highlight: Gap Analysis in Country X Determines the Need for Capacity Strengthening in Medicines Quality Assurance and Quality Control**.

Country X is among the countries with a high burden of preventable diseases, including multi-drug resistant tuberculosis; malaria; and maternal, neonatal, and child health problems. However, the root causes of substandard and falsified medicines in Country X were unclear. PQM used its Medicines Regulatory, Quality Assurance, and Quality Control Systems assessment tool to assess medicines regulation and quality assurance systems in the country. The tool was adapted from WHO's Global Benchmarking Tool and other PQM resources and has been successfully applied in many countries.

The gap analysis in Country X identified deficiencies in the capacity of the quality control laboratory to conduct compendial testing and a lack of technical laboratory expertise, among other deficiencies. PQM recognized opportunities for improvement and recommended a stepwise implementation of capacity building activities for the country's laboratory and regulatory body. PQM has been working with two QC laboratories in parallel to strengthen their QA/QC systems.

The LCMM is a tool aimed at evaluating the analytical capacity of NQCLs prior to the implementation of laboratory-strengthening efforts. This is a high-level tool that provides overarching information on the laboratory and its capacity to conduct essential services. The tool covers the technical and specialized areas necessary to provide systematic quality control services.

Together, the LCMM and SATTA tools have been used by PQM to collect baseline information on the capacity of testing laboratories. The use of these tools has led to the identification of laboratory gaps and testing priorities, and the development of quality management systems and instrument maintenance support for calibration and testing laboratories. Copies of these tools can be found in Annex 1.

4. Implementation of Laboratory Activities

After identifying country needs, gaps, priorities, and resources, an implementation plan is crafted to fit the goals of NQCLs and build stronger laboratory quality assurance systems. Using a team of technical experts, PQM works with the national agencies and NQCL to build and strengthen laboratory quality management systems, including good laboratory practices, laboratory auditing, instrument maintenance strategies, and compendial testing.

At the heart of PQM's implementation approach is the use of cost-effective and sustainable capacity building of key personnel in NQCL. PQM conducts in-service technical training and capacity building of key laboratory personnel through a train-the-trainer Collaborative Learning Model (CLM), which encourages peer-to-peer sharing of technical knowledge and skills.

To effectively implement its activities, PQM's technical approach is categorized into three overarching core competencies: 1) laboratory quality management systems strengthening, 2) short-term technical assistance support, and 3) analytical laboratory testing services.

Strengthening Quality Management Systems

Quality management systems (QMS) in NQCLs help to assure the quality of medicines using internationally recognized standards of practice. PQM leverages the long history of technical expertise developed within USP as a global standard-setting organization. PQM supports national laboratories in developing effective quality management systems, developing standard operating procedures (SOPs), assuring good documentation practices, promoting data integrity, and enabling the effective transfer of technologies. The overall outcome of this core competency is resilient and sustainable laboratory systems. Specific activities include the following:

- Assist governmental and non-governmental laboratories in developing laboratory strategic plans, quality systems documents, quality manuals, policy manuals, SOPs, and staff development curricula.
- Advise on the development of equipment/instrument qualification and maintenance strategies for continuous operation of laboratory instruments.
- Evaluate laboratory administrative, quality, and technical systems for compliance with international best practices and the requirements of USP and other acceptable compendia.
- Conduct training on topics related to the development, implementation, and maintenance of quality systems; internal auditing; management reviews; corrective and preventative actions; and root-cause analysis.

In 2010, PQM supported the Government of Liberia to enact pharmaceutical laws that set the stage for establishing a medicine regulatory agency (MRA). Along with the MRA, PQM worked with the Ministry of Health (MoH) to create a medicine testing laboratory (NQCL). PQM worked with the management and staff of the NQCL to develop a laboratory manual and more than 50 SOPs, leading to improved laboratory procedures and competency.

Another approach for scaling-up PQM's technical assistance, reducing costs, and facilitating country ownership of quality control laboratories in LMICs is the use of the Collaborative Learning Model (CLM). The CLM facilitates the transition of trainees to become trainers after technical and managerial competencies have been built. Those trained under this model act as trainers and in turn train colleagues in their own country or in other countries through South-South collaboration. This model was successfully applied to two laboratories in Nigeria. First, PQM supported the Agulu laboratory in Lagos in obtaining ISO 17025 accreditation. Following

this achievement, the Agulu laboratory staff, trained by PQM, in turn assisted the Kaduna laboratory in successfully obtaining ISO 17025 accreditation. The CLM approach reduces training costs and promotes country ownership and collaboration among laboratory staff. A detailed summary of the successful application of CLM and the lessons learned is available on request.

To foster harmonization, information sharing, and collaboration among laboratories in developing countries, PQM supports the establishment of the Network of Official Medicines Control Laboratories (NOMCoL). NOMCoL brings together NQCLs in Africa, Asia Pacific, and the Middle East/North Africa (MENA), and provides an opportunity for ministries of health and NCQLs to share best practices, quality issues, and lessons learned both regionally and internationally. NOMCoL Africa consists of 13 countries with official medicines control laboratories. The success of NOMCoL Africa prompted the development of two additional NOMCoLs, NOMCoL MENA in 2010, and NOMCoL Asia Pacific in 2013. The NOMCoLs seek to protect public health in their respective regions by strengthening the capacity of the official medicines control laboratories and promoting scientific and technical collaboration. As such, the networks help promote the safety of patients, within the general framework of the pharmaceutical legislation of each member country, so that the results given by the laboratories concerned can be used to enforce the law in another country if necessary.

Short-term Technical Assistance Support

Short-term technical assistance (STTA) is defined as the full-time training of clients in a specialized area over a short period (120 days or less).[1] PQM technical support initiatives are based on series of STTAs that span multiple visits and focus on one specific technical area at a time. This approach ensures that NQCLs continue to provide key support to stakeholders and customers with a limited disruption of services. STTA allows for the incremental progression of skills development and technical capacity toward the attainment of set targets, with defined milestones. The use of the STTA approach allows PQM to provide real-time hands-on activities at the clients' service delivery points, with minimum interruption of routine analytical works. STTA support is provided either directly or indirectly. With direct STTA, technical experts and consultants from PQM headquarters in the United States travel to the clients' site of service to conduct training and skills development (also called North-to-South). With indirect support, previously assisted NQCLs in developing countries share their technical knowledge with NQCLs in other developing countries in the same or across regions, helping the latter attain the same level of expertise as the former (also called South-to-South). Common STTA activities along the continuum of services offered by PQM's technical experts are outlined below:

- Training in the calibration and qualification of analytical equipment and optimizing the selection of appropriate instruments for efficient utilization.
- Conducting training-of-trainers (TOT) for technical staff involved in quality control and technical operations of medicine testing, compendial analysis, good pharmacopeia practices (GPhP), and the proper use of reference standards.
- Conducting quality audits, good laboratory practices (GLP) assessments, and quality control inspections of GMP.
- Training to develop a laboratory sustainability plan, using portions of the NRA strategic plan as a guide, for continuous improvement and expansion of the laboratory.

