

Inaugural Building Regional Expertise in Medicines Regulation, Information-sharing, Joint Investigation, and Enforcement (BREMERE) Meeting
Bangkok, Thailand
August 28-29, 2012

Trip Report

Román Pérez Velasco, Consultant, Southeast Asia Activities
Kennedy M. Chibwe, Senior Program Advisor
Souly Phanouvong, Manager, Asia Programs
Maria Kathrina Olivarez, Consultant, Philippines Activities
Siv Lang, Consultant, Cambodia Activities
Vuong Tuan Anh, Consultant, Vietnam Activities

Promoting the Quality of Medicines

Implemented by U.S. Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852 USA

Tel: +66-83-122-6062; +1 301-816-8582

Email: pqm@usp.org and romanperezvelasco@gmail.com

Cooperative Agreement # GHS-A-00-09-00003-00

Funding Source: USAID/PMI-RDMA

Grantee: Promoting the Quality of Medicines (PQM) Program

Author(s) Name: PQM Staff

Language: English

Date of Publication: September 27, 2012



USAID
FROM THE AMERICAN PEOPLE



This report is made possible by the generous support of the American people through the United States Agency for International Development (USAID), under Cooperative Agreement No. GHS-A-00-09-00003-00 and the President's Malaria Initiative (PMI). The contents are the responsibility of the Promoting the Quality of Medicines Program, implemented by the U. S. Pharmacopeia, and do not necessarily reflect the views of USAID, PMI, or the United States Government.

PROMOTING THE QUALITY OF MEDICINES

Executive Summary

PQM convened a regional inaugural meeting of the new initiative, “Building Regional Expertise in Medicines Regulation, Information-sharing, Joint investigation and Enforcement” (BREMERE). BREMERE aims to strengthen regional cooperation between and among the medicines regulatory authorities and law enforcement agencies in the Greater Mekong Subregion (GMS) to improve the quality of medicines. The meeting was held August 28-29, in Bangkok, Thailand.

Representatives of the relevant authorities from Cambodia, Laos, Thailand, Vietnam, Philippines, and Indonesia and of a wide range of international and scientific organizations and academia participated in the meeting. Among them were the World Health Organization (WHO), INTERPOL, United States Agency for International Development (USAID), President’s Malaria Initiative, Worldwide Antimalarial Resistance Network (WWARN), Mahidol and Chulalongkorn Universities, and the U.S. Department of State Lower Mekong Initiative (LMI).

Individual countries presented case studies on the current challenges they face tackling the problem of counterfeit and substandard medicines, in particular with inter-sectoral and inter-country cooperation. The Promoting the Quality of Medicines program, WWARN, Mahidol and Chulalongkorn, and LMI shared their experiences in providing assistance in the field.

The Terms of Reference (TOR) the group drafted encompassed BREMERE’s governance, coordination, implementation, and complementarity with other similar efforts. By the end of the meeting, participants successfully reached a consensus on the TOR, leadership of the initiative, and a timeline for future activities. Agreed-upon BREMERE objectives include:

1. Build capacity through sharing of regional expertise and provision of training and technical/financial support, with a view to creating a regional “pool of experts” who will share information and expertise in medicines regulation, registration, post-marketing surveillance, and enforcement;
2. Strengthen support and collaboration in the field of medicines quality and regulation between political bodies, i.e., Ministries, and technical agencies, such as medicines regulatory agencies and WHO, within each country and throughout the region;
3. Improve the following processes among regulatory/technical agencies and other sectors involved—customs, police, INTERPOL, prosecutors—at national and regional levels:
 - a. Information sharing, e.g., building a database;
 - b. Collective investigation, e.g., reporting alleged counterfeiters to representatives of the claimed countries of origin and agreeing upon procedures; and,
 - c. Enforcement, e.g., improving existing protocols according to best practices.

Source of Funding

USAID/Regional Development Mission for Asia through the President’s Malaria Initiative

TABLE OF CONTENTS

<u>Acknowledgements</u>	3
<u>Acronyms</u>	4
<u>Background</u>	5
<u>Purpose of Meeting</u>	5
<u>Meeting Deliberations</u>	6
<u>Opening Remarks</u>	6
<u>Highlights of Meeting Deliberations</u>	6
<u>Meeting Materials and Sources of References</u>	7
<u>Other Meetings Held</u>	8
Annexes:	
<u>Annex 1: Meeting Agenda</u>	12
<u>Annex 2: Guidelines for Taking Appropriate Enforcement Action</u>	19
<u>Annex 3: Questions for Group Discussion</u>	35
<u>Annex 4: Terms of Reference with Participants' Comments</u>	38

About PQM

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

ACKNOWLEDGEMENTS

We would like to thank:

- Dr. Wayne Stinson, Regional Malaria Advisor, President's Malaria Initiative (PMI)-United States Agency for International Development (USAID)/Regional Development Mission for Asia (RDMA)
- Ms. Sharlene Bagga-Taves, Health Officer, Office of Public Health, USAID/RDMA
- Dr. Aye Aye Thwin, Director, Office of Public Health, USAID/RDMA
- Mr. Christopher Barrett, Deputy Director, Office of Public Health, USAID/RDMA
- Mr. Joseph Taves, Officer, Regional Environment, Science, Technology and Health (ESTH) Hub for East and Southeast Asia, U.S. Embassy to Thailand
- Mr. Rick Switzer, Chief, Regional Environment, Science, Technology and Health (ESTH) Hub for East and Southeast Asia, U.S. Embassy to Thailand
- Dr. Charles Delacollette, WHO Mekong Malaria Programme (MMP)
- Dr. Klara Tisocki, Senior Technical Officer, Essential Medicines and Technology, WHO Western Pacific Regional Office
- Ms. Tammy Chan, Regional Specialized Officer, INTERPOL Bangkok
- Ms. Aline Plançon, Head, Medical Counterfeit and Pharmaceutical Crime Unit, INTERPOL
- Dr. Paul Newton, Head, Antimalarial Quality Group, Worldwide Antimalarial Resistance Network (WWARN)
- Dr. Patricia Tabernerero, Scientific Coordinator, Antimalarial Quality Group, WWARN
- Dr. Darin Kongkasuriyachai, Deputy Chief of Party, Control and Prevention of Malaria Project
- Staff of the Mahidol University School of Pharmacy, especially Dr. Somboon Jateleela, for sharing their ANEQAM experience
- Staff of the Chulalongkorn University Faculty of Pharmaceutical Sciences, in particular Dr. Pintip Pongpech (Dean), Dr. Vorasit Vongsutilers, and Dr. Bodin Tuesuwan, for co-hosting the meeting and presenting their ANEQAM activities
- Country participants from Cambodia, Indonesia, Laos, Philippines, Thailand, and Vietnam for providing their invaluable insight throughout the meeting
- Mr. Anthony Boni and Dr. Maria Miralles, USAID/Washington, for their guidance and support
- PQM's administrative and editorial staff for their assistance

ACRONYMS

ANEQAM	Asian Network of Excellence for the Quality Assurance of Medicines
ASEAN	Association of South East Asian Nations
ASEAN PPWG	ASEAN Pharmaceutical Products Working Group
BDN	Bureau of Drug and Narcotic, Thailand
BREMERE	Building Regional Expertise in Medicines Regulation, Information- sharing, Joint Investigation, and Enforcement
BVBD	Bureau of Vector Borne Disease, Thailand
CSM	Counterfeit and Substandard Medicines
DQI	Drug Quality and Information Program
FY	Financial Year
GFR10	Global Fund Round 10
GMP	Good Manufacturing Practices
GMS	Greater Mekong Subregion
IMPACT	International Medical Products Anti-Counterfeiting Taskforce
KAP	Knowledge, Attitude, and Practice
K.I. Asia	Kenan Institute Asia
MQM	Medicines Quality Monitoring
NIDQC	National Institute of Drug Quality Control, Vietnam
NQCL	National Quality Control Laboratory
PMI	President's Malaria Initiative
PQM	Promoting the Quality of Medicines Program
QA	Quality Assurance
QC	Quality Control
RDM/A	USAID Regional Development Mission for Asia
SFFC	Substandard/spurious/false-labelled/falsified/counterfeit medical products
TOR	Terms of Reference
USAID	United States Agency for International Development
USP	United States Pharmacopeia
WHO	World Health Organization
WHO-RAS	WHO Rapid Alert System
WWARN	Worldwide Antimalarial Resistance Network

Background

The U.S. Agency for International Development (USAID) and U.S. Pharmacopeia (USP) have been providing technical assistance to the Greater Mekong Subregion (GMS) since 1992, first through the USP Drug Quality and Information (DQI) program and, currently, through the Promoting the Quality of Medicines (PQM) program. In the GMS, activities have focused on (1) continuing and maintaining the effective medicines quality monitoring (MQM) sampling and testing techniques to obtain evidence-based data to support decision-making and enforcement action; (2) building the capacity of national quality control laboratories (NQCLs) in quality assurance/quality control (QA/QC) of medicines and toward compliance with ISO 17025:2005 and/or World Health Organization (WHO) prequalification standards; (3) improving the manufacturing practices of local pharmaceutical manufacturers for priority antimalarials; and, (4) raising awareness on poor-quality medicines among the general public at the grass-roots and community levels, as well as among healthcare providers, pharmaceutical industry, and retailers.

In order to strengthen national and regional capacities in medicines regulation, quality assurance, and enforcement, PQM has included among its objectives to support a regional taskforce of country inter-ministerial committees or representatives that would coordinate collective investigation and enforcement between and among countries in collaboration with INTERPOL and IMPACT, when appropriate.

Purpose of Meeting

This two-day meeting inaugurated the “Building Regional Expertise in Medicines Regulation, Information- sharing, Joint Investigation, and Enforcement” (BREMERE) initiative in the GMS. BREMERE aims to create a pool of experts in medicines regulation pertinent to pharmaceutical product registration and post-marketing surveillance, and the implementation of regulatory enforcement measures to address the problem of counterfeit and substandard medicines (CSMs). BREMERE is a component of the Asian Network of Excellence for the Quality Assurance of Medicines (ANEQAM).

The main objectives of this meeting were to:

- 1) Establish a mechanism through BREMERE to encourage information-sharing on CSMs, conduct joint investigations (where applicable), and promote collective enforcement actions within and between countries by involving medicines regulatory authorities, police, customs, prosecutors, WHO, and INTERPOL in the GMS with potential expansion to other countries in Southeast Asia; and,
- 2) Define the roles and responsibilities for the regional BREMERE with clear mandates concerning information-sharing, investigation, and regulatory action, to strengthen regional cooperation and collaboration and fortify each country’s existing enforcement activities.

