

# ASEAN PPWG meeting, MQM Follow-up audits, and PQM Technical Assistance towards WHO Prequalification for manufacturers in Indonesia

Jakarta, Nusa Dua, and Medan, Indonesia  
May 13 - June 4, 2013

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## *Trip Report*

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## **Promoting the Quality of Medicines**

Implemented by U.S. Pharmacopeia

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## **Executive Summary**

The PQM team traveled to Indonesia May 13-June 4, 2013 to participate in and present at the 20th Association of Southeast Asian Nations (ASEAN) Pharmaceutical Products Working Group (PPWG) meeting in Nusa Dua, Indonesia. During the meetings, a number of private sector manufacturers of second-line anti-TB medicines expressed interest in receiving technical assistance from the PQM program, and the team met with them individually during this trip.

The PQM team also conducted follow-up Good Manufacturing Practices (GMP) audits of three state-owned (public sector) manufacturers of anti-tuberculosis medicines in Indonesia (Phapros Indonesia, Indofarma, and Kimia Farma) as well as one private sector company (Sandoz Indonesia). The PQM team also made a supervisory field visit to Medan in Northern Sumatera which is one of the Medicine Quality Monitoring (MQM) sites. The group, accompanied by USAID/Indonesia representatives, visited a number of outlets where anti-TB medicines are available, including from both public and private sectors, and observed the Medan provincial quality control lab staff conducting data collection and basic testing on selected samples during the visit.

PQM's Mr. Christopher Raymond was appointed as a member of the national Technical Working Group for Tuberculosis under the Global Fund's Phase II Single Stream of Funding (SSF) project in Indonesia to bring attention to the importance of quality assurance of TB medicines.

In addition, PQM submitted a draft FY14 work plan to USAID/Indonesia for consideration and feedback.

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### **About PQM**

The Promoting the Quality of Medicines (PQM) program, funded by the U.S. Agency for International Development (USAID), is the successor of the Drug Quality and Information (DQI) program implemented by the United States Pharmacopeia (USP). PQM is USAID’s response to the growing challenge posed by the proliferation of counterfeit and substandard medicines. By providing technical assistance to developing countries, PQM helps build local capacity in medicine 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.

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## ACRONYMS

ACCSQ	ASEAN Consultative Committee for Standards and Quality
AMS	ASEAN Member States
ASEAN	Association of Southeast Asian Nations
AWGPD	ASEAN Working Group on Pharmaceutical Development
BA/BE	Bioavailability/Bioequivalence
BREMERE	Building Regional Expertise in Medicines Regulation, Enforcement, and Information Sharing
CRO	Contract Research Organization
CTD	Common Technical Document
DQI	Drug Quality and Information Program
GDF	Global Drug Facility
GMP	Good Manufacturing Practices
GPHF	Global Pharma Health Fund
INH	Isoniazid
MDR-TB	Multidrug-resistant tuberculosis
MOH	Ministry of Health
MQM	Medicines Quality Monitoring
MRA	Medicines Regulatory Authorities
NA-DFC	National Agency of Drug and Food Control
NOMCOL	Network of Medicines Quality Control Laboratories
PD	Product Dossier
PIC/S	Pharmaceutical Inspection Cooperation Scheme
PPOMN	National Quality Control Laboratory of Drug and Food
PPWG	ASEAN Pharmaceutical Products Working Group
PQ	Prequalification
PQM	Promoting the Quality of Medicines Program
QA	Quality Assurance
QC	Quality Control
RIF	Rifampicin
SOP	Standard Operating Procedure
TB	Tuberculosis
USAID	United States Agency for International Development
USP	United States Pharmacopeia
WHO	World Health Organization

## Background

Indonesia is considered a high-burden tuberculosis (TB) country by WHO; it has been among the top five of the 22 high-burden TB countries for years. The situation is compounded by the development of multidrug-resistant tuberculosis (MDR-TB). There is a need to improve the quality assurance system for anti-TB medicines (ATBs) being purchased and used in the TB control program and to develop and implement strict regulatory controls and measures for the sale and supply of ATBs in the private sector, a challenge for the government. None of the ATBs produced in Indonesia has achieved World Health Organization (WHO) Prequalification (PQ) status for quality or efficacy.

