

**Establishing post-market surveillance of the quality of antimalarials in Kenya; and
Training workshop on Minilab® and sampling procedures**

**Nairobi, Kenya
November 9-13, 2009; January 25-28, 2010**

Trip Report

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About PQM

The Promoting the Quality of Medicines (PQM) program, funded by the U.S. Agency for International Development (USAID), is the successor of the Drug Quality and Information (DQI) program implemented by the United States Pharmacopeia (USP). PQM is USAID's response to the growing challenge posed by the proliferation of counterfeit and substandard medicines. By providing technical leadership to developing countries, PQM helps build local capacity in medicines quality assurance systems, increase the supply of quality medicines to priority USAID health programs, and ensure the quality and safety of medicines globally. This document does not necessarily represent the views or opinions of USAID or the United States Government. It may be reproduced if credit is given to PQM and USP.

Abstract

PQM conducted several consultative meetings November 9-13, 2009 in Nairobi, Kenya with stakeholders involved in promoting the quality of medicines. The PQM team participated in meetings to gain an understanding of the stakeholders' roles in quality assurance and quality control of antimalarials in the country and used the information to propose a suitable post-market surveillance program for Kenya. Sentinel sites were selected, a sampling protocol was developed, and the medicines to be monitored were identified.

A follow up visit was conducted January 25-29, 2010 during which PQM organized a training workshop on Minilab[®] and sampling procedures at the National Quality Control Laboratory (NQCL). In addition to the workshop, PQM staff took the opportunity to meet with other stakeholders that the team was not able to meet during their first visit.

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Key Words

USAID, Kenya, Minilab[®], basic tests, sampling procedures, antimalarial, assessment, medicines quality monitoring, PPB, DOMC, NQCL

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- Our Kenyan partners from the Pharmacy and Poisons Board (PPB), Division of Malaria Control (DOMC) program, and National Quality Control Laboratory (NQCL).
- Our partners from the WHO and Management Sciences for Health (MSH) for their hospitality and their contribution to implementing the activities of our assessment.
- PQM colleagues for their valuable contribution in organizing our trip and editing this report.
- Mr. Anthony Boni and Ms. Veerle Coigneux at USAID/Washington for their guidance and helpful insight throughout the preparation the assessment and the workshop.

ACRONYMS

ACT	Artemisinin-based Combination Therapy
AL	Artemether-Lumefantrine
AM	Antimalarials
API	Active Pharmaceutical Ingredient
ARV	Antiretroviral
DHAP	DiHydroArtemisinin-Piperaquine
DOMC	Division of Malaria Control
FBO	Faith-Based Organization
GPHF	Global Pharma Health Fund
IPT	Intermittent Preventative Treatment
KEMSA	Kenya Medical Supplies Agency
MOH	Ministry of Health
MOP	Malaria Operational Plan
MQM	Medicines Quality Monitoring
MSH	Management Sciences for Health
NAMCOL	Network of African Medicines Control Laboratories
NASCOP	National AIDS & STD Control Program
NGO	nongovernmental organization
NQCL	National Quality Control Laboratory
PEPFAR	President's Emergency Plan for AIDS Relief
PMS	Post Marketing Surveillance
PPB	Pharmacy and Poisons Board
PQM	Promoting the Quality of Medicines Program
QA	Quality Assurance
QAMSA	Quality of Antimalarials in Sub-Saharan Africa
QC	Quality Control
SP	Sulfadoxine-Pyrimethamine
SPS	Strengthening Pharmaceutical Systems program
WHO	World Health Organization
TB	Tuberculosis
USAID	United States Agency for International Development
USP	United States Pharmacopeia
WHO	World Health Organization

Background

The PMI Malaria Operational Plan (MOP) for 2009 highlights the importance of drug quality control, and USAID/Kenya has selected USP PQM to assist the Ministry of Health in monitoring the quality of antimalarials available in the market. Specifically, PQM mandate as stated in the MOP FY 09 is: “Support to strengthen drug quality and post market surveillance through the procurement of self-contained kits that permit limited on-site testing of medication (Minilabs[®]) and training of technicians on evaluating drug quality.” Medicines quality determines their effectiveness and safety and, hence, the health outcome of the patient. If the quality is compromised, investments in pharmaceutical commodities, health systems, and pharmaceutical management systems are negated. Assuring medicine quality ensures that the medicine reaching the patient is efficacious, safe, and of appropriate quality for a positive health outcome.

In order to understand the quality assurance structures in Kenya and establish a sustainable post-marketing surveillance (PMS) program in the country, PQM conducted several consultative meetings with key stakeholders and partners. The meetings gave PQM a good understanding of the role of the country partners and allowed the team to develop a robust plan that fits the country context.

Review of the literature prior to the visits to Kenya revealed that a quality assurance framework document was drafted by key partners. This is an overarching document on quality assurance for all medicines in Kenya. Whereas PQM’s focus is PMS of antimalarials, the partners agreed that a comprehensive PMS structure should be developed that will be useful for all therapeutic indications. The protocol developed could be used to extend to PMS of medicines for other therapeutic indications.

Purpose of Trip

This trip report combines the November and January visits to Kenya.

PQM staff traveled to Kenya to:

- Conduct meetings with key partners to gather all needed information on medicine quality assurance systems in Kenya
- Present findings to stakeholders
- Provide criteria for sentinel site selection and tools to conduct the first round of antimalarial quality monitoring
- Develop protocol guidelines for establishing MQM as articulated in the MOP FY 09, and action plan with timelines

Source of Funding

This trip was supported with funds from USAID / PMI Kenya.

Overview of Activities

Part I: Consultative Meetings with Stakeholders to establish PMS for antimalarials

Meeting with USAID/Kenya

Participants: Kaendi Munguti, Senior Malaria Advisor; Gladys Tetteh, CDC/PMI Advisor; Patrick Lukulay and Latifa El Hadri (the “PQM team”)

The main objective of the visit was to develop a comprehensive program that is in alignment with activities run by other partners, mainly WHO and MSH and, in particular, to provide strategic planning to assess the quality of antimalarials in selected sentinel sites. At the end of the meeting, Dr. Tetteh introduced the PQM team to Karen Klimowski, PEPFAR Deputy Director, and James Batuka, HIV/AIDS Team Leader. PQM and the PEFAR team will seek joint projects for testing the quality of HIV medicines.

Meeting with the Pharmacy and Poisons Board (PPB)

Participants: Fred Siyoi and Stephen Kimatu, PPB; Andrew Nyandigisi, Division of Malaria Control (DOMC); and the PQM team

Dr. Siyoi stated that PPB will benefit from PQM's technical assistance for better functioning of their departments including registration, inspection, and drug information and pharmacovigilance departments. Dr. Siyoi sees a need for PPB to work more closely with the NQCL as they both have a common goal to protect the Kenyan people. The PQM team ensured that they will facilitate close working relationships between all key players.

The PQM team presented the Kenya work plan for FY 10 based on PMI objective to strengthen quality control of antimalarial drugs in Kenya. To ensure the success of PMI-planned activities, the PQM staff stressed the need for joint efforts of all decision makers in addition to a good partnership among the DOMC, PPB, and NQCL. For monitoring the quality of antimalarials, Dr. Nyandigisi suggested that the DOMC oversee the program while the PPB acts as the implementing partner. For good coordination and easy communication, Dr. El Hadri requested that Dr. Siyoi designate Dr. Kimatu from the Drug Information Department to be the focal point for Minilab[®] activities at sentinel sites. Dr. Kimatu was previously trained in Ethiopia on Minilabs[®] by PQM and was appointed as the focal point for the QAMSA study.

Meeting with the National Quality Control Laboratory

Participants: Hezekiah Chepkwony, Director, and George Wanganga, Deputy Director, NQCL; Stephen Kimatu and Andrew Nyandigisi, PPB; and the PQM team

Kenya's NQCL is the only public quality control lab in the sub-Saharan region which has been prequalified by WHO. Currently, the staff can carry out most quality testing and analysis of raw materials and finished dosage forms of essential pharmaceuticals for identity of active pharmaceutical ingredients (APIs): dissolution, disintegration, assay for content of APIs, sterility, and ordinary impurities. The laboratory was assigned by the PPB to conduct compendia testing for artemisinin-based combination therapy (ACT) and sulfadoxine-pyrimethamine (SP) samples collected by Malawi in the QAMSA study.

Dr. Chekwony cited other roles, including the assessment of the quality of antiretrovirals (ARVs), anti-TBs, and antimalarials submitted by the National AIDS and STD Control Program (NASCOP) and Malaria Control and National Leprosy and Tuberculosis Program. All batches of anti-TBs, antimalarials, and ARVs are subject to analysis at the NQCL before they are approved for use. The lab also embarked on random sampling of Health Center Kit Rations of drugs at Kenya Medical Supplies Agency (KEMSA) depots as part of its PMS activity.

After the overview of NQCL activities and responsibilities, Dr. Lukulay shared the work plan for monitoring the quality of antimalarials and how the lab will be involved in all steps from supervising sampling collection at sentinel sites to performing confirmatory testing at NQCL.

At the end of the meeting, Dr. Lukulay briefed Dr. Chepkwony on the Network of African Medicines Control Laboratories (NAMCOL) workshop that PQM organized in September 2009 in Ghana. Dr. Chepkwony showed interest in becoming a member of the network and requested that PQM keep him informed about the upcoming events.

Dr. Wanganga gave a laboratory tour to the PQM team, which gave good insights into NQCL's technical capacities in carrying out most quality testing and analysis for substance and finished dosage for essential medicines.



Meeting with the Management Sciences for Health (MSH SPS)

Participants: Michael Thuo and Mildred Shieshia, MSH; Andrew Nyandigisi, DOMC; Stephen Kimatu and George Muthhuri, PPB; Dr. George Wanganga, NQCL; and the PQM team

Dr. Thuo raised some concerns about the pharmaceutical sector in Kenya, one of which is the need for establishing a system that monitors and evaluates the quality of medicines in Kenya on a regular basis. The PQM team assured MSH that one of the goals of the visit is to establish a protocol for the Medicine Quality Monitoring (MQM) program for antimalarials using Minilabs[®], with the objective of expanding the program to other medicines. Dr. Lukulay emphasized that the involvement of all stakeholders and partners is crucial for a successful and sustainable program in Kenya. Following this meeting, the PQM team sent the MQM protocol to MSH to define and include their role.

