

Compendial Analysis of Anti-Tuberculosis Medicines (Lecture and Hands-on Training); Sentinel Site Visits

Tagum City, Philippines: October 15-19, 2012

Sentinel Site at Davao City, Philippines: October 22, 2012

Sentinel Site at Malolos City, Philippines: October 24, 2012

Trip Report

Sanford Bradby
Scientist IV, PQM

Lawrence Evans III, Ph.D., M.P.H.
Global Services and Standards Manager, PQM

Maria Kathrina D. Olivarez, R.Ph.
Country Consultant, PQM

Wei (Elaine) Yuan, M.D.
Program Manager Southeast Asia, PQM

Promoting the Quality of Medicines
Implemented by U.S. Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852 USA
Tel: (+1-301-230-3279)
Email: pqm@usp.org. Or exy@usp.org

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Executive Summary

PQM conducted a technical training for analysts of the Philippines Food and Drug Administration (FDA) at the FDA Satellite Laboratory for Mindanao in Tagum City from October 15-19, 2012. The goal was to train participants in compendial analysis of the fixed-dosed combination medicines comprised of rifampin, isoniazid, pyrazinamide, and ethambutol hydrochloride tablets according to the *USP* monograph. The training included scientists from FDA labs in Manila, Cebu, and Davao City, with a total of 10 people participating in the hands-on training while 16 participated in the lectures.

PQM also visited two sentinel sites in Davao and Malolos City to observe medicine quality monitoring techniques, met with management staff from the FDA to discuss future technical assistance opportunities, and briefed USAID/Philippines on project status and future plans.



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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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- Ms. Concepcion D. Regalado for sharing her knowledge and expertise throughout the laboratory training.
- Mr. Jay S. Seville, Mr. Jun T. Donalvo, and Mr. Ryan P. Deguma for extending their time and assistance during the training.
- The sentinel site staff for their determination to effectively implement the medicine quality monitoring program and its objectives.
- Ms. Maria Lourdes C. Santiago for her guidance, support, and commitment to the PQM-supported programs in the country.

ACRONYMS

CHD	Center for Health Development
DOH	Department of Health
DOTS	Directly Observed Treatment–Short Course
DQI	Drug Quality and Information Program
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
FDRO	Food and Drug Regulation Officer
GDP	Good Documentation Practices
GLP	Good Laboratory Practices
GPHF	Global Pharma Health Fund
HPLC	High Performance Liquid Chromatography
LGU	Local Government Unit
MQM	Medicine Quality Monitoring
NCDPC	National Center for Disease Control and Prevention
NTP	National Tuberculosis Program
OOS	Out of Specification
PQM	Promoting the Quality of Medicines Program
PVT	Performance Verification Test
QA/QC	Quality Assurance/Quality Control
RS	Reference Standard
RSD	Relative Standard Deviation
SOP	Standard Operating Procedure
TB	Tuberculosis
USAID	United States Agency for International Development
USP	United States Pharmacopeia
WHO	World Health Organization

Background

Since 2007, with financial support from the United States Agency for International Development (USAID), the United States Pharmacopeia (USP) has been actively providing technical assistance to the Philippines Food and Drug Administration (FDA), the Department of Health (DOH), and the National Tuberculosis Program (NTP) in an effort to strengthen medicines quality assurance and quality control (QA/QC) systems. Assistance has focused on establishing a post-marketing surveillance program—known as the medicines quality monitoring (MQM) program—to monitor the quality of anti-tuberculosis (TB) medicines available on the market and enhancing the FDA’s regulatory capacity in evaluation and registration of pharmaceutical products.

Purpose of Trip

The primary objective of this trip was to provide training in Davao, Philippines on the compendial analysis of rifampin, isoniazid, pyrazinamide, and ethambutol hydrochloride tablets using high performance liquid chromatography (HPLC) while demonstrating and implementing good laboratory practices (GLPs) and good weighing practices.

A secondary objective was to conduct sentinel site visits to assess the progress of the MQM program, motivate the sentinel site staff, clarify any technical concerns, and demonstrate the MQM work carried out at the sentinel sites to upper level management of the Center for Health Development (CHD) and the local government unit (LGU).

Source of Funding

These activities were funded by USAID/Philippines.