With financial support from United States Agency for International Development/Indonesia (USAID/Indonesia), PQM has been providing technical assistance on the following:

- Strengthening the post-marketing surveillance capacity of the National Agency of Drug and Food Control (NA-DFC) by establishing medicines quality monitoring (MQM) of ATBs in close collaboration with the National Quality Control Laboratory of Drug and Food (PPOMN)
- Conducting workshops with WHO and the Global Drug Facility (GDF) to inform manufacturers and NA-DFC about the WHO PQ Program and the technical assistance PQM provides
- Providing technical assistance directly to selected local manufacturers to improve their good manufacturing practices (GMP) and product dossier compliance, working toward WHO PQ. PQM also provides support to capacitate two contract research organizations (CROs) for conducting bioavailability and bioequivalence (BA/BE) studies for ATBs according to Good Clinical Practices and Good Laboratory Practices for acceptance into the WHO PQ Program
- Conducting research and surveys to determine medicines quality in the marketplace

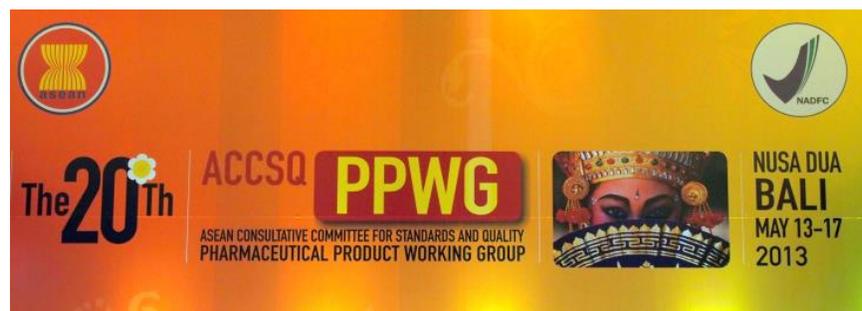
## Purpose of Trip

- Continue providing technical assistance to local manufacturers of first- and second-line ATBs
- Follow up on implementation of MQM project for ATBs
- Support the national QC laboratory to implement the MQM project
- Provide leadership and expertise at the regional level by participating in the 20<sup>th</sup> Association of Southeast Asian Nations (ASEAN) Pharmaceutical Products Working Group (PPWG) meeting

## Overview of Activities

ASEAN Consultative Committee for Standards and Quality of the Pharmaceutical Products Working Group 20<sup>th</sup> Annual Meeting in Nusa Dua, Indonesia, May 13-17, 2013

Following an initial meeting on March 21, 2013 with the ASEAN PPWG and the ASEAN Working Group on Pharmaceutical Development (AWGPD) in Jakarta, Indonesia, PQM was invited to present on its Asian regional activities at the ASEAN PPWG meeting in Nusa Dua, May 13-17, 2013. The presentations and discussions during the meeting were meant to foster a better understanding among ASEAN Member States (AMS) of potential areas for collaboration and support,



especially regarding strengthening medicines regulatory authorities (MRAs) in the region under ASEAN mutual recognition of inspectors for GMP (under the PIC/S scheme), supporting national medicines quality control laboratories, supporting training on BE capacity building for regulators, and strengthening regional initiatives for information sharing on poor quality medicines.

PQM participated in and presented at the GMP working group meeting, as well as the general assembly of the AMS with over 300 regional participants from MRAs, disease programs, and the private sector (manufacturers, etc.). PQM presented on its regional activities and identified areas of collaboration including:

- Development of a joint training and collaboration project to build capacity of GMP inspectors from AMS for mutual recognition of inspectorates under PIC/S in line with ASEAN Economic Community establishment by 2015
- Regional training initiatives for building capacity of MRAs for BE study evaluation for registration of new medicines in ASEAN
- Support for advocacy at the ASEAN Secretariat to engage Ministers of Health and other high ranking AMS officials to adopt PQM-led regional initiatives and to incorporate them into ASEAN work plans and activities.