[1] As defined by USAID's ADS Chapter 458

Analytical Laboratory Services

In instances where increased capacity is needed to employ advanced methods of laboratory testing, PQM supplements the lack of capacity by conducting laboratory testing. This support is provided by staff at any of USP's ISO 17025 accredited laboratories in Brazil, China, Ghana, India, or the U.S. Between June 2016 and July 2017, PQM conducted 52 analytical tests on 20 lots of samples collected from nine countries, including Argentina, Democratic Republic of the Congo, Kyrgyzstan, Laos, Liberia, Nigeria, Pakistan, and the U.S. Method stability studies were conducted to determine the stability of anti-TB and antimalarial medicines, a key area of need in LMICs. Although most LMICs possess the basic technology to detect falsified samples, research into stability methods is lacking, making PQM work in this area relevant.

In addition to testing services, PQM provides on-site training at its headquarters for selected personnel from developing countries through USP's Visiting Scientist Program. The Visiting Scientist Program provides opportunities for resource-limited laboratory staff to observe USP's state-of-the-art laboratory infrastructure and processes first hand. This exposes them to international laboratory quality assurance and quality control best practices. Countries that have benefited from this program include Indonesia, Liberia, Nigeria, Papua New Guinea, and Ghana. With this additional program, PQM provides on-the-job training to support the effective implementation of its programs *(see Box 3)*.

Box 3. PQM Visiting Scientist Program

In 2016, PQM supported the Quality Control Manager from Liberia's National Quality Control Laboratory to visit USP laboratories in Rockville, Maryland for two weeks. The visiting scientist worked with PQM technical experts in the laboratory to study high performance liquid chromatography (HPLC) and good laboratory practices. Upon returning to Liberia, the visiting scientist was able to implement key interventions learned from his visit to improve the detection and control of substandard medicines in his country, including the following:

- Reduced the reliance of visual inspection to assess medicine quality from 85% to below 60% in three months.
- Introduced the use of uniformity of weight for tablets and capsules as additional measures to determine sample variations prior to chemical testing.
- Implemented safety control measures, including personal protective equipment, in the laboratory
- Introduced data integrity and good documentation practices in the laboratory to improve accountability of tests.

With the exposure of working in an ISO-accredited laboratory at USP, visiting scientists are able to make a sustained impact on the quality assurance of medicines in their respective country.

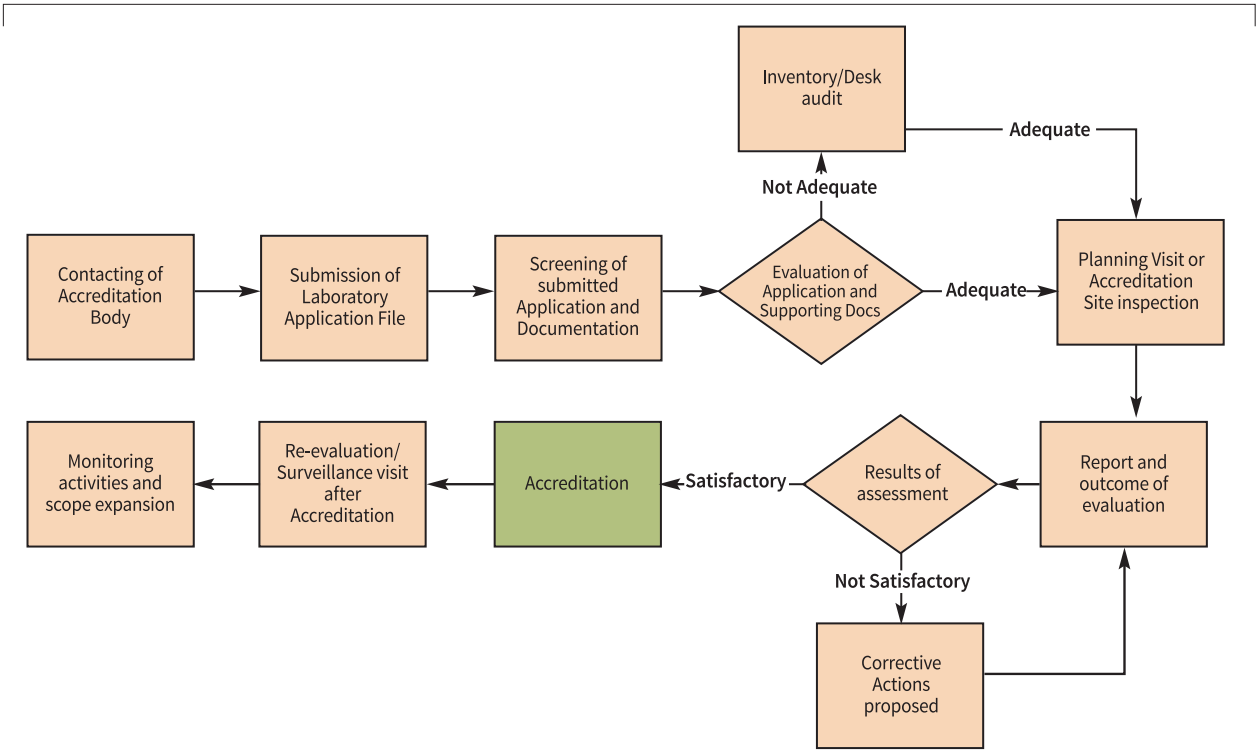
Analytical Instrumentation Support

In addition to the QMS and analytical services highlighted above, PQM supports the development and implementation of analytical instrument calibration and qualification services. The analytical instrument support program (AISP) is a new initiative of PQM aimed at ensuring the self-reliance and sustainability of NQCLs' instrument maintenance support. By building the capacity of NQCLs in instrument qualification activities and training in-house experts, NQCLs are able to effectively maintain the functionality of their instruments. Resources previously invested in service providers can now be invested back into the laboratory to meet other important demands such as consumables, personnel, and additional instrumentation. Details on PQM's analytical instrumentation support program can be found in the document *Analytical Instrumentation Support for National Quality Control Laboratories*.

Implementation Lifecycle

PQM employs a stepwise continuous improvement process to successfully implement QMS in LMICs. At the start of QMS implementation, PQM works with NQCL management, NRAs, and other relevant partners to build consensus, set expectations, agree on timelines, and allocate the resources needed to reach the goal of international recognition. The attainment of international recognition of testing services by calibration and testing accreditation organizations (ISO 17025 or WHO PQ) is the hallmark of the strong laboratory quality assurance systems. PQM therefore works with the respective NQCL and the NRA, incrementally, to complete the QMS implementation lifecycle *(Figure 1)*.