Selection of Sentinel Sites

In preparation for selecting sentinel sites and medicines to monitor, the country partners gave presentations about the current situation and their roles in ensuring drug quality in Kenya. Dr. Lukulay discussed how to establish MQM activities in sentinel sites and the criteria of selecting those sites. Dr. El Hadri presented guidelines on sampling procedures, testing at sentinel sites, and performing testing at the NQCL.

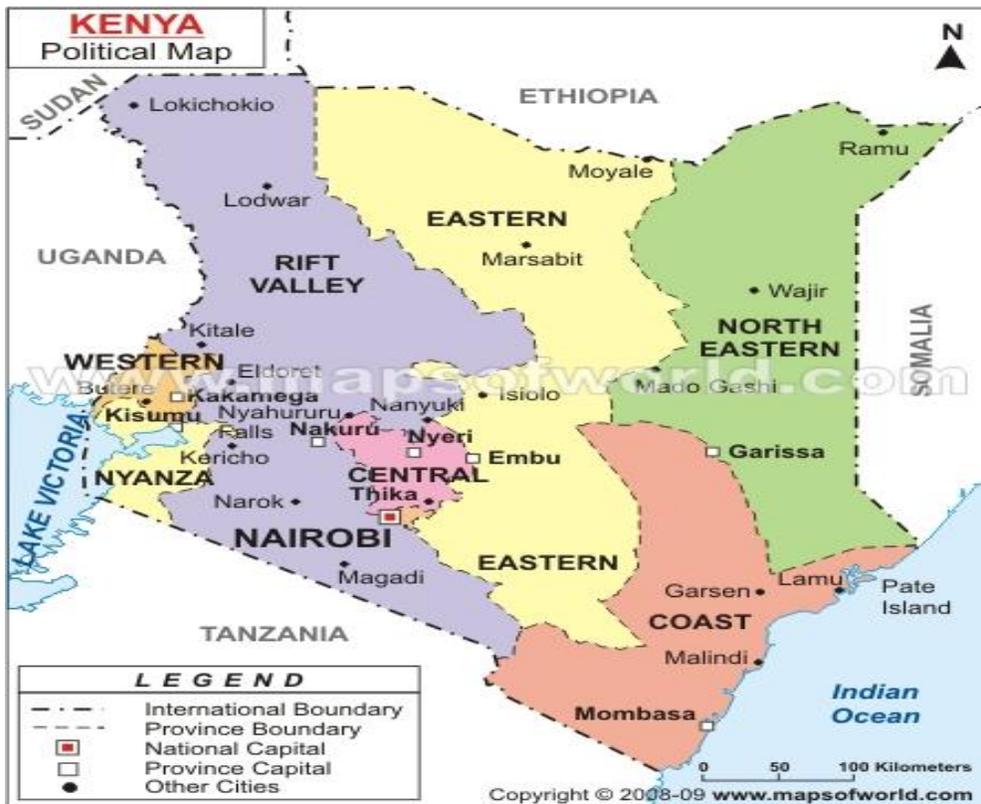
The following items were the main outcomes of PQM presentations:

Identification of five sentinel sites: Following discussions amongst the DOMC, PPB, PQM, MSH and NQCL, five sentinel sites were selected according to established criteria, such as epidemiological data demonstrating the prevalence of disease; medicine availability and accessibility for sampling; presence of all sectors (public, private, informal); and medicines circulating freely between borders with nearby countries.

The selected sites are:

- Nairobi (capital city)
- Mombasa (Coast Province)
- Kakamega (Western Province)
- Kisumu (Nyanza Province)
- Eldoret (Rift valley)

The term “sentinel site” means the identified zones: Capital City, Coast Province, Western Province, and Nyanza Province. Each zone has a number of districts that will be considered during the sampling of antimalarials.



Sources of sample collection: Samples will be collected from importers, wholesalers, Faith-Based Organization and Nongovernmental Organizations (FBOs/NGOs), central stores, regulated retailers, hospitals, private sources, and informal markets within each sentinel site.

Medicines selected for sampling: The antimalarials selected for sampling were based on the DOMC strategy for malarial control in Kenya. They include first-line and second-line treatment, intermittent preventative treatment (IPT) for malaria in pregnant women, chemoprophylaxis, and treatment for severe malaria.

- ✓ First-line treatment: artemether-lumefantrine (AL)
- ✓ Second line treatment: dihydroartemisinin-piperaquine (DHAP)
- ✓ Severe malaria: parenteral quinine, oral quinine, artemether/artesunate injection
- ✓ Intermittent preventive treatment: sulfadoxine-pyrimethamine
- ✓ Other ACTs and chemoprophylaxis: artesunate amodiaquine, artesunate mefloquine, atovaquone proguanil
- ✓ Monotherapies: Monotherapies will only be collected, not tested. This information will help to establish the monitoring of the shift from monotherapies to ACTs and to evaluate their availability on the market.

Meeting with Division of Malaria Control (DOMC)

Participants: Elizabeth Juma and Andrew Nyandigisi, DOMC; Stephen Kimatu, PPB; PQM team

Dr. Lukulay stated that this visit would allow the PQM team to assess some weaknesses and gaps in the existing quality control systems in Kenya. He also mentioned that, based on assessment findings, joint efforts of the DOMC, PPB, and NQCL are needed for a successful program. Dr. Juma agreed that monitoring of antimalarials and other medicines is performed on an ad hoc basis and expressed the need for technical support from PQM to address the existing gaps.

Meeting with USAID/Kenya

Participants: Kaendi Munguti, Gladys Tetteh, and Daniel Wacira, USAID/Kenya; Andrew Nyandigisi, DOMC; and the PQM team

The main goal of this year's activities is to bring all parties involved in quality control of medicines together and seek to create a framework for PMS of antimalarials with an aim to expand the MQM program to other sites, other USAID disease programs, and other medicines. The DOMC and PQM team debriefed USAID/Kenya on the outcome of the previous meetings and shared the need for good working relationships between the partners. Following those discussion, the PQM team presented the findings of the assessment.

- Established a protocol for monitoring the quality of antimalarials that takes into account the role of each party involved in the implementation of Minilab[®] program. The protocol also outlines the sampling strategies, testing using Minilabs[®] and analysis of nonconforming samples at the NQCL. (see attached document)
- Established a work plan (see Annex 1) according to Kenya MOP FY 09
- Selected sentinel sites based on criteria set by the PQM and DOMC
- Selected antimalarials to be sampled and tested
- Selected monotherapies to be monitored
- Agreed that samples of antimalarials will be collected from public/private and informal sectors in addition to FBOs/NGOs
- Designated Dr. Stephen Kimatu as the focal point to coordinate MQM activities between the NQCL and regional focal points at each sentinel site

- Provided timelines for the first round of MQM activities and the budget outlines to PPB

Next steps

- Identify staff from central and regional levels to be trained on basic tests using the Minilabs[®] (by December)
- Prepare coordination plan for sampling (methods, tools, sampling plans) (by December)
- Consult with the WHO team and incorporate suggestions into the protocol (by December)
- Revise the MQM protocol and send the final copy to pertinent partners (by December)
- Prepare for Minilab[®] training (decide dates, site, participants, etc.) (by December)
- Procure and deliver 3 Minilabs[®] and replenish the 2 existing ones with supplies, reagents, and chemicals (by December)
- Provide the Minilab[®] training in January
- Submit a proposal to PEPFAR/Kenya on PMS for ARVs and other health system strengthening activities that PQM could undertake in Kenya (by December)

Part II: Workshop Training on Minilab[®] and Sampling Procedures

Following the November assessment, a PQM team traveled to Nairobi January 25-29, 2010 to conduct workshop training on Minilab[®] and sampling procedures (see agenda in Annex 2). Fourteen participants from the central and regional level attended the workshop (see list of participants in Annex 3). In addition to the training, the PQM team met with the Anti-Counterfeit Taskforce, WHO, and PEPAFR to discuss collaboration and expansion of the MQM program.

Objectives of the workshop

- Hands-on training in basic tests using Minilabs[®]
- Training in sampling procedures and data reporting
- Developing a sampling plan for each sentinel site
- Defining roles and responsibilities of sentinel site and supervisory teams
- Reporting data according to MQM guidelines

January 25, 2010: Opening session at the National Laboratory of Quality Control

Participants: Dr. Daniel Wacira, USAID/Kenya; Dr. Fred Siyoi, PPB; Dr. Hezekiah Chepkwony, NQCL; Dr. Andrew Nyandigisi, DOMC; Dr. Latifa El Hadri and Dr. Mustapha Hajjou, PQM; 14 trainees from 5 sentinel sites

The opening session was chaired by Dr. Siyoi, who welcomed the participants and thanked PQM/USAID for offering their technical support in terms of training and providing resources and material to carry out the training on Minilabs[®]. Following this introduction, Dr. Siyoi gave a speech on behalf of Dr. Kipkerich Kosgei, Registrar of the PPB (see speech in Annex 4). The NQCL director thanked Dr. Siyoi for his notes and extended his thanks to Dr. Wacira, PQM staff, and personnel who came from central and regional sites to participate in Minilab[®] training. Introductions of each participant followed the NQCL director's notes, which were followed by the presentation of the training agenda by Dr. El Hadri. She highlighted the objectives of the workshop and the importance of proper sampling procedures and training on Minilab[®] basic tests as a tool to control the quality of antimalarials circulating on the Kenyan market. After the introductory remarks, the deputy director of the PPB declared the workshop open.

