U.S. PHARMACOPEIA
*The Standard of Quality℠*

# Strengthening National Capacity in Medicines Quality: Five-year Summary (2005-2009)

## Promoting the Quality of Medicines Program In Southeast Asia and the Philippines

Funded by the United States Agency for International Development
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Standards for Quality Medicines Throughout the World

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# Acronyms

| | |
|---|---|
| ABTs | Antibiotics |
| ACT | Artemisinin-based Combination Therapy |
| ADE | Adverse Drug Event |
| ADR | Adverse Drug Reaction |
| AMFm | Affordable Medicines Facility-malaria |
| AMLs | Antimalarials |
| ANEQAM | Asian Network of Excellence in Quality Assurance of Medicines |
| BDN | Bureau of Drug and Narcotic (Thailand) |
| BVBD | Bureau of Vector-borne Diseases (Thailand) |
| CMPE | Centre of Malariology, Parasitology, and Entomology (Laos) |
| CNM | National Center for Parasitology, Entomology and Malaria Control (Cambodia) |
| CPC | Cambodian Pharmacovigilance Center |
| DDF | Department of Drugs and Food |
| FDA | Food and Drug Administration |
| FDC | Fixed dose combination |
| FDD | Food and Drug Department |
| GFATM or Global Fund | Global Fund to Fight AIDS, Tuberculosis and Malaria |
| GMS | Greater Mekong Sub-region |
| GPHF | Global Pharma Health Fund e.V |
| IMC | Inter-Ministerial Committee for Eliminating Counterfeit Drugs and Illegal Health Care Services |
| IMPACT | International Medical Products Anti-Counterfeiting Taskforce, WHO |
| JPMA | Japanese Pharmaceutical Manufacturers Association |
| Lao PDR | Lao People's Democratic Republic |
| MOH | Ministry of Health |
| MQM | Medicine Quality Monitoring |
| MRA | Medicine Regulatory Authority |
| MSH | Management Sciences for Health |
| PAC | Pharmacists Association of Cambodia |
| PQM | Promoting the Quality of Medicines Program |
| NMQCL | National Medicine Quality Control Laboratory |
| PQM | Promoting the Quality of Medicines Program |
| QA | Quality Assurance |
| QC | Quality Control |
| RDM-A | USAID Regional Development Mission for Asia |
| USAID | United States Agency for International Development |
| USP | United States Pharmacopeia |
| WHO | World Health Organization |
| WIPO | World Intellectual Property Organization |

# Executive Summary

Ensuring access to good-quality essential medicines, especially in the developing world, requires commitment from individual governments, health care providers, pharmaceutical industry, and consumers. Over the past five years of this project, the Promoting the Quality of Medicines Program[1] has collaborated closely with the United States Agency for International Development (USAID)/Regional Development Mission for Asia (RDM-A), the USAID/Cambodia Mission, the USAID/Vietnam Mission, the USAID/Philippines Mission and the Ministries of Health of Cambodia, Lao People's Democratic Republic (Lao PDR), Thailand, Vietnam, and the Philippines, the World Health Organization (WHO), INTERPOL, and others. Together these organizations have worked to improve the quality of medicines circulating in these countries' markets, enabling them to reduce the prevalence of counterfeit and substandard medicines in the Mekong Region. Collaborative efforts to reduce the prevalence of counterfeit medicines among public health agencies, law enforcement, and international organizations have resulted in an increase in public awareness, arrests and seizures of counterfeits, and concomitant increases in political will to do more.[2,3]

Beginning in 2003, the PQM program initially collected data from the field on specific anti-malarial medicines, determined the quality of medicines in the marketplace, presented findings of gaps or weaknesses, and designed individualized plans for improvement based on country priorities and country context. In 2006-2007 monitoring of medicine quality expanded from antimalarial medicines to include other drug classes, including selected antibiotic, anti-tuberculosis, antiretroviral and anti-viral (Avian Influenza) medicines in both the public and private sectors. The process required cooperation and integral collaboration with each country's Ministry of Health (MOH), medicine regulatory authority (MRA), national medicine quality control laboratory (NMQCL), national priority disease control programs, surveillance site staffs, and, in some instances, community healthcare workers.

PQM's primary objectives in Southeast Asia include:

1. Building the capacity of MRAs and national quality control laboratories;
2. Obtaining evidence-based data from the field to support enforcement actions in all Greater Mekong Sub-region (GMS) countries;
3. Raising public awareness about the dangers of substandard and counterfeit medicines;
4. Conducting operational research on medicine quality, following established protocol; and,
5. Strengthening south-south collaboration and cooperation in medicine quality.

PQM has designed country-specific sampling protocols; supplied necessary laboratory equipment and reference standards for testing; increased the capacities of national medicine

[1]The Promoting the Quality of Medicines (PQM) Program, implemented by the U.S. Pharmacopeia, is the successor program to the United States Pharmacopeia Drug Quality and Information (DQI) Program. To avoid confusion, the program will be referred to as PQM throughout this report.

[2] Newton PN, Fernández FM, Plançon A, Mildenhall DC, Green MD, et al. 2008 A Collaborative Epidemiological Investigation into the Criminal Fake Artesunate Trade in South East Asia . PLoS Med 5(2): e32. doi:10.1371/journal.pmed.0050032

[3] http://www.interpol.int/Public/ICPO/PressReleases/PR2010/PR007.asp

regulators; trained nearly 2,500 individuals in sampling methodology and laboratory testing, both in the field and in NMQCLs[4]; and facilitated numerous local and regional meetings to discuss medicines quality issues in the region. This successful program has served as a model for activities in an additional 21 resource-limited countries. The country governments that have requested PQM's assistance are anxious to improve health conditions in their nations, reduce the prevalence of counterfeit and substandard medicines, and restore public confidence in their ability to ensure safe and effective medicines in the marketplace.

From 2005-2009 in the GMS, the Medicine Quality Monitoring (MQM) program has collected and sampled 3021 antibiotic, 6176 antimalarial, 625 anti-tuberculosis, and 234 antiretroviral medicines (Figure 1). By 2009, the total number of samples collected and tested reached almost 4,000 (Figure 2); working in collaboration with the Global Fund allows for the high number of samples to be collected and tested. While initial failure rates in the region averaged around 6%, there was a steady trend toward a decreasing prevalence at monitoring sites (Figure 3). Overall, when examining the results by therapeutic indication, the most frequently found counterfeit and substandard medicines were antimalarials and antibiotics (Figure 4), more than two to three times more common on average. No counterfeit antiretroviral or anti-tuberculosis medicines have been found as yet, only substandard.

Although encouraging, these results necessitate further surveillance beyond routine surveillance. Counterfeiters may become aware of monitoring activities and move their distribution elsewhere; substandard products

**Figure 1.** No. tested by therapeutic indication

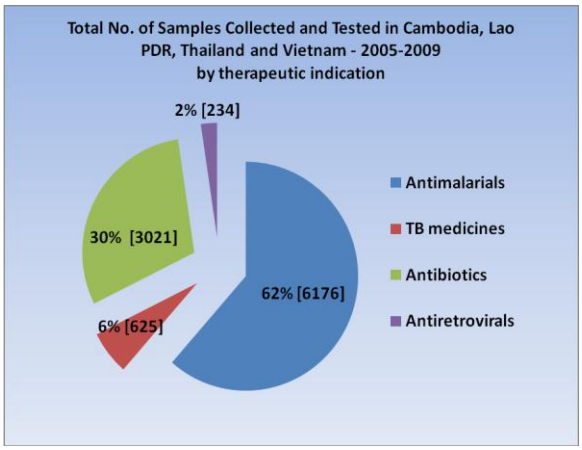



**Figure 2.** Total no. tested 2005-2009

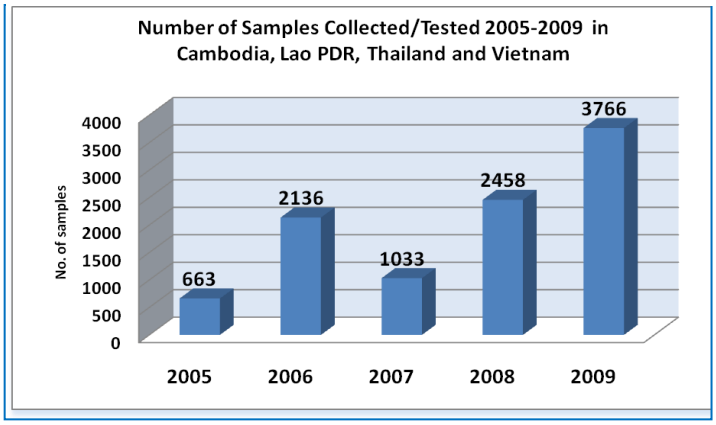
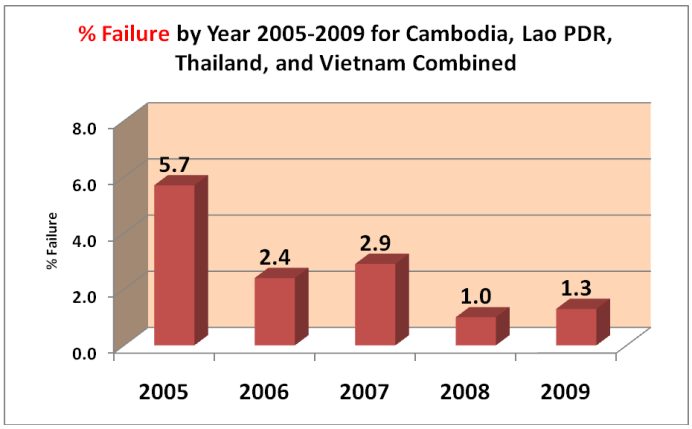


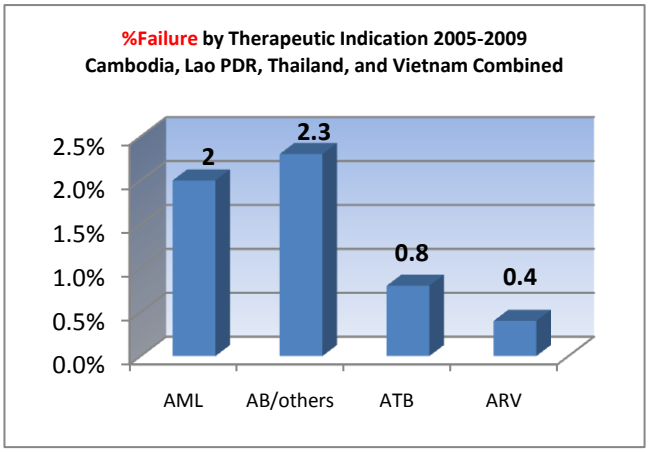

**Figure 3.** Failed products by year




[4] Alliance for Case Studies for Global Health. 2009. "Global Interagency Efforts Stem Counterfeit Drugs in Greater Mekong Asia Case Studies for *Global Health: Building relationships. Sharing knowledge.*, pp 42-49

continue to circulate in the region; and the ne pharmaceutical manufacturing sector (private and public) is an essential component of quality assurance.

**Figure 4: Failure rate by therapeutic indication**




Regional MQM activities to support building the capacity of medicine quality assurance systems have shown encouraging results, yet are not without pitfalls. This project has demonstrated the crucial need for timely follow-up, reporting, and development of strict methodology for reporting results to enforcement agencies. Difficulties in cross-border cooperation and the porous nature of international borders in the GMS further exacerbate the difficulties in regulating the pharmaceutical sector. In addition, high level buy-in on the part of central-level government agencies is required for any successful MQM program; evidence suggests that this is in need of further strengthening.

Over the next five years, the PQM program will continue to provide technical assistance to address gaps in national medicine quality assurance programs, as well as develop a robust regional network of Centers of Excellence to act as a clearinghouse and source of advanced training. Needs for the region include harmonization of data collection, increased inter-agency collaboration between ministries and private and public sectors, human resource development, strengthening of national and regional medicine quality control laboratory, and building capacity among regulatory authorities in each country.

## Background and Rationale

In the Southeast Asia/Western Pacific region, an estimated 10-35% of medicines are improperly made or illegally produced and sold.[5] The objective of the PQM medicines quality monitoring program is to reduce the prevalence of poor-quality medicines—counterfeit and substandard—available in the public, private, and informal sectors. In Cambodia, Lao PDR, Thailand, and Vietnam, PQM works closely with each country's Ministry of Health; relevant government agencies, primarily the MRAs; and national disease control programs for malaria, HIV/AIDS, and tuberculosis; NMQCLs; WHO; and INTERPOL to achieve this objective.

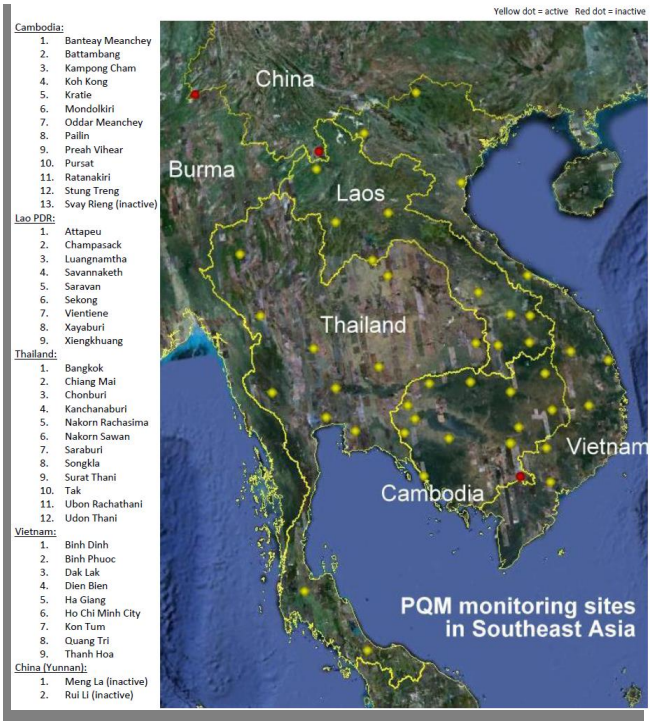
In late 2002, with financial support from USAID, PQM and WHO conducted a preliminary review of the antimalarial medicine quality situation in order to provide technical assistance to the Ministries of Health of five Southeast Asian countries: Cambodia, Lao PDR, Thailand, Vietnam, and Yunnan province of China. PQM developed a framework to support the

[5] IMPACT - International Medical Products Anti-Counterfeiting Taskforce. 2008. *Counterfeit Drugs Kill!* Fact sheet on counterfeit medicines. World Health Organization: Geneva.

governments in their quest to improve the quality assurance and quality control (QA/QC) of their essential medicines and create a comprehensive, sustainable program to build technical capacity. One of the core PQM program activities has been to establish and expand MQM to cover priority disease medicines, including antimalarial, antibiotic, anti-tuberculosis, and anti-viral products. From 2005 to 2008, the quality of HIV/AIDS medicines was also monitored.