Figure 1: *PQM's QMS Implementation Lifecycle*

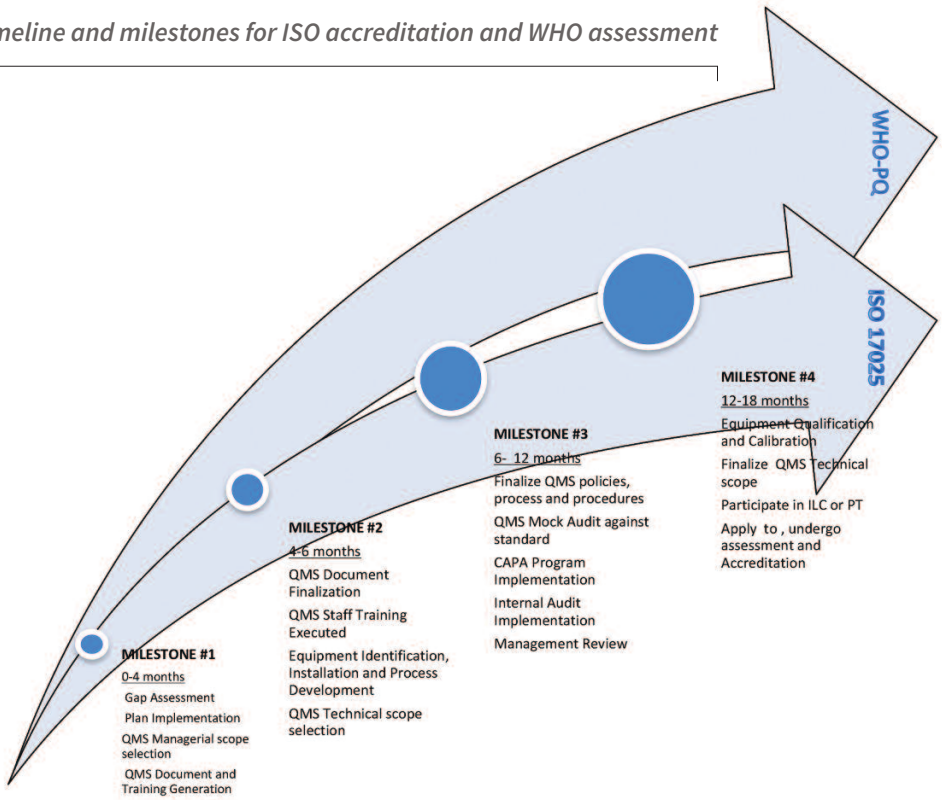


PQM works with the laboratory to develop documentation (i.e., SOPs), processes, and other relevant information to submit the initial laboratory application file for accreditation. The respective accreditation body then reviews the documents submitted by the laboratory for completeness and accuracy. When this document is found to be adequate, a site inspection may be undertaken by the accreditation body to assess the readiness of the laboratory for certification on the requested scope. Observations and reports from the accreditation body will indicate if additional corrective and preventive action (CAPA) is needed. When found satisfactory, the laboratory may receive accreditation. Throughout this process, PQM works with the laboratory as a supporting partner, with the laboratory taking ownership to drive the entire implementation lifecycle.

The initial support for accreditation or prequalification is financially and technically supported by PQM. However, following the initial accreditation, PQM advocates for the NQCL and the NRA to develop the in-house technical skills and financial responsibility to assume reaccreditation and requalification and subsequently manage the QMS contractual activities with the third-party providers.

The process of preparation, training, capacity building, and developing relevant materials to establish a strong quality management system varies considerably by laboratory. However, PQM's estimated timeline for working with an NQCL with basic laboratory infrastructure and relevant manpower to achieve initial ISO accreditation and WHO prequalification is at least 18 months *(Figure 3)*.[2] The requirements for ISO accreditation or WHO prequalification are similar; therefore, they can be performed separately or in parallel based on the needs and commitment of the laboratories.

Figure 2: *Timeline and milestones for ISO accreditation and WHO assessment*



[2] WHO prequalification is free or at limited cost for OMCL laboratories. ISO accreditation bodies charge a fee for the accreditation process. The timeline for WHO PQ is dependent on WHO's schedule. Direct contracting of ISO accreditation bodies provides greater flexibility in scheduling.

Working in a stepwise manner with clearly defined milestone indicators, PQM progressively builds the capacity of NQCLs to attain accreditation. QMS implementation is divided into multiple phases: gap assessment, documentation prioritization, implementation, basic technical training, accreditation body/WHO submission, proficiency testing, third-party visit, successful completion, additional submissions, and follow-up (see Figure 3). At each milestone, PQM works with the NQCL to implement any adjustments necessary to achieve the requirements of the subsequent milestone.

Maintaining a strong quality management system within the laboratory requires commitments and financial resources that, with proper assistance, can yield financial returns and therefore support long-term sustainability, in addition to protecting populations from poor quality medicines.

Planning for Sustainability

To further ensure prudent resource allocation, cost-effective implementation, and harmonization of technical assistance, PQM uses a comprehensive, collaborative, and integrated method for laboratory strengthening. In this methodology, five interrelated areas of NQCL operations are assessed and strengthened based on the public health risk to the country. The five related laboratory areas are:

- National health/pharmaceutical/laboratory policy,
- Risk-based service delivery,
- Medical products quality monitoring and enforcement,
- Compliance with current Good Laboratory Practices, and
- Laboratory quality management and technical principles

Each of these areas is critical to the successful implementation of effective in-country governance of quality assurance of medical products, contributing to stronger health systems.

5. Results of Laboratory Activities

For nearly 200 years, USP has been the leading organization in setting standards of practice for pharmaceutical product manufacturing and quality assurance. The PQM program is uniquely positioned to strengthen the quality control of medicines and medical products in LMICs. Unlike other providers in this space, PQM is able to capitalize on USP's technical know-how in chemistry and microbiology and apply these skills to strengthen the capacity of NQCLs to assure the quality of medical products in developing countries.

Since its inception, PQM has trained, advised, and assisted more than 30 NQCLs in a broad range of technical subjects, including general quality management systems, good laboratory and documentation practices, analytical method development and testing, and instrument maintenance and calibration. Over the years, PQM technical experts have worked in more than 30 countries globally *(Figure 4: Countries Supported by within PQM)* in key areas of technical and managerial capacity to strengthen laboratory services. This has led to significant improvements in the global detection and elimination of falsified and substandard medicines, particularly in resource-limited countries. The success of PQM in achieving these targets is partly due to the high caliber of the program's technical experts, who understand the core competencies of a functioning laboratory system.

Table 1: *Countries with laboratories that have obtained ISO 17025 or WHO PQ with PQM technical assistance (2009–2017)*

WHO-PQ	Number
S. Vietnam	1
Kenya	1
Peru	1
Thailand	1

ISO 17025 (Pharma)	Number
Ghana	1
Burma	1
Ethiopia	1
Guatemala	1
Kenya	1
Laos	1
Nigeria	3
Philippines	1
Rost-ov-Don	1
Peru	1
Bolivia	1

From 2009, the PQM program has supported over 21 laboratories and trained more than 1,000 laboratory personnel across Africa, Asia, Newly Independent States, the Middle East, and Latin America. Seventeen laboratories *(Table 1)* have achieved ISO accreditation or WHO PQ with PQM technical assistance.

The success of this work is largely due to the development of sustainable, hands-on training and skill transfer matrices, which were achieved through the technical expertise available within PQM and USP. Even with the high level of technical expertise within PQM, the program further forms strategic alliances and builds mutual relationships with accreditation bodies , WHO, regulatory agencies, USAID implementing partners, manufacturing organizations, contract research organizations, and other national and international organizations that lead the agenda for benchmarking quality assurance of medicines. As a result, PQM's implementation of quality assurance activities has been widely recognized and accepted by global stakeholders, country governments, ministries, and regulatory agencies. Country-specific success stories and lessons learned, highlighting the uniqueness of PQM's technical approaches, are available online **(here)**.

