PQM Promoting the Quality of Medicines

Analytical Instrumentation Support for National Quality Control Laboratories

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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

A2LA	American Association for Laboratory Accreditation
AISP	Analytical Instrumentation Support Program
ANAB	ANSI-ASQ National Accreditation Board
CSP	contract service provider
IML	Instrument Master List
ISO	International Organization for Standardization
LMIC	low- and middle-income country
NMI	national metrology institute
NQCL	national quality control laboratory
NRA	national regulatory authority
OMCL	official medicines quality control laboratories
PQM	Promoting the Quality of Medicines
TB	tuberculosis
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 development challenge posed worldwide by substandard and falsified medicines. There is increasing recognition of the threat these poor-quality medicines pose to public health, especially in low- and middle-income countries (LMICs), and their potential to undermine decades of investments in global health, including those made by USAID.

Using a systems-based approach, PQM offers technical assistance to LMICs tailored to fit 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 strengthen 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 Global Pharma Health Fund's Minilab™, followed by confirmatory testing in the laboratory 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 to good manufacturing practices and develop dossiers to submit to the WHO PQ program.

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

Introduction

Ensuring the quality of medicines relies on an effective and well-equipped NQCL with sufficient capacity to conduct laboratory tests that generate accurate and reliable data on a product's quality. The equipment and instruments required to conduct these tests require regular maintenance and upkeep. Additionally, laboratory staff members need to be trained to appropriately manage these instruments. These issues are particularly pronounced in LMICs.

Results from an internal PQM survey of 17 official medicines quality control laboratories (OMCLs) in sub-Saharan Africa showed that preventive maintenance and the calibration of analytical laboratory instrumentation are key challenges for these laboratories *(see Figure 1)*.

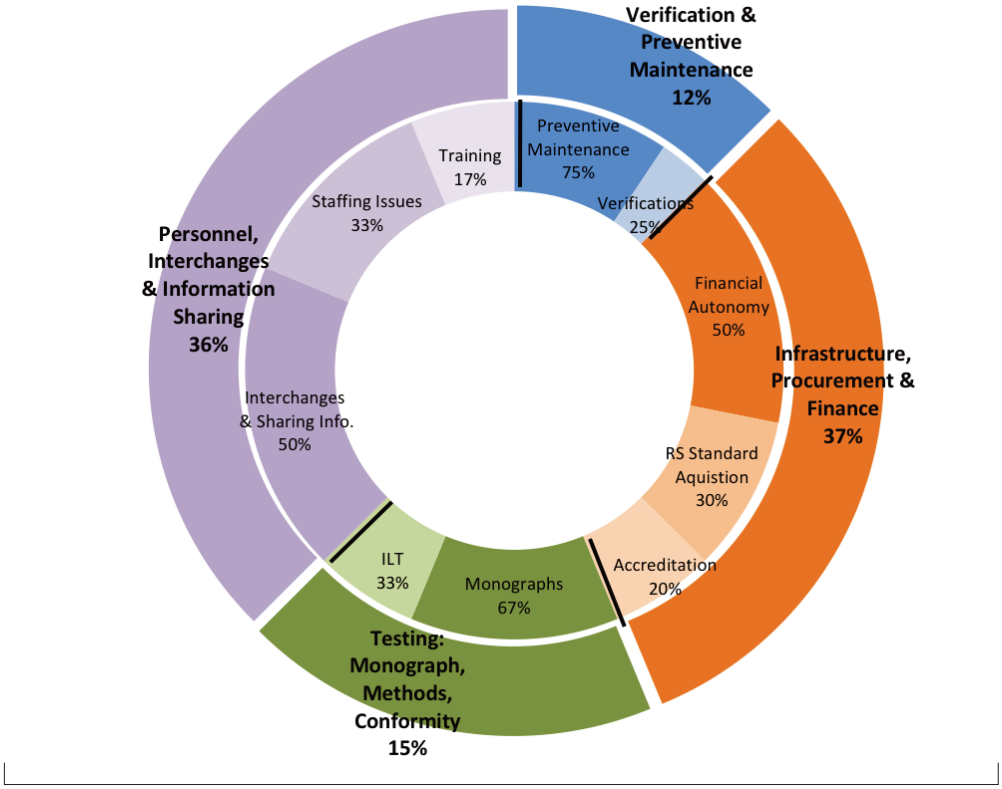


Figure 1: *Challenges Identified in 17 OMCLs in Sub-Saharan Africa*

Analytical instrument support is logistically and technically challenging for NQCLs in LMICs for a number of reasons. Initial procurement of instrumentation may or may not include a step to verify that the instrument is operating correctly, after the NQCL assumes responsibility for maintaining the instrument. Often, NQCLs in LMICs rely on outside vendors or contract service providers (CSPs) to support equipment and instrumentation maintenance activities.

Some laboratories rely on the external vendor that manufactures an instrument to provide maintenance and repair services; however, the relatively high cost and slow response times for vendor services are often problematic for NQCLs. Given that many laboratories may possess limited numbers and types of equipment, any

equipment downtime could result in the inability of a country to conduct particular tests for substandard medicines or medical products. Worse yet, testing may be performed without verification that the instrument is operating as intended, which may lead to erroneous results. The timeframe for vendor service can often span months, in part due to logistical challenges. Additionally, service calls must be set up, potentially with several different vendors, for each and every piece of instrumentation based on the required maintenance schedule, with separate appointments required for non-routine maintenance. As a result, vendor equipment servicing can be both time and cost prohibitive for most NQCLs.

CSPs are able to work on multiple instruments during the same visit; however, the cost of service remains prohibitively high for many NCQLs, and lack of prompt response times can still be factors that adversely affect the laboratory's ability to meet its mandate. In some cases, the testing performed by CSPs may be inadequate and/or not properly documented, and standards and reference materials used for testing are not traceable or are absent altogether. This may give laboratories a false sense of confidence that the instruments are operating as intended.

The need for analytical instrumentation support varies across laboratories, depending on local context, the type of instruments used, and the laboratory's size and mandate. Typically, laboratories are given disparate, disjointed, or potentially conflicting guidance from vendors, implementing partners, or other stakeholders. However, this guidance frequently does not take into consideration the interrelated systems-level challenges that come with effectively maintaining laboratory instruments. Without specific training and directed capacity-building efforts, this guidance is often not feasible or sustainable, and is insufficient to ensure appropriate functioning of instrumentation.