January 25-28, 2010: Overview of Workshop

Item	Description
Training Objectives	<ul style="list-style-type: none"> ✓ Training on sampling strategy ✓ Training on visual inspection ✓ Training on Thin Layer Chromatography (TLC) ✓ Training on simple disintegration ✓ Training on data management
Venue	NQCL, Nairobi, Kenya
Local Organizers	PPB, DOMC, and NQCL
Course Proceedings	<p>Day 1:</p> <ul style="list-style-type: none"> • Opening, Presentation on Establishing a Medicine Quality Monitoring Program ‘General Introduction’ • Presentation and work group: sampling strategy and reporting. All the participants contributed to the development of the sampling strategy for each sentinel site <p>Day 2:</p> <ul style="list-style-type: none"> • Introduction on basic tests and Minilabs[®] • Work group: visual inspection. Participants conducted the test on several samples and filled out the forms for sample collection and visual inspection • Work group: familiarization with TLC. The session was dedicated to proper pipetting and spotting. • Work group: TLC testing of fixed-dose combination of amodiaquine and artesunate samples <p>Day 3:</p> <ul style="list-style-type: none"> • Work group: TLC testing of lumefantrine • Work group: TLC testing of artemether • Work group: TLC testing of quinine sulfate <p>Day 4:</p> <ul style="list-style-type: none"> • Work group: TLC testing of sulfadoxine-pyrimethamine • Work group: review of sampling strategy for each sentinel site • General discussion <p>Participants were trained in appropriate use of reporting forms throughout the training</p>
Participants	Fourteen staff from PPB, DMC, and NQCL attended the full training workshop
Closing Ceremony	Following the closing remarks, certificates were awarded to all participants who successfully completed the course
Course Outcomes	<p>At the end of the course, participants were able to:</p> <ul style="list-style-type: none"> • Use the Basic Tests methodology covered in the course to screen the quality of antimalarial medicines available in the market; • Demonstrate good understanding of appropriate sampling procedures • Identify quality problems of antimalarial samples <p><i>It is important to note that the trainees detected a substandard sample</i></p>
Course Evaluation	Participants were asked to evaluate each of the course modules and sessions by filling out the Course Evaluation Form. (<i>See Annex 5</i>)



General Introduction on Medicine Quality Monitoring

Dr. Hajjou gave an overview of the MQM program, describing PQM's approach to PMS and the rationale behind the use of Minilabs[®] to screen medicine samples for quality. By describing the lessons learned from PQM's experience in PMS, he underlined the steps critical for the success of an MQM program. One of the most critical elements for this success is the commitment of local partners to take ownership of such a program.

Sampling Procedures

A PQM training manual was distributed to all participants. This handout covers all aspects of MQM activities in terms of sampling procedures, testing, and reporting.

Given the importance of sampling in the MQM program, and in order to ensure uniformity in the collection of antimalarials, Dr. El Hadri gave a presentation on sample definition and described the characteristics that determine a single sample (see Annex 6). The group discussed how to diversify sample collection, taking into account: 1) level of distribution (primary and secondary chain of medicines distribution); 2) different sources (wholesalers, importers, hospitals, retailers, health centers, pharmacies, etc.); 3) different sectors (public, private, and informal); and 4) different districts within the sentinel site's province.

As an exercise, Dr. El Hadri asked the participants to create a sampling plan for the sentinel site at Mombasa (coastal province). This exercise allowed the trainees to get a good grasp of sampling techniques and collection.

A template for sampling was provided to each regional focal point, and a one-to-one session was organized during the Minilab[®] training to review each sentinel site's sampling plan. Other aspects of sampling procedures were also discussed, including the number of units necessary per sample for testing with Minilabs[®] and for re-sampling in case more samples are needed for compendial testing by the NQCL.

The sampling plan for the first round of the program includes collecting around 100 samples per sentinel site, giving priority to antimalarials indicated by DOMC treatment guidelines and the most sold, used, and recommended medicines. These samples will be collected from the public, private, and informal sectors. Samples taken from FBOs/NGOs will be provided separately by participants from the PPB and DOMC.

For FY 10, one round of testing antimalarials will be carried out at the five sentinel sites. Results of this round will be submitted by early May 2010 to all stakeholders.

Sentinel site teams

A principal focal point and regional focal point for each sentinel site were designated and their roles defined. A supervisory team of four persons was also identified to ensure that the first round is accomplished according to the guidelines indicated in the Kenya MQM protocol. The personnel of this team are from the PPB (Dr. Kimatu), DOMC (Dr. Anyandigisi), and NQCL (Dr. Wanganga and Dr. Mwaura). PQM will be overseeing the activities of all sentinel site teams and will be in direct contact with the DOMC representative and principal focal point.

Forms and Data Management and Reporting

PQM staff provided all forms for managing data at the regional and central level. These forms were used by trainees during the workshop. A report template will be provided by PQM upon completion of the first round of sampling and testing of antimalarials.

Short Introduction to Basic Tests

Dr. Hajjou gave a brief introduction on basic tests using Minilabs[®], describing the three basic tests (visual/physical inspection, TLC, and simple disintegration). He explained that visual inspection can reveal irregularities in the compliance of the manufacturer with Good Manufacturing Practices (GMP) as well as indications on the quality of the product tested. TLC testing helps identify the API and gives a semi-quantitative appreciation of the amount of API present compared to the amount claimed on the label.

Dr. Hajjou emphasized safety and urged the participants to use the lab coats, gloves, and safety glasses that PQM provided for the training and for testing in the field.

Visual and Physical Inspection Test

NQCL provided several samples of antimalarial medicines for the training. Each participant received one sample antimalarial medicine along with the sampling and basic tests reporting forms. Following the completion of the test, the PQM team reviewed all the forms. One sample that failed the visual inspection test (the color of the tablets was not uniform) was circulated among the participants (see sample below in Figure 1). This training session helped the participants familiarize themselves with the reporting forms.



Figure 1: Sample of fixed-dose combination of artesunate and amodiaquine

Thin Layer Chromatography Test

Prior to the actual training on how to test medicines using TLC, the PQM team provided refresher training to the participants who needed additional help with pipetting technique using the pipette filler provided with the Minilab[®]. The participants were also familiarized with spotting on sham TLC plates.



During the laboratory training, the PQM team made sure that the trainees were following the procedures and handling the samples and the reagents appropriately.

The results showing samples failing the test were discussed with the participants (see Figure 2). The PQM team cross-examined results from different trainees regarding the same samples.

It is noteworthy to mention that by the last day of TLC training, the participants needed minimal or no supervision to conduct TLC tests.

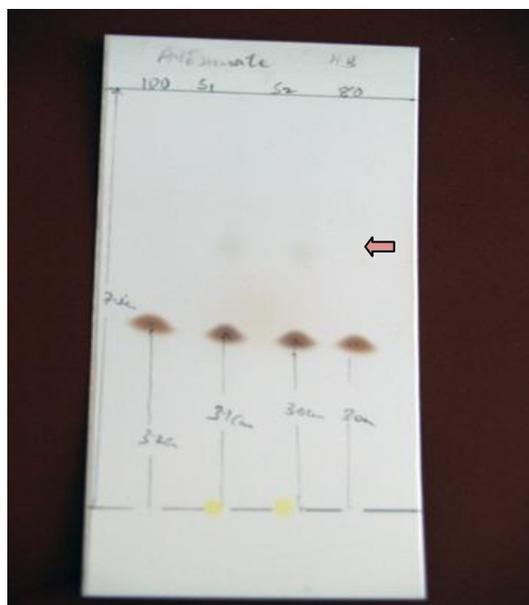


Figure 2: Sample failing TLC test because of the presence of impurities in artesunate, indicated by arrow.

Simple Disintegration Test

The PQM team set up two stations for this test, and the participants tested several samples. The PQM team explained the purpose of this test and its limitations. None of the samples used in the training failed the simple disintegration test.

Roles and Responsibilities

Three responsible positions were identified for MQM: the sentinel site team, supervisory team, and the focal point. The roles and responsibilities of each position were discussed and agreed upon during the workshop. The main activities of each are summarized in the following table:

<i>The sentinel site team will:</i>	<i>The supervisory team will:</i>	<i>The focal point will:</i>
<ul style="list-style-type: none"> • Collect samples according to the sampling plan • Handle and store collected samples • Perform Minilab[®] basic tests on collected samples from their respective SS • Report data in the specified forms and ensure their accuracy and completion • Divide samples in 3 different boxes according to Minilab[®] results (passed, failed, and doubtful) • Send boxes (each sample with collecting forms and TLC plate) to NQCL • Draft a report and send it to the focal point • Make an inventory list of the Minilabs[®] and supplies and send it to the focal point 	<ul style="list-style-type: none"> • Monitor, evaluate, and supervise sample collection and Minilab[®] testing on site • Review the data and verify its accuracy • Check the Minilab[®] components and make sure that they are well maintained, stored, and secured • Make one final report by each testing round incorporating data from the five sentinel sites and the confirmatory tests done in 	<ul style="list-style-type: none"> • Act as the main coordinator and supervisor of all activities at the regional and central level • Provide all technical support to sentinel site staff • Liaise with PQM about program activities • Keep close communication with PQM and DOMC

<ul style="list-style-type: none"> • Regional focal point will ensure that the above activities are in compliance with protocol MQM protocol guidelines and time line. • NQCL team will receive / verifying the content of the boxes and conducting conformity testing (verification and compendial analysis according to the protocol guidelines) 	<p style="text-align: center;">NQCL</p> <ul style="list-style-type: none"> • Share the report with all stakeholders • Recommend and take necessary action to deal with any fake and substandard drugs detected 	<ul style="list-style-type: none"> • Monitor and evaluate the entire process of MQM activities • Verify that all documents submitted to PQM are correct and complete
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Closing ceremony

At the end of the workshop a closing ceremony took place at the NQCL in the presence of Dr. Gladys Tetteh (USAID), Dr. Elizabeth Juma (DOMC), Dr. Fred Siyoi (PPB), Dr. Hezekiah Chepkwony (NQCL), Dr. Patrick Lukulay, Dr. Latifa El Hadri, and Dr. Mustapha Hajjou (PQM). Dr. Lukulay thanked the partners for their support of the program and the participants for successfully completing the training. He underlined the importance of collaboration between the NQCL and PPB. Dr. Siyoi thanked USAID/Kenya and PQM for their respective financial and technical support, adding that the NQCL and PPB will work jointly to ensure the success of the program. Dr. Chepkwony concurred with Dr. Siyoi and expressed his willingness and commitment to support the cooperation between the two entities. Dr. Tetteh gave an overview of the PMI activities planned for FY 10 and FY 11, and encouraged the PPB, NQCL, and DOMC to provide results of the first round by early May 2010. These baseline results will serve to build the next MOP activities for Kenya. Dr. Juma expressed that progress has been made in the malaria control effort, but more work still needs to be accomplished in terms of quality control of antimalarials and other medicines. She added that having the PQM’s technical support will be of tremendous benefit to Kenyan PMS.

The trainees expressed the need to expand Minilab[®] basic tests to other medicines. They were pleased to see how easily Minilab[®] basic tests can identify poor medicine quality relating.

At the end of ceremony, all participants were awarded a certificate of completion.