6. Monitoring and Evaluation Strategy

PQM has developed a matrix of indicators to monitor the implementation of its program. Strengthening the quality assurance of laboratories in developing countries is part of the results framework's intermediate results 1 (IR1): Medical products assurance systems strengthened. Specifically, the following sub-IRs are applicable in assuring that the quality of medical products is achieved:

- **Sub IR 1.3** – Standards of practice at national quality control laboratories sustainably improved,
- **Sub IR 1.4** – Institutional capacity for regulatory workforce sustainably improved, and
- **Sub-IR 1.5** – Capacity for post-marketing surveillance of medical products sustainably improved.

Detailed indicators and their measurements are highlighted in Annex 4. Using these indicators, PQM's strengthening of laboratory quality assurance has achieved measurable success, as highlighted by the examples below.

- Monitoring the activities of NQCLs in Ethiopia and Burma revealed that both laboratories were accredited and have now assumed financial responsibility for buying equipment, contracting vendors for maintenance and calibration, and renovating their current laboratory spaces. As these laboratories have matured, both laboratories have budgeted and built new complimentary facilities from their internally generated funds, with no financial or technical support from the PQM program. As such, these laboratories are now able to sustain their operations with internally trained experts and funding sources. This is a reflection of the commitment to quality by the management of the NRAs as they expand their testing needs to effectively monitor the quality of medical products on their market to protect public health.
- With the support of PQM in Nigeria and CIS, both countries have accredited three laboratories each to support the vast populations in these regions. Based on the strategy of parallel support, these laboratories internally communicate continuous improvement opportunities related to staffing, risk-based approaches, finances, and analytical testing. Additional technical, managerial, and continual evaluation has allowed these laboratories to maintain their accreditation and/or WHO PQ certification. The lessoned learned from one laboratory has supported the independent application of WHO PQ in other laboratories. WHO PQ and ISO 17025 accreditation allows these laboratories to test essential medicines that are procured, internally manufactured, and donated at the highest international standards. This also provides coordination in targeting risk-based activities between the laboratories and manufacturers to support their respective NRAs in pre- and post-market product testing and enforcement.
- Laboratories in Kenya and Vietnam achieved ISO 17025 accreditation and WHO PQ approval, respectively. PQM had reviewed their respective technical and managerial capabilities and provided initial technical support to both NMCLs. After evaluating their capabilities, PQM support led to them becoming ISO 17025 accredited and WHO PQ certified.

Through continuous monitoring and evaluation of quality assurance systems in developing countries, regulatory agencies have recorded substantial improvements in the quality control and surveillance of medical products. Through the efforts of PQM, regulatory bodies have developed to be independent, self-sufficient, and sustainable and are strengthening the overall health systems in their countries.

Annex 1. Laboratory Capacity Maturity Model Assessment Tool

Introduction: The Laboratory Capability Maturity Model (LCMM) is a tool used to assess the level of preparedness of laboratories prior to or during technical support visits. This tool is not a replacement for an audit or assessment tool; its purpose is to provide a snapshot of the laboratory's skills/capability maturity. The tool estimates the appropriate module of training or technical support needed for effective quality assurance services. It is intended to give analytical laboratory staff and/or the technical consultant a grade of readiness or progress along the continuum of technical support. There are five (5) levels of maturity as follows:

1. No knowledge at all – this score indicates a lack of knowledge on the topic in the laboratory.
2. Theoretical knowledge – this score is given when theoretical knowledge of the topic exists, but analysts do not have the equipment or the tools to apply this knowledge in the laboratory.
3. Some hands-on skills – this score is given when there is knowledge of the topic and its application in the lab, but the analyst requires supervision at all times.
4. Intermediate hands-on skills – this score is given when the analyst is able to conduct the test or demonstrate knowledge of the topic with limited supervision.
5. Advanced/Expert skills – This score is given when the analysts and/or the lab has an advanced level of theoretical knowledge, hands-on skills, and ability to transfer knowledge and skills to others.

Module 1 – Basic Quality Control Training

The objective of Module 1 is to offer critical routine quality control measurements that are necessary to assure the quality of pharmaceutical products at national or manufacturing quality control laboratories.

Course #	Topic	No Knowledge at all (1)	Theoretical Knowledge (2)	Some Hands-on Skills (3)	Intermediate Hands-on Skills (4)	Advancd/ Expert Skills (5)
1.	Safety in the Laboratory					
2.	Principles of Good Laboratory Practices					
3.	Data Integrity in Quality Control Laboratories					
4.	Good Documentation Practices					
5.	Principles of Good Laboratory Management – laboratory quality management system, quality policy, quality manual					
6.	Viscosity and Refractive Index & Optical Rotation					
7.	Proper Use of Pharmacopeial Standards					
8.	Good Weighing Practices					

Course #	Topic	No Knowledge at all (1)	Theoretical Knowledge (2)	Some Hands-on Skills (3)	Intermediate Hands-on Skills (4)	Advancd/ Expert Skills (5)
9.	Volumetric Solution and Analysis					
10.	Good pH Practices					
11.	Thin Layer Chromatography (TLC) Identification Method					
12.	Screening Technologies Using Point-of-Care (POC) Devices (MiniLab, Rama, CD3, etc.) for product quality					
13.	Disintegration					
14.	Friability Test					
15.	Uniformity of Weight					
16.	Uniformity of Content					
17.	Loss on Drying					
18.	Residue on Ignition					
19.	Melting Point Determination					
20.	Titrations: Aqueous, Non-Aqueous					
21.	Performance Verification of Timers					
22.	Specific Gravity					
23.	Water Conductivity					

Module 2 – Intermediate Quality Control Training

This module builds on the knowledge and skills acquired in the Basic Module to determine the quality of pharmaceutical preparations. This module employs instrument techniques and their application to quality control.

Course #	Topic	No Knowledge at all (1)	Theoretical Knowledge (2)	Some Hands-on Skills (3)	Intermediate Hands-on Skills (4)	Advancd/ Expert Skills (5)
1.	Water Determination – Karl Fischer					
2.	Principles UV/Vis Spectrometer & Best Practices					
3.	Dissolution Performance Verification Test (PVT) Including Mechanical Calibration					

Course #	Topic	No Knowledge at all (1)	Theoretical Knowledge (2)	Some Hands-on Skills (3)	Skills (4)	Skills (5)
4.	Dissolution Testing 1 (Using UV/Vis Spectrometer)					
5.	Pharmaceutical Assay Using UV/Vis					
6.	High Performance Liquid Chromatography (HPLC) – Assay and Identification					
7.	Dissolution Testing 2 (Using HPLC analysis)					
8.	Performance Verification of HPLCs/UPLCs					
9.	Uniformity of Dosage Units					
10.	Fourier Transform Infra-Red Spectrometer					
11.	HPLC – Impurities and Related Substances					
12.	Principles and Implementation of ISO17025					
13.	Atomic Absorption techniques in Pharmaceutical Analysis					
14.	Microbiological Assay – MLT					
15.	Sterility					
16.	Fluorescence Spectroscopy Techniques – General Chapter <853>					

Module 3 – Advanced Analytical Techniques

This module assumes competency of Modules 1 and 2, and that the laboratory has the advanced instrumentation necessary to undertake this module.