In early 2003, PQM launched the Antimalarial Medicines Quality Monitoring Program in the Greater Mekong Sub-region. By examining malaria disease prevalence and proximity to international transit routes and borders, PQM selected a number of provincial sites where medicine quality screening activities would be conducted. Following extensive training of local staff, each site was outfitted with a GPHF Minilab®[6]—a self-contained, semi-portable laboratory equipped to perform basic screening tests—that enables investigators to screen medicines purchased at legal or illegal drug outlets, pharmacies, and public sector facilities (public, private and informal) for identity and potency. PQM designed a protocol for the comprehensive monitoring of antimalarials and, subsequently, other infectious disease medicines. Data collected in 2004 revealed the wide availability of poor quality medicines: In some GMS countries, up to 44% of the artesunate (a commonly used, highly efficacious antimalarial) samples collected and tested contained no active ingredient. In 2008, this figure dropped below 20%; from the 358 antimalarial samples collected and tested, only 40 (11.2%) samples failed quality testing.[7] These results provided incentive for country MRAs to expand the PQM monitoring program.

**Figure 5:** Sentinel sites in GMS as of December 2009




The MQM program in the GMS region has grown from 17 sites in 2003 to 43 active sites in 2009 (Figure 5) and has broadened in scope to include antimalarial, antiretroviral, and anti-tuberculosis medicines, oseltamivir phosphate (for treatment of H5N1 and H1N1 flus) and some commonly used antibiotics. Since monitoring began, over 10,000 samples have been collected and tested.

The PQM program participates in ongoing collaboration with key partners working in the region and regularly coordinates activities with WHO program, country, and regional offices. Data on counterfeit products discovered through the MQM program is shared with law enforcement

[6] The GPHF Minilab® is a trademark-registered product of the Global Pharma Health Fund e.V (www.gphf.org), which will be referred to in this report as "Minilab(s)."

[7] USP DQI. *Annual Implementing Report on USAID/RDM-A: Malaria.* Reporting period October 1, 2007-Sept 31, 2008. Rockville, MD, 2008.

agents and customs officials at the request of the countries participating in regional investigations, such as recent INTERPOL operations.

To further build capacity in the region for a holistic quality assurance system, PQM established the Asian Network of Excellence in the Quality Assurance of Medicines (ANEQAM). Currently, three Centers have been set up; the PQM staff has worked with each to develop their capacity and train their staffs to provide regional expertise in quality control (Chulalongkorn University, Thailand), good manufacturing practices (Mahidol University, Thailand), and bioavailability/bioequivalence (CeDRES, Philippines). (Intended to provide training in advanced methods for the development of regional experts in region, ANEQAM Centers have conducted five week-long workshops for participants from Cambodia, Lao PDR, Thailand, and Vietnam.

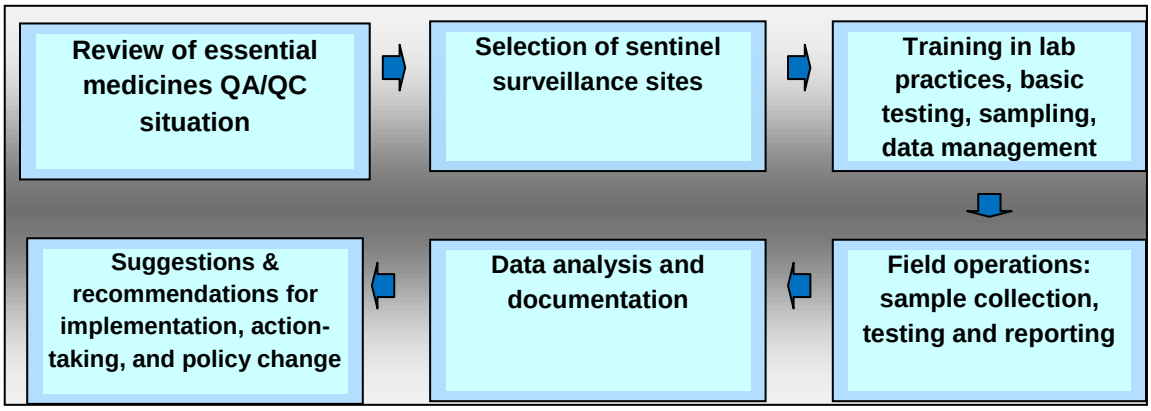
ANEQAM will continue to develop and implement regional training workshops, on-site inspections, and country visits to support the GMS as a valuable and essential resource.

## Key Activities

### Greater Mekong Sub-region (GMS) medicine quality monitoring

In collaboration with national malaria control programs (MCPs), MRAs, and NMQCLs, PQM has intensified its regional medicine quality monitoring of antimalarial, anti-tuberculosis, HIV/AIDS, oseltamivir, and selected antibiotic medicines in Laos, Thailand, Vietnam, and Cambodia over the past five years. In the Philippines, a pilot project examining the quality of anti-tuberculosis medicines began in 2008 at six sites throughout the country. Figure 6 depicts the methodological framework of medicine quality monitoring in the region.

**Figure 6:** Methodological framework for anti-infectives medicine quality monitoring




PQM has focused on conducting field visits in Cambodia, Lao PDR, Thailand, and Vietnam, assessing the performance of provincial health staff at the sentinel sites, and strengthening existing sites before expanding to other areas. After an initial assessment of the status of QA/QC systems was made in-country by PQM professional staff, sites were selected based on disease epidemiology and geography of the country. Procurement of the Minilabs with reagents and reference standards for each site was followed by training on the use of this equipment and implementation of sampling and testing protocols. These protocols—developed jointly by GPHF, PQM, and MOH staff—were used to ensure the quality of the data being generated during the

medicine quality monitoring phase. The information derived from the medicine quality monitoring program serves as the basis for enforcement action and policy changes.

Samples of medicines are routinely collected from public, private, and unlicensed sectors at various levels—wholesalers, health care facilities, retail pharmacies, and non-pharmacy outlets—in Cambodia, Lao PDR, Thailand, and Vietnam. The samples are tested[8] at sentinel sites using Minilabs; then, a proportion of the samples are verified at the national medicine quality control laboratories according to defined protocols. Recent development of harmonization protocols for sampling and testing medicines from postmarketing surveillance will ensure that data is collected in a systematic and consistent manner (Annex).

The Global Fund to Fight AIDS, TB and Malaria (GFATM) also supports the medicine quality monitoring program implemented in the GMS using PQM procedures. Three sites in Laos are partially supported with GFTAM funds; and the MQM programs in Cambodia and Vietnam are jointly supported by PQM and GFATM for monitoring antimalarial medicine quality.

**Thai-Cambodia border antimalarial medicine quality study**

The Greater Mekong Sub-region has been identified as the epicenter of *P. falciparum* resistance to antimalarial drugs globally. It is in this region that resistance to chloroquine, sulfadoxine-pyrimethamine, and mefloquine emerged before spreading to other parts of the world. Likewise, there is also a growing concern of *P. vivax* resistance to chloroquine in the GMS.[9] All six countries of the Mekong region have introduced artemisinin-based combination therapies (ACTs) as their first line of defense against malaria; ACTs are currently the only effective therapies against multidrug-resistant malaria strains.

Anecdotal evidence suggests that poor drug quality and the proliferation of unregistered and substandard antimalarial medicines may be a factor in contributing to the burden of drug resistance in the GMS.[10] Weak quality assurance and quality control of medicines, as well as inadequate supply, storage, and distribution, have been identified as factors contributing to the availability of these poor-quality medicines in this region, especially along the border provinces in Western Cambodia and Eastern Thailand.[11,12]

To assess this issue quantitatively, PQM, with financial support from USAID and the Bill and Melinda Gates Foundation (BMGF) through WHO, developed a randomized sampling protocol to estimate the prevalence of poor-quality antimalarials in the area and to better understand their use among villages in the provinces along the Cambodia-Thailand border.

[8] Each Minilab contains the equipment and reagents needed to help identify substandard and counterfeit medicines through: physical and visual inspection of labels and containers; simple disintegration to identify manufacturing defects; colorimetric reactions to identify the presence of API; and, Thin Layer Chromatography (TLC) to verify potency and identity of the labeled API.

[9] Workshop to review and plan therapeutic efficacy studies to monitor P. falciparum and P. vivax resistance to antimalarial drugs in the Greater Mekong Sub-region. Mandalay, Union of Myanmar, September 30-October 2, 2009.

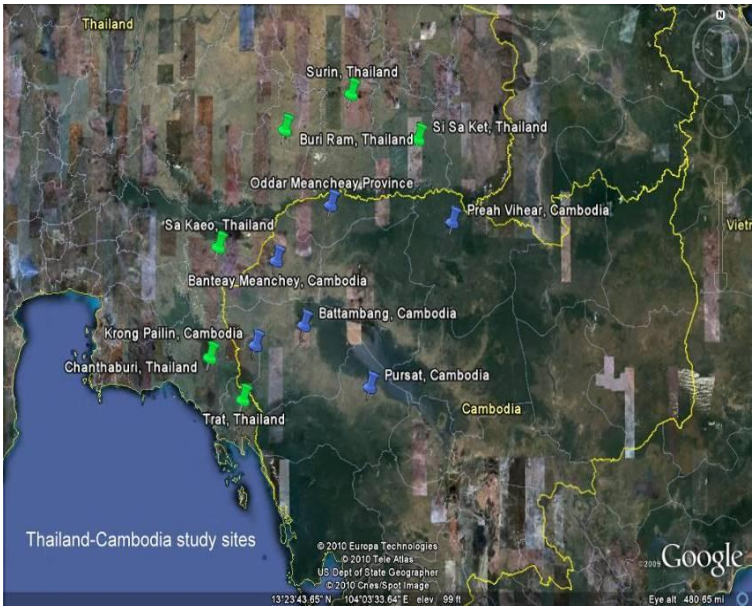
[10] Phanouvong, S., Reiss, S., and Smine, A. 2005. Why be concerned about the quality of antimalarial and ARV drugs? Poster presentation at 7th International Congress on AIDS in Asia and the Pacific, Kobe, Japan, July 1-5, 2005.

[11] BBC News, 2009. Malaria parasites 'resist drugs.' BBC NEWS | Asia-Pacific | Malaria parasites 'resist drugs.' Accessed Monday June 8, 2009: http://news.bbc.co.uk/2/hi/asia-pacific/8073118.stm

[12] Trape, J.F., Pison, G., Preziosi, M.P., Enel, C., Desgrées du Loû, A., Delaunay, V., Samb, B., Lagarde, E., Molez, J.F., Simondon, F., 1998. Impact of chloroquine resistance on malaria mortality. *C R Acad Sciences* III 321, 689–697.

The antimalarial medicine quality survey design was descriptive and cross-sectional. A randomized sampling methodology was used for both the health and household survey and the collection of antimalarials for analysis. The study population consisted of interviewees from households and health facilities, and all of the pharmacy outlets, health facilities and clinics in the public and private sectors—licensed and unlicensed selected randomly—from 12 provinces along the Cambodian-Thai border. Six Cambodian provinces (Banteay Meanchey, Battambang, Oddar Meanchey, Pailin, Preah Vihear, and Pursat) and six Thai provinces (Buriram, Chanthaburi, Sa Kaeo, Si Sa Ket/Ubonrachathani, Surin, and Trat) in the target area participated (Figure 7). The provinces were chosen based on their malaria burden, the antimalarial medicine sensitivity (indicating parasite tolerance and resistance) to *P. falciparum*, and the presence of sentinel sites for monitoring the efficacy of malaria treatment.

**Figure 7.** Twelve study sites along the Cambodian-Thai border

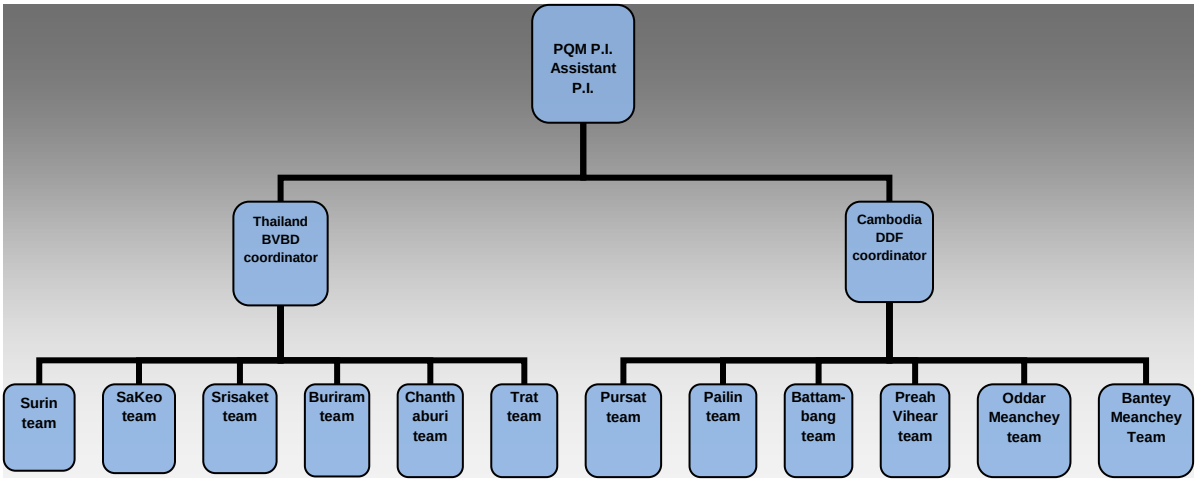



The goal of this project was to obtain evidenced-based data on the quality of antimalarial medicines circulating in the cross-border areas of Western Cambodia and Eastern Thailand. This was undertaken to help researchers, health professionals, medicines regulatory agencies, and malaria national program managers gain some understanding of the prevalence of poor-quality antimalarial medicines and the types of antimalarial medications taken by the populations that participated in the study. Toward this goal, three objectives were identified:

1. Obtain an objective estimate of the prevalence of poor-quality AML medicines in selected provincial sites along the border of Cambodia and Thailand;
2. Gain some basic understanding of the possible association between the prevalence of good- as well as poor-quality AML medicines, their availability, and use, and the types of medications that were given and/or taken by the people interviewed; and,
3. Use the findings to draw attention of appropriate government agencies to the need for policy change and/or regulatory enforcement pertaining to the quality assurance of AML medicines along the cross-border areas in both countries.