Meeting Title and Theme

Building Regional Expertise in Medicines Regulation, Information- sharing, Joint Investigation, and Enforcement (BREMERE) Initiative ([Annex 1- Agenda](#))

- BREMERE aims to strengthen regional cooperation between and among the medicines regulatory authorities and law enforcement agencies in the Greater Mekong Subregion (GMS) to improve the quality of medicines.
- Representatives of the relevant authorities from Cambodia, Laos, Thailand, Vietnam, Philippines, and Indonesia and of a wide range of international and scientific organizations and academia participated in the meeting. Among them were the World Health Organization (WHO), INTERPOL, United States Agency for International Development (USAID), President's Malaria Initiative, Worldwide Antimalarial Resistance Network (WWARN), Mahidol and Chulalongkorn Universities, and the U.S. Department of State Lower Mekong Initiative (LMI) attended the Inaugural BREMERE meeting.
- Participants expected to develop specific objectives, roles/functions, governance, implementation, and a system of coordination

Meeting Deliberations

Opening Statements

- Associate Professor Dr. Pintip Pongpech, Dean, Faculty of Pharmaceutical Sciences, Chulalongkorn University
- Dr. Wayne Stinson, Regional Malaria Advisor, PMI-USAID/RDMA
- Dr. Charles Delacollette, Coordinator, WHO- Mekong Malaria Programme (MMP)
- Dr. Kennedy M. Chibwe, Senior Program Advisor, PQM

The honored guests welcomed participants to the BREMERE meeting, and highlighted the importance of the problem of CSMs in the region: their impact on treatment efficacy, safety, development of antimicrobial resistance, and the public's trust in healthcare systems. In addition, participants were encouraged to increase their efforts to combat the presence of CSMs and to work collaboratively.

Highlights of Meeting Deliberations and Presentations

- The collaboration among the different sectors charged with the responsibility of tackling the problem of CSMs is insufficient at the country level and effective cooperation between and among countries is lacking.
- BREMERE should assist in building technical/regulatory capacity in each member country through the provision of training, technical/financial support, and sharing of regional expertise.
- There is a fundamental need to engage political support as well as technical bodies for successful outcome. Therefore, each country should have two BREMERE representatives—one political and one technical.
- There is an urgent need to improve information-sharing, collective investigation, and enforcement action across sectors, both regionally and within countries.

- It is necessary to agree upon a common working definition of “poor quality” medicines, including both counterfeit and substandard medicines, at the regional level.
- The regional BREMERE advisory committee will share information with international initiatives such as INTERPOL, WHO IMPACT, WHO Task Group on Substandard/spurious/falsely-labelled/falsified/counterfeit Medical Products (SFFC), WHO Rapid Alert System (WHO-RAS), WWARN, or ASEAN Pharmaceutical Products Working Group (PPWG), ensuring no duplication of efforts.

Next Steps

- ▶ PQM will incorporate the country participants’ comments into the draft TOR and distribute the revised document (Sept 15 2012);
- ▶ Country participants will provide feedback to PQM on the revised TOR (Oct 30 2012);
- ▶ PQM will incorporate the additional comments provided by country participants (Oct-Nov 2012);
- ▶ PQM will submit the finalized TOR to BREMERE country representatives, who will coordinate with their respective agencies to obtain buy-in and support (Nov 2012);
- ▶ PQM, in collaboration with country partners, will develop an action plan for implementing BREMERE (Dec 2012); and,
- ▶ The BREMERE initiative will be formally launched by convening a face-to-face meeting (Jan 2013).



Meeting Materials and Sources of References

The PQM presentations and working documents, as well as the slide presentations by conference presenters ([Annex 1-Agenda](#)) can be obtained upon request from PQM staff (pqm@usp.org and romanperezvelasco@gmail.com).

Other Meetings

Briefing with PMI-USAID at USAID/RDMA Office– Aug 27, 2012

Participants:

Dr. Wayne Stinson, Senior Malaria Advisor, PMI-USAID/RDMA
Dr. Kennedy M. Chibwe, Senior Program Advisor, PQM
Dr. Souly Phanouvong, Manager, Asia Programs, PQM
Dr. Vuong Tuan Anh, Consultant, Vietnam Activities, PQM
Ms. Siv Lang, Consultant, Cambodia Activities, PQM
Dr. Román Pérez Velasco, Consultant, Southeast Asia Activities, PQM

The PQM team met Dr. Wayne Stinson to:

1. Formally introduce to the Mission the new PQM Regional Project Coordinator, Dr. Román Pérez Velasco;
2. Introduce the PQM team attending the BREMERE meeting;
3. Brief PMI-USAID staff on the BREMERE meeting, including agenda, objectives, and expected outcomes;
4. Briefly update PMI-USAID staff on PQM FY12 regional activities:
 - MQM activities: Global Fund Round 10 (GFR10) with Kenan Institute Asia (K.I. Asia) and Bureau of Vector Borne Disease Control (BVBD), Thailand
 - Comparative survey preparation
 - Myanmar activities
5. Discuss awareness-raising activities with the U.S. Embassy in Laos and with the National Institute of Drug Quality Control (NIDQC) in Vietnam;
6. Submit the proposal for FY13 PQM work plan activities; and,
7. Discuss other topics, e.g., PQM ceiling, interview request for regional documentary film.

Highlights

The inauguration of the BREMERE initiative was welcomed by Dr. Stinson, who agreed on the objectives and accepted the invitation to attend on behalf of PMI-USAID/RDMA.

The PQM team updated him on FY12 activities, in particular:

- The delay in conducting the comparative study of MQM vs. non-MQM sites in Thailand, Laos, Cambodia, and Vietnam, due to competing agendas in target countries;

- The progress of the project on antimalarial medicines quality in malaria clinics and posts with K.I. Asia and BVBD, in which 80% of samples were already collected;
- The efforts to hire a local consultant for Myanmar activities and establish a PQM office;
- The progress with a Knowledge, Attitude, and Practices (KAP) survey of pharmacy staff in Laos to obtain information for the design of awareness-raising materials, in collaboration with the U.S. Embassy; and,
- Recent activities conducted in Vietnam (collaboration with partners) and Cambodia (banning of poor quality drugs).

PQM also provided a brief overview of its FY12 proposed workplan, highlighting the systems perspective taken and the more strategic approach to activities, such as medicines sampling.

Finally, Dr. Stinson informed the PQM team that USAID/DELIVER (JSI) will receive funds to procure necessary equipment for the activities in Burma.

Meeting on GFR10 PQM Technical Assistance with K.I. Asia, BVBD, and Bureau of Drug and Narcotic (BDN) at BVBD Office–August 30, 2012

Participants:

- Ms. Jiranya Ratchinda, Program Manager-Corporate Social Responsibility, K.I. Asia and Focal person for GFR10 implementation
- Ms. Sakolsri Satiyathiwat, Asst. Consultant, Business & Economic Development, K.I. Asia
- Ms. Sansanee Rojanapanas, Technical Officer, Malaria, BVBD
- Ms. Suravadee Kitchakarn, Technical Officer, Malaria, BVBD
- Ms. Sasida Yoosuk, Specialized Quality Control Pharmacist, BDN
- Ms. Withinee Kongsuk, Specialized Quality Control Pharmacist, BDN
- Dr. Kennedy M. Chibwe, Senior Program Advisor, PQM
- Dr. Souly Phanouvong, Manager, Asia Programs, PQM
- Dr. Román Pérez Velasco, Consultant/Regional Project Coordinator, PQM

This meeting was organized to follow up on the implementation of GFR10 PQM technical assistance to monitor the quality of antimalarials at malaria clinics/posts of the 22 high-priority provinces in Thailand. PQM provides technical assistance and monitoring and evaluation to K.I. Asia, which implements activities to strengthen existing mechanisms for the early detection of poor quality antimalarials in order to eliminate artemisinin-resistant parasites.

The objectives of the meeting were as follows:

1. Introduce the working team and their roles;
2. Update the status of lab testing by BVBD and BDN;
3. Discuss the next steps—testing results, report, meeting in the next financial year;
4. Discuss logistics and administrative work; and
5. Discuss other issues.

Highlights

The group reviewed the progress of the project—plan for testing, number of samples, way to proceed with primaquine samples—and agreed upon the next steps as follows:

- BDN will provide information on their medicines testing cost structure and capacity (Sept 10, 2012);
- BVBD will collect results (Sept/Oct 2012);
- K.I. Asia will draft a request for committed activity budget increase in Quarter 2 to Global Fund;
- PQM will meet with BDN to discuss a budget for testing and a format for the certificate of analysis (mid-Oct 2012); and,
- BVBD will give presented documents, sample collection forms, and Minilab[®] testing report forms to PQM for review (Sept 15, 2012).

Finally, it was agreed to give a small stipend to the BVBD staff for the additional administrative support they have been providing for this project and to possibly hire administrative support for the PQM staff in Southeast Asia to help coordinate the project.

Meeting on ANEQAM activities with the Dean and key staff at the Faculty of Pharmaceutical Sciences, Chulalongkorn University–September 24 and 31, 2012

Participants:

Dr. Pintip Pongpech, Dean, Faculty of Pharmaceutical Sciences, Chulalongkorn University
Dr. Vorasit Vongsutilers, Head of Medicinal Analytical & Pharmaceutical Chemistry
Research Unit, Faculty of Pharmaceutical Sciences, Chulalongkorn University
Dr. Bodin Tuesuwan, Deputy Head of Medicinal Analytical & Pharmaceutical Chemistry
Research Unit, Faculty of Pharmaceutical Sciences, Chulalongkorn University
Dr. Kennedy M. Chibwe, Senior Program Advisor, PQM
Dr. Souly Phanouvong, Manager, Asia Programs, PQM
Dr. Román Pérez Velasco, Consultant for Southeast Asia Activities, PQM

The objectives of the meetings were as follows:

1. Discuss the implementation plan for collaborative activities in FY13;
2. Discuss potential work for FY12 to promote ANEQAM in the region (e.g., fingerprint library for profiling counterfeit antimalarials in the region);
3. Visit the Pilot Manufacturing Unit at the Faculty;
4. Discuss the BREMERE meeting, thank the Faculty for co-hosting the meeting, and discuss the possibility of a Thai partner (either Thai FDA or the Faculty of Pharmaceutical Sciences) to be the first BREMERE co-Chair.

As in the previous meeting, the Dean spoke highly of the PQM team, recognizing them for their work, to which the PQM team expressed their appreciation.