Why Is Analytical Instrumentation Important?

Analytical instrumentation is at the heart of compendial testing of pharmaceuticals for safety and purity. Along with liquid chromatography, dissolution can not only determine when the active ingredient is present, but can also verify that the claim on the product's label is accurate. Receiving a non-therapeutic dose can often be inferior to receiving no dose at all by increasing the resistance of bacteria to antibiotic therapy. Worse still is receiving an adulterated product that contains a toxic substance that causes patient harm. As the trust of the public erodes, attitudes can shift in favor of remedies that are untested or directly harmful.

As can be seen, compendial testing has the central role to play in systematically maintaining the health of the public at large. This testing relies on analytical instrumentation, such as dissolution baths, balances, titrators, and spectrophotometers. In turn, these instruments must be in good working order, fit for their intended purpose, and as reliable as the pharmaceuticals they test.

Calibration, qualification, and verification activities form the basis through which instruments are proven to be fit for their intended purpose of testing pharmaceuticals. Preventive maintenance and repair activities are necessary for the proper functioning of instrumentation. When these activities are neglected, incorrect results will occur and risk adverse public health outcomes. The Analytical Instrumentation Support Program (AISP) will provide procedure-based training on performance verification and maintenance for major analytical instrumentation.

AISP was formed to address the unmet needs currently experienced by NQCLs. To date, PQM has worked to strengthen analytical instrumentation capacity in several countries in Africa and Asia, including Bangladesh, Burkina Faso, Mali, and Mozambique. Over 50 pharmacists have been trained in analytical instrumentation and performance verification procedures have been adapted in five countries. As NQCLs begin to develop

extensive expertise in analytical testing through the PQM program, support for secondary activities as outlined above play an ever-important role in maintaining the progress achieved.

Purpose of this Document

This document outlines the PQM program's approach to supporting NCQLs in managing and maintaining their analytical instrumentation and outlines strategies for building in-house expertise of NQCL staff, strengthening the capacity of national metrology institutes (NMIs), and strategically partnering with CSPs to share resources and calibration reference standards. Based on a laboratory's existing capacity and needs, a combination of these strategies may be warranted. Annex A. reviews each of these strategies in greater detail.

Technical Approach

With extensive relationships with NQCLs across the world, PQM provides a wide array of timely solutions for implementation backed by the rigor of USP verification testing standards for major analytical instrumentation.

PQM has trained, advised, and assisted NQCLs on a broad range of technical subjects, including quality management systems, good laboratory and documentation practices, analytical method development and testing, and instrument maintenance and verification. Since 2009, the USP PQM program has supported over 64 laboratories and trained over 1,105 laboratory personnel from 19 countries across Africa, Southeast Asia, Latin America, newly independent states, and the Middle East. With PQM assistance, 27 laboratories attained compliance with international standards and achieved ISO accreditation and/or WHO PQ. By providing support to NQCLs for instrumentation maintenance, the impact of the other areas of support to NQCLs is maximized and also made more sustainable.

The PQM approach for instrumentation support is primarily aimed at ensuring building long-term local capacity for instrument support. This added capacity can help NQCLs reduce expenses and better manage limited resources. Costs previously incurred by using service providers can now be invested back into the laboratory to address other important demands, such as procuring consumables, hiring personnel, and obtaining additional instrumentation.

The effectiveness of PQM's approach is rooted in:

- Dedicated personnel to instrument support
- Training those closest to the process
- Verifying performance of instrumentation in-situ
- Local ownership of instrumentation management

Ultimately, PQM supports laboratories in attaining compliance with globally recognized standards, namely ISO 17025 and WHO PQ. Compliance with ISO 17025 is evaluated by outside accreditation associations such as the ANSI-ASQ National Accreditation Board (ANAB) and the American Association for Laboratory Accreditation (A2LA).

Instrument Categorization

NQCLs use a wide range of instrumentation and equipment, which varies based on the testing performed and laboratory scale of advancement. USP General Chapter <1058> Analytical Instrumentation Qualification gives broad-based suggestions on dividing instrumentation into three categories (Table 1). PQM uses this same categorization to draft procedures based on NQCL instrumentation currently in use. These procedures are further customized based on individual laboratory requirements.

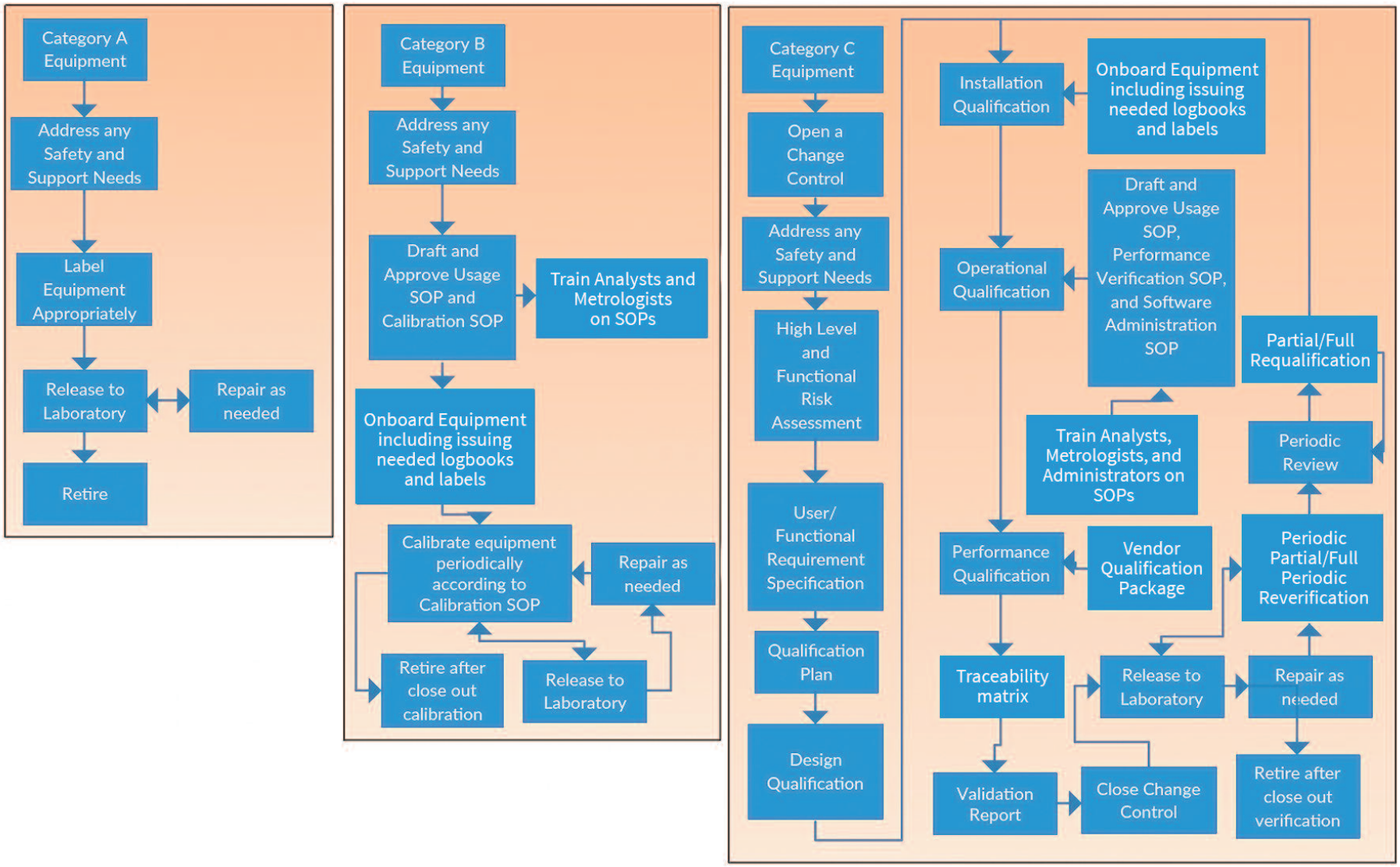
Table 1: *Examples of Instrument Categorization*