Country study investigating teams, led and supervised by a principal and an assistant investigator from PQM, were formed—one for Cambodia and one for Thailand. Each country team consisted of central and provincial investigators; the provincial investigators were responsible for carrying

**Figure 8:** Cambodia-Thailand country study investigation teams




out the study in their respective provinces, while the central level investigator coordinated the study and monitored progress (Figure 8).

## Avian Influenza

Oseltamivir phosphate is an antiviral medicine that is currently effective against avian influenza (AI) caused by the H5N1 virus, as well as the H1N1 virus and is a principal pharmacotherapy for reducing the morbidity and mortality in humans. Due to high demand and long lead times for manufacture and procurement, stockpiling oseltamivir has been a central strategy of many ministries of health plans for preparedness against AI should a pandemic occur. The true shelf-life of oseltamivir product is uncertain, ranging between three and six years, depending on the formulation and storage conditions. Consequently, the quality of all stockpiled and circulated oseltamivir products should be tested periodically, in order to establish its quality at any given time.[13,14]

In addition to routine monitoring of a variety of drug products in Cambodia, Lao PDR, Thailand, and Vietnam, PQM's work also involved monitoring, sampling, and testing oseltamivir. Formal clearance from relevant authorities in Laos, Thailand, and Vietnam is underway to monitor and check the quality of AI products stockpiled in individual countries and at the regional level. PQM's ongoing activities on AI include:

- Initiating a regional surveillance project on the quality of oseltamivir phosphate, as an integral part of overall anti-infectives medicine quality monitoring and encouraging regulatory agencies to use data for advocacy and appropriate action;

[13] USP DQI, 2008. *Survey of the Quality of Stockpiled and Circulated Oseltamivir Products in the USAID RDM-A Region: Instructions for Oseltamivir Sampling*

[14] USP DQI and Collaborators, 2009. Quality Specifications of Oseltamivir: Technical Guidelines [Working Document]

- Providing reference standards for the Minilab, chemical reagents, and reference materials to support continuous program activities related to oseltamivir monitoring;
- Developing an oseltamivir sampling protocol and piloting a project on sampling and testing in Lao PDR;
- Mapping suppliers and distributors of oseltamivir and producing a final report on the manufacture, procurement, distribution, and stockpiles in GMS.
- Developing guidelines, in collaboration with WHO and others, on how to maintain quality from acquisition to the point of use.

**Building regional capacity: Establishing a network of Centers of Excellence**

In order to tackle the lack of institutional expertise and experience in medicine quality and information in the region, PQM established the Asian Network of Excellence in Quality Assurance of Medicines (ANEQAM) to serve as a regional resource for the quality assurance of medicines. The ANEQAM centers include:

- Chulalongkorn University Faculty of Pharmaceutical Sciences Quality Control Laboratory (Thailand)—provides expertise in quality control of medicines;
- Mahidol University Faculty of Pharmacy (Thailand)—focuses on providing expertise in good manufacturing practices (GMP); and,
- University of Santo Tomas Center for Drug Research, Evaluation, and Studies (CeDRES) (Philippines)—expertise in bioavailability/bioequivalence (BA/BE).

The PQM program has been building institutional capability through regional trainings at the Centers of Excellence, training staff from Cambodia, Lao PDR, the Philippines, Thailand, and Vietnam. The ongoing interactions between participating institutions during trainings have fostered an atmosphere of cooperation and collaboration, leading to more effective regional interaction among professional staff.

**Pharmacovigilance**

Pharmacovigilance—the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications—is an essential and cost-efficient means of detecting and minimizing injury to patients. It guards against the undetected use of ineffective, substandard or counterfeit medicines; assists in the promotion of rational drug use; and helps prevent medication errors or inadvertent overdose.

In 2008, PQM, WHO, the Cambodian MOH, and the Department of Food and Drugs (DDF) recognized the importance of establishing a national pharmacovigilance program in Cambodia and subsequently organized a workshop coordinated by pharmacovigilance experts. Government officials met to develop a national action plan for monitoring the safety of medicines in the Cambodian market. More than 40 representatives from international, nongovernmental, universities and humanitarian organizations met with members of the Cambodian Ministry of Health, hospital directors and national and provincial public health leaders to create the structures needed for the Cambodian Pharmacovigilance Center (CPC). PQM and its partners have continued to work with the Cambodian MOH to overcome challenges that might have prevented some pharmacovigilance activities from being fully implemented.

### Raising awareness about substandard and counterfeit medicines

In most GMS countries, patients go first to the community pharmacy for medicines and medical advice; yet many pharmacy staffs are not educated on the consequences of poor-quality medicines and may not recognize substandard or counterfeit medicines. In some countries, there is a lack of enforcement or an inability to disseminate information on poor-quality medicines to healthcare workers or the general public. In collaboration with NGOs that provide community-based services, PQM attempts to raise public awareness through community outreach, sometimes reaching out to the public through alternative routes, such as public service announcements and films. In that way PQM can communicate not only to policymakers but to health professionals and the general public to increase awareness about the dangers of substandard and counterfeit medicines and encourage vigilance against their further proliferation.

## Progress and Results

### Cambodia

PQM's scope of work in Cambodia encompasses four main objectives: Improving detection of poor-quality medicines, strengthen medicine quality assurance systems, improving access to quality information, and raising awareness about medicine quality issues among regulators, health care professionals and the public. To improve detection methods and QA systems, PQM has been providing technical assistance to Cambodia to support postmarketing surveillance of the quality of antimalarial medicines through the medicine quality monitoring program.

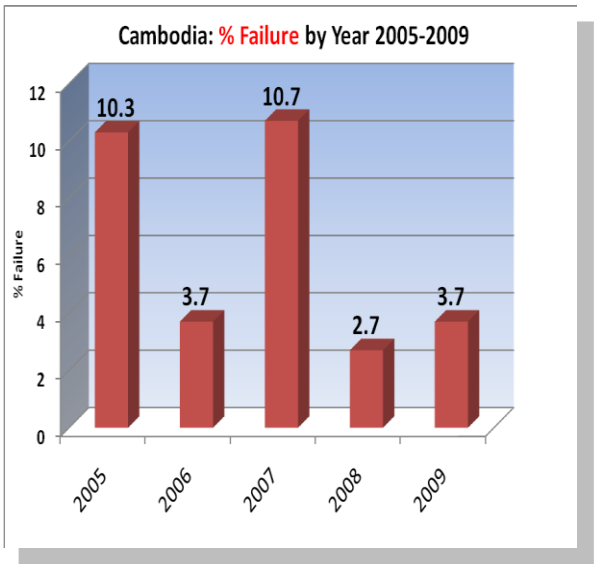
**Figure 9:** Sentinel sites in Cambodia

From seven sites in 2005, the MQM project had grown to 13 sites by 2009, covering as many provinces, and its scope had expanded to include testing of other infectious disease medicines, specifically, antibiotic, anti-TB, and antiretroviral products (Figure 9). PQM has also provided Cambodia's NMQCL with essential laboratory equipment—a high performance liquid chromatography (HPLC) system, dissolution tester, and spectrofluorometer—and training to improve their capacity to perform compendial pharmaceutical analysis in accordance with the *International Pharmacopoeia* and *U.S. Pharmacopeia* standards to confirm results of testing in the field.

From 2005-2009, the Department of Drugs and Food (DDF) working together with PQM, has consistently found counterfeit and substandard antimalarial, antibiotic, and antiretroviral medicines among those sampled. From 2005-2007, 9.4% of the 470 samples collected from seven provinces did not pass quality testing. From 2007-2009, the failure rate decreased to 3.4% of the 1,716 samples collected from among 12 provinces.

Figure 10 shows the failure rate for each year from 2005-2009 for Cambodia testing. Of all the GMS countries PQM actively works, the largest amount of poor quality medicines are consistently found in Cambodia. Despite decreasing failure rates, counterfeit and substandard medicines continue to be a very important public health challenge for Cambodia.

**Figure 10:** Failure rate for Cambodia 2005-2009




Activities are supported cooperatively by PQM and by the GFATM (for antimalarial medicines) in ongoing sampling and testing rounds.Through this collaborative monitoring program, the DDF, National Centre for Malariology, Parasitology, and Entomology (CNM), and PQM have exposed unscrupulous manufacturers and distributors of counterfeit medicines, tracing them to manufacturers in China, Thailand, and Vietnam.

PQM has supported a number of initiatives with the Cambodian MOH to strengthen their QA/QC systems which has resulted in development of an inter-Ministerial action plan to eradicate counterfeit and substandard medicines and creation of the Cambodian Pharmacovigilance Center (CPC). PQM furnished the CPC with all the necessary equipment and supported the training of one staff member at the WHO Uppsala Monitoring Center. With continued support from PQM, WHO and experts in the field, the Cambodian MOH, also formed an Advisory Committee of health professionals from various disciplines who help the CPC analyze adverse drug event reports and collectively make decisions on actions to be taken.

In 2009 PQM became a member of the National Task Force for the Containment of Artemisinin-resistant Malaria in Cambodia. The Task Force monitors implementation of the malaria containment project in zones 1 and 2 in Western Cambodia, near the Thai border, where emergence of drug-resistant strains of malaria necessitate the mobilization of resources from donor partners, primarily the Bill and Melinda Gates Foundation and the Global Fund. PQM's role on the Task Force is to ensure that medicine quality assurance remains a component of the ongoing implementation of the containment project. In addition, PQM supports activities of the Inter-Ministerial Committee for Eliminating Counterfeit Drugs and Illegal Health Care Services (IMC), the national body authorized to take enforcement actions against substandard and counterfeit medicines imported, produced, or found circulating in the Cambodian market.

In collaboration with the DDF, PQM identified a need for technical support in order to build the capacity of Cambodia's pharmaceutical sector in areas of registration, licensing, GMP standards application, supply chain inspection, import control, laboratory testing, and quality control

systems for medicines in procurement and distribution. Subsequently, PQM conducted a GMP training course for DDF inspectors and QA/QC staff and internal auditors from three pharmaceutical manufacturers combining hands-on visits to each for practical experience. Participants learned the importance of maintaining GMP and how to conduct and document a successful GMP audit.

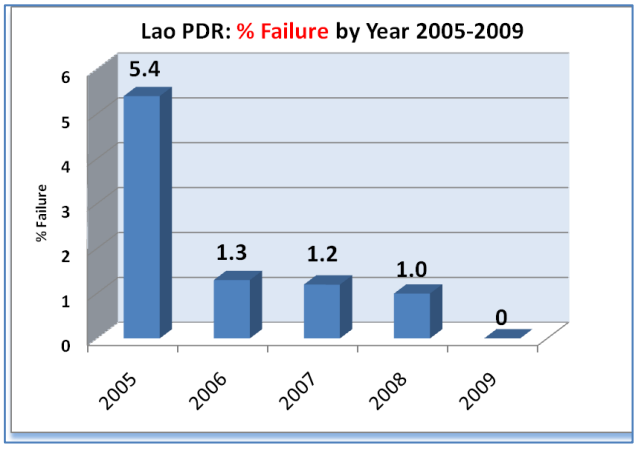
## Lao PDR

Lao PDR medicine quality monitoring activities are implemented through a partnership with the Food and Drug Quality Control Centre (FDQCC) laboratory and PQM focal points at the Food and Drug Department (FDD), the Medical Product Supply Centre (MPSC), and the Centre for Malariology, Parasitology and Entomology (CMPE). Antibiotic, antimalarial, antiretroviral, and anti-TB medicines are sampled and tested at six sites in Laos and, occasionally, from adjacent provincial sites nearby.

**Figure 11:** Sentinel sites in Lao PDR

PQM supports the FDQCC by providing laboratory equipment for advanced analysis, including HPLC and dissolution apparatus, reagents and reference standards, and Minilabs for six sites (Figure 11), among others. PQM supports routine postmarketing surveillance at the sites through the FDD. Figure 12 shows the failure rate of medicines collected from 2005-2009. A clear decrease in the number of poor quality products found at the sentinel sites and neighboring provinces can be observed.

**Figure 12: Failure rate for Lao PDR**




In collaboration with the MOH, FDD, FDQCC, and provincial health authorities, PQM held a meeting in August 2006 in Vientiane, Laos, on Strengthening Collaboration and Coordination of Key Stakeholders in Addressing the Problems of Counterfeit and Substandard Medicines. The meeting resulted in recommendations which, upon further development, were incorporated into the National Plan of Action on combating counterfeit and substandard medicines, including:

- Increase inspection activities;
- Increase law enforcement, especially by undertaking strict sanctions and punishment against violations according to law and regulations;
- Increase local pharmaceutical manufacturing capacity;

- Establish appropriate procurement practices;
- Improve drug dispensing practices;
- Increase medicine quality control at local and regional levels;
- Improve the medicine quality information system; and,
- Develop appropriate support systems (external cooperation, budget, tools, and strategies).

In collaboration with local partners, PQM organized and facilitated two training workshops in hot-spot areas for HIV/AIDS—Vientiane, Laos, and Ho Chi Minh City, Vietnam—on HIV/AIDS Medicines Quality, Safety and Information. Experts from the USP Center for the Advancement of Patient Safety Department, USP International Health Expert Committee, University of California, and PQM in facilitating the workshops to educate community pharmacists on the importance of medicine quality, how to recognize substandard or counterfeit medicines, and how to convey this information to their patients.

**Philippines**

The Philippines has a high burden of tuberculosis (TB) and many new cases arise every year, a problem further complicated by burgeoning resistant strains of TB. At the request of USAID/Philippines, and working with the country's Department of Health (DOH) and FDA, PQM established an MQM program for tuberculosis medicines. In May 2008, a program staff trained participants from the FDA, Center for Health Development (CHD), and local government on the basics of sampling and testing with Minilabs to monitor the quality of TB medicines and their fixed dose combinations (FDC). Sample collection and testing began in early 2009 at six sentinel sites (Figure 13); after six months of monitoring anti-TB medicines, none have been found to be substandard, but compendial testing on the second round is still ongoing.

**Figure 13:** Sentinel sites in the Philippines

In addition to the monitoring project, PQM has provided technical assistance to strengthen the FDA laboratories in the Philippines, conducted a training workshop at the FDA on Good Laboratory Practices (GLP), HPLC, and dissolution testing on four FDC TB medicines. FDA analysts at the main FDA site and satellite laboratories in Cebu and Davao were taught the necessary analytical skills to determine the quality of TB medicines through compendial testing and were supplied with the needed reference standards and reagents for testing.