Annexes

Annex 1: Meeting Agenda

Annex 2: Guidelines for Taking Appropriate Enforcement Action Against Substandard and Counterfeit Medicines

Annex 3: Questions for Group Discussion

Annex 4: Terms of Reference, with Participants' Comments



Building Regional Expertise in Medicines Regulation, Information-sharing, Joint Investigation, and Enforcement

**An Inter-sectoral Initiative for the Greater Mekong Sub-region
August 28-29, 2012 ♦ Novotel Bangkok on Siam Square ♦ Bangkok, Thailand**

Tentative Agenda

Day 1: August 28, 2012 (Tuesday)

Time	Topic	Presenter	Moderator
8:00-8:30	Participant Registration	All	Bodin Tuesuwan
8:30-9:00	Welcome and Opening Remarks	Chula FPS: Dean Pintip Pongpech USAID: Wayne Stinson or Christopher Barrett WHO: Charles Delacollette PQM: Kennedy Chibwe	
9:00-9:30	Overview of medicines quality situation in Mekong Sub-region	Souly Phanouvong	Narueporn S.
9:30-9:50	Brief overview of ANEQAM and Introduction to BREMERE (aim, objectives, roles/functions, coordination)	Souly Phanouvong	
9:50-10:30	ANEQAM recent activities related to QC area ANEQAM recent activities related to GMP	Chula FPS Mahidol FPS	
10:30-11:00	Group photo and coffee break	All	
11:00-11:30	WHO Rapid Alert System, Updates [via call-in]	WPRO Representative	
11:30-12:00	WWARN Drug Quality Surveyor Database	Paul Newton	
12:00-13:00	Lunch	All	

13:00-15:00 [30 mins each]	Country presentations: Case studies and current challenges in inter-sectoral and inter-country cooperation on tackling the problems of counterfeit and substandard medicines	Cambodia Laos Myanmar Philippines	WHO or USAID
15:00-15:30	Coffee break	All	
15:30-16:30 [30 mins each]	Country presentations: Case studies and current challenges in inter-sectoral and inter-country cooperation on tackle the problems of counterfeit and substandard medicines	Thailand Vietnam	
16:30-17:00	The Lower Mekong Initiative and Counterfeit Medicines	U.S. State Dept. Representative	
17:00-17:15	Wrap-up and planning for Day 2 discussions	PQM	

Day 2: August 29, 2011 (Wednesday)

Time	Topic	Presenter	Moderator
8:30-10:00	<ul style="list-style-type: none"> • Presentation on draft BREMERE T.O.R and Coordination Mechanism • Focused discussion: <ol style="list-style-type: none"> 1. T.O.R, organizational structure (secretariat, appointment of focal points for each working group: e.g., evidence data verification, investigation, initiation of enforcement); governance; operation mechanism (coordination, communication, cooperation); and funding. 2. Activities, with clear mandate on communication and coordination protocols 3. Implementation issues at national and regional levels (could be discussed further in the small group sessions); complementarity with other regional and international efforts (e.g., INTERPOL, FSP, and LMI) 	All	PQM presents
10:00-10:30	Coffee break	All	
10:30-12:00	Small group inter-sectoral discussions by country on practical implementation of BREMERE activities, confidentiality issues, data-sharing, joint investigations	Group break-out discussions	To be elected by each group a moderator and a rapporteur
12:00-13:00	Lunch	All	
13:00-14:00	Continued discussion and drafting from above	Group break-out discussions	

14:00-15:00	Convene plenary session and brief presentation from groups		
15:00 -15:30	Coffee break	All	
15:30-17:00	<ul style="list-style-type: none">• Incorporation of small group comments in the draft on implementation issues• Consensus on adoption of BREMERE's organization, governance, roles and responsibilities, TORs, annual planned activities	All	
17:00-17:15	Meeting wrap-up, next steps	PQM	

Guidelines for Taking Appropriate Enforcement Action Against Substandard and Counterfeit Medicines

June 4, 2010

Cooperative Agreement # GHS-A-00-09-00003-00
Sponsoring USAID Missions: USAID/Cambodia
Grantee: Promoting the Quality of Medicines (PQM) Program
Author(s) Name: PQM Staff
Language: English
Date of Publication: June 4, 2010



This report is made possible by the generous support of the American people through the United States Agency for International Development (USAID), under Cooperative Agreement No. GHS-A-00-09-00003-00. The contents are the responsibility of the Promoting the Quality of Medicines Program and do not necessarily reflect the views of USAID or the United States Government.

1. ACKNOWLEDGEMENTS

PQM would like to express sincere thanks and appreciation to the following experts and country officials who provide inputs to this final document:

- Dr. Somthavy Changvisommid, Director General, Food and Drug Department, Ministry of Health, Lao PDR.
- Dr. Sivong Sengaloundeth, Deputy Director, Food and Drug Department, Ministry of Health, Lao PDR.
- Dr. Heng Bunkiet, Director, Food and Drug Department, Ministry of Health, Cambodia.
- Mr. Tey Sovannarith, Chief, Technical Division, National Health Product Quality Control Laboratory, Cambodia
- Mr. Som Sam Nang, inspector, Food and Drug Department, Ministry of Health, Cambodia.
- Dr. Chheang Sena, Deputy Director, Provincial Health Department of Kampong Cham, Cambodia.
- Ms. Mam Boravann, Project Coordinator, National Center for Parasitology, Entomology and Malaria Control, Ministry of Health, Cambodia.
- Mr. Aphichai Hoonchamlong, Chief of Inspectorate Unit, Drug Control Division, FDA, Ministry of Public Health, Thailand.
- Ms. Ms. Saowanit Vijaykadga, Senior Technical Officer, Malaria Cluster, Bureau of Vector Borne Diseases Department of Disease Control, Ministry of Public Health, Thailand.
- Mr. Trinh Ngoc Hai, Chief, Pharmaceutical Division, Institute of Malariology, Parasitology, Entomology, Ho Chi Minh City, Vietnam.
- Assoc. Prof. Dr. Sauwakon Ratanawijitrasin, Faculty of Social Sciences and Humanities Mahidol University & Pharmaceutical System Research & Intelligence Center, PhaReD Foundation, Thailand
- Ms. Nguyen Thi Hoang Lien, Deputy Director, National Institute of Drug Quality Control, Ministry of Health, Vietnam.
- Ms. Maria Lourdes C. Santiago, Chief, Laboratory Services Division, Food and Drug Administration, Ministry of Health, Philippines.
- Ms. Rosario D. Dalangin, Food & Drug Regulation Officer III, Food and Drug Administration, Ministry of Health, Philippines.

Our thanks and gratitude go to the following staff of the United States Agency for International Development: Mr. Anthony Boni, Dr. John MacArthur, Mr. Jonathan Ross, Ms. Kate Crawford, Dr. Aye Aye Thwin, Dr. Chansuda Wongsrichanalai, Dr. Corazon Manaloto, and Dr. Chantha Chak.

2. INTRODUCTION

It is common knowledge that substandard and counterfeit medicines (SCMs) can cause serious harm and even death. They contribute to treatment failure, prolonged hospitalization and treatment and, in some cases, may lead to the emergence of microbial drug resistance. Consequently, these medicines waste already-scarce financial resources—at both governmental and individual levels—that could have been used to address other priority health issues.

3. BACKGROUND AND RATIONALE

One main objective of the Promoting the Quality of Medicines (PQM) program is to strengthen the quality assurance systems of national medicines regulatory authorities (MRAs), enabling them to combat the availability of SCMs. In achieve this goal in various countries, with financial support from the United States Agency for International Development (USAID), PQM has provided technical assistance to establish medicines quality monitoring (MQM) programs in selected sentinel sites in each of the countries in the Greater Mekong Subregion. These activities serve to obtain evidence-based data on the quality of essential medicines. This data will support administrative and, more importantly, regulatory actions. PQM's determination to reduce the availability of SCMs in the region has contributed tremendously to the strategic objectives of USAID, World Health Organization (WHO), and other partners to address multi-drug resistant malaria, tuberculosis, and HIV/AIDS.

In the past, each MRA in the region has strived to take action on SCM cases found from routine post-marketing surveillance and MQM activities. Help from other law enforcement agencies, such as police and customs officers, is crucial to these efforts. The effectiveness of the actions and the swiftness of with which they are taken varies from one country to another. Among the key challenges faced in carrying out actions are: (a) vague definitions and legal provisions regarding counterfeit medicines; (b) lack of appropriate power, authority, capacity, and resources; and, perhaps most notably, (c) inadequate procedural instructions and practices for an MRA to follow in order to take action.

International organizations and programs—such as PQM, WHO, INTERPOL, Wellcome Trust Foundation, and others—have observed that MRAs in different countries have been slow to act and have not done enough to address the problems of SCMs in their respective countries. In addition, the lack of inter-country alerts or communication when SCMs are detected remains a significant barrier to effective reduction of these products. Inadequate institutional, financial, technical, and human resources among MRAs in many developing countries, including those in the Greater Mekong Sub-region, restrict MRAs in their ability to safeguard the quality, safety, and efficacy of medicines in the market. Further, combating the transnational trade in SCMs requires interventions at regional and international levels as well, which requires coordination and cooperation among national authorities, relevant regional mechanisms, international organizations, and other stakeholders.

4. AIM AND SCOPE OF GUIDELINES

This document is generically designed to be adapted as needed by individual countries in a manner that complements their existing regulatory procedures and practices concerning

enforcement on SCMs, regardless of postmarketing surveillance activities. The primary target audience includes MRAs and police and customs officials dealing with pharmaceutical trade regulation and enforcement.

The scope of these guidelines explains the background and rationale and suggests a step-by-step course of action for MRAs and other key stakeholders at all levels to enable swift and effective administrative and regulatory actions if a substandard or counterfeit medicine sample is suspected. Suspected samples may originate in routine postmarketing surveillance or from medicine quality monitoring mechanisms within a given country.

5. REPORTING AND ENFORCEMENT PROCEDURES

In areas where sampling and testing is routinely conducted, procedures are already in place on what actions should be taken when a collected sample looks suspicious. It is *imperative* that the sentinel site staff conduct basic tests on **all** suspected samples immediately after collection or detection, **within twenty-four to forty-eight (24-48) hours** (1-2 working days). If test results on **any sample exhibit the characteristics described in Box 2** below, the sentinel site staff should send the sample to the national quality control laboratory (NQCL).