Next Steps

Budget: After the training, PQM distributed a template to determine the budget for the first round for each sentinel site, including:

- a. Cost to buy the samples from different sectors
 - b. Transportation to the site and within the site
 - c. Per diems for sample collection/testing onsite with Minilab[®] confirmatory testing at NQCL/supervision
 - d. Sampling tools (zipper bags, cartons, markers, stickers, etc.)
 - e. Postage
- The PPB and DOMC will finalize the sampling plan and all relevant guidelines to collect antimalarial samples at the five selected sites
 - Budget for sampling and testing will be submitted to PQM
 - Sampling and testing with Minilab[®] tests will start in March

Minilab[®]: Three new Minilab[®] tests were procured by PQM and delivered in January 2010 to the NQCL with all reference standards, reagents, and supplies to carry out MQM activities in the field. PQM also replenished the two existing Minilabs[®] at the NQCL with necessary supplies. These Minilabs[®] will be shipped to the five selected sentinel sites and will be the responsibility of the regional focal point.



January 25, 2010: Meeting with the Kenyan Anti-Counterfeiting Taskforce

Dr. Lukulay and Dr. Kimatu met with the Kenyan Anti-Counterfeiting Taskforce at the Ministry of Industrialization. The objective of the meeting was to brief the taskforce about planned activities in support of the PPB and the Malaria Control Program with special emphasis on PMI-supported PMS of the quality of antimalarials in Kenya. The taskforce pledged to work with PQM to take appropriate actions and asked for PQM support beyond antimalarials, requesting training for field staff in the detection of counterfeits at border posts and other points of entry. Dr. Lukulay discussed special hand-held spectrometers that could be used to authenticate

products at border posts and indicated that these tools would be valuable in detecting counterfeits of brand name and popular generic drugs entering Kenya illegally.

January 26, 2010: Meeting at PPB with WHO Staff

Participants: WHO; PPB; DOMC; PQM

The objective of the meeting was to discuss how the PQM's work fits into the overall WHO strategy on quality assurance and quality control of medicines in Kenya. The WHO team emphasized that PQM should coordinate activities with WHO in the area of quality assurance and quality control so that there is no duplication of efforts. They also stressed that the planned PMS activities should be planned in such a way that the practice would ultimately be institutionalized and consistent with the Quality Assurance Framework document that was drafted by various stakeholders for Kenya. The PQM team volunteered to help finalize the framework document by reviewing and providing any necessary feedback.

The PQM team thanked WHO for their useful review of the MQM protocol and pledged to coordinate work and to share all MQM findings with WHO and all key stakeholders in Kenya. The PQM team also shared the timeline for data collection and testing.

Meeting with PEPFAR at USAID/Kenya

Participants: James Batuka, Alice Micheni, and Stanley Bii, PEPFAR; PQM team

Dr. Lukulay described the technical assistance that PQM could provide to support PEPFAR objectives in Kenya. The technical assistance would focus on supporting local manufacturers of medicines against opportunistic infections to comply with GMP requirements, support PPB by strengthening drug registration, and expand the PMS program to include antiretrovirals.

Dr. Batuka indicated that PEPFAR had been reviewing the entire portfolio of technical assistance to quality assurance with an emphasis on cost effectiveness and building local capacity. He pointed out that PEPFAR's focus is on the priorities of the Ministry of Health in the next five years. He also mentioned that those priorities do not include medicines QA.

At the end of the meeting, Dr. Batuka promised to share the proposed activities with his director and send feedback to PQM.

Next steps

PQM will ensure the implementation of the MQM protocol by:

- Wiring the funds for the first round of the MQM program
- Monitoring the progress of sample testing at the sentinel sites and NQCL
- Communicating with the PPB, NQCL, and DOMC to ensure that MQM activities follow protocol guidelines
- Disseminating MQM first round results to relevant stakeholders

Conclusion

Establishing a PMS program for Kenya will enable PPB and DOMC to conduct quality control for antimalarials in a coherent and coordinated fashion. The established program can be extended to other critical, life-saving medicines as well.

Providing technical assistance and training using the most cost efficient tools will contribute to strengthening local capacity in medicines quality and in early detection of counterfeit and substandard products circulating in Kenya.

DETAILED WORK PLAN – KENYA
September 30, 2009 – October 1, 2010

Objective	Activities	Expected results	Timeline	Estimated budget
Strengthening quality and post marketing surveillance of Antimalarials	<ul style="list-style-type: none"> Conduct a comprehensive assessment on the capability of PPB in testing the quality of Antimalarial 	Assessment conducted	Q1	15,000.00
	<ul style="list-style-type: none"> Develop protocol for post marketing surveillance of Antimalarial in selected sentinel sites 	Protocol developed and sentinel sites identified	Q1	
	<ul style="list-style-type: none"> Procure 3 minilabs and supplies for existing minilabs 	3 minilabs procured and supplies provided to replenish the 2 existing ones	Q1	20 ,000.00
	<ul style="list-style-type: none"> Provide 1 week minilab training for staff from DOMC, PPB and NQCL. Training include <ul style="list-style-type: none"> a - Documentation, lab coats, supplies, transportation, lunch, drinks, lodging for personnel coming outside Nairobi and per diem for participants b- Expense for 2 PQM staff trainers 	Training provided for 16 participants	Q2	15,000.00
	<ul style="list-style-type: none"> Organize one round of testing of antimalarial in 5 sentinel sites <ul style="list-style-type: none"> Provide reagents, reference standards and chemicals for minilab testing at sentinel sites Procuring medicines for testing Transportation to the sites Transportation within the sites Purchasing of small materials, distilled water, photocopies Per diem for samplers and analysts Coordination, supervision, work in the field, data management 	300 samples collected and tested by Minilab	Q2 & Q3	40,000.00
	<ul style="list-style-type: none"> Provide NQCL with supplies and RS to perform confirmatory testing 	Non conform samples tested at NQCL	Q3	10,000.00
	<ul style="list-style-type: none"> Monitor and evaluate the implementation of the protocol 	Evaluation accomplished	Q2 & Q3	
	<ul style="list-style-type: none"> Issue a final report to stakeholders 	Report finalized and presented to stakeholders	Q4	
Total				100,000.00

PQM

Nairobi / Kenya: January 25-29, 2010

Tentative Agenda

January, 2010	Location	Purpose
25 <i>Morning</i>	NQCL	<ul style="list-style-type: none"> • Opening session of the training workshop by PPB Registrar
25 <i>Afternoon</i>	NQCL	Minilab training on Antimalarial medicines for staff from PPB, DOMC, and NQCL <ul style="list-style-type: none"> • General introduction • Sampling strategies and sample collection • Presentation of Minilab kits
26-28	NQCL	Training on minilab basic tests: <ul style="list-style-type: none"> • Visual and Physical Inspection • Simple Disintegration • Thin Layer Chromatography
28*	Office of Anti-counterfeit agency.	Meeting with Anti-counterfeit agency. Time between 10.00am and 11.00
29 <i>Morning</i>	NQCL	Training evaluation and distribution of certificates
29** <i>Morning / Afternoon</i>	PPB / USAID mission	<ul style="list-style-type: none"> • Meeting with WHO rep, Regina Mbindyo, at 9:00AM • Meeting with PEPFAR team, Karen Klimowski and James Batuka, at 11:00 AM • Debrief USAID mission on the outcome of the above activities, meetings, and discuss the next action plan. Time: TBD

Note:

- * on January 28th Patrick will be meeting with Anti-counterfeit Agency
- ** On January 29th, Patrick will meet with Regina and PEPFAR team. PQM training team will join Patrick to debrief USAID mission.

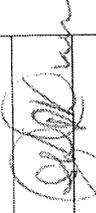
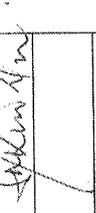
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Monday - 25 / 01 / 2010

MINILAB TRAINING HELD ON JANUARY 25- 29, 2010 AT NQCL

LIST OF PARTICIPANTS.

<u>NAME</u>	<u>P/NO</u>	<u>ORGANIZATION</u>	<u>TEL. NO</u>	<u>EMAIL</u>	<u>SIGNATURE</u>
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OPENING SPEECH FOR THE REGISTRAR FOR THE MINILAB TRAINING TO BE HELD IN NQCL FROM JANUARY 25 TO JANUARY 29, 2010.

To the USP team, Mustafa and Latifa, Director NQCL, representatives from the WHO, MSH, DOMC, USAID, PPB, facilitators and participants of the training, ladies and gentlemen, it gives me a great pleasure to be part of this Minilab training workshop.

As a regulatory authority, one of the important functions involves ensuring that medicines in circulation in the country are safe, efficacious and of good quality. The quality of medicines determines their effectiveness and safety and hence the health outcome of the patient. If the quality of medicines is compromised, investments in pharmaceutical commodities, health systems and pharmaceutical management systems are negated.

As a country and in line with the Vision 2030, having a healthy population is very critical to achieve this. Currently, world over, the issue of counterfeit medicines has become a major concern and Kenya is not spared either. Studies have shown that counterfeit medicines are more in the developing countries compared to the developed world.

The Board has been involved in active surveillance to reduce the counterfeit medicines circulating in our market through the inspectorate department. In addition, the Board is working on developing a routine post-marketing surveillance strategy to ensure quality of medicines.

The Board has identified and recommended to customs for gazettment the ports of entry of medicines in Kenya and it is working to ensure that medicines batches are tested before they are allowed in the market at the ports of entry. This will be done by having Minilabs at these ports of entry.

I am aware that this training will equip our staff with the basic skills required to use the Minilabs and this will help the Board a lot in meeting this obligation.

On this note, I would like to thank United States Pharmacopeia (USP) for their support on this Medicines Quality Monitoring programme. This will go a greater length to ensure that we have quality medicines in the market. The Government of Kenya through the Ministry of Medical services is very keen to partner with USP and we promise our total commitment on this project.

I would also like to thank other partners who have been working with the Board like WHO and MSH for their support and government departments like DOMC, NASCOP, NQCL and NLTP.

With those few remarks, I wish to thank all of you and declare this workshop officially open.

DR.KIPKERICH C. KOSGEI

REGISTRAR.

Evaluation by Participants

Nine participants returned the evaluation form.

Indicator	Strongly Agree	Agree	Disagree Somewhat
1. Course objectives were relevant to my needs	14		
2. I was able to understand the content of the materials presented	13	1	
3. Overall the course was useful and will help me do my job better	13	1	
4. There were enough practical exercises to facilitate understanding of the course	11	3	
5. The pacing of sessions was appropriate for my understanding of course materials	11	3	
6. The instructors were knowledgeable on the subject	14		
7. The instructors allowed an appropriate level of participation in the class	14		

Any other comments/suggestions:

1. Which topic(s) or aspects of the course should not be included in future workshops?

The majority expressed the importance of Minilab training in their daily activities at regional level. They expressed their wish to extend this training to other medicines mainly Anti-TB and ARVs.