Category	Category Description	Examples
Category A	Includes standard equipment with no measurement capability or usual requirement for calibration, where the manufacturer's specification of basic functionality is accepted as user requirements. Conformance of Group A equipment with user requirements may be verified and documented through visual observation of its operation.	Equipment examples: • Nitrogen evaporators • Magnetic stirrers • Vortex mixers • Centrifuges
Category B	Includes standard equipment and instruments providing measure values, as well as equipment controlling physical parameters (e.g., temperature, pressure, or flow) that need calibration, where the user requirements are typically the same as the manufacturer's specification of functional and operational limits. Conformance of Group B instruments or equipment to user requirements is determined according to the standard operating procedures for the instrument or equipment, and documented during IQ and OQ.	Equipment examples: • Muffle furnaces • Ovens • Refrigerator-freezers • Water baths • Pumps • Dilutors Instrument examples: • Balances • Melting point apparatus • Light microscope • pH meters • Variable pipets • Refractometers • Thermometers • Titrators • Viscometers
Category C	Includes instruments and computerized analytical systems, where user requirements for functionality, operational, and performance limits are specific for the analytical application. Conformance of Group C instruments to user requirements is determined by specific function tests and performance tests. Installing these instruments can be a complicated undertaking and may require the assistance of specialists. A full qualification process should apply to these instruments.	Instrument examples: • Atomic absorption spectrometers • Differential scanning calorimeters • Dissolution apparatus • Electron microscopes • Flame absorption spectrometers • High-pressure liquid chromatographs • Mass spectrometers • spectrometers • UV/Vis spectrometers • Inductively couples plasma-emission spectrometers • Densitometers • Microplate readers • Thermal gravimetric analyzers • X-ray fluorescence spectrometers • X-ray powder diffractometers • Diode-array detectors • Elemental analyzers • Gas chromatographs • IR spectrometers • Near-IR spectrometers • Raman spectrometers

The Lifecycle Approach

PQM provides assistance to laboratories for all phases of the instrument lifecycle, including procurement, installation, qualification, ongoing verifications and preventive maintenance, troubleshooting and repairs, requalification, and decommissioning. Understanding the appropriate interventions throughout the equipment lifecycle provides the most long-term value based on cost, time, and resource requirements. The categorization of instruments and equipment helps to define the type of support required for appropriate management and maintenance. Figure 2 illustrates how the lifecycle management work flows vary for instruments and equipment categories A, B, and C.

Figure 2: *Lifecycle Management Work Flow*



Key Phases of Support

PQM works to support NQCLs to build instrumentation capacity in four phases: Assessment, Prioritization, Deployment, and Follow-Up *(Figures 3 and 4)*. The development of materials will be procedure-based with hands-on instruction (see Annex C) and in line with program priorities and activities.

Figure 3: *Phases of Analytical Instrumentation Support*

Assessment

An initial inventory of all the instrumentation, equipment, and standards currently possessed by the NQCL is the first step in an assessment. An Instrument Master List (IML) needs to be populated (database, spreadsheet, or software package) with the following information:

- Instrument ID (internal laboratory name for instrument)
- Type
- Manufacturer
- Model
- Serial Number
- Location (Building and Room)
- Picture (hyperlinked to photo)
- Calibration/Verification outsourced or in-house
- Mobility (movable, non-movable)
- Status (retired, out-of-service, in-service)
- Categorization (A, B, C)
- Usage Procedure
- Performance Verification/Calibration Procedure
- Software Administration Procedure
- Last Calibration/Verification Date
- Calibration/Verification Due Date
- Qualification Date
- Logbooks (Yes, No)

An in-depth room-by-room, drawer-by-drawer, box-by-box assessment should be made. This activity can span multiple days depending on the size and organization of the NQCL. This list will serve multiple functions: planning, compliance, tracking, procurement, and gap analysis.

Prioritization

Once the IML is complete the instrumentation can be categorized as A, B or C and the gaps in instrument documentation, qualification, and verification/calibration can be assessed. The highest risk instrumentation should be prioritized first for gap remediation (i.e., Category C instrumentation).

Deployment

Training should be given first for instrumentation that is high priority/risk for in-house verification/calibration Category C instrumentation. Performance verification draft procedures used during initial training must be customized, approved, and trained on by the NQCL.