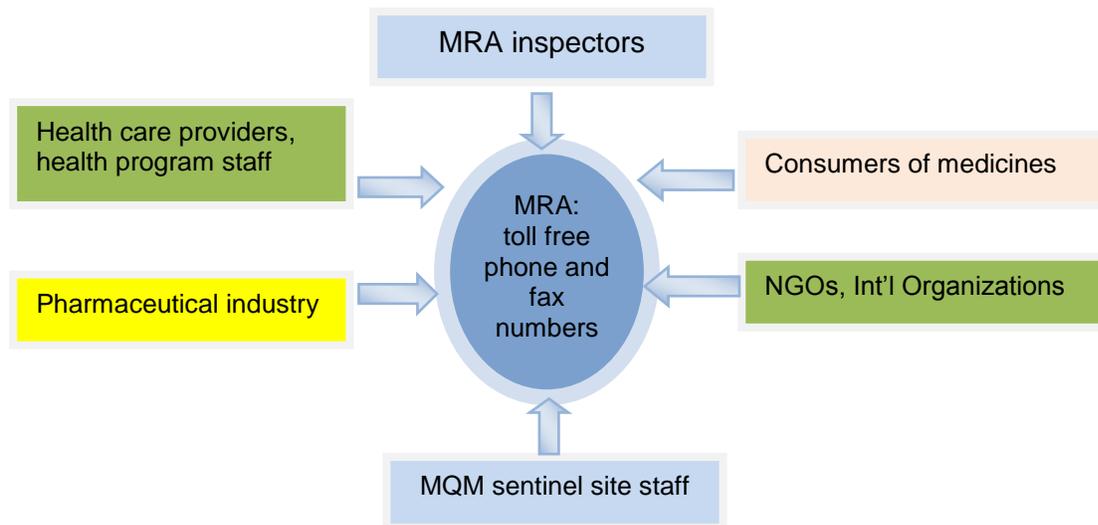
Where basic testing facilities are unavailable—in most inspection cases that occurs in areas outside the MQM sentinel sites—the suspected samples should be sent directly to the regional laboratory or NQCL for complete analysis. In countries where the pharmaceutical sector and control authority system is decentralized, police, customs, and provincial inspectors may send samples directly to the regional lab or NQCL for testing, bypassing the national MRA. The regional lab or NQCL can then send test results to regulatory agencies at both the national and provincial levels for timely enforcement action.

Reporting of suspected poor-quality medicines should not only be the responsibility of MRA personnel, but rather should also include:

- All healthcare providers in both public and private sectors—general practitioners, hospital and health center clinicians, pharmacists, nurses, and paramedics
- Health programs personnel—disease program officers and non-clinician public health staff
- Pharmaceutical industry—manufacturers, importers, distributors/wholesalers, retail pharmacy outlet attendants
- Non-governmental organizations (NGOs) and international organizations
- Medicine quality monitoring sentinel site staff
- Consumers and the general public.

These individuals have a legal, moral, or professional obligation to report any and all suspected medicines to the appropriate authorities—national, provincial or district MRA personnel (Figure 1).

Figure 1: Illustration of Key Stakeholders in Reporting of Suspected Medicines



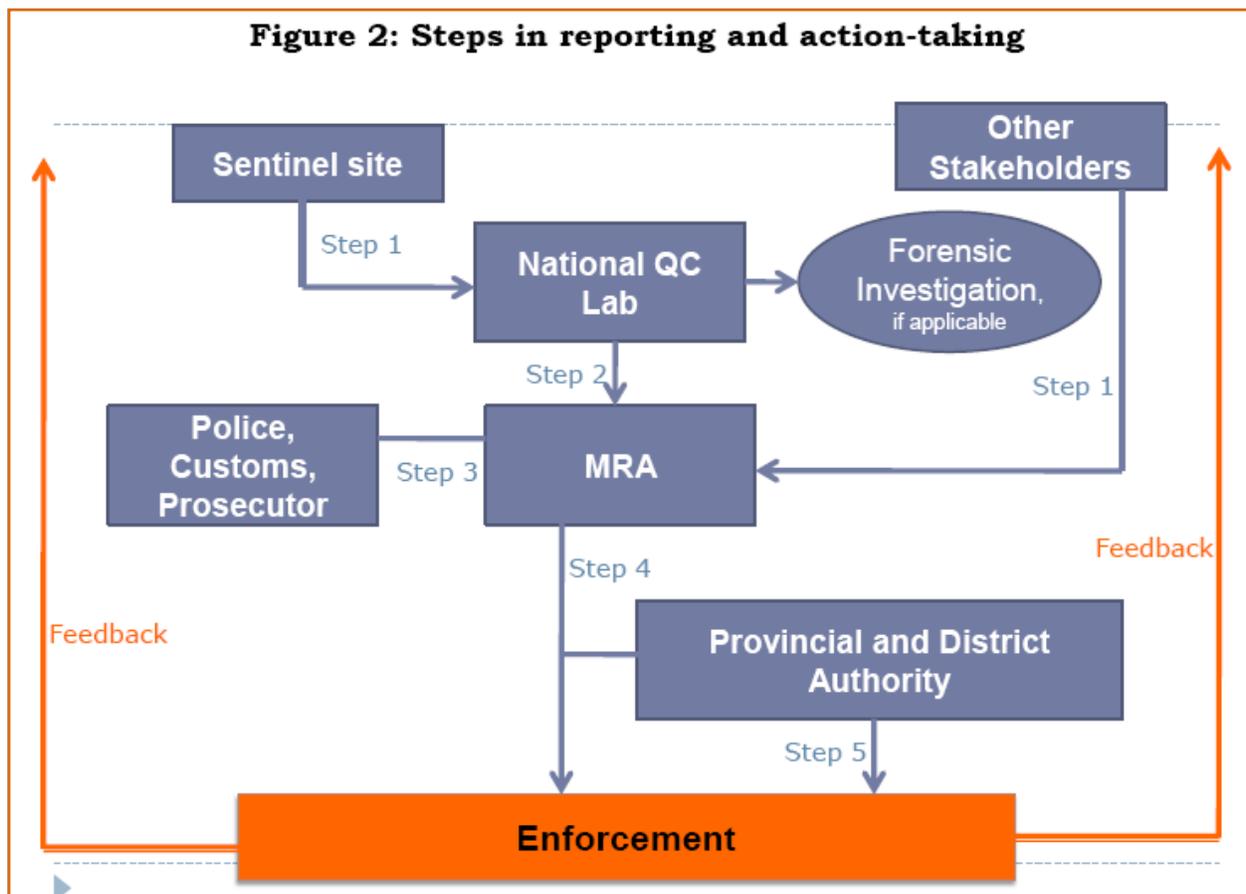
It is strongly recommended that the MRA provide toll-free telephone and fax numbers so that all stakeholders can easily report suspected pharmaceutical products. While reporting can be done anonymously, the individual or organization reporting a suspected product should provide the key information listed in Box 1 to the authorities.

Box 1: Key Product Information to Report

1. Name of the product: both the brand name and generic names (INN)
2. Name and address of manufacturer as claimed on the label, if available
3. Description of physical appearance
4. Lot/batch number, if applicable
5. Dosage form
6. Registration number, if applicable
7. Manufacturing and expiry dates, if applicable
8. Name of importer, distributor or wholesaler, if applicable
9. Location where the sample was found/seen/sold/obtained; and
10. Indication whether or not the sample was in its original packaging, if applicable.

The sections below describe the procedural steps that the MQM sentinel site staff and the MRA inspectors need to take when reporting suspected medicines samples, as illustrated in Figure 2.

Reporting suspected medicines



Step 1: It is critical that sentinel sites in the field report all quality defects or suspected counterfeit and substandard samples to the regional or national QC lab by following these procedures:

- **Immediately¹ [within twenty-four (24) hours]** after obtaining the basic test results for those samples that are highly suspected of having quality defects. These samples can be classified as ‘*critical quality defect*’ which are potentially life threatening or could cause serious risk to health and fall under any of the characteristics stated in Box 2.
- **Within forty-eight (48) to seventy-two (72) hours [two-three (2- 3) working days]** after obtaining the basic test results for those samples that are classified as ‘*major quality defects*’ which could cause illness or mistreatment but are not life-threatening. Examples are: 1) Incorrect labeling; for example, wrong or missing text or figures; 2) Missing or incorrect information on the packaging label, leaflets, or package inserts; and 3) Microbial, physical or chemical contamination with potential medical consequences.

¹ In many countries, an effective method to ensure immediate attention/action by authorities is to “stamp” the cover page of the request with “*Urgent*” or “*Priority*.”

- **Within ninety-six (96) to one-hundred-twenty (120) hours [four-five (4-5)] working days]** after obtaining the basic test results for those samples that are classified as ‘*minor quality defects*’ which are not likely to pose a significant hazard to health. These may include 1) faulty packaging, for example, wrong or missing batch number or manufacturing or expiry date; 2) faulty closure; and 3) breaking capsules.

Box 2: “Critical Quality Defect” Characteristics

1. No active pharmaceutical ingredient(s) (APIs); and/or,
2. Incorrect or wrong API(s); and/or,
3. API(s) content greater than one hundred twenty per cent (120%) or less than eighty per cent) 80%² (based on observation of the TLC spot intensity); and/or,
4. Failed visual and/or physical inspections, including packaging and labeling, suspicion of being counterfeited; and/or ,
5. Failed simple disintegration and/or,
6. Illegal or unregistered (no legal registration number on label); banned and/or previously recalled/withdrawn products.³

Upon receiving the samples, the regional lab or NQCL conducts confirmatory analysis. The samples should be submitted with as much information as available. (See Annex A-1: Sample Collection Form; Annex A-2: Basic Test Analysis Form; and, Annex A-3: Test Request Form.)

The same procedure should be applied to suspect samples collected from routine inspections and/or targeted investigations by the MRA inspector(s). In such cases, submission of sample(s) and necessary information should come from the respective inspector(s) or the inspectorate division.

Step 2: The NQCL (or MRA’s contract QC Lab) must assign top priority to analysis of the suspected samples submitted by performing the confirmatory analysis ***within seventy-two (72) to one-hundred-twenty (120) hours [three to five (3-5) working days]***. Note that if additional quantity/volume of the sample is needed for testing, the NQCL should ask the sentinel site to collect more, or the MRA inspector(s) themselves should travel to the original sampling location to collect additional samples. At least fifty to one hundred (50-100) additional units per sample of the suspected product should be collected from the same batch, and if applicable, from the same location. Funds should be taken from the MRA or donor sponsor for these samples for both the price of the collected sample and

² Most countries in the Mekong Subregion consider that less than 80% and more than 120% API content classifies a pharmaceutical product as counterfeit or substandard. If API content is lower than the minimum or higher than the maximum standards prescribed in the formula registered with the MRA by more than 20%, the sample is classified as counterfeit. If the API content is between 80.10% and 119.90%, the sample is defined as substandard, assuming that all other quality characteristics are in compliance with the specifications.