## Next Steps

- AMS, with Singapore as lead, will submit a concept note for a regional project on GMP inspectors' trainings under PIC/S for eight priority focus areas to PQM for consideration of support. [completed]
- PQM will support a number of MRA participants from selected AMS to attend a training workshop on BE study evaluation to be held in Manila, Philippines in September 2013. [completed]
- PQM will meet with the ASEAN Secretariat (PPWG and AWGPD) during Q4 to identify further areas of collaboration and models for sustainability for regional PQM-led initiatives for the upcoming fiscal year.

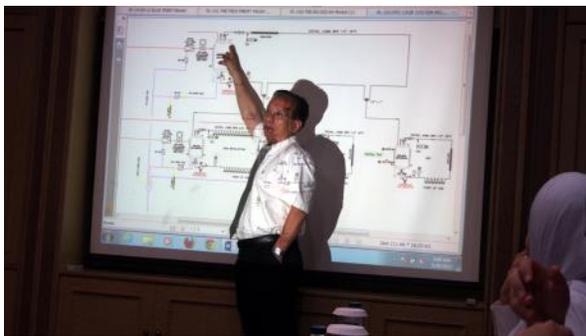
## Kimia Farma GMP follow-up audit and consultation, May 20-21, 2013

PQM Senior GMP specialists conducted a follow-up audit of the facility, evaluated the corrective and preventive action (CAPA) plan, and reviewed blueprints for facility upgrades at Kimia Farma, a state-owned manufacturing company producing ATBs located near Jakarta, Indonesia. The PQM team spent two days reviewing CAPA implementation (on 2FDC and 4FDC manufacturing facilities) since the previous audit, held in 2011. During this visit, Kimia Farma re-initiated its participation in the PQM

technical assistance program with the intention of submitting its product dossier to WHO PQ for a 2FDC (RIF 150, INH 150) product by the end of 2013, followed thereafter by 4FDC products. The GMP team also provided feedback on the blueprints for the proposed facility renovation.

### Next Steps

- Kimia Farma will establish a GMP team to communicate with PQM according to the timeline and milestones established during this audit, and Kimia Farma will submit a letter of commitment to the PQM team. [completed]
- Kimia Farma will regularly submit updates on CAPA implementation, stability data, BE study protocols, blueprint revisions, and other documents. [in process]
- Kimia Farma will need to reformulate their 2FDC (the priority) and 4FDC; also need stability data, dissolution profile, updated BE protocol [in process]
- PQM will source and provide comparator products and reference standards to Kimia Farma for their 2FDC product. [complete]
- Kimia Farma will begin compiling the product dossier [targeted submission date is Feb 2014]
- Kimia Farma will complete the registration batch, and PQM will assist in selecting a CRO for BE studies (either San Clin EQ or Equilab)



### Indofarma GMP follow-up audit and consultation, May 22-23, 2013

The PQM team, together with a representative from the Indonesian Medicines Regulatory Authority (BPOM), conducted an on-site audit and document review at the Indofarma manufacturing facility, a state-owned enterprise, in south Jakarta May 22-23, 2013. Specifically, the PQM team reviewed CAPA implementation and provided feedback on the proposed blueprint designs for a new production facility. Additionally, the PQM team established an implementation timeline for submission of Indofarma's product dossier for a 2FDC product, with a target submission date of February 2014. Based on discussions held on day one, Indofarma redesigned the blueprints for discussion on day 2, including amending materials and waste flows/buffer rooms, personnel flow, Validation Master Plan, and temperature and humidity amendments. The BPOM representative agreed to fast-track approval on the redesigned plans, and the Indofarma team agreed on the implementation timeline for submission to WHO PQ.