Course #	Topic	No Knowledge at all (1)	Theoretical Knowledge (2)	Some Hands-on Skills (3)	Intermediate Hands-on Skills (4)	Advancd/ Expert Skills (5)
1.	Gas Chromatography (including Head Space)					
2.	Ultra-Pressure Liquid Chromatography (UPLC)					
3.	Atomic Absorption Spectrometry (AAS)					
4.	Ion-Exchange Chromatography (IEC)					
5.	Electro-thermal Analysis (Thermogravimetric Analysis, TGA, or Digital Scanning Calorimetry, DSC)					
6.	GC-Mass Spectrometry (GC-MS)					
7.	Liquid Chromatography- Mass Spectrometry (LC-MS)					
8.	Stability Studies (photo and chemical stability – real time, accelerated)					
9.	Analytical Method Development and Validation & Verification					
10.	Equilibrium Dialysis Studies					
11.	Repair, Preventative Maintenance and Troubleshooting of HPLCs/ UPLCs					
12.	Chemometric techniques in drug analysis					
13.	HPTLC (High Performance Thin Layer Chromatography) method development and validation					

Course #	Topic	No Knowledge at all (1)	Theoretical Knowledge (2)	Some Hands-on Skills (3)	Intermediate Hands-on Skills (4)	Advancd/ Expert Skills (5)
14.	Developing and Validating Dissolution Method General Chapter <1092>					
15.	Elemental Impurities Limit – General Chapter <232> and Elemental Impurities Procedure <233>					
16.	ICP-OES and ICP-MS (Inductively Coupled Plasma) – Based on the Elemental Impurities Procedure <233>					
17.	NMR (Nuclear Magnetic Resonance) Spectroscopy – General Chapter <761					
18.	Laboratory Instrument Verification or Qualification					

Annex 2. List of Courses for Technical Assistance

Introduction: Providing technical assistance in quality control and quality assurance is critical for achieving global health mandates and USP's mission of improving global health through public standards and related programs to ensure the quality, safety, and benefit of medicines and foods. Over the years, the PQM Technical Assistance groups worked with developing countries to strengthen their quality control and quality assurance systems. Due to the increasing demand for ALS's services globally and the diversity of our technical experts, it is important to standardize our programs and/or service offerings in order to progressively impact the health of our clientele. To this end, a modular course approach is proposed in this document for the consideration of technical staff in order to assure the consistent quality of our technical training curriculums.

Generally, our approach is to use four modules as follows:

1. **Module 1** – *Basic Quality Control Training*. In this module, a quality control laboratory is given training in basic but critical quality control activities that, if neglected, can adversely affect the output of analytical work. This includes proper weighing techniques, pH measurement, and understanding pharmacopeial requirements and good laboratory practices. This module should be chosen when a laboratory first requests the services of ALS.
2. **Module 2** – *Intermediate Quality Control Training*. This is a follow-up to the basic training in Module 1. The intent of this module is to build on the success of the basic training to provide additional content in quality control testing. Common content in this module includes principles and best practices in UV/Vis spectrometry, Dissolution PVT, and the proper application of HPLC.
3. **Module 3** – *Advanced Quality Control Training*. In the advanced module, it is assumed that a laboratory has graduated from the basic and intermediate modules and is ready to undertake additional content in complex analytical tests.
4. **Module 4** – *Customized Module*. In cases where a laboratory cannot wait to undergo the modular approach to services, or does not have the requisite capacity and human resources to progressively graduate through the multiple stages of capacity building, the team could work on a specific module to support the lab. In doing this, ALS will work with the laboratory to identify their current capacity and training gaps using the Capacity Maturity Module and create an a-la-carte module for the laboratory. It should be noted that to benefit from the standardized curriculum, the specific topic selected must include a combination of our existing modules.

Module 1 – Basic Quality Control Training

The objective of Module 1 is to offer critical routine quality control measurements that are necessary for assuring the quality of pharmaceutical products at national or manufacturing quality control laboratories.

Course #	Topic	Duration	Curriculum Reference
1.	Safety in the Laboratory	3.0 hrs Power Point Discussions & Training Videos	This course addresses basic safety issues in the laboratory, including the separation of chemicals based on their properties, the use of MSDS, and the proper disposal of laboratory chemicals.
2.	Principles of Good Laboratory Practices	3.5 hrs Power Point Discussion & Training Videos	WHO GPPQCL_TRS957_Annex-1 WHO/TDR GLP Manual
3.	Data Integrity in Quality Control Laboratories	3.5 hrs Power Point Discussion & Training Videos	WHO New Guideline_TRS_996_ Annex5 Data Integrity and 9.5-FDA UCM495891_draft Data Integrity
4.	Good Documentation Practices	3.0 hrs Power Point Discussions & Training Videos	Good Documentation Practices Guideline USP General Chapter 1029
5.	Principles of Good Laboratory Management – laboratory quality management system, quality policy, quality manual	40.0 hrs Power Point Discussions & Training Videos Hands-on laboratory audits	ISO 17025, USP and WHO Clinical Laboratory Management Guide ISBN 978 92 4 154827 4 Assumes 8 hr/day of work, translating to 5 days of training
6.	Viscosity and Refractive Index & Optical Rotation	8.0 hrs Power Point Discussions & Training Videos Hands-on laboratory work	USP General Chapter <429>

Course #	Topic	Duration	Curriculum Reference
7.	Proper Use of Pharmacopeial Standards	3.5 hrs Power Point Discussions & Training Videos	This course addresses the use of the different pharmacopeias, their interpretation, and how to follow the specific or general chapters of a pharmacopeia.
8.	Good Weighing Practices	16 hrs Power Point Discussions & Training Videos Hands-on laboratory work	This course will address the daily calibration of weighing scales, develop weighing skills, and address deviations in weighing. USP <41>
9.	Volumetric Solution and Analysis	16 hrs Power Point Discussions & Training Videos Hands-on laboratory work	This course will address the different definitions of solutions, how to prepare them, and the proper labeling of reagents and analytical solutions USP CP – (Reagents)
10.	Good pH Practices	16 hrs Power Point Discussions & Training Videos Hands-on laboratory work	This course highlights the daily calibration of pH meters, the calculation of deviations, the use of pH meters in compendial monographs, and data interpretation <791>
11.	Thin Layer Chromatography (TLC) Identification method	4.5 hrs Power Point Discussions & Training Videos Hands-on laboratory work	This course highlights the basics of separation methods in pharmaceutical preparations. <201>
12.	Screening Technologies Using point-of-Care (POC) devices for product quality – MiniLab, Rama, CD3, etc.	16 hrs Power Point Discussions & Training Videos Hands-on laboratory work	This course provides training on the basic use of emerging technologies to identify pharmaceutical product quality. Ref: GPHF for MiniLab

Course #	Topic	Duration	Curriculum Reference
13.	Disintegration	2.5 hrs Power Point Discussions & Training Videos Hands-on laboratory work	Introduction to tablet disintegration as a method of determining tablet strength. <701>
14.	Friability Test	2.5 hrs Power Point Discussions & Training Videos Hands-on laboratory work	Introduction to testing mechanical effect of tablets during transporting and other external effect.
15.	Uniformity of Weight	1.5 hrs Power Point Discussions & Training Videos Hands-on laboratory work	Application of weighing skills to determine the weight variation of tables.
16.	Uniformity of Content	1.5 hrs Power Point Discussions & Training Videos Hands-on laboratory work	Application of weighing skills to determine the weight variation of capsules content.
17.	Loss on Drying	2.5 hrs Power Point Discussions & Training Videos Hands-on laboratory work	Application of weighing to determine the amount of loss after drying a drug substance.
18.	Residue on Ignition	3.0 hrs Power Point Discussions & Training Videos Hands-on laboratory work	Application of weighing to determine the residue on ignition of a drug substance.