³ To ascertain and confirm that a medicine product is illegal or unregistered, banned and/or previously recalled or withdrawn, the sentinel site staff should contact the relevant division of the MRA, e.g., Registration Division or Section.

the cost of the analysis. Depending on the confirmatory test results, the steps to be done by the QC Lab should be as follows:

1. If confirmatory test results from the NQCL determine that the sample is nonconformant with quality specifications **and** that they can be characterized as “critical” based on Box 2, the NQCL (or MRA’s contract QC Lab) **must immediately submit** a report of findings and send it with the Certificate of Analysis (CoA) to the appropriate section of the MRA to alert them for further action as necessary. If available, the QC lab should also send a sample of the medicines analyzed along with the CoAs to the national MRA **within twenty-four (24) hours**. The QC lab should retain a sample of the tested medicine, stored under proper conditions, for future reference.
 - For those samples that can be classified as having “major quality defects” or “minor quality defects,” the same procedures should be followed under Step 1 above.
 - Passed samples should be retained for six (6) months. Failed samples, on the other hand, should be retained for at least eighteen (18) months.

If the non-conformant sample involved is a genuine pharmaceutical product which failed established quality specifications (terms of API content, it should not be lower than the minimum or higher than the maximum allowable specifications by 20%), the sample should be classified as substandard.⁴ The follow-up regulatory action, in this case, will differ slightly from the above procedure: the QC Lab should prepare the report of findings and submit it to the national MRA within **two to three (2-3) working days**, along with the CoA.

Box 3: Key information to Provide to Law Enforcement Authorities

1. Name of the product both brand and INN
2. Name and address of manufacturer as claimed on label, if applicable
3. Lot/batch number, if applicable
4. Dosage form
5. Registration number, if applicable
6. Manufacturing and expiry dates, if applicable
7. Name of importer, distributor or wholesaler, if applicable
8. Sampling location where samples were collected, if applicable
9. Final conclusions of confirmatory analytical results, reasons for sample failure; and
10. A sample of the actual sample in its original packaging, if available

2. If the confirmed results from the QC Lab show that the sample conforms with established standard specifications (highly unlikely considering all the characteristics

⁴ A substandard medicine is a legally branded or generic pharmaceutical product produced by an authorized/licensed manufacturer that does not meet official standards for identity, quality, purity, strength, packaging, and labeling.

described in Box 2), the QC Lab can report the results to the MRA on a regular or routine basis (monthly, quarterly, etc.). The QC Lab, however, should provide feedback on the confirmatory results to the respective sentinel site(s) and/or inspector(s) who initially submitted the suspected samples for QC testing either by telephone, email, facsimile, and/or by post-mail.

Step 3: Once the QC test results are received by the relevant MRA division (in most countries this is the Medicine Control Division), the findings should be ratified against the technical and legal requirements and a formal notice with key information prepared, as in Box 3. The MRA should subsequently communicate with relevant law enforcement agencies, such as customs, police, and prosecutors, who would then determine the appropriate enforcement actions. In countries where MRAs have full power and authority, Step 3 will not be applied. In other settings, there may be an Inter-Ministerial Committee at the central level that might issue regulatory orders or notices for national enforcement actions.

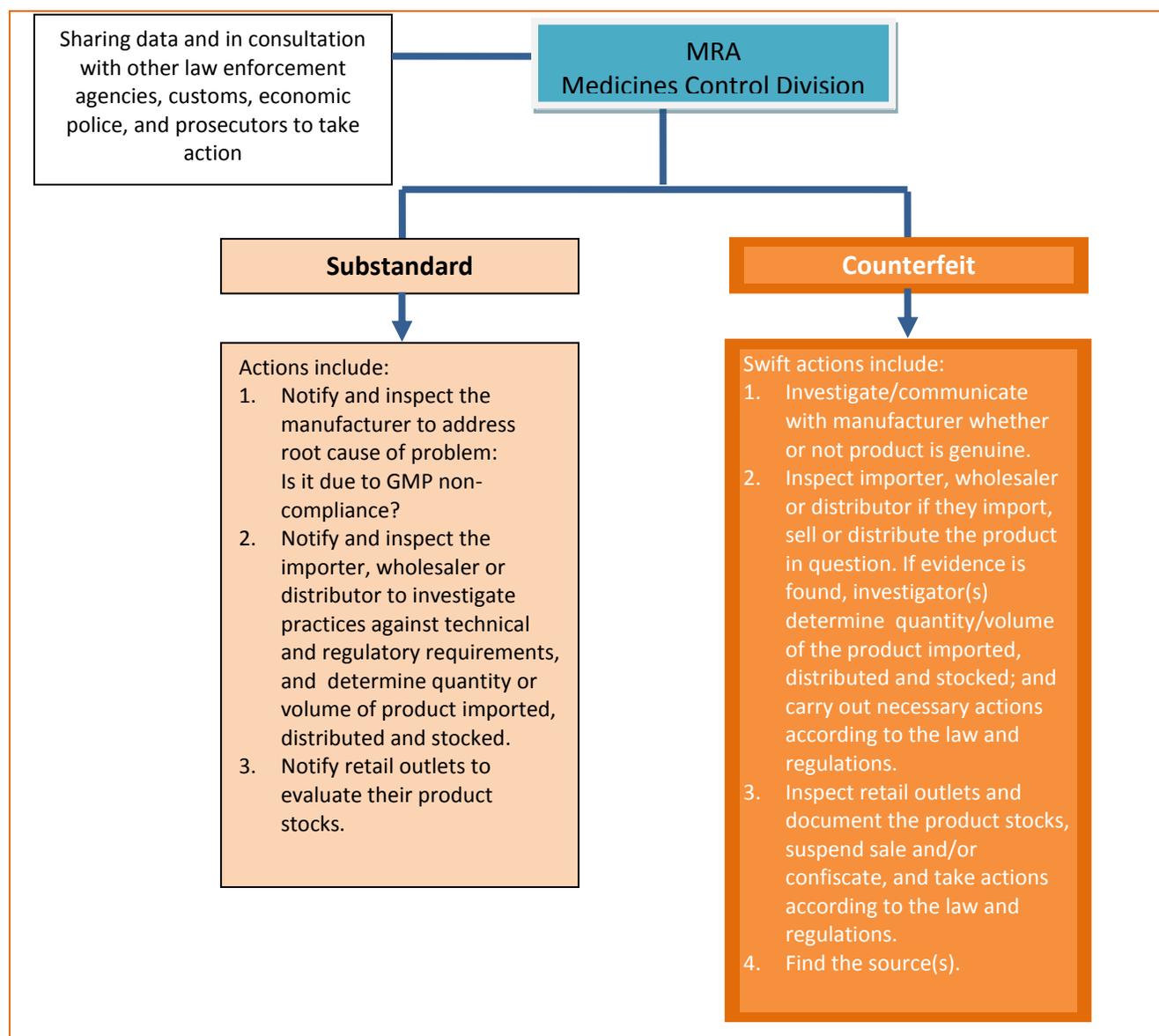
Step 4: Once the MRA has arrived at a decision (in close consultation with the Inter-Ministerial committee or involved stakeholders), the responsible MRA division issues an official regulatory notice, circular, or executive order with credible information, as described in Box 3, to relevant sub-national, municipality, or provincial level MRAs to take action. If the suspected product is found in multiple provinces or transnationally, the national MRA should conduct the follow-up, coordinating with MRAs from other countries where the product has been discovered. There are two possible algorithms for enforcement actions to be taken which depend on findings as described in Figure 3 below.

What action is taken for a confirmed substandard product depends on the seriousness of the quality defect and the potential impact to patient health. The defect may be classified into three categories—critical, major, or minor—depending on country regulations. Each category has procedures and criteria for action; however, in this document, the simplified approach can be adapted and used to streamline the enforcement process according to the defined criteria described in Step 1 above.

Step 5: If, following receipt of enforcement orders, the enforcement actions are not carried out directly by the national level, the sub-national, municipality, or provincial authorities must coordinate with appropriate law enforcement agencies (investigation teams) to immediately take action by investigating the case(s) in close collaboration with respective authorities at the district level. Investigations may involve police, customs, and other law enforcement officers, if necessary.

Feedback: The investigation team (either at provincial or district levels) must report investigation results to the superior level of authority *within forty-eight to seventy-two (48-72) hours [two to three (2-3) working days]*. For example, the district investigation team must report its outcomes/findings to the provincial authority. Findings and a report on actions taken by the investigation team must be submitted by the provincial level authority to the central or national MRA.

Figure 3: Investigation on confirmed substandard or suspected counterfeit medicines



Transnational MRA Coordination: For substandard or counterfeit products which are known to have foreign origins, MRAs should develop protocols for direct follow-up between countries in accordance with national legislation for data sharing, intellectual property laws, etc. This mechanism should involve PQM reporting and/or the WHO Rapid Alert System, as available. For Association of Southeast Asian Nations (ASEAN) member countries, substandard medicinal products may be reported through the Post Marketing Alert System.

5. ENFORCEMENT ACTIONS

Each country will have legislative and regulatory sanction requirements pertinent to administrative and enforcement actions against violators that manufacture, distribute, and/or sell

substandard and counterfeit medicines. Depending on the nature of the violation in each case, the following sanctions are commonly applied by most MRAs:

1. Initial warning requiring violator(s) to meet with MRA officials to receive general education and specific information about the violation and to sign an agreement ensuring that a similar incident will not occur in the future;
2. Warning notice, levy of fines, and confiscation and withdrawal of offending product;
3. Levy of fines and suspension or revocation of market authorization license or registration certificate, confiscation of offending products, and closure of outlet/pharmacy;
4. Levy of fines and suspension or revocation of manufacturing license and GMP certificate, confiscation of products and closure of manufacturing plant;
5. Prosecution according to the national law and regulations; or
6. All of the above and imprisonment or appropriate punishment.

6. REPORTING ENFORCEMENT ACTIONS TO PQM AND INTERESTED PARTIES

PQM requires that country MRAs submit reports on a regular basis, preferably quarterly, regarding any regulatory enforcement actions taken in their respective country by the MRA and/or other law enforcement agencies on all actions that occur as a result of data obtained from PQM-supported activities (monitoring, support, etc). The report helps PQM to present the case and provide justification to donor(s) for future financial support to address the problems of substandard and counterfeit medicines. PQM is also interested in obtaining information on enforcement measures taken as a result of other organizations' programs, such as investigations or seizures by police, customs, etc., which are deemed relevant.