2. What are your recommendations/suggestions for improvement of the course?

- **More practical training needed**
- **Request by trainees to have a follow-up post training**
- **Need to have supervisory visit at regional level**
- **Requested training for other partners mainly pharmacists at regional level**
- **Train more people on the site**
- **Need to go over logistics for sampling and testing**
- **Provide presentation using Video to see how other countries are performing their MQM activities**
- **Provide soft copy of the course**

The participant evaluations and experience of the facilitators during the course will be used to update the training materials at a later date.



Guidelines to Establishing a Protocol for Medicine Quality Monitoring

Latifa El Hadri, Ph.D.

Program Coordinator, USP Drug Quality and
Information Program





Objective

USP Drug Quality and Information Program

**Create a uniform protocol for all
procedures undertaken in Medicine
Quality Monitoring (MQM)**





Main Sections

USP Drug Quality and Information Program

- ◆ Background and Introduction
- ◆ Main Objective/ specific objectives
- ◆ Main Activities
 - > sample collection: public, private, informal
 - > Test sampled medicines;
 - > Analyze MQM findings
 - > Write report, after each round,,
 - > Implement corrective and preventive actions





Responsibilities of Stakeholders Involved in MQM

USP Drug Quality and Information Program

- ◆ List all stakeholders involved in each activity.
- ◆ Define clearly the role of each stakeholder within the program.
- ◆ Designate a principal focal point for all sentinel sites
- ◆ Designate a focal point for each sentinel site, if applicable.
- ◆ Roles of focal point:
 - ▶ Development of a sampling and analysis plan;
 - ▶ Supervise the implementation of the sampling strategies and the sample collection;
 - ▶ Ensure that samples are analyzed according to the protocol;
 - ▶ Ensure that testing results are analyzed accordingly;
 - ▶ Write and disseminate the report;



Methodology

◆ **Sampling strategies**

The planning for sampling should take into consideration: Potential limitations, budget, human resources; availability of medicine in all sectors—public, private, and informal, accessibility, and levels of distribution

◆ **Site selection**

- > consult with key health officials and partner
 - > 5 sites will be determined according to the following factors:
 - > Budget;
 - > Human resources;
 - > Epidemiological data;
 - > Medicine availability and accessibility for sampling;
 - > Presence of all sectors (public, private, informal);
 - > Medicines circulating freely between borders with nearby countries
 - > Proven or anecdotal evidence of poor-quality medicines circulating in the market;
 - > Other relevant factors.





- ◆ **Medicine selection for testing**
- ◆ **Sample definition**

To ensure uniformity in the collection of medicines, clearly define the attributes that determine a single sample.

The variables comprising a single sample are:

- > Active ingredient or API (i.e., chloroquine, amodioquine, artesunate, etc.)
- > Dosage form (i.e., tablet, capsule, oral solution, etc.)
- > Lot/Batch number
- > Collection site



Sampling

USP Drug Quality and Information Program

Estimate number of samples to be collected per round

Ideally 100 samples per sentinel site/ round .

Sampling techniques

- ▶ If expired medicines are found, collect a minimum number of units
- ▶ conceal the identities of the sampling team.
- ▶ Arrange to replace samples collected from government and other facilities as appropriate.
- ▶ Practice key questions to be asked at informal
- ▶ If a government vehicle is used for transport, keep it out of sight of medicine dealers; use public transportation to reach to the site if needed.



Sampling

◆ Number of units to collect per sample

Initial Sampling		
Minimum Units	Maximum Units	Comments
20	40	If the “minimum” of 20 units is not feasible, collect what is available but no less than 5 units
Re-sampling for Compendial Testing (if necessary)		
50	100	If the “minimum” of 50 units is not feasible, refer to the Number of Units Needed in Table 1: Guidelines for Compendial Testing





Sampling

USP Drug Quality and Information Program

- ◆ Secure each collected sample in a plastic container or sealable plastic bag (e.g., Ziploc®) and attach its corresponding *Sample Collection Form*
- ◆ Sample transportation and handling
Pack, transport, and store collected samples in such a way as to prevent any deterioration, contamination, or adulteration.



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Sampling Analysis

USP Drug Quality and Information Program

- ◆ Conduct Minilab® Basic Tests at sentinel sites on ALL Verification of Basic Tests at National Quality Control Lab
- ◆ Confirmatory Testing with Compendial Methods
- ◆ 100% Fail, 100% Doubtful, 10% Pass ◆ Complete Annex 5
- ◆ Record results in MQM Excel Reporting Datasheet



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Reporting

USP Drug Quality and Information Program

- ◆ write report according to MQM template
- ◆ Disseminate results
- ◆ Action to be taken on Non Confirm samples



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Sentinel Site (Nairobi)						
Monitoring the Quality of Antimalarials						
<i>Sampling procedure</i>						
Sector	Sites of collection /	Name of sites / address	List of Antimalarial by API	Commercial / Brand Name	Number of samples to be collected	Total
Public	Kemsa	Warehouse	-Quinine (tablet, injectable) -SP -Lumefantrine+artemether tabs	Coartem or Artefan	8	40
	Hospitals	Mbagathi D. Hosp. Kayole D. Hosp. Pumwani Hosp. Ngong Sub D. Hosp	- Quinine (tablet, injectable) -SP -Lumefantrine+artemether tabs	Coartem or Artefan	16	
	Health Centres	Lang'ata HC, Kangemi HC, Makadara HC, Kasarani HC	- Quinine (tablet, injectable) -SP -Lumefantrine+artemether tabs	Coartem or Artefan	16	

Private	Importers/Distributors	2 (1 in Westlands and 1 in Central business District)	- Quinine (tablet, injectable) -SP -Lumefantrine+artemether tabs -Dihydroartemisinin/ Piperaquine tabs	Coartem, Artefan, Lonart, Coartesiane, Fantem, Artheget, Lumerax, Lumether, Lufanate, Co-Max, Lufenart, Co-Mether and Co-Falcinum	8	60
	Wholosalers	2 (1 Central Business District and one in Easleigh)	-Quinine (tablet, injectable) -SP -Lumefantrine+artemether tabs -Dihydroartemisinin/ Piperaquine tabs	Coartem, Artefan, Lonart, Coartesiane, Fantem, Artheget, Lumerax, Lumether, Lufanate, Co-Max, Lufenart, Co-Mether and Co-Falcinum	8	
	Hospitals	4 (Nairobi west, Aga Khan, Marter hospital and Getrudes)	-Quinine (tablet, injectable) -SP -Lumefantrine+artemether tabs -Dihydroartemisinin/ Piperaquine tabs	Coartem, Artefan, Lonart, Coartesiane, Fantem, Artheget, Lumerax, Lumether, Lufanate, Co-Max, Lufenart, Co-Mether and Co-Falcinum	20	

	Pharmacies	3 in Nairobi, 1 in Kajiado and 1 in Thika	-Artemether/Artesunate inj - Quinine (tablet, injectable) -SP -Lumefantrine+artemether tabs -Dihydroartemisinin/ Piperaquine tabs	Coartem, Artefan, Lonart, Coartesiane, Fantem, Artheget, Lumerax, Lumether, Lufanate, Co-Max, Lufenart, Co-Mether and Co-Falcinum	10	
	Clinics	3 in Nairobi, 1 in Thika and 1 Kajiado	Quinine (tablet, injectable) -SP -Lumefantrine+artemether tabs	Coartem, Artefan, Lonart, Coartesiane, Fantem, Artheget, Lumerax, Lumether, Lufanate, Co-Max, Lufenart, Co-Mether and Co-Falcinum	8	
	Shops & Kiosks	3 in Nairobi, 1 in Kajiado and 1 in Thika	Quinine (tablet, injectable) -SP -Lumefantrine+artemether tabs	Coartem, Artefan, Lonart, Coartesiane, Fantem, Artheget, Lumerax, Lumether, Lufanate, Co-Max, Lufenart, Co-Mether and Co-Falcinum	6	
Total						100 samples



PROTOCOL FOR POST-MARKETING SURVEILLANCE OF ANTIMALARIALS IN KENYA



Acronyms

ACT	Artemisinin-based combination therapies
DOMC	Division of Malaria Control Program
FP	Focal Point
IEC	Information Education and Communication
IPT	Intermittent Preventive Treatment
KEMSA	Kenya Medical Supplies Agency
MEDS	Mission of Essential Medicines Services
MHS	Management Sciences for Health
MQM	Medicines Quality Monitoring
NASCOP	National Aids and STI Control Program
NHSSP II	Second National Health Sector Strategic Plan
NLTP	National Leprosy and Tuberculosis Program
NQCL	National Quality Control Laboratory
PPB	Pharmacy and Poisons Board
PQM	Promoting the Quality of Medicines
ToR	Terms of Reference
USAID	United States Agency for International Development
USP	United States Pharmacopeia

PROTOCOL FOR POST-MARKETING SURVEILLANCE (PMS) OF ANTIMALARIALS IN KENYA

1. Background and Introduction

Medicines regulation is a complex process which comprises the totality of measures – legal, administrative and technical – which governments take to assure the quality, safety and efficacy of medicines for the population. An important role of a medicine regulatory authority involves ensuring that medicines in circulation in the country are safe, efficacious and of good quality. The quality of medicines determines their effectiveness and safety and, hence, the health outcome of the patient. If the quality of medicines is compromised, investments in pharmaceutical commodities, health systems and pharmaceutical management systems are negated, and patient safety is jeopardized

The Pharmacy and Poisons Board (PPB) is the National Drug Regulatory Authority of Kenya, established in 1957 by the Pharmacy and Poisons Act. The PPB is charged with the responsibility of regulating the practice of pharmacy and trade in medicines. The PPB's core mandate is to ensure the provision of quality, safe and efficacious pharmaceutical products and services. This is done through evaluation and registration of pharmaceutical products, promotion of rational use of medicines, inspection and surveillance activities, licensing of personnel and institutions, clinical research authorization, and advising the government on any matter relating to regulation of medicines and poisons. Registration of medicines requires thorough quality control testing in order to ensure that the product meets quality specifications. The National Quality Control Laboratory for medicines and medical devices, established in 1992, is a serves as the technical arm of PPB and is mandated by the Pharmacy and Poisons Act as a testing facility for pharmaceuticals and medical devices. Post-marketing surveillance requires collaboration and coordination of activities between the PPB, the quality control laboratory and various disease programs, including Division of Malaria Control (DOMC), National AIDS and STI Control Program (NASCOP), and Division of Leprosy TB and Lung Disease (NLTP). A primary strategic objective of the malaria control program is to monitor and evaluate the effectiveness of their case management strategies in the field and this requires monitoring the effectiveness and safety of antimalarials. Thus, post-marketing surveillance is critical to ensuring that various commodities used are effective, impactful and beneficial for controlling diseases in the community.