To support NQCLs in meeting their analytical instrumentation needs, PQM has developed or is in the process of developing short courses on equipment performance verification, preventive maintenance, troubleshooting and repair, and laboratory procedures *(Box 1)*.

Box 1. PQM Analytical Instrument Support Services

Instrument Courses	Performance Verification	Preventive Maintenance	Troubleshooting/ Repair
High-performance liquid chromatograph	●	●	●
Timer	●	●	●
UV spectrometer	●	●	●
Balances (analytical and micro)	●	●	●
pH meters	●	●	●
FTIR	●	●	●
Gas chromatograph	●	●	●
Headspaces	●	●	●
Dissolution baths	●	●	●
Karl Fisher	●	●	●
Titrators	●	●	●
Disintegration apparatus	●	●	●

Procedure Courses

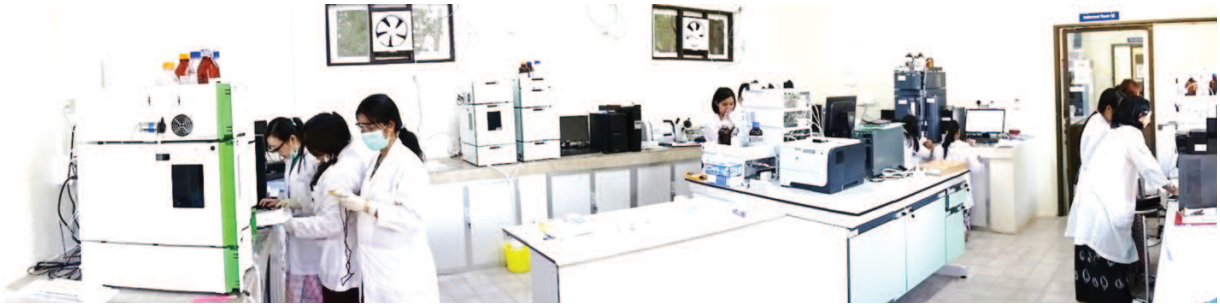
- Audit trails, user administration, and data integrity
- Developing standard operating procedures for usage, verification, and software administration
- Process mapping and procurement of parts and instrumentation
- Population of instrument master lists and onboarding of instrumentation
- User requirement specification generation for analytical instrumentation
- General knowledge of analytical instrument qualification

Follow-up and Monitoring

Next steps identified during the assessment and subsequent technical assistance trainings need to be followed up by the on-the-ground presence. Metrics can be used to show the progress the NQCL is making toward compliance.

When all gaps have been remediated, the program can be closed and transitioned into the monitoring phase.

Case Study: PQM Supports a National Quality Control Laboratory in Southeast Asia



In an effort to maximize the impact of combating poor quality, USP was contacted by WHO and asked to conduct a training on the performance verification of high-performance liquid chromatography (HPLC)/ ultra-performance liquid chromatography (UPLC) instruments.

During a pre-assistance meeting, the Assistant Director of the NQCL outlined the current issues they faced, including the cost, availability, and timeliness of the performance verifications that were outsourced to third-party vendors, such as HPLCs/UPLCs and timers.

Before this training, timer verifications had been handled by a third-party vendor. The timers themselves needed to be shipped out of the country to verify their accuracy. This process took months, and calibration along with shipping costs approached approximately 800 USD per timer per verification. PQM drafted a Performance Verification Procedure and trained personnel to execute their own verifications in a timely manner by comparing their timers to a national standard via Voice over Internet Protocol (VoIP). This procedure provided a clear cost, time, and compliance advantage as compared to sending out timers to third-party vendors.

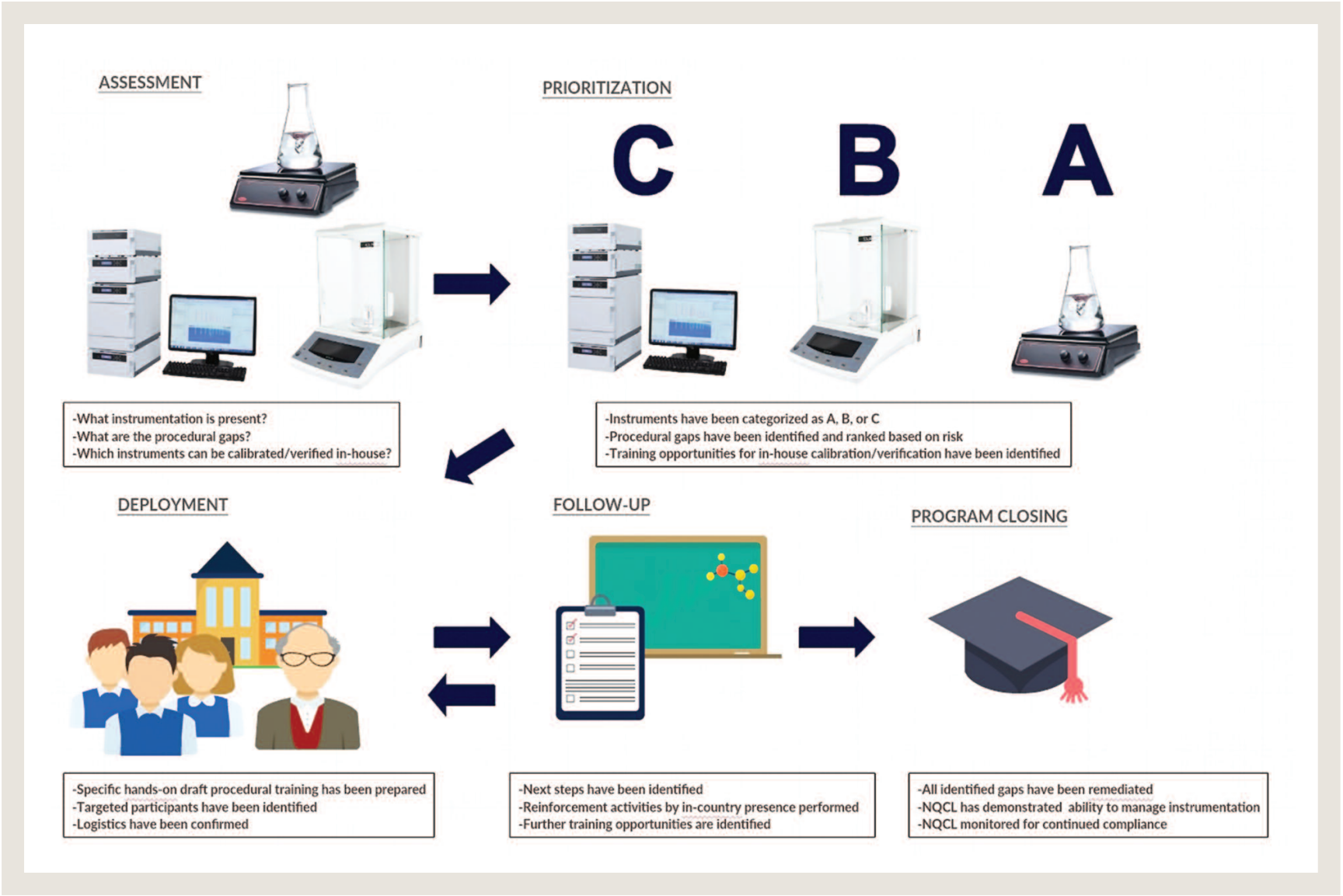
Annual Cost Savings:[1] approximately $1,600 USD