The report on regulatory enforcement should be included in routine MQM reporting and should contain detailed testing results, progress, achievements, challenges and issues encountered, lessons learned, and suggested solutions from each round of MQM activities. (See Annex 4: MQM Guidelines for further details). Responsible PQM staff will work closely with each country's MRA on data and report dissemination to interested audiences at regional and international levels.

7. CONCLUSION

Timely follow-up and reporting through the correct channels is essential for successful enforcement actions when substandard or counterfeit medicines are found in national health programs or in the marketplace. Lack of quick follow-up or action can lead directly to increased public exposure to dangerous medicines, impacting public health, health expenditures, and a loss of consumer confidence in health care systems. Coordination and cooperation among stakeholders at multiple levels and bureaus within the Ministries of Health is a vital aspect of a successful medicine quality monitoring system and medicines quality assurance network. Ensuring public health through provision of good-quality medicines depends on each link in the chain extending from the consumer to the highest levels of relevant Ministries. This document is intended to streamline the processes of reporting enforcement actions for MQM and routine MRA postmarketing surveillance for long-term sustainability and commitment for all involved in the quality assurance of medicines.

Annex A-1

**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 (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: <ul style="list-style-type: none"> • Type of package (blister pack/card, bottle, others specify) • Number of units/pack • Presence of insert/leaflet 	
Check one:	<input type="checkbox"/> taken in original package <input type="checkbox"/> 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.

Annex A-2

**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

Have any corrections and/or additions been made to Sample Collection Form (Annex 2):

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: DISINTEGRATION²

Time of observed disintegration (minutes)	Did the drug pass the disintegration test?	
1. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	
2. _____		
3. _____		

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.

TEST 3: TLC	
<p>Did the sample have a spot?</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>Rf Standard: _____</p> <p>Rf Sample: _____</p> <p>Rf % Sample difference ³</p> <p>_____</p>	<p>Intensity of sample spot compared to standard:</p> <p><input type="checkbox"/> Less than 80%</p> <p><input type="checkbox"/> Between 80 – 100%</p> <p><input type="checkbox"/> More than 100%</p> <p>_____</p> <p>Were there any contaminants/impurities present?</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>Observations:</p>
FINAL RESULTS	
<p><input type="checkbox"/> The sample conformed with basic tests</p> <p><input type="checkbox"/> The sample did not conform with basic tests (Reason: _____)</p> <p><input type="checkbox"/> The sample is considered doubtful (Reason: _____)</p> <p>How many units are remained after basic tests: _____</p>	
<p><u>REPORT REVIEWED BY⁴:</u></p> <p>Date: _____</p> <p>Name: _____</p> <p>Signature: _____</p>	

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 = ((| 0.55 - 0.57 |) / 0.55) x 100 = (0.02/0.55) x 100 = 3.6 %

⁴ If applicable

Test Request Form

Request submitter:	For National Lab Use Only
Contact details: Telephone: Fax: Email: Street address:	Project or Receipt Number:
	Receiving Officer:
	Date:
Date of request:	
Type of request: (check where applied)	
<input type="checkbox"/> Verification testing <input type="checkbox"/> Confirmation testing <input type="checkbox"/> Others (specify).....	
Tests request for: (check where applied) <input type="checkbox"/> Identification of active ingredient(s) (API)(s) <input type="checkbox"/> Dissolution <input type="checkbox"/> Assay for content of active ingredient(s) (API)(s) <input type="checkbox"/> Others (specify).....	
Suggested Method to be used (check where applied) <input type="checkbox"/> International Pharmacopeia (specify Edition number or Year) <input type="checkbox"/> U.S. Pharmacopeia (specify Edition number or Year) <input type="checkbox"/> Other (specify).....	
Desired Completion Date:..... Provide reasons for the date:.....	
Attachments and/or materials provided with this Request Form: <input type="checkbox"/> Samples (if more than one sample, attach a separate list of the samples with names and other details e.g. sample code) <input type="checkbox"/> Sampling Receipt Form(s) <input type="checkbox"/> Others (specify).....	
Please send invoice/bill of testing charge to:..... Telephone: Fax: Email: Street address:	

Questions for Group Discussion

1. Structure:

Are any modifications/changes necessary to the proposed BREMERE Structural Formation? Refer to Figure 1 in the 'Working Document' or 'Presentation'

If any, please specify and give reasons.

2. Goal and objectives:

Goal:

Objectives:

3. Representation:

a. Country Representative to be a BREMERE member:

1. Political representative or technical representative?
2. Should the country representative be the same person who currently serves as INTERPOL focal point?
3. Should the country-appointed representative serve at both the regional and national levels to coordinate BREMERE activity implementation? Or
4. Should there be a separate appointed person to coordinate at the country level?
5. If yes to Question 3, then discuss the following.

b. Country Focal Points for BREMERE Activities at Country Level (Country BREMERE Team)

Single individual or team? Suggest a team with representatives from each of the following agencies with the MRA representative playing the coordinating role:

1. MRA
2. Police
3. Customs
4. Prosecutor?

Provide briefly the reasons:

4. Reporting and Feedback mechanism between Countries and BREMERE

Figures 2 and 5

Any comments/suggestions on the process (Figures 3, 4, and 5), what information (Boxes 1 and 2) and who should report to whom?

- a. Within a country
 - On *highly suspected cases* of poor-quality medicines requiring timely action

 - *On regular cases*
- b. Between two countries:
 - What, when, and who
- c. Between country and BREMERE (Figure 5)
 - What, when, and who

5. BREMERE and Its Partners: Data-sharing and Dissemination

- a. Beyond BREMERE countries? (**Figure 6**) and with partners, including the
 1. INTERPOL
 2. WHO IMPACT and SSFC
 3. WHO RAS
 4. WWARN
 5. Others?
- b. Submit information to WHO Regional Alert System (RAS); **How** will this be done and **who** will facilitate this? (Figure 6)
- c. Make data and final outcomes of the investigation available on countries MRA websites and perhaps USP's MQDB, as well as WHO IMPACT and the EDQM, and/or WWARN?

6. Additional questions for discussion:

- a. To ensure regular and effective coordination and continuity of the operation of BREMERE, it is suggested that BREMERE have a Chairperson with a two-year term. The Chairperson would be selected by member countries' representatives and the chairmanship rotated every two years among the GSM countries, while the Philippines and Indonesia could join as associate members or observer.

QUESTION:

Would this option be acceptable?

- b. The USP PQM program (and other potential partners and donors) will provide technical assistance and limited financial support for the first two to three years of BREMERE operations.

Question:

Would the countries be able to gradually include BREMERE activities in their annual and/or strategic operational plans for government support?

ANNEX 4

Building Regional Expertise in Medicines Regulation, Information Sharing, Joint Investigation and Enforcement: An Inter-sectoral Initiative for the Greater Mekong Sub-region in an Effort to Address the Poor-Quality Medicines

PROPOSED TERMS OF REFERENCE—with meeting comments incorporated; to be finalized after the draft is circulated among participants for additional feedback.

1. What is BREMERE?

- a. Is a mechanism to strengthen regional cooperation and collaboration in monitoring the quality of medicines and addressing poor-quality medicines— this will be done to support national/regional efforts in containing their adverse effects to public health and preventing the spread of resistance of malaria, tuberculosis and other infectious diseases.
- b. Is an additional component to the Asian Network of Excellence in Quality Assurance of Medicines (ANEQAM), established in 2006 to promote technical expertise and skill sharing among countries and institutions within the region. It will focus on the areas of medicines quality assurance (QA) and quality control (QC).
- c. Is a regional ‘pool of experts’ who specialize in medicines regulation, registration, post-marketing surveillance and regulatory enforcement action.
- d. Is a mechanism to provide technical support through training in QA/QC, Good Manufacturing Practices (GMP), bioavailability/bioequivalence (BA/BE), product dossier evaluation for registration, and the exchange of information related to the quality of medicines, joint action and combating substandard and counterfeit medicines.
- e. In the long term BREMERE can become one of the priorities of the Association of South East Asian Nations (ASEAN) Health Ministers’ agenda concerning quality, safety and efficacy of medicines that are manufactured, procured, supplied and used in the region.
- f. Does not replace the existing administrative and/or regulatory processes and procedures, and practices of the countries in the region. It simply provides an avenue for cooperation and collaboration between and among country agencies in the area of medicines quality.
- g. Does not act as enforcement or policing body or supersede a country’s existing rules and regulations.

2. Goal and objectives of BREMERE

Goal: To strengthen regional cooperation and collaboration for improving the quality of medicines, information sharing, collective investigation and enforcement in the Greater Mekong Sub-region (GMS).

Objectives:

1. To build capacity through sharing of regional expertise, provision of training (e.g., in QA/QC, GMP, BA/BE) and technical/financial support (e.g., testing of special cases of poor-quality medicines), with a view to create a regional 'pool of experts' who share information and expertise in medicines regulation, registration, post-marketing surveillance and enforcement.
2. To strengthen support and collaboration in the field of medicines quality and regulation between political—i.e., Ministries—and technical bodies—Medicines Regulatory Agencies (MRAs), World Health Organization (WHO)- country, regional and central levels—within each country and the region.
3. To improve the following processes among regulatory/technical agencies and other involved sectors (Customs, Police/Interpol, Prosecutors) at national and regional levels:
 - information sharing (e.g., building a database),
 - collective investigation (e.g., reporting alleged counterfeiters to the representatives of the claimed countries of origin and agreeing on procedures), and
 - enforcement (e.g., improving existing protocols according to best practice)

3. How Does the Organizational Structure of BREMERE Look Like?

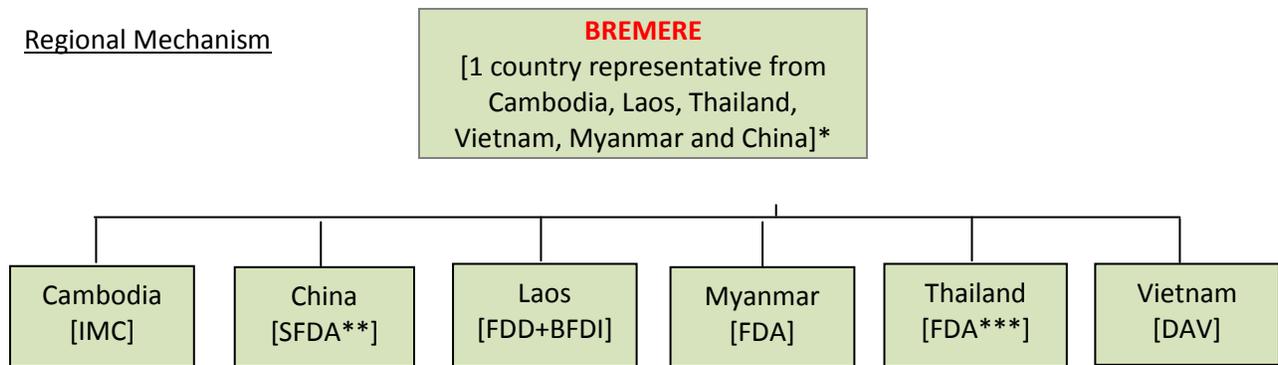
To minimize administrative and logistics costs every effort should be made to keep this BREMERE mechanism small, effective and efficient. Each country's law enforcement agencies on medicinal products in the GMS (and associate member countries) will *appoint* two representatives to be the country focal persons for BREMERE. Ideally one country representatives should be technical and come from the medicines regulatory authority (MRA) (e.g., Food and Drug Administration, Food and Drug Department, Drug Administration, etc.) because of the nature and functions the MRA plays concerning the quality, safety and efficacy of medicines and its fundamental responsibility to safeguard the public health from poor-quality medicines. Another country representative should have a political profile and may come from the MRA or another relevant department within the Ministry of Health, because it is easier for a person with this profile to communicate with other sectors (e.g., Customs, Police, Prosecutors) and promote enforcement action.