The PPB is participating in an ongoing initiative to harmonize technical requirements for medicines regulation within Africa, and specifically among the EAC partner states. This initiative aims at developing common approaches, technical documents and closer networking for key regulatory functions among the partner states. A national PMS system therefore needs to take into account, as well as to inform, other market surveillance activities in the sub-region, in order to assure the safety of consumers in the sub-region.

Situation Analysis

Within the last few decades, there has been a growing increase in awareness and safety concerns, such as:

- 1 Counterfeits/substandard medicines
- 2 Medication errors
- 3 Lack of efficacy reports
- 4 Use of medicines for indications that are not approved and for which there is inadequate scientific basis
- 5 Case reports of acute and chronic poisoning
- 6 Assessment of drug-related mortality
- 7 Abuse and misuse of medicines
- 8 Adverse interactions of medicines with chemicals, other medicines, and food

Various studies have been undertaken on the quality of medicines in Kenya. These continue to inform current and future initiatives towards a comprehensive PMS system. Some of the studies are highlighted below:

- a) A nationwide study of antimalarials by the Pharmacy and Poisons Board in collaboration with DOMC in May 2006, found that a wide range of antimalarials existed in the market, and the majority were not in the national malaria treatment guidelines; that a large proportion (42.6%) of antimalarial medicines were not registered, and that some antimalarial medicines found in the market did not meet quality standards -. The survey enabled an innovative approach to the regulation of medicines for priority conditions, with the regulator and disease control programme working collaboratively to address an issue of public health importance.
- b) During 2009, NASCOP and DLTLD undertook similar studies on quality of ARVs and TB medicines respectively. The studies were modelled along the 2007 AM survey, with modifications and adaptations to suit the context of ARVs and TB medicines. The results of both studies are being finalized, and are expected to inform further strategies for post-market surveillance of HIV and TB medicines.
- c) PPB and DOMC also participated collaboratively in a multi-country study on quality of antimalarials in Africa (QAMSA) in 2008. The results of QAMSA study showed that a number of ACTs and SPs were non-conform. Report of this study will be communicated soon by WHO to all stakeholders
- d) For ARVs, a WHO multi-country study undertaken in 2005 did not demonstrate any failures of ARVs sampled from Kenya, which comprised both imported and locally produced ARVs.

These findings may not be limited to antimalarials and therefore it is necessary to establish the registration status of all other products, and provide updated information on the quality of essential medicines circulating in the market

The PMS System

Post-marketing surveillance encompasses the **pro-active** and **reactive** collection of information on quality, safety and performance of medicines, medical devices, complementary medicines, cosmetics, and related substances after they have been introduced in the market (after registration).

Regulation of prescription and non-prescription medicines is critically important in protecting the health and safety of citizens. However, the approval process for new medicines cannot adequately predict the full extent of harmful or unexpected effects of a drug once it is on the market. Consequently, a post-marketing surveillance system is necessary for medicines, medical devices and diagnostic reagents. It is also in line with the Second National Health Sector Strategic Plan (NHSSP II) objective of enhancing the regulatory capacity of the Ministry of Health. Such a system will be able to detect harmful and unexpected effects of medicines and devices in a timely manner to avoid delay in follow-up and intervention measures. It also helps to improve the protection of health and safety of patients, users and others by reducing the likelihood of the same type of adverse incident being repeated in different places at different times. Thus greater consumer involvement will considerably improve the effectiveness of the post-marketing surveillance system.

2. Main Objective of PMS

The primary objective of the post-marketing surveillance system in general is to monitor the safety of medicines and conformity with established specifications for quality specifications as declared in the registration dossier or recognized pharmacopeial specifications. It will provide regular information on the quality of medicines circulating in the country.

In this study, post-marketing surveillance will focus on: 1) assessing the quality of antimalarials in selected sentinel sites which are part of the strategic plan of the division of malarial control and are part of the treatment guidelines; and 2) monitoring the shift from mono-therapies to Artemisinin-based combination therapies (ACTs).

This protocol can be expanded to include post-marketing surveillance of medicines for other disease programs.

3. Specific Objectives

The specific objectives that will be met under the post-marketing surveillance activities include the following:

- Estimate the proportion of the use of Mon therapies versus ACTs in selectes sites
- Obtain information on the quality of subsequent batches of registered antimalarial products in circulation in public , private and informal sectors
- Obtain information of the proportion of unregistered products in the selected sites
- Develop a medicine information database on the quality of medicines in circulation
- Disseminate information on the quality of medicines to stakeholders involved in medicines procurement, use, and regulation
- Promote communication and cooperation between stakeholders involved in medicines procurement, use, and regulation
- Provide evidence-based data for enforcement actions
- Propose possible strategies and implementation plans to address the problems identified in the study

4. Main Activities

- Collect selected antimalarial medicines from the public, private, and informal sectors
- Test sampled medicines
- Analyze MQM findings and results as indicated in Figure 2 – MQM Flow Chart
- Write report, after each round, describing overall MQM results
- Disseminate results and enforcement actions

5. Responsibilities of Stakeholders Involved in MQM

The stakeholders involved in MQM activity are:

Pharmacy and Poison Board (PPB)

- Will have oversight of the post-marketing surveillance activities
- Facilitate sample collection from each site
- Ensure that all samples collected conform to sampling protocol and verify samples sent to NQCL
- In the case that non conform samples are encountered in each round, PPB can 1) impose sanctions as defined in law; 2) issue product recalls if deemed necessary to protect public health; or 3) reprimand manufacturers, importers, distributors, wholesalers, retailers and pharmaceutical reps
- Gather all information for writing the report
- Disseminate the MQM report to all stakeholders, including all relevant authorities within MOMS, MOPHS and the advisory committee
- Present results of MQM at national and international fora to raise awareness

National Quality Control laboratory (NQCL)

- In charge of conducting inventory of Minilabs[®] on each site
- Examine and test medicines received from sentinel sites
- Perform QC testing as presented on MQM Analysis Flow Chart after validation by the focal point (FP)
- Submit the results to FP with a short summary on conducted analysis
- FP may request additional testing if needed (non conform samples); FP needs to coordinate with NQCL for re-sampling if more testing is required
- Ensure that all designated annexes are completed appropriately
- Store received samples in NQCL lab and reference them for future use

Division of Malaria Control (DOMC)

DOMC, in consultation with technical working group (PPB and NQCL), will:

- Develop MQM budget
- Manage travel logistics, including transportation to and within the sites
- Oversee MQM activities on site
- Support FP in gathering all samples from sites and ensure their delivery to NQCL
- Provide the list of samples to be collected

- Prepare sampling strategies (number of samples per site/sector/source)
- Liaise with FP and other partners as needed
- Share the results and invite IEC responsible persons to meetings, conferences, etc.
- Present results of non conform samples to IEC to raise awareness among the population

Advisory Committee for MQM activities

The PPB will establish an advisory committee. This committee will:

- Provide technical expertise on action to be taken on non-conform samples encountered in the market
- Make appropriate recommendations to the Registrar upon receipt of the results of MQM activities

Specific Terms of Reference (TOR) for the Board Research committee and PMS-committee will be developed.

Management Sciences for Health (MSH)

- Participate in the discussion and dissemination of MQM results
- FP will share planned MQM activities for each round
- FP and DOMC rep will request TA from MSH as needed
- MSH/SPS will support the DOMC by playing a collaborative role and providing TA on PMS issues related to supply chain strengthening and improving access and availability of ACTS.

World Health Organization (WHO)

- Technical support to development of comprehensive PMS strategy and system in line with ongoing regulatory strengthening
- Strengthening technical and collaborative linkages between MRA, disease control programs and other regulators
- Development, adaptation and adoption of relevant norms and standards
Support to consensus building at various stages; harmonization of regulatory systems (including PMS) within the sub-region

Promoting the Quality of Medicines (PQM)

Provide technical and financial assistance in regards to implementing all MQM activities

- Review MQM results at each level (Minilab[®], QC at NQCL) and final report
- Disseminate report and share results with relevant partners
- Ensure follow up, monitoring, evaluation, and execution of MQM protocol
- Review the budget and prepare contract and wire funds
- Provide supervisory visits and training as needed

Kenya Medical Supply Agencies (KEMSA)

- Make samples available to sampling team to test KEMSA supply
- Provide samples to sampling team to replenish samples withdrawn from public sectors if necessary
- Participate in discussion of MQM findings

Focal Point (FP)

The Focal Point (FP) of MQM activities is Stephen Kimatu, Head of the Medicine Information Department at PPB, and he will be in charge of:

- Coordinating MQM activities with all stakeholders
- Communicate directly with PQM staff
- Ensuring the development of a sampling and analysis plan
- Supervising the implementation of sampling strategies and sample collection
- Ensuring that samples are analyzed according to the protocol
- Ensuring that testing results are analyzed accordingly
- Writing and disseminating the report to all stakeholders