The same issues were faced with the verification of HPLCs/UPLCs. The Assistant Director communicated that the laboratory currently spent approximately 8,000 USD for the performance verification of its HPLCs/UPLCs per system per instance utilizing outside vendors. With seven HPLC/UPLC systems, the laboratory bears an annual cost of approximately 56,000 USD for the performance verification of all its systems. This created a significant hurdle for compliance and cost-effective management of its limited resources. USP drafted a Performance Verification Procedure for the laboratory's HPLC/UPLCs, which formed the basis of the training provided.

Annual Cost Savings: approximately $56,000 USD

[1] Costs saving assumes a zero-dollar cost to labor from the laboratory, as verification responsibilities would be assigned to laboratory analysts and would be absorbed as a cost of daily operation. Initial one-time startup costs for needed equipment are not included, as they are not representative of the continuing cost of reverification. Preventive maintenance costs are excluded to allow for accurate comparison with vendor costs. Reference standards costs were excluded, as they may be prepared fresh from laboratory supplies.

Figure 4: *AISP Implementation*



Annex A. Review of Analytical Instrumentation Strategies

AISP Strategies	In-house	National Metrology Institute	Contracy Service Provider	Partner
Aim	To build capacity for NQCLs in instrument qualification activities by bringing the process in-house	To support NMIs in achieving accreditation in support of NQCLs	To support in-country CSPs in achieving ISO 17025 accreditation in support of NQCLs	To partner with local CSPs to provide calibration services to NQCLs
Scope	NQCLs	NQCLs and local manufacturers	NQCLs	NQCLs
Intended Impact	To eliminate the cost of having CSPs perform the verification of analytical instrumentation. These savings, as outlined in the Case Study, can reach upwards of 8,000 USD per instrument for major analytical instrumentation.	By expanding the scope of accreditation of NMIs, PQM can decrease the total cost of compliance for NQCLs and local manufacturers. Additionally, an NMI that is accredited increases the fundamental infrastructure needed for local manufacturers to setup manufacturing sites.	By expanding the scope of accreditation, PQM can increase the capacity for local calibrations to both NQCLs and local manufacturers. Local CSPs could be used at a lesser cost since they would not need to travel internationally to calibrate fixed equipment.	By partnering with a local CSP and signing a memorandum of understanding, PQM can offer calibration services to our PQM partner NQCLs worldwide and issue certificates for instruments that are calibrated.
Estimated Budget	79,000 USD for parts (proposed to begin activities)	30,000 USD per training, not including procurement of standards	30,000 USD per training, not including procurement of standards	Revenue positive, depending on agreement not including cost of training and standards
Applicable Instrumentation	• High-Pressure Liquid Chromatographs • Ultraviolet Chromatographs • Dissolution Testers • Disintegration Testers • Balances • pH meters • Karl Fischer Titrators	• Balances • Thermometers • Pressure gauges • Tachometers • Calipers • Pipettes	• Balances • Thermometers • Pressure gauges • Tachometers • Calipers • Pipettes	• Balances • Thermometers • Pressure gauges • Tachometers • HPLCs • UVs • Calipers

AISP Strategies	In-house	National Metrology Institute	Contracy Service Provider	Partner
Process Steps	• **Step 1: Assessment** > What countries are served? > What laboratories are served in each country? > What instrumentation exists in each country? > What instrumentation is in the process of being procured? > What is the status of those instruments?	• **Step 1: Assessment** > What instrumentation exists at the NMI already? > What instrumentation will be needed? > Who will procure it? > What is the status of existing equipment? > What is the NMI accreditation process? > Who will be needed to be trained and on what? > What procedures are necessary? > What infrastructure is necessary? > Will the NMI be able to cover the majority or their calibration needs?	• **Step 1: Assessment** > What instrumentation exists at the CSP already? > What instrumentation will be needed? > Who will procure it? > What is the status of existing equipment? > Who will be needed to be trained and on what? > What procedures are necessary? > What infrastructure is necessary? > Will the CSP be able to cover the majority or their calibration needs?	• **Step 1: Assessment** > What instrumentation exists at the CSP already? > What instrumentation will be needed? > Who will procure it? > Who will be needed to be trained and on what? > What procedures are necessary? > What infrastructure is necessary? > Will the CSP be able to cover the majority or their calibration needs?
	• **Step 2: Prioritization** > Which instruments get used the most? > Which instrument brands are the most prevalent? > Which instruments will be the easiest to support? > What type of instrument support will give us the biggest impact? > What type, kind, and amount of instrumentation and software should be procured?	• **Step 2: Prioritization** > What equipment is the most important to NQCL operation? > Which NQCLs will be supported?	• **Step 2: Prioritization** > What equipment is the most important to NQCL operation? > Which NQCLs will be supported?	• **Step 2: Prioritization** > What equipment coverage is the most important to NQCL operation? > Which NQCLs will be supported?