In countries where there is an existing Interpol focal point at the MRAs, this person could act as the technical representative for BREMERE.

Both technical and political representatives of each country, who will work closely, will coordinate the BREMERE activity implementation at both national and regional levels.

The technical and political representatives of each country will seek support and organize a network of collaborators or advisory committee from institutions such as official quality control labs (OQCLs) (e.g., NHQC/Cambodia, BDN/Thailand, NIDQC/Vietnam), Police (e.g., Economic Police Dept/Laos, Consumer Protection Division/Thailand, Drug Enforcement Agency/Philippines), Customs, and prosecutors where relevant. The collaborators should have a clear demarcation of roles within the network. This is necessary because MRAs have limited power for enforcement action and need the support of other sectors.

Figure 1: Formation of BREMERE

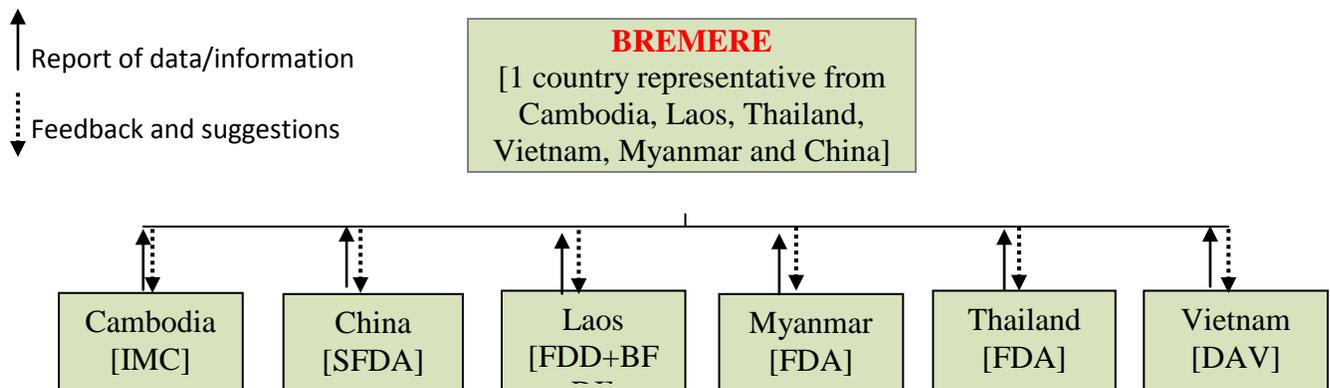


*In the associate member countries Indonesia and Philippines, the responsible agencies would be NAFDC and DG-PMDS, and FDA, respectively.

** It is possible that the Yunnan FDA is also represented.

***The Bureau of Drug Control and the Technical and Policy Administration Division are the responsible departments within the Thai FDA.

Figure 2: Reporting/Feedback



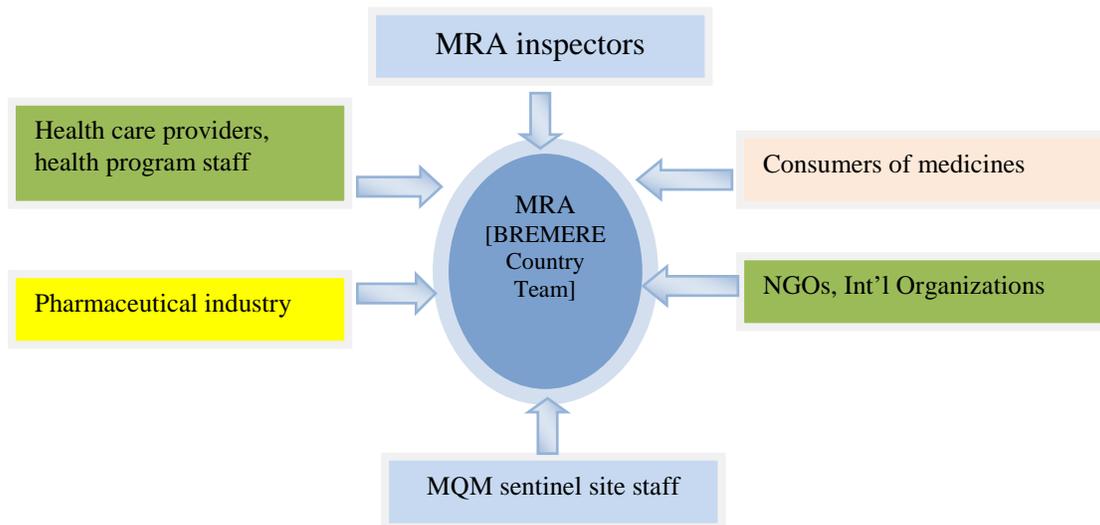
4. Reporting: the Process

a. Within Country

Reporting of suspected poor-quality medicines should not only be the responsibility of MRA personnel, but rather should also include:¹

- All healthcare providers in both public and private sectors—general practitioners, hospital and health center clinicians, pharmacists, nurses, and paramedics
- Health programs personnel—disease program officers and non-clinician public health staff
- Pharmaceutical industry—manufacturers, importers, distributors/wholesalers, retail pharmacy outlet attendants
- Non-governmental organizations (NGOs) and international organizations
- Medicine quality monitoring sentinel site staff
- Consumers and the general public.

Figure 3: Illustration of Key Stakeholders in Reporting of Suspected Medicines



The following information should be provided as described in Box 1 below. It is strongly recommended that the MRA provide toll-free telephone line and fax numbers so that all stakeholders can easily report suspected pharmaceutical products. Once the intelligence

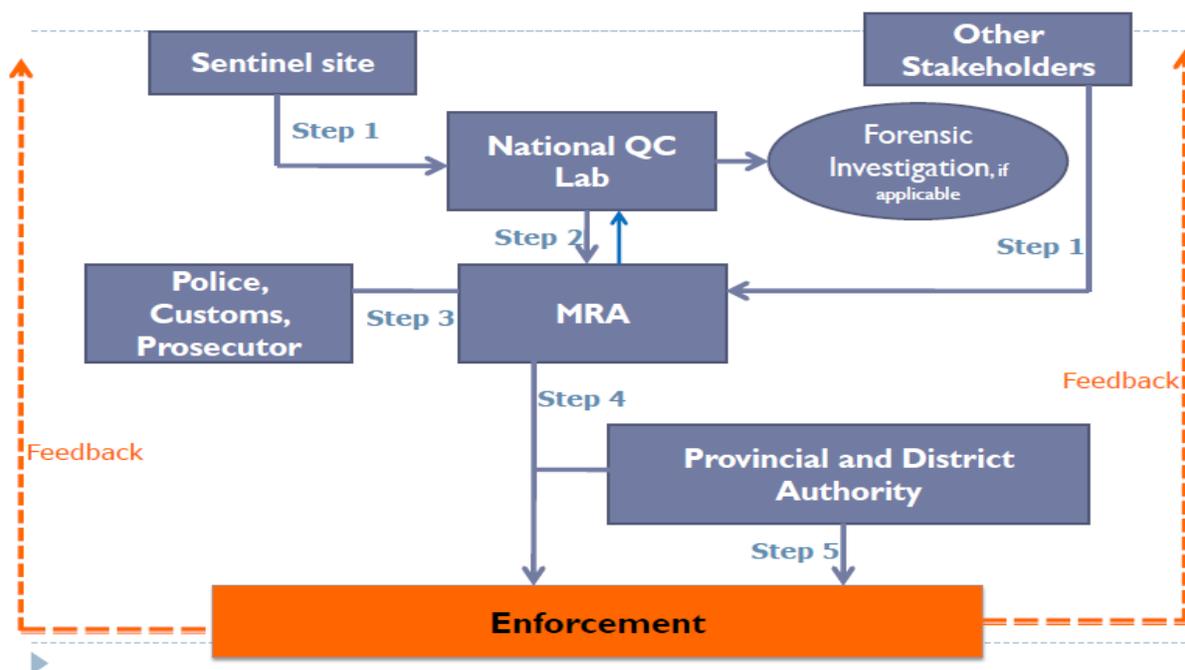
¹ Promoting the Quality of Medicines Program, 2010: Guidelines for Taking Appropriate Enforcement Action Against Substandard and Counterfeit Medicines, June 2010, page 5.

collected, the MRA should collect samples for investigation using the necessary steps as described in Figure 4.

Box 1: Key Product Information to Report

1. Name of the product: both the brand name and generic names (INN)
2. Name and address of manufacturer as claimed on the label, if available
3. Description of physical appearance
4. Lot/batch number, if applicable
5. Dosage form
6. Registration number, if applicable
7. Manufacturing and expiry dates, if applicable
8. Name of importer, distributor or wholesaler, if applicable (first reported to country of origin)
9. Location where the sample was found/seen/sold/obtained
10. Indication whether or not the sample was in its original packaging, if applicable
11. Pictures of falsified and original products, if applicable
12. Number of samples/units found and collected
13. Type of outlet where the sample was found, if applicable
14. Number and identity of expired products

Figure 4: Reporting Steps²



Notes:

It is necessary to agree upon a common working definition of poor-quality medicines (including both counterfeit and substandard medicines) at regional level.

On highly suspected cases of poor-quality medicines, the MRA in close collaboration with the country’s BREMERE team should report to the relevant authorities. On regular cases, the mechanism will be defined as BREMERE’s experience develops.