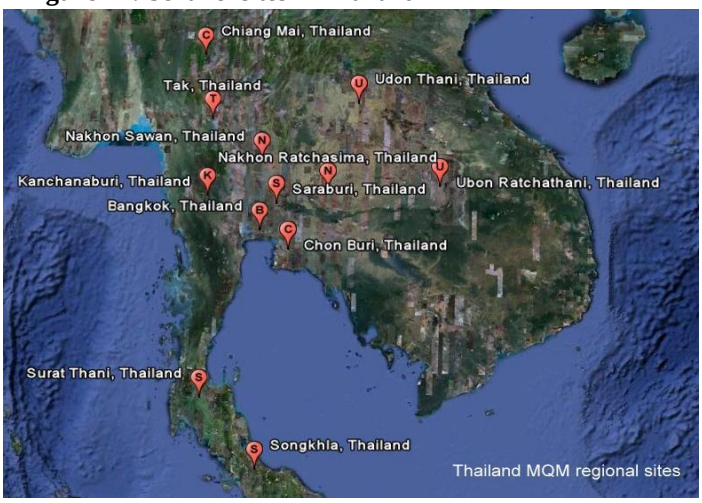
A number of challenges to the monitoring program—insufficient human resources, difficulties performing verification tests, inadequate time for sampling and testing, and reporting issues—

have been successfully addressed by the FDA, USAID, and PQM. Changes to the protocol are being implemented that will extend sampling to wholesalers in Manila and in the public sector. Sampling will also be collected from the informal outlets where antibiotics are sold illegally. In the future, MQM activities may expand to other geographical areas as well include additional antibiotics used to treat TB co-infections.

## Thailand

Since 2005, PQM-supported sites throughout Thailand (Figure 14) have collected and tested 3,747 medicine samples. Working with the Bureau of Vector-borne Diseases (BVBD) of the Department of Disease Control, the Thai FDA, and the Bureau of Drugs and Narcotics (BDN) Quality Control Laboratory, PQM has provided technical assistance to scale up antimalarial medicine quality monitoring throughout the country. In 2007, sampling and testing expanded to include medicines for TB, HIV/AIDS, Avian Influenza, and antibiotics. Figure 15 shows the failure rate for medicines colleted from 2005-2009.

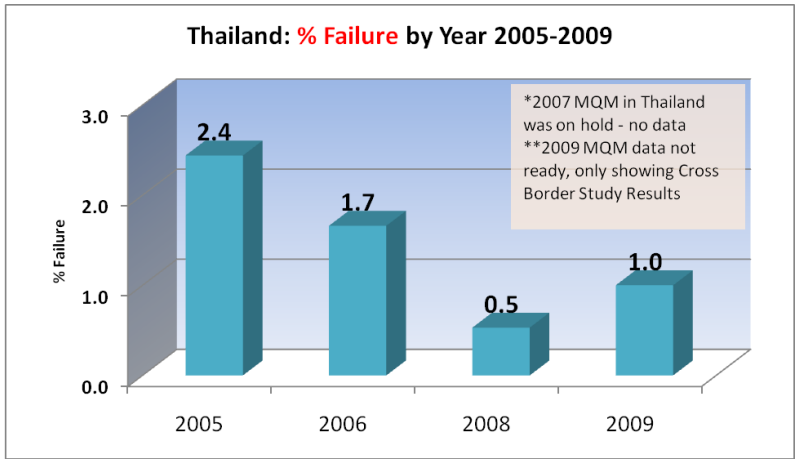
**Figure 14:** Sentinel sites in Thailand




During 2008-2009, the BVBD, FDA, and BDN also implemented the Thai-Cambodia cross-border study on antimalarial medicine quality.

PQM, together with other local NGOs, helped develop the Global Fund Round 9 proposal for malaria for the Thai MOH. In order to assure that drug quality assurance is integrated into malaria containment projects, PQM has been invited to provide technical assistance during the next proposal development for Round 10 in Thailand.

**Figure 15:** Failure rate in Thailand



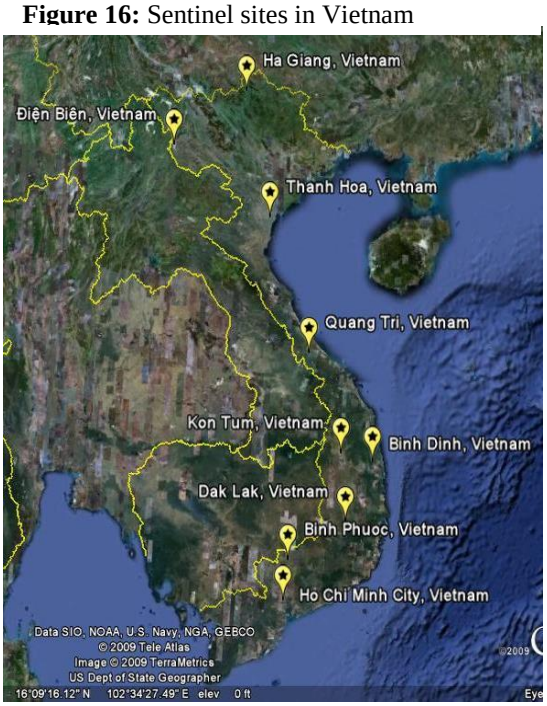

Thailand also hosts two of the ANEQAM institutions building regional capacity for medicine quality assurance, one of which—the Pharmaceutical System Research & Development (PhaReD)—helped PQM in 2008 develop the document, "Mapping the Supply of Avian Influenza Medicines in Thailand." As a producer and importer of oseltamivir phosphate (Tamiflu®), Thailand plays an important role in the region where there are a number of H5N1- and H1N1-endemic countries. The mapping document tracks the structures and processes provided for the flow of oseltamivir through the system in Thailand, from making it available in the country to delivering

it to the patient. The pharmaceutical supply and management of oseltamivir were examined including registration, procurement, distribution, and use. This mapping exercise provided a framework for addressing the supply management of medicines for preparedness for pandemic influenza at the national level.

**Vietnam**

The MQM program in Vietnam launched in March 2003 at a regional workshop in Bangkok, Thailand, on "Establishing Medicine Quality Monitoring of Antimalarials in the Mekong Delta Region.' It would be implemented by the Ministry of Health's National Institute of Malariology, Parasitology, and Entomology (NIMPE), National Institute of Drug Quality Control (NIDQC) Laboratory in Hanoi, and the Drug Administration of Vietnam (DAV).

**Figure 16:** Sentinel sites in Vietnam




Sentinel sites were established in four provinces—Lai Chau (now Dien Bien), Quang Tri, Dak Lak and Binh Phuoc—to sample and test antimalarial medicines. PQM suppli ed each sentinel site with a Minilab and conducted a "training of trainers" workshop for staff from NIDQC, DAV, and NIMPE on good laboratory practices, basic tests using the Minilab, and data reporting. They, in turn, trained personnel for all the sentinel sites, and in July 2003, the first round of sampling and testing began. In 2005, PQM assisted NIMPE to develop a section on medicines quality in the country's proposal seeking aid from the Global Fund. The funds obtained supported expansion to five additional sentinel sites in Thanh Hoa, Ha Giang, Kon Tum, Binh Dinh and Ho Chi Minh City (Figure16).

**Figure 17:** Failure rate for Vietnam

Almost 3,000 drug samples have been collected and tested according to PQM protocols in the nine provincial sites throughout Vietnam since 2003. Figure 17 shows the failure rate of medicines collected from 2005-2009. Samples collected at the provincial and district hospitals, warehouses, and clinics and from private sector pharmacies include available antimalarial, anti-tuberculosis, anti-viral, and antiretroviral medicines and selected antibiotics. The sampling and testing has resulted in the discovery of many products not meeting quality specifications, providing evidence for

NIMPE and the DAV to take corrective actions. Data generated from the MQM project have also been used in three INTERPOL operations to combat the proliferation of counterfeit medicines in Southeast Asia.

PQM has increased the capacity of national institutions in a variety of ways, from assisting in the successful application for GFATM grant Round 6 to providing needed reference standards, analytical reagents, solvents, lab ware, and pharmacopeial monographs to the NIDQC and sentinel sites. Beyond teaching analysts and sentinel site staff in basic testing, PQM has trained community pharmacists on HIV/AIDS medicines quality and information to assist patients to detect dubious products; DAV medicine registration staff in BA/BE for dossier review; and, in collaboration with the ANEQAM program, NIDQC analysts in advanced compendial methods.

To assist regional efforts, PQM also convened a meeting with stakeholders to encourage them to strengthen their collaborations and coordinate data reporting on the Project on Antimalarial Medicines Quality Assurance. The two-day meeting allowed participants to discuss collective efforts and approaches among MOH, police, customs officials, and prosecutors in the fight against counterfeit medicines in Vietnam.

**Thai-Cambodia cross-border antimalarial medicine quality study**

Before conducting the survey, PQM provided Minilabs, dissolution testers, and other necessary lab supplies to participating study sites. The PQM staff then trained the national and provincial project teams on the sampling method, principles of good laboratory practices (GLP), basic test methods used with the Minilabs, data documentation, and reporting. The protocol had been translated into the Khmer and Thai languages to make it easy to follow the directions. Sampling teams mapped sampling locations, using a GPS device, when necessary, and collected and recorded products from public and private outlets. Private outlets were sampled by "mystery shoppers"; however, public sector outlets were sampled in a transparent manner, with authorization from local authorities. All sampling operations were performed with care.

All samples were initially screened at sentinel sites following precise protocols for Minilab testing. Each country examined different antimalarial products, and different numbers of samples were collected and tested based on availability and prevalence of use. All failed samples from Minilab testing were subjected to verification testing to determine the reason for failure. A certain percentage of the samples—those that failed, passed, or were doubtful—were then selected for verification testing by compendial or pharmacopeial specifications and/or validated in-house methods.

The verification tests were performed at the NLDQC in Cambodia, the BDN Laboratory in Thailand, and the NIDQC in Vietnam. The latest edition of the *United States Pharmacopeia, International Pharmacopoeia, 4th edition* (2006), the *Pharmacopoeia of the People's Republic of China,* and/or in-house validated analytical methods were used. A sample was considered

failed if it did not pass any of the tests, including identity of active pharmaceutical ingredient (API), disintegration, dissolution, assay for content of API or any major physical defects such as broken tablets, non-uniform color and improper labeling. The results of verification tests for each sample were reported using a form provided in the protocol.

The study revealed failure rates of antimalarial medicines to be 1% (7 failed out of 716 tested) for Thailand and 12.3% (46 failed out of 374 tested) for Cambodia. This study was the first of its kind to determine statistically—using a randomized sampling protocol—the prevalence of poor-quality antimalarial medicines along the cross-border areas of Cambodia and Thailand which, for many years, has been identified as a "hot spot" of drug-resistant malaria. The investigators believe that this project will provide an exemplary study methodology for other researchers, one that MRAs can adapt as needed to determine the magnitude of poor quality medicines in any particular health or pharmaceutical situation, and in any geographical area.

**Avian Influenza**

*Monitoring the Quality of Oseltamivir Products Stockpiled In Laos*

Oseltamivir is available in the public sector hospitals only and is strictly controlled by the Lao Government. This medicine has not been imported even though it has already been registered with the FDD by a local company. The Lao Government received donations of oseltamivir phosphate capsules in blister-pack forms from the World Health Organization (WHO) in February 2007, as Tamiflu® capsules. After distribution to ten provincial hospitals, the oseltamivir that had been kept in stockpile was analyzed for quality according to protocols developed by PQM. The protocol used, S*urvey of the Quality of Stockpiled and Circulated Oseltamivir Products in the RDM-A Region: Instructions for Oseltamivir Sampling*, instructed drug inspectors on how to collect samples for testing. Subsequently, samples underwent testing at the FDQCC laboratory using the PQM/ GPHF monograph-*Testing Manual for Basic Testing of Oseltamivir Capsules.* All 22 stockpiled oseltamivir samples from 16 public sector hospitals passed quality testing using basic tests.

**ANEQAM**

The Asian Network of Excellence in Quality Assurance of Medicines serves as a regional resource for training and sharing expertise in the areas of QA/QC, GMP, and BA/BE studies. Successful

Participants from Lao PDR and Cambodia, lecturers of the program and

workshops have been conducted by all three Centers of Excellence, providing valuable training for professional staff throughout the GMS. The trainings conducted in collaboration with ANEQAM partners, included:

- GMP workshops at Mahidol University Faculty of Pharmacy (Thailand) included:
  - Good Manufacturing Practices for inspectors from Lao PDR and Cambodia (August 2009)— offered fundamental knowledge on the principles and practices of GMP compliance and hands-on experience in GMP inspection during actual site visits
  - GMP for Thai inspectors and manufacturers from public and private sectors (May 2008)—trained on basic GMP, validation, and risk management in the pharmaceutical industry
- QA/QC workshops at Chulalongkorn University Faculty of Pharmaceutical Sciences (Thailand):
  - Advanced Testing of Tuberculosis (TB) Medicines for drug quality control laboratory technical staffs from Lao PDR, Cambodia, Vietnam, and Thailand (July 2009)—hands-on training in HPLC, UV, microbial assay, and dissolution of anti-TB FDCs according to compendial methods
  - Quality Control of Antimalarials for drug quality control laboratory technical staff from Laos, Cambodia, Vietnam, and Thailand (December 2007)—hands-on training and classroom lectures on HPLC and dissolution testing of artesunate
- BA/BE workshop by University of Santo Tomas CeDRES (Philippines) on statistical analysis used in BA/BE studies for analysts and lab staff from Cambodia and Vietnam (November 2007, in Cambodia)—in-depth instruction and hands-on training on complex statistical methods for analyzing BA/BE study results using software developed by UST.

**Raising public awareness about the dangers of counterfeit medicines in Southeast Asia**

The *Pharmacide* project has produced a series of public service announcements (PSAs) for public broadcast in the GMS countries to address the lack of public education about the dangers of counterfeit drugs. Five versions were created to be culturally and linguistically appropriate for Cambodia, Lao PDR, Thailand, and Vietnam, as well as an English version for broadcast on regional channels and use by USAID and PQM. The PSAs will air in Vietnam, Lao PDR and Thailand in local languages on local TV channels after clearance is obtained from the authorities.

The PSAs were recently selected by the World Intellectual Property Organization (WIPO) for global distribution as an excellent example of using media to inform the public of this health threat.

In addition, PQM recently produced a 20-minute dramatic documentary film that outlines field operations related to the detection of counterfeits, laboratory analysis, and the public impact of -using counterfeit and substandard medicines which affects the lives of many of the rural poor in the GMS. A fictional dramatization that captures the realities of

discovering counterfeit medicines, investigations, testing, and outcomes, the film is meant to be used for MQM training and to raise awareness of stakeholders and policymakers in a visually effective manner.