Course #	Topic	Duration	Curriculum Reference
19.	Melting Point Determination	1.5 hrs Power Point Discussions & Training Videos Hands-on laboratory work	The use of physical techniques for the identification of thermally unstable molecules.
20.	Titrations: Aqueous, Non-aqueous	8 hrs Power Point Discussions & Training Videos Hands-on laboratory work	Determining the amount of drug substances using acid-base reactions in aqueous and non-aqueous media.
21.	Performance Verification of Timers	8 hrs Power Point Discussions & Training Videos Hands-on laboratory work	Hands-on practicum on performing periodic performance verification of timers using VOIP to connect to a traceable timer source.
22.	Specific Gravity	2 hrs Power Point Discussions & Training Videos Hands-on laboratory work	General Chapter <841>
23.	Water Conductivity	2 hrs Power Point Discussions & Training Videos Hands-on laboratory work	General Chapter <645>

Module 2 – Intermediate Quality Control Training

This module builds on the knowledge and skills acquired in the Basic Module for determining the quality of pharmaceutical preparations. This module employs instrument techniques and their application to quality control.

Course #	Title	Duration	Curriculum Reference
1.	Water Determination – Karl Fischer	2 days Power Point Discussions & Training Videos Hands-on laboratory work	USP–NF <921>
2.	Principles UV/Vis Spectrometer & Best Practices	2.5 hr Power Point Discussions & Training Videos Hands-on laboratory work	USP–NF <581> + USP–NF <1857>
3.	Dissolution Performance Verification Test (PVT) including Mechanical Calibration	1 day Power Point Discussions & Training Videos 4-5 days Hands-on laboratory work	USP–NF <711>
4.	Dissolution Testing 1 (Using UV/Vis Spectrometer)	4 hrs Power Point Discussions & Training Videos 2-3 days Hands-on laboratory work	USP–NF <711>
5.	Pharmaceutical Assay Using UV/Vis	4 hrs Power Point Discussions & Training Videos 2-3 days Hands-on laboratory work	USP–NF <581>

Course #	Title	Duration	Curriculum Reference
6.	High Performance Liquid Chromatography (HPLC) – Assay and Identification	4 hrs Power Point Discussions & Training Videos 2-3 days Hands-on laboratory work	USP–NF <621>
7.	Dissolution Testing 2 (Using HPLC analysis)	3-4 days	USP–NF <711>
8.	Performance Verification of HPLCs/UPLCs	3 days Power Point Discussions & Training Videos Hands-on laboratory work	Hands-on practicum on performing periodic performance verification of HPLC/UPLC systems (Waters, PE, Shimadzu, Agilent)
9.	Uniformity of Dosage Units	2 days Power Point Discussions & Training Videos Hands-on laboratory work	USP–NF <905>
10.	Pharmaceutical Assay Using UV/Vis	4 days Power Point Discussions & Training Videos Hands-on laboratory work	USP–NF <584>
11.	HPLC - Impurities and Related Substances	2-3 days Power Point Discussions & Training Videos Hands-on laboratory work	USP–NF <621>

Course #	Title	Duration	Curriculum Reference
12.	Principles and implementation of ISO:17025	5 days Power Point Discussions & Training Videos Hands-on laboratory work	ICH – 1SO:17025:2016
13.	Atomic Absorption techniques in pharmaceutical analysis	2.5 days Power Point Discussions & Training Videos Hands-on laboratory work	USP –NF <852>
14.	Microbiological assay – MLT	10 days	Antimicrobial effectiveness testing USP–NF <51>
15.	Sterility	5 days	USP–NF <71>
16.	Fluorescence Spectroscopy Techniques – General Chapter <853>	2 days Power Point Discussions & Training Videos Hands-on laboratory work	USP–NF <853>

Module 3 – Advanced Analytical Techniques

This module assumes competency of Modules 1 and 2, and that the laboratory has the advanced instrumentation necessary to undertake this module.

Course #	Title	Duration	Curriculum Reference
1.	Gas Chromatography (including Head Space)	3-4 hrs Power Point Discussions 2-3 days Hands-on	USP–NF <621>
2.	Ultra-Pressure Liquid Chromatography (UPLC)	3-4 hrs Power Point Discussions 3-4 days Hands-on	USP–NF <621>
3.	Atomic Absorption Spectrometry (AAS)	4-5 hrs Power Point Discussions 3-4 days Hands-on	USP–NF <852> and USP–NF <1852>
4.	Ion-Exchange Chromatography (IEC)	1 day Power Point Discussions 5 days Hands-on minimum	USP–NF <1065>
5.	Electro-thermal Analysis (Thermogravimetric analysis, TGA, or Digital Scanning Calorimetry, DSC)	1 day Power Point Discussions 5 days Hands-on minimum	USP–NF <891>
6.	GC-Mass Spectrometry (GC-MS)	1 day Power Point Discussions 5 days Hands-on minimum	USP–NF <621> and USP–NF <736>

Course #	Title	Duration	Curriculum Reference
7.	Liquid Chromatography-Mass Spectrometry (LC-MS)	1 day Power Point Discussions 5 days Hands-on minimum	USP –NF <621> and USP –NF <736>
8.	Stability Studies (photo and chemical stability – real time, accelerated)	2 days Power Point Discussions 10 days Hands-on	Research Material
9.	Analytical Method Development and Validation & Verification	1 or 2 days Power Point Discussions 10 days Hands-on	General Chapter <1025>
10.	Equilibrium Dialysis Studies	1 day Power Point Discussions 15 days Hands-on minimum	Research material
11.	Repair, Preventative Maintenance and Troubleshooting of HPLCs/UPLCs	1 day Power Point Discussions 5 days Hands-on minimum	Hands-on practicum on repairing commonly worn-out items such as pump seals, injector seals, lamps, etc., with instructions for troubleshooting common problems (Agilent, Waters)
12.	Chemometric techniques in drug analysis	1 day Power Point Discussions 3 days Hands-on minimum	Research Material

Course #	Title	Duration	Curriculum Reference
13.	HPTLC (High Performance thin layer chromatography) method development and validation	1 day Power Point Discussions 2 days Hands-on minimum	General Chapter <203>
14.	Developing and Validating Dissolution Method	1 day Power Point Discussions 2.5 days Hands-on minimum	General Chapter <1092>
15.	Elemental Impurities Limit	1 day Power Point Discussions 3 days Hands-on minimum	General Chapter <232> and Elemental Impurities Procedure <233>
16.	ICP-OES and ICP-MS (Inductively Coupled Plasma)	5 days	Based on the Elemental Impurities Procedure <233>
17.	NMR (Nuclear Magnetic Resonance) Spectroscopy	5 days	General Chapter <761>
18.	Laboratory Instrument Verification or Qualification	1 day Power Point Discussions 2 days Hands-on minimum	General Chapter <1058>

Annex 3. Material Considerations for QMS Implementation

One aspect of supporting the strategic planning of LMICs is the development of sustainability plans by the OMCL. These plans incorporate the general costs of staffing, infrastructure upkeep, equipment, reagents, and building or expanding a laboratory.