## Next Steps

- Indofarma will submit a revised timeline for 2FDC [completed]
- Indofarma will submit a revised plant design for PQM review and feedback, including any subsequent changes to the design [completed]
- Following PQM review and feedback, Indofarma will submit blueprint redesigns to BPOM for approval of construction [in process]
- Indofarma will submit monthly CAPA implementation accomplishments [in process]
- PQM will send comparator products to Indofarma [in process], as well as Guidelines for Changes to Plant for Validation Master Plan (WHO) & Variation Guidelines [completed]

## Initial meetings with Indonesian manufacturers expressing interest in receiving assistance from PQM May 24, 2013 (some meetings initiated during ASEAN PPWG meeting May 13-17, 2013)

The PQM team met with a number of local manufacturers to follow up on initial contacts made during the ASEAN PPWG meeting and the CPhI workshop held in March in Jakarta:

### *PT Metiska Farma*

Metiska Farma expressed interest in receiving technical assistance from PQM for their levofloxacin 500mg tablets. The potential submission to WHO PQ could be by the end of 2013.

### *PT Dexa Medica*

Dexa Medica, the parent company of CRO Equilab (a company receiving PQM technical assistance for BE studies) is in the process of assessing their readiness for WHO PQ for their potential product dossier submission.

### *Novell Pharmaceutical Laboratories*

The PQM team met with the Director and senior management of Novell Pharmaceutical Laboratories regarding their ofloxacin, moxifloxacin, and levofloxacin products for use in second-line treatment of TB. Since they are currently being audited by TGA, South Africa, and EMA, they do not have the resources to commit to applying for WHO PQ this year. However, they requested that we revisit the option in 2014 with them.

### *PT Zenith Pharmaceuticals*

Zenith Pharmaceuticals was approached during the ASEAN PPWG meeting and expressed interest in receiving technical assistance from PQM for their levofloxacin 500mg tablets. The PQM team has

received their product information questionnaire and expression of interest, and will soon schedule an initial meeting and assessment of their capacity to apply for WHO PQ.

### **Next Steps**

- PQM team will schedule an initial assessment of Zenith Pharmaceuticals and Metiska for October 2013 to follow up on the product questionnaire submitted to PQM in July [in process]
- PQM team will follow up with Dexa Medica and Metiska regarding submission of an expression of interest and product questionnaire to PQM [in process]

### Medicines Quality Monitoring Supervisory Field Visit to Medan, Sumatera, May 27-29, 2013

The PQM team—together with Dr. Kendra Chittenden of USAID/Indonesia and Dra. Ati Setiawati from the NA-FDC QC lab in Jakarta—conducted a two-day supervisory field visit to Medan, Sumatera. The team met with the Medan BBPOM provincial authorities and visited sampling sites from both the public and private sectors in the province of North Sumatera, including the provincial hospital and dispensary, a specialized public-sector Lung Hospital, and private sector pharmacies to sample ATBs for testing at the BBPOM lab. Medan is one of five provincial sites that PQM has equipped with Minilabs<sup>®</sup> and is part of a network of ten provincial BBPOM sites involved in the PQM-led Medicines Quality Monitoring (MQM) project for ATBs in Indonesia. During Round 1 of sampling and testing, 160 anti-TB and antibiotic medicines were tested at Medan BBPOM using basic tests performed with the Minilab<sup>®</sup>. The total number of samples tested in five provincial BBPOM sites under MQM in Round 1 was 869 (see Annex 1 for data details and Annex 2 for a selection of photos from the visit to Medan). Confirmatory testing is currently underway in five other parallel BBPOM sites, and plans are being made for Round 2 of sampling and testing for this year.



The supervisory team observed the Medan BBPOM laboratory staff conducting basic tests on the samples collected during the site visit, including both first- and second-line products. Doubtful samples were re-tested and subsequently sent for confirmation at the Padang BBPOM laboratory, in accordance with the MQM protocol. The team also collected samples of streptomycin 1g powder for injection to use for method development for basic tests.