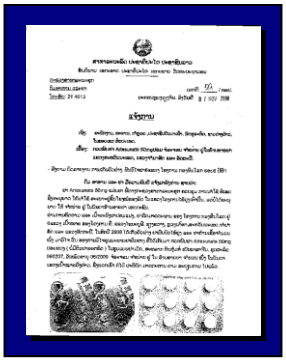
Currently, a proposal is under development for an hour-long, regional documentary film which takes an in-depth look at the manufacture, distribution, and delivery of counterfeit medicines in the region, as well as what is being done about it. This film, meant for public education, is part three in the part *Pharmacide* series.

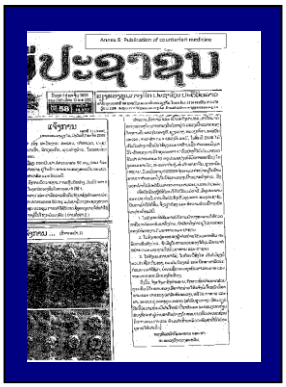
## Highlights of Successes

### Cambodia

The Cambodian MOH recently took steps to close illegal drug outlets throughout the country, a result of the IMC following data from PQM- and GFATM-supported monitoring and WHO-supported Rapid Alert activities. A decree by the Secretary of State has resulted in the closure of 424 illegal drug shops since November 2009. Additionally, recent actions by the Cambodian Economic Police division led to the seizure of a counterfeit medicine storage and distribution operation in the capital city of Phnom Penh. Close collaboration and providing evidence through monitoring, testing, and follow-up activities are producing an increase in both public awareness and political will at the highest levels in Cambodia. This is an encouraging step forward toward ensuring medicine quality in Cambodia.

### Confiscations and recalls in Laos





Regulatory notices were issued regarding counterfeit artesunate tablets and substandard erythromycin tablets to affected provincial and district authorities of Champasak, Saravan, Phongsaly, and other provinces notifying them to conduct thorough inspections and investigations at retail outlets. Similar notices were issued for counterfeit, non-registered ampicillin capsules found in the provinces of Sayabuly and Luang Prabang, and the capital, Vientiane. Provincial authorities investigated the origin of the products; pharmacy owners were educated, warned, and fined according to the Lao PDR Law on Drugs and Medical Products; and the Vientiane-based distributor was investigated, educated, warned, and fined. The remaining stocks of ampicillin capsules were seized.

The pharmacy owners and distributor involved were also required to sign an agreement stating that they will strictly follow the Law on Drugs and Medical Products and other regulations, recognizing that, if they commit future violations, they will face serious punishment.

The Food and Drug Department (FDD) convened law enforcement officials from central and provincial levels (MRAs, economic police, customs, and trade) to attend awareness-raising and collective action planning meetings in Vientiane and Borikhamxay to address issues surrounding counterfeit medicines.

Photos and information on the products involved were published in local newspapers (*Vientiane Mai* and *Pasaxone*) and will also be reported on the FDD website and in its bulletin.

**Data harmonization**

PQM has developed a tool to harmonize the data generated by MQM testing that will standardize reporting despite language differences, regulatory and legislative variations between countries, different medical products, etc. Incorporating various data sources from monitoring into a single document for multiple countries has proven difficult in the past. With the initiation of MQM harmonization, future data collection should be more easily incorporated into a global database. This database, currently under development at USP, will synthesize all medicine quality data from the field around the world, and provide countries and stakeholders with timely information. The recently finalized MQM harmonization document and associated data collection forms will be used by all countries involved in the PQM monitoring programs.

**Inter-agency cooperation**

PQM works collaboratively with the World Health Organization on numerous projects in the GMS to ensure the availability of and access to good quality medicines to treat endemic diseases such as malaria, tuberculosis, and HIV/AIDs. The following highlights key accomplishments in this arena

- Involved in conceptualization, framework development, and reporting for WHO Rapid Alert (RAS) system.
- Shared MQM data from GMS region with WHO Western Pacific Regional Office (WPRO) to facilitate Operation Jupiter-Asian Region, the first of its kind for collective effort among health professionals, academia, INTERPOL, and customs agents which led to identification of the source of counterfeit artesunate.[15]
- Participated in the ARC-III research group collaborative study in GMS that examined artemisinin resistance along the borders of Thailand and Cambodia, focusing on the quality component, among many key factors that play a role in the failure rates of first-line antimalarials and parasite resistance to artemisinin-based combination therapy (ACT) AMLS used for treating patients with *P. falciparum* malaria. The study was implemented by WHO and funded by BMGF.
- Collaborated with the WHO/Uppsala Monitoring Center, a recognized leader in the field, to develop a pharmacovigilance programs in Cambodia.

PQM has been involved with INTERPOL-coordinated operations to combat counterfeit medicines in the GMS where, in one study, 49.9% (195/361) of the artesunate samples collected were counterfeit.[16] The packaging had fake holograms and the artesunate tablets contained little

[15] Paul N Newton, Facundo M Fernández, Aline Plançon, Dallas C Mildenhall, Michael D Green, Li Ziyong, Eva Maria Christophel, Souly Phanouvong, Stephen Howells, Eric McIntosh, Paul Laurin, Nancy Blum, et al. 2008. A Collaborative Epidemiological Investigation into the Criminal Fake Artesunate Trade in South East Asia. PLoS Medicine, February 2008, Vol. 5, Issue 2, e32. http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371%2Fjournal.pmed.0050032.

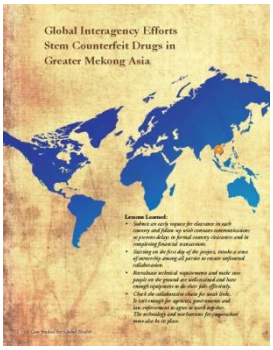
[16] Ibid

or no artesunate. During Operations Jupiter[17] and Storm I[18], PQM provided data from MQM programs in Cambodia, Lao PDR, Thailand, and Vietnam to country customs and police agents during regional exercises. The data were used in conjunction with other intelligence to effect enforcement actions throughout the region including arrests and seizures of over $9.5 million worth of counterfeit medicines throughout Southeast Asia.

PQM facilitated and participated in a Collaborative Training Workshop on Establishing Antimalarial Drug Quality Monitoring for Selected Provinces in Philippines and Indonesia, jointly organized by the Department of Health Bureau of Food and Drugs, Research Institute for Tropical Medicine (RITM), and ACTMalaria (August 2006).

PQM has collaborated with the Kenan Institute Asia's (KIAsia) Border Action Against Malaria (BAAM) program and the new Greater Mekong Subregion Responses to Infectious Diseases (GMS-RID) project in Thailand. KIAsia provided assistance to the Thai BVBD to implement MQM activities during 2005-2006 and has contributed funds towards the purchase of Minilabs used in routine monitoring in Thailand. In addition, the KIAsia office houses the PQM regional office for the GMS. KIAsia and PQM partner to develop Global Fund proposals for malaria for Thailand, and future plans include harmonizing surveillance sites in the RDM-A region for enhanced cooperation over the next five years of project implementation.

Additionally, PQM has provided technical assistance to Laos, Vietnam, and Thailand in drafting proposals to the Global Fund for AIDS, TB and Malaria. Technical assistance has also been provided for development of proposals to the Bill and Melinda Gates Foundation. PQM also has leveraged funds from private foundations and other sources to help implement projects in GMS.




**Case Studies in Global Health**

PQM staff submitted a case study on medicine quality monitoring to the Global Health Case Study Initiative, a project to identify ways in which key stakeholders are addressing global health concerns sponsored by The Bill & Melinda Gates Foundation, World Health Organization's Special Programme for Research and Training in Tropical Diseases (TDR), Global Health Progress (GHP), International AIDS Vaccine Initiative (IAVI) and Association of University Technology Managers (AUTM). The PQM case study, "Global Interagency Efforts to Stem Counterfeit Drugs in the Greater Mekong Asia," was accepted and published in October 2009 as part of a book containing 35 case studies. A book launch and presentation of the case study took place during the 2009 American Society of Tropical Medicine and Hygiene (ASTMH) annual meeting in Washington, DC.

[17] Paul N Newton, et al. 2008. A Collaborative Epidemiological Investigation.

[18] http://www.interpol.int/Public/ICPO/PressReleases/PR2008/PR200865.asp

## Challenges and Lessons Learned

### Challenges encountered

Challenges faced by the PQM program during the five-year report period included:

- Medicines regulatory agencies (MRAs) in the region seem to lack the required authority and, consequently, were unable to effectively enforce the laws and regulations pertaining to violations of selling and distributing poor quality medicines.
- Ineffective coordination and communication between stakeholders in some countries in the region, especially among law enforcement agencies (e.g., MRAs, economic police, prosecutors, trade, customs), impeded their taking appropriate and timely actions against violators that distributed and sold poor quality and counterfeit medicines found in the field.
- Obtaining comprehensive and accurate data on medicine quality from the monitoring sites continually proved a challenge to PQM efforts.
- The turnover of staff at the sentinel monitoring sites and the need for repeated trainings presented delays and hindered effective operations.
- Inconsistent use of proper basic testing techniques at some sentinel sites using the Minilab protocol and monographs threatened the validity of the data collected.

Some of the program implementation issues encountered include:

- Delays in obtaining formal concurrence from the countries' relevant authorities for agreed-upon work plans, which often took longer than anticipated, in turn, delayed PQM transfer of funds to those countries to carry out program activities.
- Delays in obtaining country reports after each round of sample collection and testing, due to in-country personnel constraints, among other issues, were experienced.
- New USP regulations which require that all funds being transferred to any institution or entity required a signed legal agreement with that institution to first be in place delayed fund transfers and, subsequently, delayed activities.

### Key lessons learned

Lesson 1: Slow implementation of the MQM activities at the country level, at least initially

**Possible causes**

- Time-consuming formal clearance
- Additional workload for the program, lab, and MRA
- Different countries, different QA/QC systems
- Financial support arrangements
- Language barrier–material translation takes time
- Training of trainers–takes more time

**Suggested solutions**

- Obtain buy-in of the relevant government agencies, institutions, and malaria programs

- Fully incorporate the MQM project into national program activities
- Direct training

Lesson 2: Technical issues surrounding sampling procedure and testing

**Possible causes**

- Some rural area sites had difficulty collecting the required quantity of sample
- Some countries lack adequate equipment at their national laboratory to carry out verification tests

**Suggested solutions**

- Apply revised sampling procedure
- Build capacity by equipping and training national lab staff

Lesson 3: Weak coordination and cooperation among key partners participating in the project

**Possible causes**

- Lack of political will, common goal, and motivation
- Lack of financial resources for collaborative activities

**Suggested solution**

- Encourage commitments for funding
- Encourage collaboration and cooperation among stakeholders and partners

Lesson 4: Untimely information-sharing among law enforcement agencies within the country when a counterfeit or substandard sample is discovered in the field leading to further delays in enforcement action

**Possible causes**

- Lack of human resource and technology
- Lack of regulatory procedures
- Poor interagency coordination

**Suggested solution**

- Improve communication system and means e.g. Internet access and email
- Develop and implement regulatory procedures
- Increase coordination and cooperation among agencies involved in enforcement

Lesson 5: Weak information-sharing between countries and among regional MRAs

**Possible causes**

- Lack of effective mechanisms for collaboration, cooperation and communication
- Human resource and technology constraints
- Unwillingness to disclose data

**Suggested solutions**

- Strengthen inter-country and regional collaboration and cooperation, may be under the umbrella of the ASEAN guidelines on pharmaceutical products
- Build up a regional network for information-sharing among DRAs for counterfeit and substandard medicines
- Encourage MRAs in the region to report to WHO/WPRO Rapid Alert System once it is up and running again

Lesson 6: Weak law and regulatory enforcement at country level

**Possible causes**

- Inadequate laws and regulations
- Weak penal sanctions
- MRAs not adequately empowered

**Suggested solution**

- Revise drug laws and regulations
- Empower DRAs and/or establish an effective national committee embracing all relevant law enforcement agencies to deal with counterfeit medicines
- Consider forming a regional committee

## Looking to the Future

Plans for the next five years implementing the Promoting the Quality of Medicines cooperative agreement with USAID include the following:

- Develop concrete plans to integrate and institutionalize MQM activities as part of normal MRA function. This is necessary for sustainability of this important activity.
- Build capacity of local manufacturers in GMP compliance.
- Assist NMQCLs to reach ISO accreditation, enabling them to generate revenues from testing for NGOs and multilaterals such as the Global Fund.
- Provide technical assistance to initiate a medicine quality monitoring project in Burma/Myanmar, including procurement of equipment, training, protocol implementation, and continued support. A study to provide baseline data in various sites in Burma/Myanmar will be implemented following Congressional approval to expend USAID funds within that country.
- PQM intends to re-engage the former MQM sites in Yunnan province of China, collaborating closely with the Chinese authorities and WHO, as part of a comprehensive regional program for harmonizing data collection for medicine quality in the GMS.
- Following up country requests, PQM intends to expand MQM sites and intensify data collection and enhance capacity of national authorities to take appropriate enforcement actions.
- PQM will participate in upcoming Global Fund proposal development for the region.

- PQM intends to provide technical assistance to INTERPOL and local customs and police officials to develop training and protocols for combating the spread of counterfeit medicines, especially in cross-border provinces and point-of-entry sites throughout the GMS.
- PQM will continue to develop high-quality and relevant media products to increase public awareness about counterfeit and substandard medicines and engage policymakers and stakeholders.

## Conclusion

The Promoting the Quality of Medicines Program (and its predecessor, the USP DQI program) in the Greater Mekong Subregion of Southeast Asia has successfully established a model for ensuring medicine quality throughout the region. PQM synergizes efforts among key partners in Ministries of Health, bi-lateral and multi-lateral aid agencies, and international organizations such as the Global Fund for AIDS, TB and Malaria, INTERPOL and the WHO. It has been instrumental in fostering an environment of collaboration and exchange of information, ideas, and insights into the complexities of developing and strengthening functional medicine quality assurance systems for the region.

PQM has lent its expertise and technical assistance in the form of provision of commodities and training to national drug quality control laboratories, and has trained and equipped dozens of provincial and regional level monitoring sites in six countries in Southeast Asia. Development of medicine quality databases, establishment of pharmacovigilance centers, and training in advanced pharmaceutical quality assurance systems and good manufacturing practices are among other key activities and accomplishments by PQM over the past five years. Creating and supporting a regional network of Centers of Excellence for the GMS attests to PQM's commitment for long term sustainability of the programs, as well as enhancing staff capabilities and building capacity of laboratories and educational institutions. The PQM program has encouraged a collaborative spirit among national regulatory authorities, drug quality control laboratories, and relevant vertical disease programs for more effective follow up, enforcement, and data sharing.