ISO 17025 Requirements	Laboratory Activities/ Requirements for ISO 17025 Accreditation	Rationale/Justification
ISO 17025 :Administrative Requirements		
1	Accreditation Body (Location)	To become an ISO 17025 accredited laboratory, must be assessed by an ILAC-approved accreditation body. This accreditation will be recognized globally.
2	Accredit Calibration Provider (Equipment)	Prior to becoming an ISO 17025 accredited laboratory, must select an ISO 17025 accredited calibration provider. This provider will calibrate equipment related to their scope of accreditation to certify that the equipment is operational, functioning as designed, and meets the specification or qualifications of the vendor and the laboratory. The laboratory will be provided documentation by the ISO 17025 accredited calibration provider as proof of activity.
3	Accredited PT Provider (Personnel)	Prior to becoming an ISO 17025 accredited laboratory, must select an ISO 17025 accredited Proficiency Test (PT) provider, if available. This provider will provide test and samples related to the laboratory's future scope of accreditation. Successful completion of the proficiency testing certifies the staff has the correct procedures, can operate the equipment as designed, and generates data that meets the specifications or qualifications of the sample provided. The laboratory will be provided documentation by the ISO 17025 PT provider as proof of activity. The information will also be registered with the PT provider and readily available to the public upon request.
	ISO 17025 Standard (2) EN/FR (Documentation)	The laboratory needs to purchase its own approved copy of the current ISO 17025 standard as the official reference for the laboratory. This will allow the laboratory to provide internal communication and guidance using the standard to train the staff.

ISO 17025 Requirements	Laboratory Activities/ Requirements for ISO 17025 Accreditation	Rationale/Justification
MINIMAL ESSENTIAL EQUIPMENT REQUIREMENTS based on WHO pharmaceutical laboratory critiera		
1	HPLC (2)	The laboratory must have one functioning unit.
		The laboratory needs two HPLCs, preferably of the same brand, w/ autosampler. For the Laboratory to add this to their scope of accreditation, there must be evidence of at least one working instrument. Providing two instruments will ensure that if one fails, the laboratory will still be capable of performing the activities using the other.
2	Karl Fisher (2)	The laboratory must have one functioning Karl Fisher Unit.
		The laboratory needs two KF units, preferably of the same brand. For the laboratory to add this to their scope of accreditation, there must be evidence of at least one working instrument. Providing two instruments will ensure that if one fails, the laboratory will still be capable of performing the activities using the other.
3	Refrigerator (1)	The laboratory must have one functioning refrigerator which should not cycle.
		The laboratory needs one. For the laboratory to add this to their scope of accreditation there must be evidence of at least one working instrument. The laboratory must show that they can store samples, standards, and reagents in a controlled refrigerated environment at 5 + 3°C.
4	Freezer (1)	The laboratory can have a freezer in their immediate area.
		The laboratory needs one. For the laboratory to add this to their scope of accreditation there must be evidence of at least one working instrument. The laboratory must show that they can store samples, standards, and reagents in a controlled refrigerated environment at -20 + 10°C.

ISO 17025 Requirements	Laboratory Activities/ Requirements for ISO 17025 Accreditation	Rationale/Justification
MINIMAL ESSENTIAL EQUIPMENT REQUIREMENTS based on WHO pharmaceutical laboratory critiera		
5	pH (2)	The laboratory must have one functioning pH meter
		The laboratory needs two. For the laboratory to add this to their scope of accreditation, there must be evidence of at least one working instrument. The laboratory must show that they can test the pH of samples at a range between 2, 4,7,10 and 14.
6	Oven w/ Vacuum (1)	The laboratory can have one oven.
		The laboratory needs a second oven w/pressure. For the laboratory to add this to their scope of accreditation, there must be evidence of at least one working instrument. The laboratory must show that the oven reaches temperatures of at least 250°C under vacuum.
7	Dissolution Calibration Kit (1)	The laboratory must have two dissolution apparatuses.
		The laboratory needs a certified calibration kit. For the laboratory to add this to their scope of accreditation there must be evidence of at least one working instrument. The laboratory must show that they can perform this calibration using this equipment.
8	Reference Standards (2)	The laboratory must have one set of reference weights and a reference thermometer.
		The laboratory needs two reference standards of each, preferably of the same brand. For the laboratory to add this to their scope of accreditation, there must be evidence of at least one reference standard instrument. Providing two instruments will ensure that if one fails, the laboratory will still be capable of performing the activities using the other.
9	Equipment and Infrastructure Service Contract	Maintenance and calibrations that cannot be completed or documented by the in-house laboratory calibration and metrology groups must be conducted by an authorized vendor and service provider. Cost varies based on the amount of equipment and the size of the laboratory infrastructure (water, HVAC, electricity, and waste disposal programs).

List of Laboratory Equipment and Their Estimated Cost (as of 2016-2017)	
Type	**Estimated Cost**
Dissolution system (one additional)	$25,000
GC columns	$10,000
HPLC (one additional)	$130,000
HPLC columns (C8 and C18 most common)	$10,000
KF Titrator	$15,000
KF Titrator parts/consumables	$4,000
FTIR	$20,000
FTIR supplies/parts	$5,000
Large Hood (with exhaust)	$6,000
Large Sonicators (bath combo)	$2,000
Laundry machine/Dryer combo (washing lab coats)	$5,000
PC/Monitor/software – 21 CFR 210 211	$3,500
pH Meter	$1,500
Refrigerator and Freezer combo	$10,000
Safety Shower combo	$5,000
Security Door	$2,000
Storage cabinets – various sizes	$4,000
Storage cabinets –for lab consumables	$2,000
Uninterrupted Power Supply systems (4–6)	$60,000
UV lamp (short and long)	$2,000
UV-Vis system	$45,000
Various Lab reagents/solvents	$10,000
Viscometer	$10,000
Vortex	$600
Washing Machine (Glassware)	$11,000
Standard Mass	$3,000
Waste drums or Waste	$2,000