AISP Strategies	In-house	National Metrology Institute	Contracy Service Provider	Partner
Process Steps *(continued)*	• **Step 3: Development** > What standard should be used? > What procedures/protocols are needed? > What reference material is needed? > What calibration/verification instrumentation is needed? > What logistical processes are needed to support recertification of reference material? > What do the laboratories need most?	• **Step 3: Development** > What procedures are needed? > What personnel are needed? > What reference material is needed? > What logistical processes are needed to support recertification of reference material?	• **Step 3: Development** > What procedures are needed? > What personnel are needed? > What reference material is needed? > What logistical processes are needed to support recertification of reference material?	• **Step 3: Development** > What procedures are needed? > What reference material is needed?
	• **Step 4: Deployment** > How will laboratories be prioritized? > What deliverables are provided first? > How to provide these deliverables?	• **Step 4: Deployment** > What is the timeline for bringing in new equipment? > At what point will the NMI be able to calibrate the NQCL equipment?	• **Step 4: Deployment** > What is the timeline for bringing in new equipment? > At what point will the CSP be able to calibrate the NQCL equipment?	• **Step 4: Deployment** > At what point will the AISP resource be able to calibrate the NQCL equipment?
	• **Step 5: Follow-Up** > What to do if laboratories cannot maintain compliance? > What to do if laboratories lose key people? > What to do if our deliverables are insufficient for certification? > How to measure success?	• **Step 5: Follow-Up** > What happens if the NMI loses accreditation? > What happens if NMI loses key people? > What happens if our deliverables are insufficient for accreditation? > How is success measured?	• **Step 5: Follow-Up** > What happens if the CSP loses ISO accreditation? > What happens if CSP loses key people? > What happens if our deliverables are insufficient for accreditation? > How is success measured?	• **Step 5: Follow-Up** > How is success measured?

AISP Strategies	In-house	National Metrology Institute	Contracy Service Provider	Partner
Deliverables	• **General SOPs:** > Onboarding new instruments and categorization > Instrument labeling > Change control > Reference Standard management • **Instrument Specific SOPs**: > Usage > Verification/Calibration > Software Administration • **Instrument Protocols**: > High-Level Risk Assessments > User Requirement Specifications > Functional Requirement Specifications > Design Qualifications > Installation Qualifications > Operational Qualifications > Performance Qualifications > Validation Plans > Validation Summary Reports > Traceability Matrixes • **Training** > Video training modules > In-person training modules (hands-on) > General presentations • **Reference Standard procurement list** • **Instrument Master List** • **AISP Work Plan for dissemination** • **Laboratory profiles including points of contact** • **Preferred vendor list for procurement**	• List of instruments needed • List of infrastructure needed • List of personnel needed • Facilitation meetings • AISP Work Plan for dissemination • Laboratory profiles including points of contact • Instrument Master List for NQCLs	• List of instruments needed • List of infrastructure needed • List of personnel needed • Facilitation meetings • AISP Work Plan for dissemination • Laboratory profiles including points of contact • Instrument Master List for NQCLs	• List of instruments needed • List of standards needed • Memorandum of understanding • Facilitation meetings • AISP Work Plan for dissemination • Laboratory profiles including points of contact • Instrument Master List for NQCLs

AISP Strategies	In-house	National Metrology Institute	Contracy Service Provider	Partner
Indicators	• **Process Indicators:** > Number of standard operating procedures or curriculum modules developed and implemented to support a fully functional NQCL > Number of quality control laboratories receiving technical assistance in instrument qualification	• **Process Indicators:** > Number of standard operating procedures or curriculum modules developed and implemented to support a fully functional NMI > Number of NQCL labs receiving calibration assistance for their instrumentation	• **Process Indicators:** > Number of standard operating procedures or curriculum modules developed and implemented to support a fully functional CSP > Number of NQCL labs receiving calibration assistance for their instrumentation	• **Process Indicators:** > Number of instruments calibrated by AISP for NQCLs
	• **Outcome Indicators:** > Adopting of procedures into NQCLs quality management system > Number of NQCLs in compliance with international standards of practice such as ISO 17025 and WHO PQ accreditation	• **Outcome Indicators:** > Fully accredited or increased scope for NMI	• **Outcome Indicators:** > Fully accredited or increased scope for CSP	• **Outcome Indicators:** > Ability for AISP to issue calibration certificates
	• **Impact Indicators:** > Increased analytical instrumentation up-time and an increase in the number of samples processed	• **Impact Indicators:** > Increased analytical instrumentation up-time and an increase in the number of samples processed	• **Impact Indicators:** > Increased analytical instrumentation up-time and an increase in the number of samples processed	• **Impact Indicators:** > Increased analytical instrumentation up-time and an increase in the number of samples processed

AISP Strategies	In-house	National Metrology Institute	Contracy Service Provider	Partner
Advantages	• Immediate roll-out • Not dependent on outside stakeholders • Real and immediate measureable deliverables • Sustainable	• Coverage for multiple laboratories at the same time	• Coverage for multiple laboratories at the same time	• Ability to issue calibration certificates • Ability to calibrate instrumentation quicker • Ability to combine laboratory visits with instrument calibration • Not having to rely on a vendor for calibration services
Disadvantages	• Singular approach (can be mitigated by involving multiple laboratory personnel from multiple sites) • Focused on NQCLs • Time is required to develop procedures and training materials	• Only certain calibrations performed • Will NOT cover analytical instrument calibrations • Cost to acquire equipment is high • Current expertise is out of scope	• Only certain calibrations performed • Will NOT cover analytical instrument calibrations • Cost to acquire equipment and expertise is high • Significant conflicts of interest may arise • Current expertise is out of scope	• Creating a dependency on USP for instrument calibrations • USP's reputation would be at risk from an association with a contract laboratory • USP would have to use the contract laboratory's procedures, documentation, and reference materials • Contract laboratories may not calibrate all analytical equipment • Reference materials are needed for contract laboratory calibrations • Significant conflicts of interest may arise