Despite some of the challenges encountered during implementation of the program such as lack of centralized authority among regulators, difficulties in correctly implementing MQM protocols in the field, lack of streamlined and efficient communication among partners, delays in country reporting following data collection, and others, PQM will continue to address these challenges by evolving strategies to meet the needs of the country partners. Working closely with international agencies, Inter-ministerial agencies in-country, and continuing to refine protocols and develop harmonized data collection methods, PQM will continue to support the strengthening of medicine quality assurance systems in the GMS countries. Due to its international reputation as a leader in medicines QA, PQM is a vital partner to provide necessary support to the countries of Cambodia, Laos, the Philippines, Thailand, and Vietnam over the next five years of project implementation.

ANNEX

U.S. PHARMACOPEIA
*The Standard of Quality℠*

# Guidelines to Establishing a Medicine Quality Monitoring Program

Promoting the Quality of Medicines Program

March 2010

Standards for Quality Medicines Throughout the World

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## Acronyms

| | |
|---|---|
| ACT | Artemisinin-based Combination Therapy |
| API | Active Pharmaceutical Ingredient |
| CAPA | Corrective and Preventive Action |
| DQI | Drug Quality and Information Program |
| M & E | Monitoring and Evaluation |
| MQM | Medicine Quality Monitoring |
| MRA | Medicine Regulatory Authority |
| NGO | Non-governmental Organization |
| NMCP | National Malaria Control Program |
| NQCL | National Quality Control Laboratory |
| PQM | Promoting the Quality of Medicines Program |
| S/P | Sulfadoxine-Pyramethamine |
| TLC | Thin Layer Chromatography |
| USAID | United States Agency for International Development |
| USP | United States Pharmacopeia |
| WHO | World Health Organization |

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# Guidelines to Establishing a Medicine Quality Monitoring Program

The purpose of this Guide is to help authorities create a uniform protocol for all procedures undertaken in Medicine Quality Monitoring (MQM) programs, including medicines sampling, testing, and reporting. This Guide and the annexed forms are designed to be adapted as needed by the individual country.

## 1. Background and Introduction

Provide a brief introduction on the importance of using good-quality medicines to the country's health system and to morbidity and mortality caused by specific disease(s). A statement could address the rationale of why conducting MQM in each country is important.

## 2. Main Objective

List the overall purpose of establishing the MQM program.

## 3. Specific Objective(s)

List the specific objectives to be achieved by the MQM program.

## 4. Main Activities

List the specific activities that will allow the accomplishment of the specific and main objectives, for example:

- Collect selected 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; and,
- Implement corrective and preventive actions (CAPAs) as necessary.

## 5. Responsibilities of Stakeholders Involved in MQM

- List all stakeholders involved in each activity.
- Define clearly the role of each stakeholder within the program.
- Designate a principal focal point, if possible, to coordinate all MQM activities to ensure good communication and smooth operations within all sentinel sites. Designate a focal point for each sentinel site, if applicable.
    - Ensure the focal point coordinates with each stakeholder to complete the following:
        - Ensure the 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; and,
        - Implement CAPAs as necessary.

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## 6. Methodology

### 6.1 Sampling strategies

The planning for sampling should take into consideration:

- Main and specific objectives of the project;
- Potential limitations of the study methodology;
- Budgets;
- Human resources;
- Availability of medicine in all sectors—public, private, and informal;
- Accessibility of sampling sites; and,
- Levels in the distribution chain and sectors (manufacturers, central warehouse, wholesalers, regional warehouses, public and private hospitals, retailers, etc.)

The rationale for utilizing the chosen sampling strategy should be defined in the protocol.

### 6.2 Selection of Region/Sentinel Sites

When selecting geographical regions where samples will be collected, consult with key health officials and partners. For example, in the case of antimalarial medicines, select the regions jointly with the National Malaria Control Program (NMCP), local U.S. Agency for International Development (USAID) Mission, Drug Quality and Information/Promoting the Quality of Medicines Programs (DQI/PQM), Medicine Regulatory Authority (MRA), National Quality Control Laboratory (NQCL), and any other pertinent stakeholders.

The number of regions/sites will be determined according to the following factors:

- Available budget;
- Available human resources;
- Epidemiological data demonstrating prevalence of the disease;
- 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; and,
- Other relevant factors.

Of the cited criteria, epidemiology, access, and availability of medicines generally are first taken into consideration. Other criteria can also be integrated and prioritized depending upon the main objective of the project.

Involve all relevant stakeholders in choosing where to locate the sentinel site for each region. Typically, the site is selected because it is centrally located within the geographical region where sampling will be conducted; accessibility and availability of staffing must also be taken into consideration. At times, however, the geographical region for sampling is determined by the location of an existing sentinel site. Either way, how suitable the facility is for use as a laboratory must always be considered, since all samples collected within a geographical region will be sent to the sentinel site for preliminary testing (Basic Tests with Minilabs®).

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After identifying and justifying the selection of regions/sites, locate the respective sentinel sites on a national map with enough detail to allow samplers to prepare the logistics of traveling to each point of the sample collection. On the sampling plan for each site, list the types of sources from which the samples will be collected (e.g., importers, wholesalers, nongovernmental organizations (NGOs), central stores, manufacturers, regulated retailers, hospitals, private sources, and informal markets).

### 6.3 Medicine selection for testing

Involve the pertinent national health program authorities in development of the list of medicines to be collected for sampling and testing. For example, if the project concerns antimalarial medicines, discuss with the NMCP, MRA, and NQCL which medicines are most frequently used. Specify if the selected medicines were chosen according to the national health therapeutic program.

### 6.4 Sample definition

To ensure uniformity in the collection of medicines, clearly define the attributes that determine a single sample. A sample comprises of a given medicine with the same characteristics as given below:

- Active ingredient or API (i.e., chloroquine, amodioquine, artesunate, etc.)
- Dosage form (i.e., tablet, capsule, oral solution, etc.)
- Dose (i.e., 200 mg, 50 mg/ml, 1,000,000 I.U., etc.)
- Lot/Batch number (i.e., 80001-A, PGX-001, etc.)
- Collection site (i.e., private pharmacy in Town A, private pharmacy in Town B, private pharmacy in Town C, etc.).

Any difference in any one of these variables indicates that the medicine collected must be considered ***a separate sample***.

Combining collected samples of the same product (same presentation) from multiple locations or sources to create one pooled sample does not constitute a valid sample and is not permitted.

### 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.

The following example of sample collection applies to solid dosage forms (tablets and capsules) only. Details for sampling of oral suspension, injectable, or other dosage forms should be discussed during the protocol development on a case-by-case basis.

| 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 |

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| Re-sampling for Compendial Testing (necessary to take regulatory actions) | | |
|---|---|---|
| Minimum Units | Maximum Units | Comments |
| 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 |

### 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., 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).

If diversification is not possible, provide justification or explanation of why not. State the priority of the medicines and the number of samples to be collected.

### 6.8 Estimating the number of samples to collect per round

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

If private and/or informal sectors are to be included in the study, approximately 20-30% of the total budget should be allocated to purchasing samples.

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If it is not possible to collect 100 samples, collect samples according to the available human and financial resources and the market availability. Justification should be provided to indicate why the ideal number of samples was not collected.

### 6.9 Sampling technique

- 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. Expired samples should not be tested, but they should be reported to the MRA.
- Caution should be taken when sampling medicines with 2-3 months until expiration. Each protocol should clearly define how these samples will be handled to ensure expired medicines are not tested.
- In specific instances—particularly in the private and informal sectors—it is crucial to conceal the identities of the sampling team. The following are some suggestions to remain anonymous while collecting medicines from these sectors:
  - Whenever possible, adopt the "mystery shopper" technique when collecting samples—essential at informal market and private collection sites. Arrange to replace samples collected from government and other facilities as appropriate.
  - Practice key questions to be asked at informal market in order to collect the needed target samples.
  - 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.

### 6.10 Collection technique

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 be classified as "fail or doubtful" and should there be the need for regulatory action.

### 6.11 Sample 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.

## 7. Sample Analysis

Once samples have been collected, they need to be tested in three stages or levels (Figure 1). Protocols may define "stages" or "levels" differently. The term "level" is used in these

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guidelines; however, individual protocols should clearly indicate the terminology to be utilized and its specific meaning.

**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.

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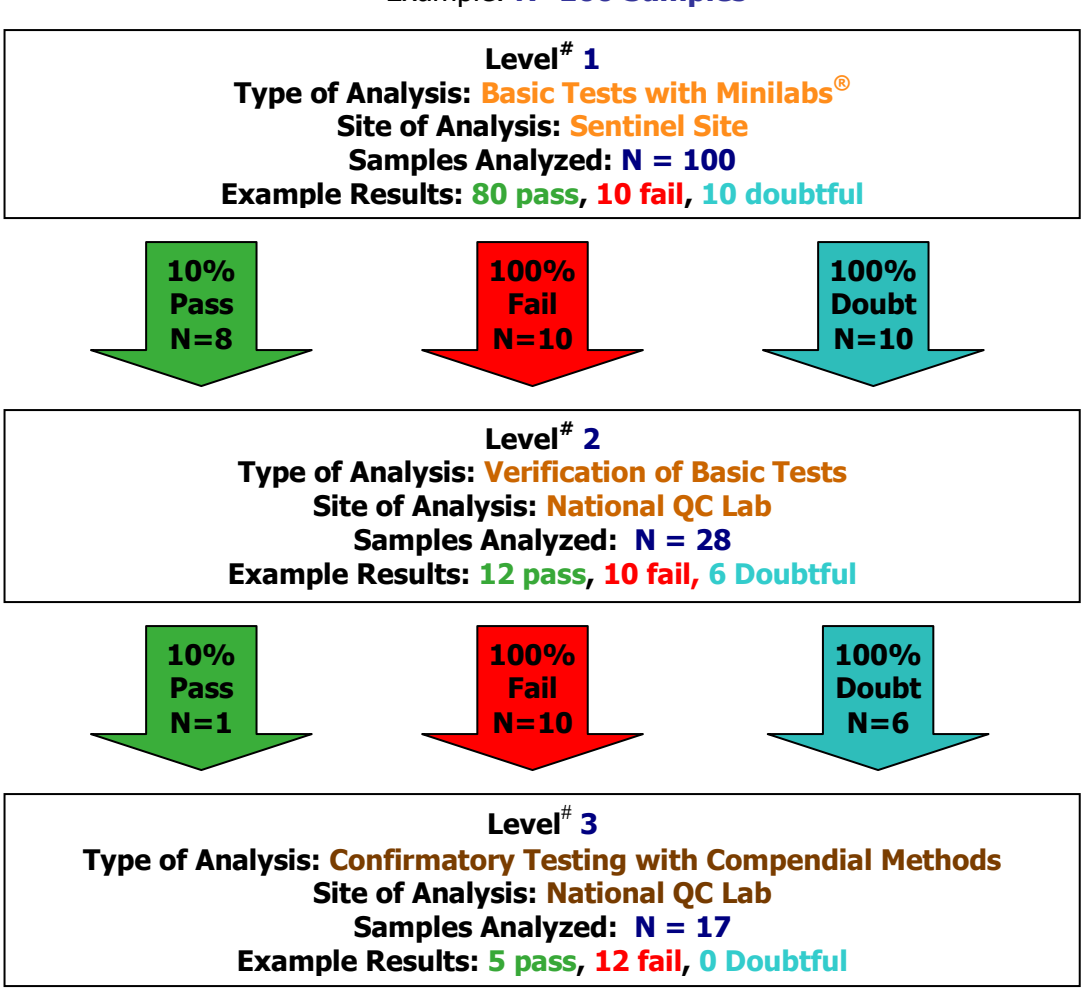
## 7.1 Levels 1 & 2: Basic Tests

### 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**




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

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- Record clearly the test results for each sample on the *Basic Tests Analysis Form for Sentinel Site Staff* (Annex 3).
- Once testing has been finalized, send all samples with their respective forms attached (*Sample Collection Form* and *Basic Tests Analysis Form for Sentinel Site Staff*) and TLC plates to the NQCL. It is important for all samples to be sent to the NQCL for retention purposes.
- The samples sent to NQCL should be separated into two categories:
  - Subset of samples for verification and confirmatory testing
  - All remaining samples for retention purposes
- The subset of samples for verification testing is defined 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***

.

**7.1.2.** Level 2: Verification of Basic Tests at NQCL

NQCL: Perform verification testing by repeating basic tests on the subset of samples. If Level 1 and Level 2 tests are properly performed, the majority of results for passed and failed samples should correlate between Level 1 and Level 2.

- 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 which are known to be prone to dissolution failures
    - Since S/P tablets are known to have high dissolution failure rates, always perform compendial analysis on S/P tablets.
  - 50-100% of Artemisinin-based combination therapy (ACT) tablets/capsules which are known to be prone to related-compound (impurities) failures
    - Since ACTs are known to have high related-compound failure rates, always perform compendial analysis on ACT tablets/capsules..

  * 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:

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- 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 sourc**e, 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 | • Pass or Fail, proceed to Step 2 | • 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 | • Pass, proceed to Step 3<br>• Fails, STOP | • If sample Fails Step 2, you can conclude: Sample does not conform to compendial specifications |
| 3 | Content | Assay | 20 | • Pass, proceed to Step 4<br>• Fails, STOP | • If sample Fails Step 3, you can conclude: Sample does not conform to compendial specifications |
| 4 | Disintegration | Dissolution | 24 | • Pass, proceed to Step 5<br>• Fails, STOP | • 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 | • Pass, proceed to Step 6<br>• Fails, STOP | • 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.<br>• If sample Fails Step 5, you can |

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| | | | | | |
|---|---|---|---|---|---|
| | | | | | conclude: Sample does not conform to compendial specifications |
| 6 | If the sample passes Steps 1-5 and there are sufficient units, proceed to remaining monograph tests. | | | | • If sample Fails Step 6, you can conclude: Sample does not conform to compendial specifications |

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.
2 The number of units needed for each test depends on the individual monograph.
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.)