### **Next Steps**

- PQM will provide the Medan BBPOM lab with the USP36-NF31 and with USP Streptomycin reference standards [complete]

- PQM will work with the BPOM national QC lab on inventory and supply needs for Round 2 [in process]
- Medan BBPOM and Padang BBPOM will report test results to the BPOM national quality control lab and follow up on failed products according to protocol, as well as compile results into an annual report [following completion of Round 2]
- PQM will send anti-TB reference standards and USP-NF documentary materials to the National quality control lab for distribution to the provincial BBPOM sites involved in the MQM project [complete]

#### Kimia Farma Dossier Compilation Training, May 27-28, 2013

Mr. Edwin Toledo conducted a two day, on-site Dossier Compilation Training for Kimia Farma in preparation for their application for their 2FDC anti-TB product for WHO PQ. The training was well-attended by senior management and staff responsible for dossier compilation, including from Regulatory Affairs.

#### **Next Steps**

- PQM will continue to provide technical assistance to Kimia Farma and follow up on agreed-upon timelines towards application for WHO PQ by the end of 2013 [in process]

#### Sandoz Indonesia GMP follow-up audit and consultation, May 30-31, 2013

The PQM team conducted a two-day audit at Sandoz Indonesia, and a separate audit review report was submitted to them.

#### **Next Steps**

- PQM will continue to work with Sandoz to implement the agreed-upon timeline for application to WHO PQ, provide feedback on documentation, and procure comparator products and reference standards, as requested [complete]

#### PQM team debriefing for USAID/Indonesia, May 30, 2013

The PQM team debriefed USAID/Indonesia on recent and upcoming activities, including a discussion on coordination and collaboration with Phase II of the Global Fund grant for TB in Indonesia. The PQM team also submitted the first draft work plan for FY14 to the USAID team for consideration.

#### **Next Steps**

- Mr. Raymond will be appointed to the national technical working group (TWG) for the TB portfolio for the Global Fund's Phase II Single Stream of Funding (SSF) project in Indonesia [completed]
- USAID will review the submitted draft work plan and provide feedback [in process]

#### Phapros Indonesia GMP follow-up audit and consultation, June 3-4, 2013

The PQM team conducted a two-day audit at Phapros Indonesia, and a separate audit review report was submitted to them.

#### **Next Steps**

- PQM will review the submitted documents and provide feedback to Phapros [in process]
- PQM will provide comparator products and reference standards to Phapros [in process]

## Annex 1

**Total number of anti-TB and antibiotics sampled in Indonesia in Round 1 from five provincial MQM sites**

No	Nama sediaan	BBPOM di Medan	BBPOM di Serang	BBPOM di Surabaya	BBPOM di Mataram	BBPOM Makassar	
1	Rifampicin tablets/capsules and FDCs	44	55	24	45	21	
2	Isoniazid tablets	10	6	9	5	13	
3	Ethambutol tablets	15	5	11	7	11	
4	Pyrazinamide tablets	13	3	6	7	13	
5	Levofloxacin tablets/capsules	8	8	12	5	11	
6	Moxifloxacin tablets/capsules	1	1	-	-	1	
7	Ethionamide tablets	-	-	-	-	1	
8	Cycloserine tablets	-	-	-	-	1	
9	Amoxicillin tablets/capsules	21	25	23	47	21	
10	Ciprofloxacin tablets	14	15	17	43	13	
11	Cotrimoxazole tablets	10	21	18	42	14	
12	Chloramphenicol tablets/capsules	10	19	15	32	10	
13	Cefixime capsules	12	9	10	29	2	
14	Streptomycin serbuk injeksi	2	-	3	-	-	total
	<b>TOTAL</b>	<b>160</b>	<b>167</b>	<b>148</b>	<b>262</b>	<b>132</b>	<b>869</b>

Trip photos from Medan