Annex 4. Monitoring and Evaluation Indicators

Sub-IR	Indicator	Means of verification
Sub-IR 1.3 Standard of practices at national quality control laboratories sustainably improved	**Indicator 1c.1**: Number of quality control laboratories that have passed the proficiency test	Proficiency Test Report
	Indicator 1c.2: Number of quality control laboratories accredited or reaccredited	Proficiency Test Report
	Indicator 1c.3: Number of quality control laboratories with expanded scope of accreditation	Proficiency Test Report
Sub-IR 1.4 Institutional capacity for medical products' quality assurance workforce sustainably improved	**Indicator 1d.1:** Number of PQM-supported local institutions and organizations providing training services or technical assistance in QA/QC systems strengthening	Survey of local institutions and organizations
	Indicator 1d.2: Number of PQM-supported quality control laboratories that are able to generate income	Interview of quality control laboratory staff
	Indicator 1d.3: Number of pre-service or in-service training curricula developed or reformed to address QA/QC topics	Curricula
	Indicator 1d.4: Number of individuals trained in key QA/QC-related technical areas	Attendance List
	Indicator 1d.5: Number of individuals completing training in key QA/QC-related technical areas	Post-training Assessment
	Indicator 1d.6: Percent of institutions/entities with staff trained by PQM that report an improvement in workforce capacity	Follow-up Training Evaluation
IR 1.5 Capacity for post-marketing surveillance of medical products sustainably improved	**Indicator 1e.1:** Number of medical product samples tested	Sampling Reports from sentinel sites and quality control laboratories
	Indicator 1e.2: Average turn-around time per sample tested from sampling, to first level testing, to lab confirmatory testing, and to final report	Sampling Reports from quality control laboratories
	Indicator 1e.3: Number of sentinel sites added for MQM/PMS activities by the MRA	Trip Reports

Annex 5. Frequently Asked Questions

Question
Why does the National Quality Control Laboratory need a strong Quality Management System (QMS)?

Answer
A strong QMS ensures that the managerial and technical activities are at their highest level, building in quality continuously throughout the testing process. The QMS, along with the technical training, demonstrates that the laboratory can conduct testing and generate reliable data at an international level.

Question
What is the benefit of the National Quality Control Laboratory having accepted and recognized policies, processes, and procedures when building a QMS?

Answer
To ensure that the policies, practices, and procedures meet expectations on a global level, they must be standardized and validated to ensure competency and proficiency in the laboratory and compared to other laboratories. Valid procedures supported by reliable and valid data promote continuous improvement and confidence among customers.

Question
How do standard operating procedures (SOPs) help to build the laboratory QMS?

Answer
The foundation of a QMS is the standardized, approved, and effective procedures that serve as objective traceable evidence of compliance with regulations, laws, or standards. SOPs are used by organization staff as guidance to ensure that best practices, current methodology, and data generation and review are conducted in the same fashion by all laboratory staff.

Question
What is the difference between Certification, WHO Prequalification, and ILAC Accreditation Bodies?

Answer

1. **Certification** – The official notification by document proving that an individual or organization has successfully completed a course or process requirement, especially for a standard or particular profession, or attesting to a status or level of achievement.
2. **WHO Prequalification (PQ)** – The World Health Organization PQ program is the laboratory assessment program for active pharmaceutical ingredients, finished pharmaceutical products, and laboratory safety of quality control laboratories. This program is also used for the qualification of GMP manufacturers. In this case, the assessment of laboratories is made through a comprehensive evaluation of the quality of their chemical and microbiological testing services, based on information submitted by the NQCLs and inspection of the corresponding NQCL premises. The WHO PQ laboratory process is specific for QC testing laboratories and directly instructs the laboratory on what to do, how to comply, and why the laboratory must have a quality management system. There are no or minimal costs incurred by laboratories seeking WHO PQ.
3. **ILAC Accreditation Bodies** – ILAC is the international organization for accreditation bodies operating in accordance with ISO/IEC 17011 and is involved in the assessment and accreditation of calibration laboratories (using ISO/IEC 17025), testing laboratories (using ISO/IEC 17025), medical testing

laboratories (using ISO 15189), and inspection bodies (using ISO/IEC 17020). The accreditation process is broad and applied for testing, calibration, facilities, and multiple other sectors. Because this process is broad, accreditation does not directly state how the laboratories must develop their policies, processes, or procedures, but the laboratory must show competency at a global level through proficiency and continuous improvement. There is a substantial cost for ISO accreditation that varies based on the accreditation body, the location of the laboratory, and the time at which a laboratory is seeking ISO 17025:2005 accreditation from an ILAC AB.

Question
Is a laboratory required to be WHO Prequalified or ISO 17025 accredited?

Answer
A laboratory is not required to be qualified or accredited. It is the responsibility of the laboratory management to build in quality systems and technical and managerial capabilities, and to develop or continuously improve the quality management system of the organization.

Question
What is the goal of the GPH PQM program in providing technical support to the NRAs and NQCLs?

Answer
The goal of PQM is to help public and private entities in developing countries to strengthen systems to ensure the quality, safety, and efficacy of pharmaceutical and medical supplies, to strengthen regulatory systems, to increase the availability of quality medicines, and to support evidence-based decision-making.

Question
What sets apart PQM technical and managerial experts from other providers in the space?

Answer
The PQM program distinguishes itself from other providers by helping partners to address weaknesses in quality assurance systems that lead to the proliferation of poor-quality medicines. By focusing on strengthening quality systems — such as resolving systemic weaknesses in the regulation and manufacture of medical products — our partners are making meaningful improvements to their overall health systems. By increasing the efficiency of the regulatory systems, health systems can increase their responsiveness and sustainability. PQM helps its partners to strategically harness these opportunities and deliberately build quality into processes and products.

Question
Why is in important for an NQCL to generate reliable, valid, reproducible, and defendable data for its customers?

Answer
The NQCL or OMCL mandate is to analyze drug products and to support medicines registration to ensure their quality, protect the public health, and strengthen the medicines supply in the country.

Through collaboration with country authorities to strengthen medicines evaluation, inspection, and quality surveillance functions, the laboratory can reliability provide data to identify impurities and substandard or misbranded products for legal action and public protection.

Question

Who is responsible for sustaining the QMS laboratory system and developing the strategic plan for continued maintenance, improvement, and success?

Answer

The Senior Management of the MOH or MRA is responsible for developing the strategic plan, which incorporates the laboratory staff. All laboratory staff are responsible for maintaining the QMS system and the sustainability of the lab.

Question

What is the difference between the strategic plan and sustainability plan of the NQCL?

Answer

The strategic plan, developed by the NRA or MOH and NQCL Senior Management, is the 3- to 5-year rolling plan and overall activities surrounding the interaction between the NRA and the laboratory.

The sustainability plan, developed by the NQCL Senior Management, is the 5- to 7-year rolling plan for laboratory operations, finances, human resource capacity, customer development, and growth.

References

[i] WHO. List of Prequalified Quality Control Laboratories. Available at: https://extranet.who.int/prequal/sites/default/files/documents/PQ_QCLabsList_23.pdf.

[ii] Hernandez S, Nkansah P. (2017). *Analytical Instrumentation Support for National Quality Control Laboratories*. Rockville, MD: U.S. Pharmacopeial Convention, Promoting the Quality of Medicines Program.