It is important to emphasize that all highly suspected medicinal products with safety and efficacy concern and quality defects should be taken out of the market and/or program as quickly as possible to prevent the harms that they can cause to users. Therefore the MRA or the BREMERE country team should investigate as soon as possible within a 24 hours’ timeframe.

A medicine sample can be classified as ‘critical quality defect’ which is potentially life threatening or could cause serious risk to health and fall under any of the characteristics stated in Box 2.

² For more details on necessary steps, refer to the Promoting the Quality of Medicines Program, 2010: Guidelines for Taking Appropriate Enforcement Action Against Substandard and Counterfeit Medicines, June 2010, pages 7-10.

Box 2: “Critical Quality Defect” Characteristics

1. No active pharmaceutical ingredient(s) (APIs); and/or,
2. Incorrect or wrong API(s); and/or,
3. API(s) content greater than one hundred twenty per cent (120%) or less than eighty per cent) 80%³ (based on observation of the TLC spot intensity); and/or,
4. Failed visual and/or physical inspections, including packaging and labeling, suspicion of being counterfeited; and/or ,
5. Failed simple disintegration and/or,
6. Illegal or unregistered (no legal registration number on label); banned and/or previously recalled/withdrawn products,⁴

Additional information to take into account:

- i. Number of tests conducted,
- ii. Number of samples collected / Number of samples failed,
- iii. Cut-off for testing or pharmacopoeia followed.

Confirming Analytical Results

1. The analysis should be conducted by each country’s OMCL.
2. For joint investigations the sample should be reconfirmed by the involved countries’ OMCL, by an independent OMCL that the United States Pharmacopeia (USP) Promoting the Quality of Medicines program (PQM) recommends, or by the USP PQM QC lab – using pharmacopeial specifications. If there is no pharmacopeial monograph available, validated methods and procedures should be used.

Note: If there is a discrepancy in the analysis results between the reporting country’s OMCL and the involved country’s, the sample(s) will be re-confirmed at the USP PQM QC lab or any other recommended and ISO/IEC-17025 accredited laboratory.

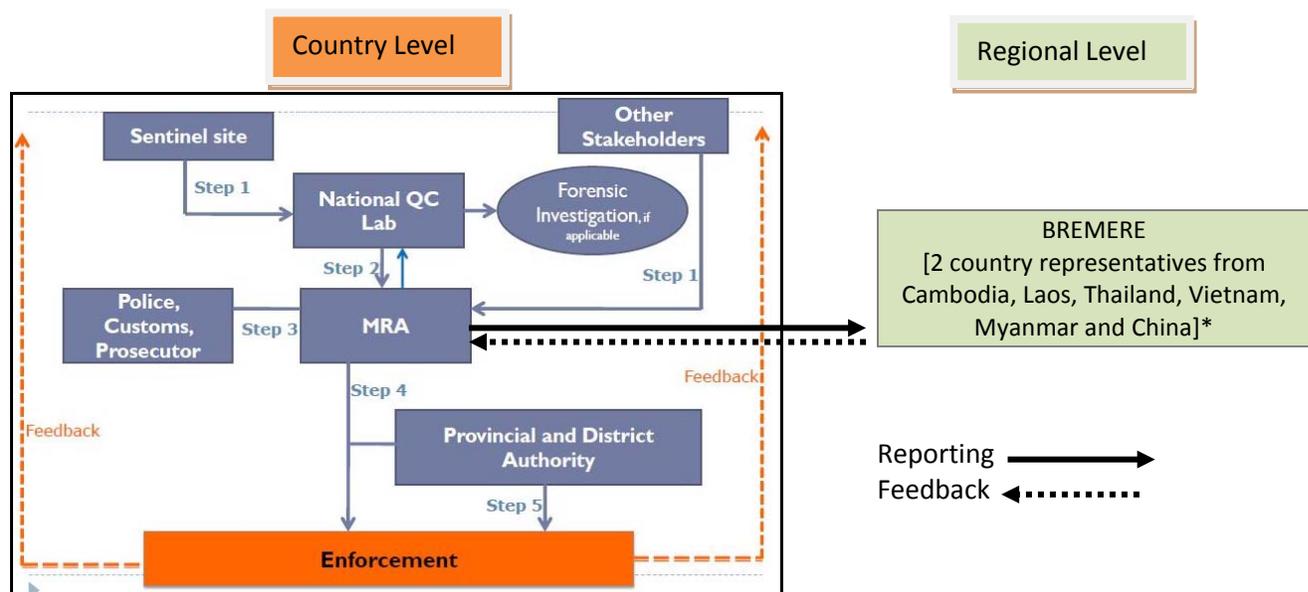
³ Most countries in the Mekong Sub-region consider that less than 80% and more than 120% active pharmaceutical ingredient (API) content classifies a pharmaceutical product as counterfeit or substandard. For example in Thailand, if API content is lower than the minimum or higher than the maximum standards prescribed in the formula registered with the MRA by more than 20%, the sample is classified as counterfeit.

⁴ To ascertain and confirm that a medicine product is illegal or unregistered, banned and/or previously recalled or withdrawn, the sentinel site staff should contact the relevant division of the MRA, e.g., Registration Division or Section.

5. Working Relationship Between Country and Regional Level

- a. Country BREMERE technical representative (with supervision from the political representative) reports to Regional BREMERE after having confirmed test results
- b. Regional BREMERE discusses and consults with its members (country reps) via face-to-face meeting
- c. Regional BREMERE notifies and advises the country BREMERE representatives on the case and suggests steps to take (Figure 5). This could involve:
 - Reconfirmation of results, and
 - Suggest appropriate next steps which include:
 - i. Investigate internally between the Country BREMERE team led by MRA
 - ii. Investigate externally between countries involved in the product (e.g., a medicine labeled as manufactured in Vietnam but found in Laos –the Country BREMERE team led by the MRA coordinates the investigation in cooperation with the involved parties.
- d. The outcomes of the investigation will be shared between the two countries' BREMERE teams as well as via the Regional BREMERE in the form of 'Letter of Notification' to all members in the region, and potentially via a regional online database where countries can submit/upload standardized data forms Information should be shared at least monthly.
- e. Eventually, each country will then take appropriate measures in line with their current rules and regulations – e.g., recall, seizure, delist from registration, license revocation, etc.

Figure 5: Reporting and Feedback Mechanism between Country and Regional BREMERE Teams



*Philippines and Indonesia as associate members.

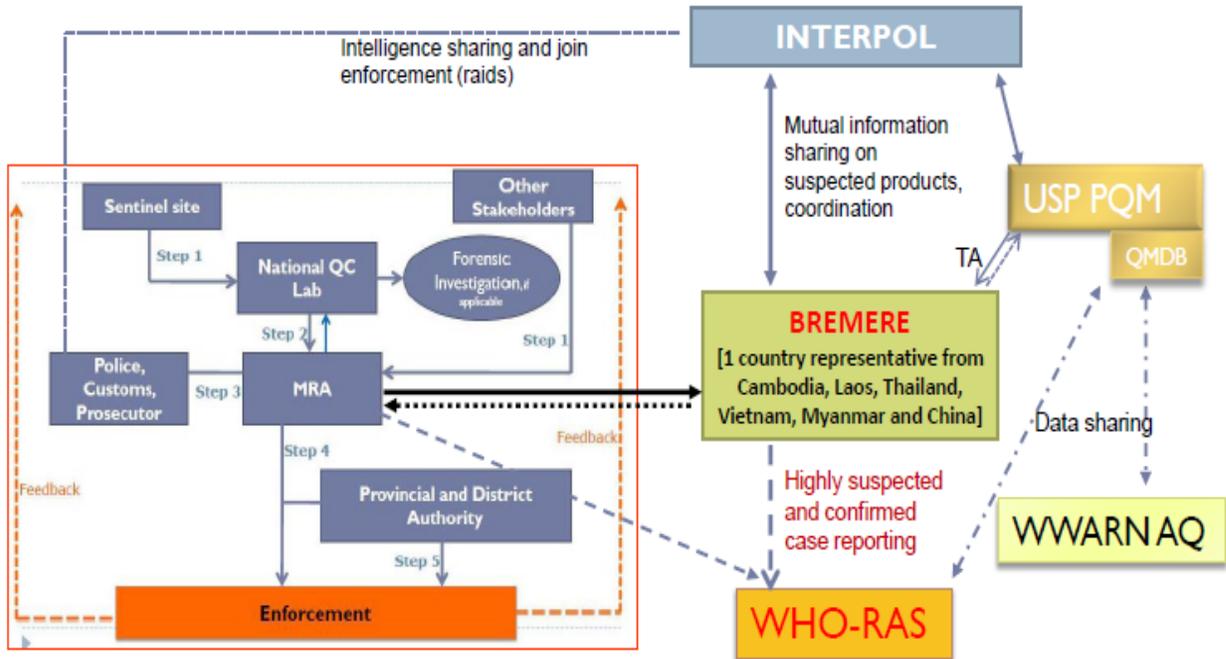
6. BREMERE and Its Partners: Data Sharing and Dissemination

The regional BREMERE will share information with international initiatives such as Interpol, WHO International Medical Products Anti-Counterfeiting Taskforce (IMPACT) and Substandard/spurious/falsely-labelled/falsified/counterfeit Medical Products (SFCC), WHO Rapid Alert System (WHO-RAS), Worldwide Antimalarial Resistance Network (WWARN), ASEAN Pharmaceutical Products Working Group (PPWG), and the World Customs Organization (WCO).

In particular, the mode of submission of data of highly suspected and confirmed cases to WHO-RAS still depends on the improvement of the alert system, and may be done by the country BREMERE representatives or the regional BREMERE chairperson.

Data will also be published in the member countries' MRA websites, which will potentially have a weblink to a common BREMERE online database. WWARN can provide technical assistance in the construction of this database.

Figure 6: Sharing/Dissemination of Information beyond BREMERE to other partners



* each BREMERE member country should have 2 representatives

7. Chairperson

1. To ensure regular and effective coordination and continuity of the operation of BREMERE, BREMERE will have a Chairperson with a 2-year term. The Chairperson will be selected by member countries' representative. The chairmanship will be rotated every two years among GMS countries, while the Philippines and Indonesia can join as associate members.
2. In the first term, a country's representative will be the Chairperson, assisted by a representative from another country acting as Co-Chairperson. The Co-Chairperson will be selected until the system is fully operational.

The USP PQM program (and other potential partners and donors) will provide technical assistance and limited financial support for the first 2-3 years of BREMERE operations. Thereafter, member countries will try gradually including BREMERE activities in their annual and/or strategic operational plans for government support.