6. Methodology**6.1 Sampling Strategy**

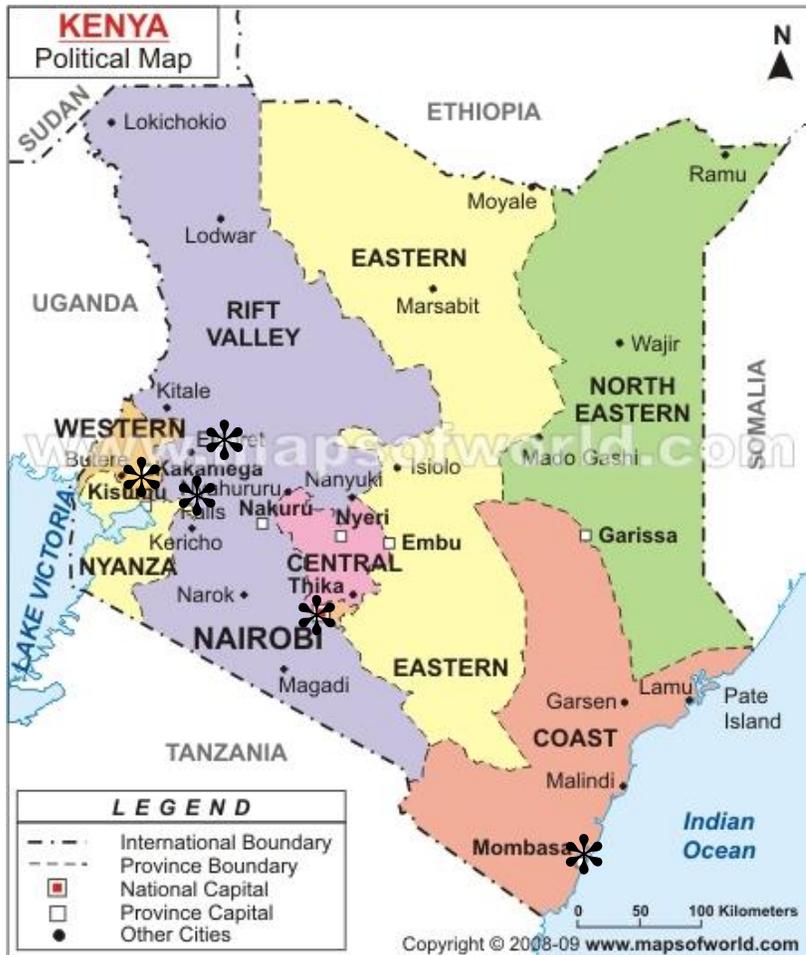
The sampling strategy involves convenience sampling from the various levels in the distribution chain including public (KEMSA, public health facilities, health centers), nongovernmental organizations (NGOs), faith-based organizations (such as Mission of Essential Medicines Services (MEDS), private for-profits (pharmacies), hospitals (private and public), and illicit markets. Samples will be collected using “mystery shoppers” in the private sector to simulate the real life situation in how patients access medicines. avoid alerting traders who might hide products. For the purpose of the malaria control program, samples will be collected from five sentinel sites defined in the sample site selection section. This strategy ensures that samples are obtained from all sectors where patients are likely exposed to medicines.

6.2 Site Selection

For the purpose of the Division of Malarial Control, five sites have been identified in collaboration with PPB, NQCL, and MSH for sample collection based on epidemiological data demonstrating prevalence of the disease, medicines availability and accessibility, medicines circulating freely originating from border towns, ports of entry, and availability of human resources. The sites where sampling will be done include:

- Nairobi (capital city)
- Mombasa (Coast Province)
- Kakamega (Western Province)
- Kisumu (Nyanza Province)
- Eldoret (Rift valley)

Map of Kenya showing sentinel site locations



Sentinel Sites

- Kisumu (Nyanza)
- Kakamega (Western)
- Eldoret (Rift valley)
- Mombasa (Coastal)
- Nairobi (capital city)

Samples will be collected from importers, wholesalers, Non-Governmental Organizations (NGOs), central stores, regulated retailers, hospitals, private sources, and informal markets.

6.3 Medicines selected for sampling

The antimalarial medicines selected for sampling are based on the division of malarial control program strategy for malarial control in Kenya. They include first-line treatment, second-line treatment, intermittent preventive treatment (IPT) for malaria in pregnant women, chemoprophylaxis, and treatment for severe malaria.

- **First-line treatment**
 - Artemeter Lumefantrine (AL)
- **Second-line treatment**

- Dihydroartemesinin & Piperaquine (DHAP)
- **Severe malaria**
 - Parenteral quinine
 - Oral quinine
 - Artemether/Artesunate injection
 - Rectal Artesunate
- **Intermittent Preventive Treatment (IPT)**
 - Sulphadoxine & Pyrimethamine (SP)
- **Chemoprophylaxis**
 - Doxycycline
 - Atovaquone I Proguanil
- **Other ACTs**
 - Artesunate Amodiaquine
- **Monotherapies**
 - Monotherapies will only be only collected, not tested (this information will help to establish the monitoring of the shift from monotherapies to ACTs and to evaluate their availability in the market)

6.4 Sample Definition

For the purpose of this study, a sample is defined as a medicine with a given API, dosage form, strength, and lot number from a given level in the distribution chain. Samples with the same attributes above and including the same lot number may only be collected if they are from a different level in the distribution chain, such as wholesaler versus retailer, etc. The same lots should not be collected from similar or same level institutions (for example, two pharmacies or retailers).

6.5 Number of units to collect per sample

The number of units collected per sample will determine the types of conclusions which can be drawn regarding product quality. Refer to table below.

The following example of sample collection applies to solid dosage forms (tablets and capsules) only. Sampling of oral suspension, injectable, or other dosage forms should be discussed in consultation with PQM.

Initial Sampling		
Minimum Units	Maximum Units	Comments
20	40	<ul style="list-style-type: none"> ● If the “minimum” of 20 units is not feasible, collect what is available but no less than 5 units

Re-sampling for Compendial Testing (if necessary)		
Minimum Units	Maximum Units	Comments
50	100	<ul style="list-style-type: none"> ● If the “minimum” of 50 units is not feasible, refer to the Number of Units Needed in Table 1: Guidelines for Compendial Testing

6.6 Criteria for prioritization of sampling

The protocol should have a clearly defined list of priority medicines to sample.

Priority should be given to the following APIs and Dosage forms:

- First-line treatment at the national level in the National Health Program (i.e., National Malaria Control Program (NMCP)) treatment guidelines;
- Most-sold medicines;
- Most commonly-used medicines to reflect the reality of consumed medicines from all available sectors; and,
- Medicines known or suspected to be counterfeit or sub-standard

Budget considerations should also be considered.

6.7 Criteria for diversification of sampling

An attempt should be made to try and diversify the samples collected from each site to reflect the availability in the market.

Consider the following characteristics to diversify the sampling:

- Different brands of the same API;
- Different batch/lots numbers;
- Multiple dosage forms (tablets, capsules, oral suspensions, injectables, suppositories, etc.);
- Different sectors (private/public/informal);
- Different sources or outlets of same product with same lots from different sources or outlets;
- Suspicious medicines;
- Improperly stored medicines at the sampling site (exposed to sunlight, humid/wet conditions, etc.); and,
- Different packaging of same product (i.e., blister vs. bulk).

Estimating the number of samples to collect per round

Ideally each round of sampling should contain approximately 100 samples per sentinel site.

6.8 Sample collection

- Provide a Sampling Checklist (Annex 1) to samplers prior to their departure to collection sites and emphasize the need for its consistent use.
- If expired medicines are found, collect a minimum number of units
- Conceal the identities of the sampling team
- Arrange to replace samples collected from government and other facilities as appropriate
- Practice key questions to be asked at informal sites
- If a government vehicle is used for transport, keep it out of sight of medicine dealers; use public transportation to reach the site if possible.

Secure each collected sample in a plastic container or sealable plastic bag (e.g., Ziploc®) and attach its corresponding *Sample Collection Form* (Annex 2). The *Sample Collection Form* is an essential element to the sampling process. As the “passport” for each collected sample, the form contains all traceable data that will accompany the sample from the site of the collection to the site of Minilab® testing and then to the quality control laboratory for confirmatory testing. This maintains a traceable record of the identity of the sample should it test “fail or doubtful” and should action need to be taken.

6.9 Sampling transportation and handling

Pack, transport, and store collected samples in such a way as to prevent any deterioration, contamination, or adulteration. Store and transport collected samples in their original sealed containers, according to the storage instructions for the respective product. Take appropriate measures and adequate care to ensure that samples reach the test site – whether for Minilab® or confirmatory testing – without any physical or chemical damage. Pack samples in a container filled with cotton, foam, or other suitable material to protect them during transport; then seal and label the containers appropriately. Ensure that samples are stored in the appropriate environmental condition at all times.

7.0 Sample Analysis

Once samples have been collected, they need to be tested in three stages or levels (Figure 1). Level 1 is the sentinel site minilab tests, level 2 is the verification test carried out in the lab using minilab to verify sentinel site data and level 3 is the confirmatory testing done using full compendial testing.

Safety & Environmental Considerations

Sample analysis should be performed taking into consideration any possible safety and environmental consequences. Safety guidelines should be followed per Part Four of the WHO Technical Report Series, No. 902, Annex 3. Waste disposal shall follow the country’s national legislation. If a country does not have the relevant legislation it is recommended to follow WHO Health Care Waste Management guidelines.

7.1 Levels 1 & 2: Basic Tests

7.1.1. Level 1: Basic Tests with Minilabs® at Sentinel Site

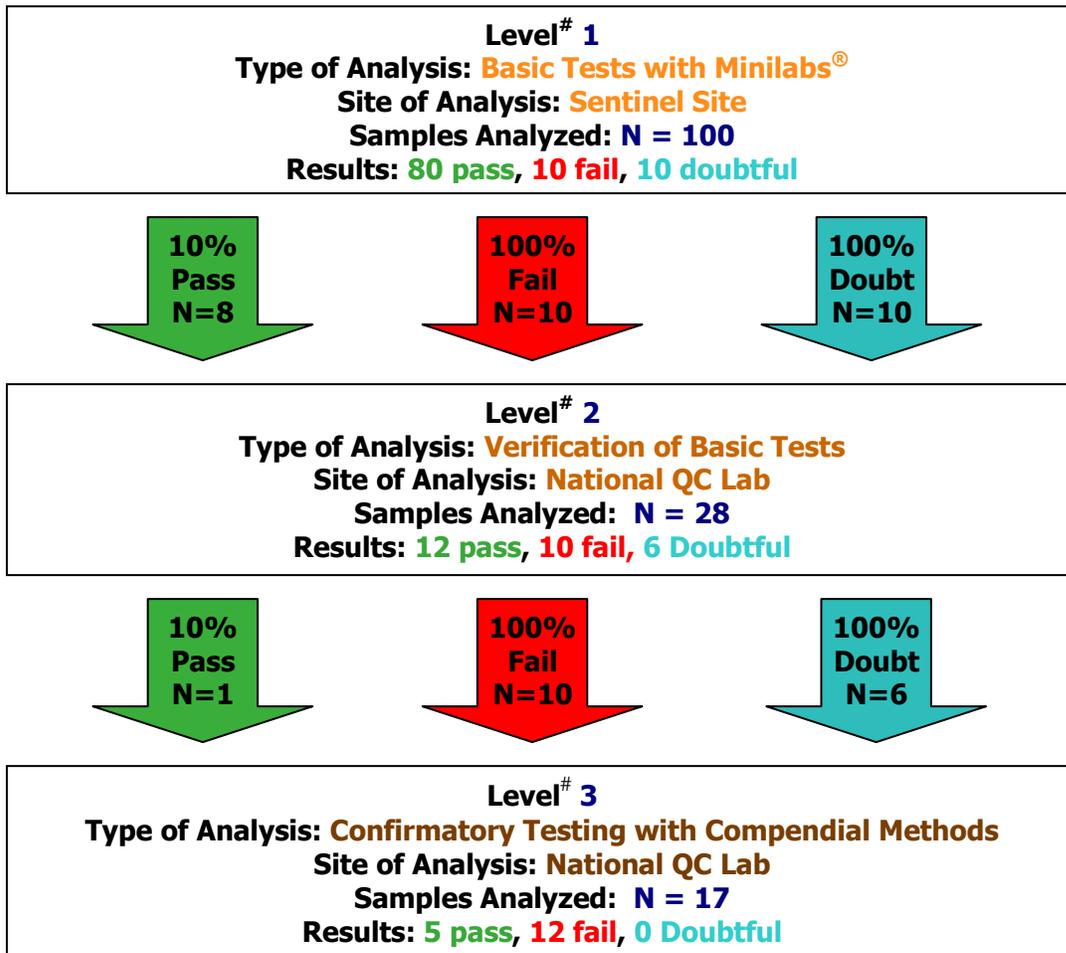
Basic tests include Physical/Visual (P/V) Inspection, Disintegration, and Thin Layer Chromatography (TLC)

- Test each collected sample at the sentinel site using the Minilab®. (Sentinel site staff should have been trained, prior to sampling, in the use of the Minilab® for testing and on interpretation of basic tests.)