Annex B. Examples of Calibration Standards and Tools

Instrument	Specification Source	Test	Specification	Equipment Needed
HPLC	vendor documents	Temperature	Varies	Thermometer
HPLC	vendor documents	N/A	N/A	Union
HPLC	vendor documents	N/A	N/A	Lamps: UV
HPLC	vendor documents	N/A	N/A	Seals: pump, injector, solvent lines, face
HPLC	vendor documents	N/A	N/A	Check valves
HPLC	vendor documents	N/A	N/A	Needles
HPLC	vendor documents	N/A	N/A	Needle seats
HPLC	vendor documents	N/A	N/A	Frits
HPLC	vendor documents	N/A	N/A	Syringes
HPLC	vendor documents	N/A	N/A	Flow meter
HPLC	vendor documents	N/A	N/A	Glassware
HPLC	vendor documents	Flow Rates	Varies	Timer
HPLC	vendor documents	N/A	N/A	Capillary Column
HPLC	vendor documents	N/A	N/A	Column
HPLC	vendor documents	N/A	N/A	Flow cells
HPLC	vendor documents	N/A	N/A	Tubing
HPLC	vendor documents	N/A	N/A	Injector assemblies
HPLC	vendor documents	Precision	Varies	Caffeine standards
HPLC	vendor documents	GPV Testing	Varies	GPV standards
HPLC	vendor documents	Precision	Varies	Injection standards
HPLC	vendor documents	Wavelength Accuracy	Varies	Wavelength standards
HPLC	vendor documents	N/A	N/A	multimeter
HPLC	vendor documents	N/A	N/A	(degasser) tubing cutter
HPLC	vendor documents	N/A	N/A	(degasser) solvent tubing 5 meters
HPLC	vendor documents	N/A	N/A	(degasser) solvent filter
HPLC	vendor documents	N/A	N/A	open ended wrenches
HPLC	vendor documents	N/A	N/A	open ended wrenches
HPLC	vendor documents	N/A	N/A	Tweezers
HPLC	vendor documents	N/A	N/A	10 ml syringe for pulling solvent line vaccuum
HPLC	vendor documents	N/A	N/A	Small barb luer
HPLC	vendor documents	N/A	N/A	Mirror
HPLC	vendor documents	N/A	N/A	Micro screw driver set
HPLC	vendor documents	N/A	N/A	Macro screw driver set
HPLC	vendor documents	N/A	N/A	Hex set metric
HPLC	vendor documents	N/A	N/A	Hex set standard
HPLC	vendor documents	N/A	N/A	Torx set
UV	USP <857>; USP <1857>, vendor documents	Stray Light	Varies	OQ/PV standards kit-1, Stray light
UV	USP <857>; USP <1857>, vendor documents	Wavelength Accuracy	Varies	OQ/PV standards kit-2 Wavelength Accuracy
UV	USP <857>; USP <1857>, vendor documents	Transmittance	Varies	SRM 930e Set: 10, 20 & 30 %T Neutral Density Filters and blank holder
UV	USP <857>; USP <1857>, vendor documents	N/A	N/A	Cuvettes and MCT adjustment tool
UV	USP <857>; USP <1857>, vendor documents	N/A	N/A	Deuterium lamp
UV	USP <857>; USP <1857>, vendor documents	N/A	N/A	Tungsten lamp
UV	USP <857>; USP <1857>, vendor documents	N/A	N/A	Macro screw driver set

Annex C. Sample Draft Verification Procedure

National Quality Control Laboratory Name, Location *National Quality Control Laboratory Name*		SOP Number- XXX-SOP-XXX
		Version No. 01
Title: Performance Verification of Timers and Stopwatches	Approved Date: TBD	Effective Date: TBD

PURPOSE/SCOPE	Purpose: The purpose of this procedure is to describe the process to verify the performance of timers and stopwatches. Scope: This procedure is applicable to timers and stopwatches located at the National Quality Control Laboratory Name in Location. When an outside ISO certified vendor is used to verify the performance of an instrument the vendor procedure and acceptance criteria will supersede this procedure.
ISO STANDARD	ISO/ IEC 17025:2005 section 5.6
BACKGROUND	None
SUPERSEDES	New
REFERENCES	NIST Handbook for the calibration of stopwatches and timers
ACRONYMS	NIST – National Institute for Science and Technology SOP- Standard Operating Procedure ISO- The International Organization for Standardization IEC- The International Electrotechnical Commission
DEFINITIONS	None Applicable
MATERIALS AND EQUIPMENT	None Applicable
SAFETY	None Applicable
RESPONSIBILITIES	Analyst – Perform the Performance Verification Reviewer – Review the Performance Verification Approver – Approve the Performance Verification
1.0 Performance Verification Interval 1.1. Refer to XXX-SOP-XXX 2.0 Labeling of Instrument 2.1. Refer to XXX-SOP-XXX	

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Page 1 of 5

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This procedure is the property of the National Quality Control Laboratory Name, Location.

National Quality Control Laboratory Name, Location *National Quality Control Laboratory Name*		SOP Number- XXX-SOP-XXX
		Version No. 01
Title: Performance Verification of Timers and Stopwatches	Approved Date: TBD	Effective Date: TBD

3.0 Forms

3.1. XXX-SOP-XXX-F01 – Performance Verification of Timers and Stopwatches Form

4.0 Applicable Instruments

4.1. Timers (all models)

4.2. Stopwatches (all models)

5.0 Mobility

5.1. Fully Mobile

6.0 Signature Record

6.1. Record the Name, Signature, Initials, and Date of each Analyst performing the verification

6.2. When the performance verification is reviewed record the Name, Signature, Initials, and Date of the Reviewer

6.3. When the performance verification is approved record the Name, Signature, Initials, and Date of the Approver

6.4. Record applicable comments

7.0 Maintenance Checklist

7.1. Record the event as scheduled maintenance or non-routine maintenance

7.2. Clean the unit and remove any unnecessary stickers when present

7.3. Replace the battery when user accessible

7.4. Record the instrument symptoms when applicable

7.5. Record the corrective action taken when applicable

8.0 Equipment Identification

National Quality Control Laboratory Name, Location *National Quality Control Laboratory Name*		SOP Number- XXX-SOP-XXX
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Title: Performance Verification of Timers and Stopwatches	Approved Date: TBD	Effective Date: TBD

from the Source Time Start

11.7. Compare the Source Time Delta to the Set Time Point acceptance criteria

11.8. Record the instrument time

11.9. Calculate the absolute difference between the Source Time delta and the Test Instrument Elapsed Time as displayed on the timer

11.10. Compare the result to the acceptance criteria

11.11. Indicate a Pass or Fail result

11.12. Repeat the above steps for the remaining time points

11.13. Enter Performance Verification Date Initiated as the first day of procedure execution

11.14. Enter the Performance Verification Due Date as per XXX-SOP-XXX

12.0 Remedial Action

12.1. When the instrument does not pass the acceptance criteria the analyst will verify the procedure was executed correctly.