## 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 authorities 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

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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

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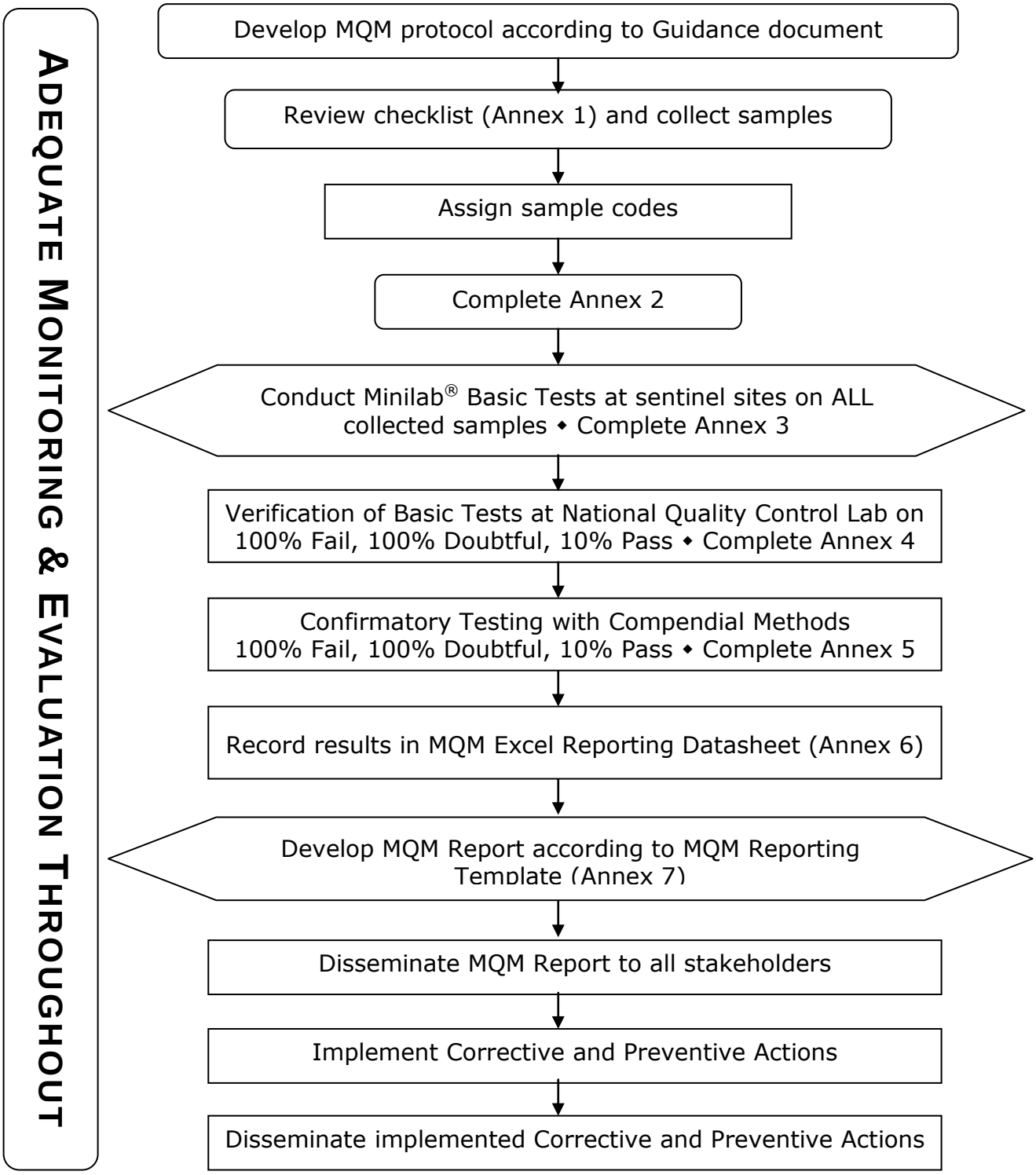
**Figure 1: Medicine Quality Monitoring Workflow**

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**Annex 1**

## Guide to Establishing a Protocol for Medicine Quality Monitoring

# Sampling Checklist

Before departing for sentinel sites with the intention of sampling for a Medicine Quality Monitoring (MQM) program, check that you have all the items listed below.

| ✓ | Task |
|---|---|
| | **1. Sufficient Sampling Forms**<br>*Fill out one form for each sample.* |
| | **2. Sampling Plan**<br>*Prepare a sampling plan in accordance with the MQM protocol and plan ahead for each day of sampling.* |
| | **3. Sampling Tools**<br>*Each sampling team must have the following tools:* |
| | • New plastic or glass, opaque, clean containers to store and transport samples |
| | • Map for the designated site with listed sources of sample collection |
| | • Scissors, gloves, clean spatula or spoon, forceps, tape, watch, labels |
| | • Indelible markers for labeling the sampling containers |
| | • Indelible pens to complete forms |
| | • Cardboard box(es) to store collected samples. |
| | |
| | **4. Notebook**<br>*(one per sampling team)*<br>*Use a notebook dedicated to only MQM collections to record additional information about sampling activities.* |
| | |
| | **5. Logistics**<br>*Money for transportation, purchasing samples, food, lodging, and other incidentals.* |
| | |
| | **6. Optional items**<br>*Digital or conventional camera, mobile phone, global positioning system device, and other items as necessary.* |

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## Guide to Establishing a Protocol for Medicine Quality Monitoring

# Sample Collection Form

| | |
|---|---|
| **Date (day/month/year)** | |
| **Name of Site** | |
| **Name of Collector** | |
| **Signature of Collector** | |

| **SAMPLE INFORMATION** | |
|---|---|
| Sample code [1] | |
| Complete site address<br>(Name of location, street address, contact information, if applicable) | |
| Sector of site (public, private or informal) | |
| Description of dispensing site (pharmacy, health clinic, hospital, warehouse, etc.) | |
| Commercial drug name | |
| INN[2] | |
| Pharmaceutical presentation (tablet, capsule, injectable, etc.) | |
| Dosage (mg) | |
| Manufacturer name | |
| Manufacturer's batch or lot number | |
| Manufacturing date (if present) | |
| Expiry date | |
| Registration or license number (if applicable) | |
| Manufacturer address | |
| Number of units collected[3] | |
| Package description:<br>• Type of package (blister pack/card, bottle, others specify)<br>• Number of units/pack<br>• Presence of insert/leaflet | |
| Check one: | ☐ taken in original package ☐ taken from bulk container |
| Instructions to store sample (e.g., keep medicine away from light and at 25°) | |
| Storage conditions at site[4] | |

[1] Adapt according to program or country needs, suggested will be (A/B/C/D/E): A: Name of Country, B: INN/API, C: Collection Site; D: Date of Collection; E: Sequential Number.

[2] INN is the International Non-proprietary Name of a drug product, also known as Active Pharmaceutical Ingredient (API)

[3] If fewer than the number required by the protocol, please explain.

[4] Please describe the general storage conditions of the sampling site (e.g., medicines exposed to sun and/or air, no temperature and/or humidity control, water visible in storage room, medicines stacked inappropriately, etc.)

* Sample collection form should be attached to the sample and additional copies should be retained as indicated in the project protocol.

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**Annex 3**

## Guide to Establishing a Protocol for Medicine Quality Monitoring

# Basic Tests Analysis Form for Sentinel Site Staff

| | |
|---|---|
| **Sample Code** | |
| **Date of Analysis (day/month/year)** | |
| **Sentinel Site of Analysis** | |
| **Name of Analyst** | |
| **Signature of Analyst** | |

| **TEST 1: VISUAL & PHYSICAL INSPECTION** | |
|---|---|
| **Visual Inspection:** | |
| Please confirm that all of the recorded information in the Sample Collection Form (Annex 2) is consistent with the packaging and labeling of the medicine. Correct the Sample Collection Form (Annex 2) if there are any errors and/or omissions.[1]<br><br>Have any corrections and/or additions been made to Sample Collection Form (Annex 2):<br><br>☐ Yes ☐ No | |
| Other Comments (description of hologram, any print on the backing foil, etc.) | |
| **Physical Inspection:** | |
| Shape (circular, oval, flat sides, other) | |
| Uniformity of shape | |
| Uniformity of color | |
| No physical damage (cracks, breaks, erosion, abrasion, sticky) | |
| Other observations (no foreign contaminant, dirty marks, proper seal - for capsule) | |
| **TEST 2: DISINTEGRATION[2]** | |

[1] If any corrections and/or additions were made to the Sample Collection Form (Annex 2), please initial and date all added information.

[2] Disintegration tests are 30 minutes; for testing at sentinel sites perform only 3 tablets/capsules. If one or more units do not disintegrate classify the sample as failing basic tests and send for confirmatory tests. For confirmatory testing please refer to the testing protocol.

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| | |
|---|---|
| Time of observed disintegration (minutes)<br><br>1. _____<br>2. _____<br>3. _____ | Did the drug pass the disintegration test?<br><br>☐ Yes ☐ No |

**TEST 3: TLC**

| | |
|---|---|
| Did the sample have a spot?<br><br>☐ Yes ☐ No<br><br>Rf Standard: _____<br><br>Rf Sample: _____<br><br>Rf % Sample difference [3]<br><br>_____ | Intensity of sample spot compared to standard:<br><br>☐ Less than 80%<br>☐ Between 80 – 100%<br>☐ More than 100%<br>_____<br><br>Were there any contaminants/impurities present?<br><br>☐ Yes ☐ No<br><br>Observations: |

**FINAL RESULTS**

☐ The sample conformed with basic tests

☐ The sample did not conform with basic tests (Reason_____)

☐ The sample is considered doubtful (Reason:_____)

How many units are remained after basic tests: _____

REPORT REVIEWED BY[4]:
Date: _____
Name: _____
Signature: _____

[3] Rf % Sample Difference = [(| Rf (standard) - Rf (sample) |) / Rf (standard)] x 100.
In this formula | Rf (standard) - Rf (sample) | represents the absolute value of the difference between the Rf's of the standard and the sample.
Ex: In a TLC run the following values are obtained: Rf (standard) = 0,55, Rf (sample) = 0,57;
The Rf % Sample Difference = ((l 0.55 - 0.57 l) / 0.55) x 100 = (0.02/0.55) x 100 = 3.6 %
[4] If applicable

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## Guide to Establishing a Protocol for Medicine Quality Monitoring

# Basic Tests Analysis Form for National Quality Control Lab Staff

| | |
|---|---|
| **Sample Code** | |
| **Date of Analysis (day/month/year)** | |
| **Sentinel Site of Analysis** | |
| **Name of Analyst** | |
| **Signature of Analyst** | |

| **TEST 1: VISUAL & PHYSICAL INSPECTION** | |
|---|---|
| **Visual Inspection:** | |
| Please confirm that all of the recorded information in the Sample Collection Form (Annex 2) is consistent with the packaging and labeling of the medicine. Correct the Sample Collection Form (Annex 2) if there are any errors and/or omissions.[1]<br><br>Have any corrections and/or additions been made to Sample Collection Form (Annex 2):<br><br>☐ Yes ☐ No | |
| Other Comments (description of hologram, any print on the backing foil, etc.) | |
| **Physical Inspection:** | |
| Shape (circular, oval, flat sides, other) | |
| Uniformity of shape | |
| Uniformity of color | |
| No physical damage (cracks, breaks, erosion, abrasion, sticky) | |
| Other observations (no foreign contaminant, dirty marks, proper seal - for capsule) | |
| **TEST 2: DISINTEGRATION[2]** | |

[1] If any corrections and/or additions were made to the Sample Collection Form (Annex 2), please initial and date all added information.

[2] Disintegration tests are 30 minutes; for testing at sentinel sites perform only 3 tablets/capsules. If one or more units do not disintegrate classify the sample as failing basic tests and send for confirmatory tests. For confirmatory testing please refer to the testing protocol.

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**Guide to Establishing a Protocol for Medicine Quality Monitoring**
**NQCL Basic Tests Analysis Form**

| | |
|---|---|
| Time of observed disintegration (minutes)<br><br>1. _____<br>2. _____<br>3. _____ | Did the drug pass the disintegration test?<br><br>☐ Yes ☐ No |

**TEST 3: TLC**

| | |
|---|---|
| Did the sample have a spot?<br><br>☐ Yes ☐ No<br><br>Rf Standard: _____<br><br>Rf Sample: _____<br><br>Rf % Sample difference [3]<br><br>_____ | Intensity of sample spot compared to standard:<br><br>☐ Less than 80%<br>☐ Between 80 – 100%<br>☐ More than 100%<br>_____<br><br>Were there any contaminants/impurities present?<br><br>☐ Yes ☐ No<br><br>Observations: |

**FINAL RESULTS**

☐ The sample conformed with basic tests

☐ The sample did not conform with basic tests (Reason_____)

☐ The sample is considered doubtful (Reason:_____)

How many units are remained after basic tests: _____

REPORT REVIEWED BY[4]:
Date: _____
Name: _____
Signature: _____

[3] Rf % Sample Difference = [(| Rf (standard) - Rf (sample) |) / Rf (standard)] x 100.
In this formula | Rf (standard) - Rf (sample) | represents the absolute value of the difference between the Rf's of the standard and the sample.
Ex: In a TLC run the following values are obtained: Rf (standard) = 0,55, Rf (sample) = 0,57;
The Rf % Sample Difference = ((l 0.55 - 0.57 l) / 0.55) x 100 = (0.02/0.55) x 100 = 3.6 %
[4] If applicable

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**Annex 5**

**Guide to Establishing a Protocol for Medicine Quality Monitoring**

# Confirmatory Tests Using Compendial Methods Form

| | |
|---|---|
| **Sample Code** | |
| **Date of Analysis (day/month/year)** | |
| **Name of Lab** | |
| **Name of Analyst** | |
| **Signature of Analyst** | |

## Test Methods and Results

| | |
|---|---|
| 1. **Methodology:** | |
| a. Pharmacopeia: | |
| i. Volume: | |
| ii. Monograph: | |
| | |
| b. Other validated method (e.g., manufacturer's or lab) | |
| i. If yes, please note method: | |
| ii. If no, please explain: | |
| | |
| 2. **Tests Performed:** | |
| a. **ID:** | |
| i. A: | |
| ii. B: | |
| iii. C: | |
| iv. Other: | |
| | |
| b. **Assay:** | |
| i. Test limit: | |
| ii. Assay results: | |
| | |
| c. **Dissolution:** | |
| i. Test limit: | |
| ii. Vessel results: | |
| 1. | |
| 2. | |
| 3. | |
| 4. | |
| 5. | |
| 6. | |

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| | |
|---|---|
| | |
| d. **Uniformity of Dosage Units:** | |
| i. Test limit(s): | |
| ii. Test results: | |
| | |
| e. **Related Compounds:** | |
| i. Test limit(s): | |
| ii. Test Results: | |
| | |
| f. **Other:** | |
| i. Test limit(s): | |
| ii. Test Results: | |
| | |
| **3. Comments:** | |
| **4. Final Results:** | |