Note: Samples collected that have expired, or are within two to three months of expiration, should not be tested.

Figure 1: Medicines Quality Monitoring (MQM) Analysis Flow Chart

Example: **N=100 Samples**



Protocols may define “stages” or “levels” differently; individual protocols should clearly indicate the terminology to be utilized and its specific meaning.

- Record clearly the test results for each sample on the *Basic Tests Analysis Form for Sentinel Site Staff* (Annex 3).
- Send a subset of samples to the NQCL for verification testing, as follows: (Refer to Figure 1—MQM Analysis Flow Chart.)
 - 10% of samples that passed*
 - 100% of samples that failed**
 - 100% of samples that are doubtful***
- Send the selected subset of samples with their respective forms attached (*Sample Collection Form* and *Basic Tests Analysis Form for Sentinel Site Staff*) to the NQCL for verification and confirmatory testing.

7.1.2. Level 2: Verification of Basic Tests at NQCL

NQCL: Perform verification testing by repeating basic tests on the subset of samples.

- Record clearly the results of each sample on the *Basic Tests Analysis Form for National Quality Control Laboratory Staff* (Annex 4).
- For any samples that fail or are doubtful, continue to the third stage of analysis by performing complete compendial testing.
- Perform compendial testing on the following samples:
(Refer to Figure 1—MQM Analysis Flow Chart.)
 - 10% of samples that pass verification testing*
 - 100% of samples that fail verification testing**
 - 100% of samples that are doubtful for verification testing***
 - 50-100% of sulfadoxine-pyramethamine (S/P) tablets/capsules and other medicines with known dissolution failures
 - ◆ Since S/P tablets are known to have high dissolution failure rates, always perform compendial analysis on S/P tablets.

* Pass: Conforms to all three (3) tests

** Fail: Does NOT conform to at least one (1) of the three (3) tests

*** Doubtful: Conflicting or inconclusive results for at least one (1) of the three (3) tests

7.2 Stage/Level 3: Confirmatory Testing with Compendial Methods at NQCL

If compendial testing must be conducted and there are insufficient units, more units of the same sample should be collected, preferably using the following procedure:

- Ideal: Collect the same product with the same lot number from the same original source. If possible, collect samples of the same lot number from other sources to ensure that the cause of failure is not due to storage conditions of the original source.
- Alternative: If the same lot number **cannot be found** at the **original source**, then collect the same lot from other sources.

In both situations, ensure that a sufficient number of units are collected to perform compendial testing.

Note: Should the country MRA suggest using different methods of sample collection for compendial testing, justify using those procedures in the protocol.)

- Confirmatory testing should be done in logical sequence, rather than carrying out the full compendial testing all at once (Table 1).
 - Priority should be given to compendial tests that evaluate quality attributes that yielded failed or doubtful results during Basic Tests.
- Implementing Corrective and Preventive Actions (i.e., fines, lot withdrawals, etc.) on failed samples is subject to the national regulations of the individual country.
- For samples with no official compendial method, discuss with DQI and any other pertinent stakeholders to identify a valid quality control method of analysis.

- Record clearly the results of compendial analysis on the *Confirmatory Tests Using Compendial Methods Form* (Annex 5) for each sample tested.

Table 1: Guidelines for Compendial Testing (Solid Dosage Forms) ¹					
Step	Failed Basic Test	Suggested Compendial Method	Number of Units Needed ^{2, 3}	How to Proceed	Comments
1	Physical/Visual Inspection	Physical/Visual Inspection	10	<ul style="list-style-type: none"> Pass or Fail, proceed to Step 2 	<ul style="list-style-type: none"> Although P/V Inspection is not required by compendial tests, it is recommended to prior to beginning Steps 2-6
2	ID	ID(s)	5	<ul style="list-style-type: none"> Pass, proceed to Step 3 Fails, STOP 	<ul style="list-style-type: none"> If sample Fails Step 2, you can conclude: Sample does not conform to compendial specifications
3	Content	Assay	20	<ul style="list-style-type: none"> Pass, proceed to Step 4 Fails, STOP 	<ul style="list-style-type: none"> If sample Fails Step 3, you can conclude: Sample does not conform to compendial specifications
4	Disintegration	Dissolution	24	<ul style="list-style-type: none"> Pass, proceed to Step 5 Fails, STOP 	<ul style="list-style-type: none"> If sample Fails Step 4, you can conclude: Sample does not conform to compendial specifications
5	Impurity	Related Compound and/or Impurity test	See Comments	<ul style="list-style-type: none"> Pass, proceed to Step 6 Fails, STOP 	<ul style="list-style-type: none"> Some related compound and/ or impurity tests can be performed as part of the Assay. Other monographs may require additional units, which should be discussed on a case-by-case basis. If sample Fails Step 5, you can conclude: Sample does not conform to compendial specifications
6	If the sample passes Steps 1-6 and there are sufficient units, proceed to remaining monograph tests.				<ul style="list-style-type: none"> If sample Fails Step 6, you can conclude: Sample does not conform to compendial specifications
<p>1 This example applies to solid dosage forms (tablets and capsules) only. Details for testing oral suspension, injectable, or other dosage forms should be discussed during protocol development on a case-by-case basis.</p> <p>2 The number of units needed for each test depends on the individual monograph.</p> <p>3 Use the available units and follow the sequence indicated in the table. (For example: If only 50 units are available, begin performing Steps 1-3. Do not wait for re-sampling to occur.)</p>					

8. Reporting Data

Reporting data on the *MQM Reporting Excel Datasheet* (See Annex 6 for a visual representation of the Excel file) should be assigned to a sentinel site team leader or to the MQM focal point. In either case, the final MQM reporting Excel Datasheet should be reviewed and completed by MQM focal point. A copy of this document should be sent along with a final report of MQM activities to the PQM program manager for review.

9. MQM Report

Generate a report summarizing the data resulting from the MQM round. Follow the guidelines provided in the *Reporting Template for Medicine Quality Monitoring* (Annex 7), adapting appropriately to the unique needs and project specifications of the country program. Send the MQM report to the PQM program manager for final review.

Disseminate the MQM report to all partners involved in the project, and present results for discussion to determine what actions the medicines regulatory authority should take if counterfeit/substandard medicines are discovered.

10. Monitoring & Evaluating

As depicted in Figure 2, Monitoring and Evaluation (M & E) should be performed throughout the entire process of MQM activities. This process should be performed by a team designated by the MQM focal point. M&E should be conducted according to tools set by the PQM program manager and performed throughout the entire MQM process.

Adequate monitoring of MQM activities will allow the pertinent stakeholders to remediate or prevent any inconsistencies with the protocol. Additionally, an objective evaluation of the protocol's success should be performed after completing each round to allow for implementation of lessons learned, thus improving subsequent MQM activities.

As part of the M&E process, PQM suggests utilizing the *M&E Tool: Deviations, Changes & Recommendations from Guidelines to Establish a MQM Program* (Annex 8). This tool will help track any deviations and changes to the protocol and will also allow PQM to improve the guidelines based on partner recommendations.

11. MQM Overview

The following overview summarizes the steps involved in the MQM process and the forms that should be completed at various steps. (A visual representation of the MQM overview is presented in Figure 2.)

- Protocol Development—including a sampling and analysis strategy
- Sampling
 - Sampling team prepares for travel by completing *Sampling Checklist* (Annex 1)
 - Sampling team assigns sample codes as indicated in *Sample Collection Form* (Annex 2)
 - Person responsible for sampling records all pertinent information (i.e., details of packaging and point of purchase) on *Sample Collection Form* (Annex 2)
- Basic Tests Analysis at Sentinel Site
 - Sentinel site staff perform Basic Tests using the Minilab® and record results on *Basic Tests Analysis Form for Sentinel Site Staff* (Annex 3)
 - Upon completion of field testing, sentinel site or study focal point sends remaining samples, with their respective *Sample Collection Forms* and *Basic Tests Analysis Forms*, to NQCL for verification testing
- Verification of Basic Tests at NQCL

- NQCL staff performs verification tests and record results on Basic Tests Analysis Form for National Quality Control Laboratory Staff (Annex 4)
- If compendial testing must be conducted for failed and/or doubtful samples and there are insufficient units, more units of the same sample should be collected using a new *Sample Collection Form* (Annex 2)
 - These samples, with their Sample Collection Forms, are sent to NQCL for confirmatory testing
- Confirmatory Testing with Compendial Analysis at NQCL
 - NQCL staff performs confirmatory tests and records results on Confirmatory Tests Using Compendial Methods Form (Annex 5)
- MQM focal point records or reviews (if other analysts entered data) the *MQM Reporting Excel Datasheet* (See Annex 6 for a visual representation of the Excel file)
- MQM focal point should designate a team to conduct M & E
 - MQM focal point and PQM staff perform M & E throughout entire process as necessary
- MQM focal point writes and disseminates final report
 - The report should follow the guidelines indicated in the Reporting Template for Medicine Quality Monitoring (Annex 7). These guidelines can be altered as needed for individual country protocols.
 - National stakeholders implement CAPAs as necessary
 - National stakeholders disseminate implemented CAPAs

Figure 2: Medicines Quality Monitoring Flow