12.2. When upon investigation the instrument did not pass the acceptance criteria and the procedure was executed correctly the instrument will be retired from service.

12.3. Any Out of Specification result will be investigated and cross referenced on XXX-SOP-XXX-F01

National Quality Control Laboratory Name, Location *National Quality Control Laboratory Name*		SOP Number- XXX-SOP-XXX
		Version No. 01
Title: Performance Verification of Timers and Stopwatches	Approved Date: TBD	Effective Date: TBD

RECORDS AND DOCUMENT HISTORY

RECORDS –Refer to XXX-SOP-XXX for the Record Retention period.	
TYPE OF RECORD	**LOCATION**
Document Master List	Hardcopy
Instrument Log Book	Hardcopy
Performance Verification of Timers and Stopwatches Form	Hardcopy

Document History

Revision	Document Issue Date	Document Change Number	Summary of Changes
NA		NA	New SOP

APPROVAL LOG

TITLE	NAME	SIGNATURE	DATE
AUTHOR			
REVIEWER			
QA			
DEPARTMENT HEAD			

End of the Document

National Quality Control Laboratory Name, Location *National Quality Control Laboratory Name*		SOP Number- XXX-SOP-XXX-F01
		Version No. 01
Title: Performance Verification of Timers and Stopwatches Form	Approved Date: TBD	Effective Date: TBD

TYPE: TIMER/STOPWATCH **Instrument ID:** _____

Signature Record

Analyst (1)			
Name (print)	Signature	Initials	Date (DD/MMM/YY)
Analyst (2) N/A ☐			
Name (print)	Signature	Initials	Date (DD/MMM/YY)
Analyst (3) N/A ☐			
Name (print)	Signature	Initials	Date (DD/MMM/YY)

Reviewer			
Name (print)	Signature	Initials	Date (DD/MMM/YY)

Approver			
Name (print)	Signature	Initials	Date (DD/MMM/YY)

Comments N/A ☐

_____

_____

_____

_____

_____

_____

Page 1 of 3 **Initials:**_____ **Date:**_____

National Quality Control Laboratory Name, Location *National Quality Control Laboratory Name*		SOP Number- XXX-SOP-XXX-F01
		Version No. 01
Title: Performance Verification of Timers and Stopwatches Form	Approved Date: TBD	Effective Date: TBD

TYPE: TIMER/STOPWATCH **Instrument ID:** _____

Maintenance Checklist

Scheduled maintenance: ☐ or Nonroutine Maintenance: ☐

Task	Yes	No	N/A	Date
Clean timer and remove any unneeded stickers when present	☐	☐	☐	
Replace battery when user accessible	☐	☐	☐	

Instrument Symptoms N/A ☐

Corrective Action N/A ☐

Page 2 of 3 **Initials:**_____ **Date:**_____

National Quality Control Laboratory Name, Location *National Quality Control Laboratory Name*		SOP Number- XXX-SOP-XXX-F01
		Version No. 01
Title: Performance Verification of Timers and Stopwatches Form	Approved Date: TBD	Effective Date: TBD

TYPE: TIMER/STOPWATCH **Instrument ID:** _____

Equipment Identification

Component	Manufacturer	Model Number	Serial Number
Timer/Stopwatch			

Equipment Location

Building	Room

Operational Testing

Description	Pass	Fail	N/A
All input buttons functional	☐	☐	☐
Alarm funcitonal	☐	☐	☐
Count up functional	☐	☐	☐
Count down functional	☐	☐	☐
Channels keep separate time	☐	☐	☐

Performance Verification

Traceable source used: _____

Phone number of source: _____

Set Time Point (HH:MM:SS)	Time Zone of Source Time	Source Time Start (HH:MM:SS)	Source Time End (HH:MM:SS)	Source Time Delta (HH:MM:SS)	Test Instrument Elapsed Time (HH:MM:SS)	|Delta| (seconds)	Pass	Fail
00:02:00							☐	☐
01:00:00							☐	☐
04:00:00							☐	☐

Passing Acceptance Criteria:
Set Time Point = Source Time Delta +/- 1 minute
|Delta| <= 2 seconds

Performance Verification Date Initiated: _____

Performance Verification Date Due: _____

Page 3 of 3 **Initials:**_____ **Date:**_____

Annex D. Definitions

calibration – the act of comparing a measurement device against a known and traceable standard and adjusting it into tolerance when required. Examples of instruments that are normally calibrated include multi-meters, micrometers, weights, thermocouples, humidity sensors, pressure gauges, and tachometers. This term is used colloquially as a phrase to describe instrument support activities.

change control – a documented process through which changes to instrumentation are captured

installation qualification – a protocol that verifies the installation requirements of the instrument, such as dimensional, vibrational, humidity, light, electrical, HVAC, gasses, waste, fluidics

operational qualification – a protocol that verifies the operational requirements of the instrument. Examples of HPLC operational tests include gradient, flow rate, noise, drift, wavelength accuracy, and column temperature accuracy.

performance qualification – a protocol that verifies the performance of the instrument. Normally this is accomplished by running a method and comparing it to known specifications.

performance verification standard operating procedure – a procedure executed periodically that describes the process of checking that the instrument can meet predefined specifications

periodic review – a process of reviewing an instrument and risk-assessing the need for requalification based on past non-routine maintenance, corrective actions, out-of-tolerance results, prior qualifications, associated change controls, logbooks, and all associated paperwork present in the instrument file

preventive maintenance – a documented process whereby wear items are replaced before failure

qualification – the holistic process of ensuring that an instrument is fit for intended use, including calibration, verification, standard operating procedure drafting (usage, verification, and software administration), training, vendor protocols, and user requirement specifications

software administration standard operating procedure – a procedure that describes the process of adding and deleting users, backing up and restoring data, turning on audit trails and assessing them, defining and setting up password requirements, and other administrative processes

traceability matrix – a document that matches the testing done during the qualification with each user requirement specified

usage standard operating procedure – a procedure that defines the use of an instrument. Default parameters, as well as any daily maintenance or verification requirements, are defined.

verification – the act of ensuring an instrument meets predefined specifications. Examples of instruments that are normally verified include HPLCs, UVs, GCs, Dissolution Baths, FTIRs, and KFs.