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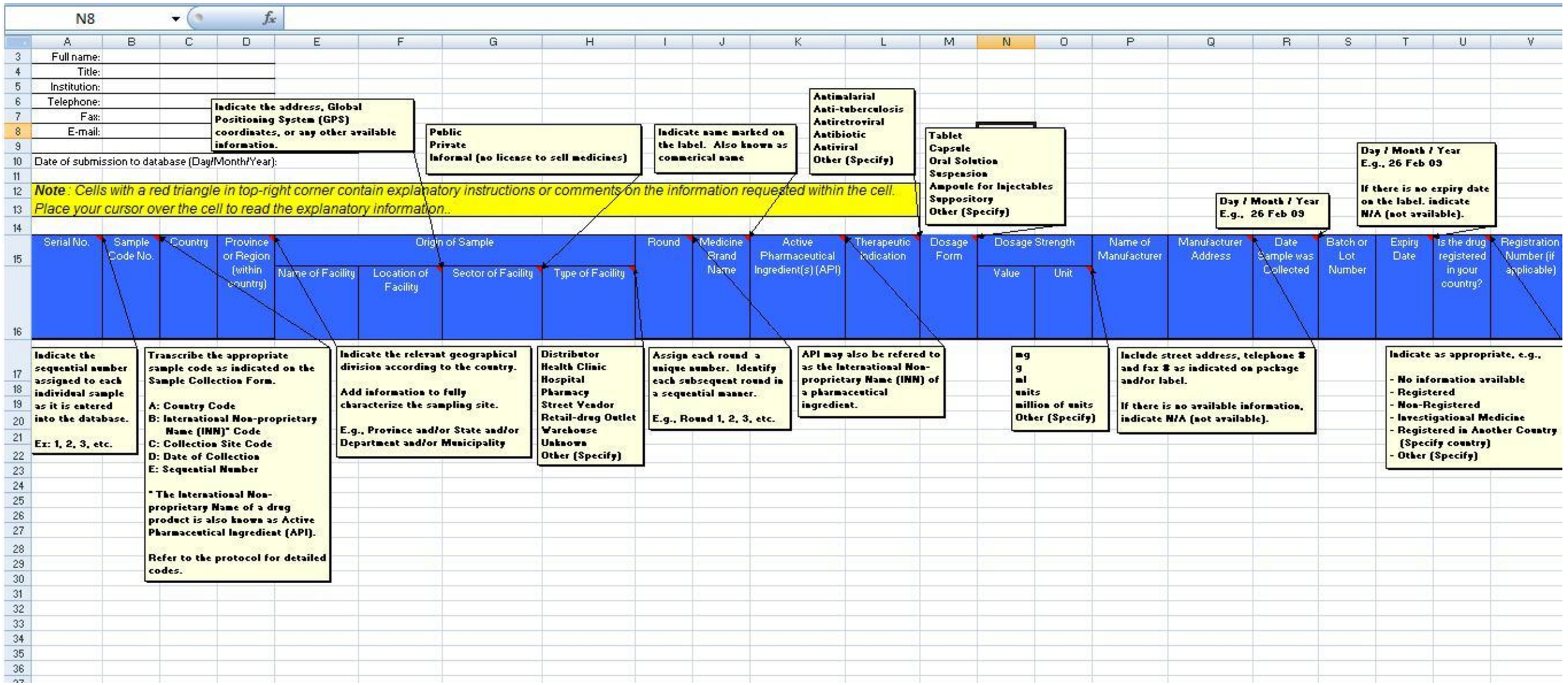
## Guide to Establishing a Protocol for Medicine Quality Monitoring

# MQM Reporting Excel Datasheet (Visual Representation)

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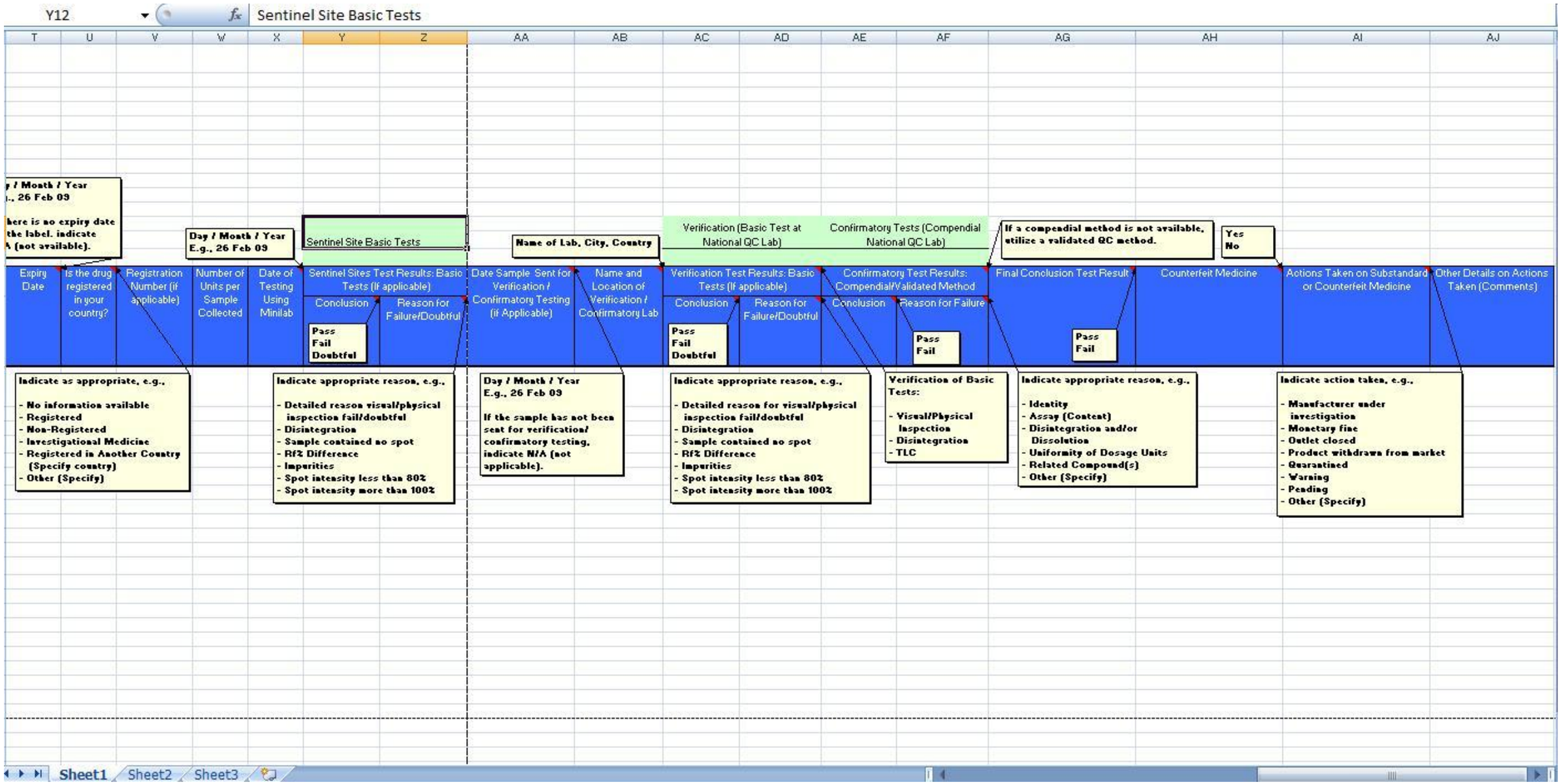


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# Report Template for Medicine Quality Monitoring

One single report should be compiled that incorporates test results from all of the sentinel sites (Minilab® and verification testing) and from the national quality control laboratory (confirmatory testing). If any actions were taken by the medicines regulatory authority (MRA), the specifics should also be captured in the report.

**Protocol corrections**
Any deviations made from the original protocol for Medicine Quality Monitoring (MQM) should be described.

**Layout, format, and presentation**

1. Book format, using a soft binding;
2. Approximately 10-50 pages maximum, including attachments;
3. Cover or front page to include the following information:

   "[Anti-infective] Medicines Quality Monitoring Program Report
   Round number month/year/country name"
   **Optional:** Logos of your Ministry of Health, department or institution, WHO, etc.
   (Note: If *any* logos are added, the USAID and PQM logos must also be added.)

4. Test results presented in tables, figures, or graphics, e.g., pie chart, columns, and/or bar graphs;
5. Data on all samples collected and tested (including a hard copy of the MQM Reporting Excel Datasheet in the bound publication);
6. Discussion, including objectives, methodology, and results; and,
7. Text and symbols in Times New Roman font, 11- or 12-point size.

## Content of report

**Table of contents**
Acknowledgements, list of acronyms, project summary, background, main objective, specific objectives, methods, results, discussion, recommendations, conclusion, next steps, and annexes.

**Acknowledgements**
Acknowledge all partners involved in MQM:

- Funding organization (USAID through DQI/PQM);
- Names of individuals and local/national institutions contributing to project implementation, including those from DQI/PQM and WHO offices, if any; and,
- Others you wish to acknowledge.



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## List of acronyms

List any acronyms used in the report and their meaning.

## Project summary

Provide a one-page summary that briefly describes the history of MQM in the country.

## Background

Include information about the country, such as the location, population, and sites (provinces, regions, etc.) where malaria, tuberculosis, and/or HIV/AIDS is most prevalent. (This depends on what you are monitoring. If you are monitoring the quality of only antimalarials, only include information related to malaria). Also mention the geographical locations where substandard and counterfeit medicines have been found or are suspected to be prevalent. Describe how or why mortality and morbidity might be related to the quality of medicines. Also include a brief summary of any previous studies or projects related to MQM and the main results obtained.

## Main objective

State the main purpose of the program.

## Specific objectives

List the specific objectives intended to be achieved by implementing the MQM program. Specific objectives could include a list of main activities in the program and/or a follow-up of previous rounds of MQM.

## Methods

Highlight the selection criteria used for choosing the sentinel sites; list the names of sites and provide a map of their locations; indicate the number of personnel involved in sampling and testing the collected samples. Describe the sampling strategies, sample collection, and sample testing along with the departments involved in the process.

## Results

The MQM project involves several variables including sites of collection, sources of sampling, and sector of sampling. Results should be presented according to the individual protocol objectives. It is also important to report results in a clear manner to avoid confusion.

A hard copy of the MQM Reporting Excel Datasheet will be included in the report, which has a detailed listing of all medicines collected and tested, and the results at all three levels of testing: Minilab®, verification, and confirmatory.

***Minilab® results (optional: to be determined by each country if Minilab® testing results should be part of the report):*** Illustrate results for each Minilab® basic test per drug/site/test. Then prepare a summary table (drug/site/final Minilab® conclusion). If a sample fails at least one test, it should be considered failed and counted only one time.

***Verification and Confirmatory testing results:*** Present the results of samples that were considered for verification and confirmatory testing. Results can be illustrated as:



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drug/failed test/QC results. Example: chloroquine/failed assay/substandard.

Use a graph, if possible, to effectively present the overall results of total samples collected versus conforming and non-conforming samples. When bar graphs are used to illustrate non-conforming versus conforming samples for all tested medicines, it is important to include "N=" (number of samples) per medicine on each bar. Tables, which allow more variables to be analyzed, can be used for the same purpose, for instance, looking at a particular drug/sector of collection (private, public and informal)/particular sentinel site.

It is recommended to calculate the overall failure rate by dividing the number of samples that failed confirmatory testing (Level 3) by the original number of samples collected.

**Example #1:**

| | |
|---|---|
| 1. Sampled and sent to sentinel site (Level 1) | 100 samples collected |
| **2. Results of Level 1 Testing** (Basic Tests w/Minilabs®) | **10 failed, 10 were doubtful, 80 passed** |
| 3. Sent to NQCL for verification (Level 2) | 28 samples: 10 failed, 10 doubtful, 8 passed |
| **4. Results of Level 2 Testing** (Verification of Basic Tests) | **15 failed, 3 were doubtful, 10 passed** |
| 5. Sent to NQCL for confirmatory testing (Level 3) | 19 samples: 15 failed, 3 doubtful, 1 passed |
| **6. Results of Level 3 Testing** (Confirmatory Testing using Compendial methods) | **15 samples failed, 4 samples passed** |
| **Failure Rate** | 15/100= **15%** |

**Example #2:**

- 100 samples collected ➔ 18 failed Confirmatory Testing w/Compendial Methods at NQCL (Level 3).
- Failure Rate = (18/100) * 100 = 18%

  Note: Failure rates can be modified by variable (i.e.: API, site of collection, sector, etc...); however, the same approach should be performed.

**Example #3:**

- 100 samples collected. Of these 25 are Artesunate.
- 5 Artesunates failed Confirmatory Testing w/Compendial Methods at NQCL (Level 3).
- Failure Rate for Artesunate = (5/25) * 100 = 20%

  Note: Details of how the data will be presented in the final report should be clearly discussed and defined by the focal points of the study and PQM. This information should be shared with in-country USAID mission before submitting the final report.



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**Discussion**

Discuss the testing results, highlighting their relevance to the main and specific objectives. Specifically, list which medicines failed quality testing and what actions were (or will be) taken by the MRA (alerts, withdrawal or confiscation of product, closing down illegal outlets, etc).

**Recommendations**

Suggest what can be done to improve implementation at the country level:

1. How can we better coordinate between the country and PQM in terms of funding, reporting, etc.?
2. What lessons have we learned? What obstacles have we overcome? What issues have we resolved in the process?
3. Does the MRA, or any other pertinent stakeholder, have any suggestions for improving regulatory actions for non-conforming medicines?

**Conclusion**

Highlight the main results of the MQM project.

**Next steps**

List recommendations for the next round of MQM and timelines for upcoming activities. Attach tables, figures, and annexes, if any.

Note: List the name of the person to contact if information is needed.



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**Annex 8**

**Guide to Establishing a Protocol for Medicine Quality Monitoring**

# Monitoring & Evaluation Tool: Deviations, Changes and Recommendations from Guidelines to Establish an MQM Program

**Deviations from Guidelines**

Please identify any deviations from the PQM guidelines and provide justification:

| Section of Guidelines | Justification |
|---|---|
| | |
| | |
| | |

**Changes in Country Specific Protocol**

Please identify changes that were implemented for subsequent MQM rounds:

| Section of Protocol | Justification |
|---|---|
| | |
| | |
| | |

**Recommendations to Improve Guidelines**

Please provide any relevant recommendations to the Guidelines:

| Section of Guidelines | Recommendation |
|---|---|
| | |
| | |
| | |

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