Overview of Activities

The training activities are summarized in the following table:

Item	Description
Specific Objectives	Train participants on: <ul style="list-style-type: none">• HPLC analysis of anti-TB medicines using compendial methods• Handling out-of-specification results• Good laboratory practices• Good weighing practices
Venue/Location	FDA Satellite Laboratory for Mindanao, Tagum City, Philippines
Organizers	PQM and FDA Satellite Laboratory for Mindanao
Sponsors	PQM
Trainers and Facilitators	Sanford Bradby, Lawrence Evans III, Elaine Yuan, and Maria Kathrina Olivarez of PQM
Trainees	16 FDA participants (10 for hands-on training) See Participant List in <i>Annex 1</i> for detailed information
Agenda	See Agenda in <i>Annex 2</i> for detailed information
Opening Ceremony	<ul style="list-style-type: none">• Concepcion D. Regalado, Chief – FDA Satellite Laboratory for Mindanao gave the welcome and opening comments• Elaine Yuan gave an overview of the PQM program

Modules	<ul style="list-style-type: none"> • High Performance Liquid Chromatography • Good Laboratory Practices • Good Weighing Practices <p>Note: PQM was informed that the lab's dissolution instrument failed the USP performance verification test (PVT) twice the week prior to the training. PQM reviewed their data and found a calculation error. Troubleshooting provided by PQM revealed that the dissolution instrument passed the PVT test once the results were properly calculated.</p>
Closing Ceremony	<ul style="list-style-type: none"> • Concepcion D. Regalado gave closing comments • Lawrence Evans and Sanford Bradby gave a summary of the training • Certificates of completion were given to the participants
Training Evaluation	See participant evaluations of each module in <i>Annex 3</i>
Outcomes/Conclusion	<ul style="list-style-type: none"> • Participants noted that the hands-on demonstrations were especially helpful in learning proper techniques and that the use of small groups for the laboratory component was conducive to grasping the techniques being taught. • Participants asked for additional training in interpretation and handling of results.
Next Steps	<ul style="list-style-type: none"> • PQM will provide contact information for the USP Global Health Impact Programs Manager to the FDA so that the lab can submit an application to participate in USP's Technical Alliance Program • PQM will host a conference call by the end of February 2013 regarding post-training activities (establishing due dates, expectations, and requirements) • PQM will send reference standards to the lab for performing post-training analyses of anti-TB medicines (due date will be determined in the conference call) • The lab will submit post-training analysis results to PQM for review and feedback (due date will be determined in the conference call)

Training commentary

Lawrence Evans and Sanford Bradby reviewed the agenda and presented the training objectives and expected outcomes during the opening ceremony. The PQM training team also requested and documented each of the participants' individual expectations. Some of the expectations expressed included:

- Develop more expertise in analyzing anti-TB medicines
- Improve ability to troubleshoot analysis problems
- Handle out-of-specification (OOS) results



- Improve skills and knowledge to be able to meet system suitability
- Generate precise and accurate results
- Properly use standards for analyzing fixed-dose combination anti-TB medicines containing 2 or 4 active pharmaceutical ingredients
- Improve skills in weighing practices

Throughout the training, the PQM team addressed each expectation in either the laboratory or lecture setting and revisited each topic during the final question and answer session to ensure the participants' individual expectations were met.

The training was originally devised to address the technical challenges communicated by the FDA. These included the inability to meet the relative standard deviation (RSD) system suitability requirement in the assay for ethambutol hydrochloride and the inability to meet the RSD and column efficiencies system suitability requirements in the assay for rifampicin, isoniazid, and pyrazinamide.

During the training, both teams of participants were able to meet system suitability and, subsequently, perform the HPLC analysis and achieve precise and accurate results. PQM was able to provide solutions as to why the lab was previously unable to meet the system suitability requirements and demonstrate the proper techniques to ensure success going forward. The participants' performance was monitored throughout the hands-on lab component and was also evaluated via a quiz on the topics taught and discussed during the week. The average score was 85% correct.

As indicated in the "Next Steps", the lab's post-training activities will be discussed in early 2013. Until then, the lab is expected to implement the practices and techniques provided during the training and seek assistance from PQM when a question arises. The post-training activities will require the lab to test an anti-TB medicine and provide the results to PQM for evaluation.

Sentinel Site Visits

In addition to the laboratory training, Dr. Elaine Yuan and Maria Kathrina Olivarez visited sentinel sites in Davao City and Malolos City on October 22 and 24, respectively. The PQM team spent time with the sentinel site staff at each location, observing their techniques, inspecting the Minilabs[®] to see what supplies need to be replenished, and making suggestions to improve techniques and methods, as necessary. Details of the sentinel site visits are included in *Annex 4*.

PQM plans to visit all eight sentinel sites at least once a year with the aim of monitoring the MQM activities, observing and teaching techniques, and providing the supplies that each site needs. Site visits are a unique opportunity for PQM to collaborate with LGUs and the CHD to jointly identify specific issues and concerns related to medicine quality at each site and to monitor and improve staff techniques.



Additional activities

During this trip, PQM met with management staff from the Philippines FDA to discuss current challenges and the ways PQM can provide technical assistance to continue strengthening the capacity of the Philippines FDA.

PQM also met with USAID/Philippines to debrief Mission staff on PQM's accomplishments in the past year and to present the draft work plan. The Mission officer provided guidance, advice, and direction regarding work plan development.

PARTICIPANT LIST (HANDS-ON TRAINING)

1. ARIETE, MARILOU J.	ANTIBIOTICS SECTION SAT LAB FOR MINDANAO
2. TUBOG, MARY BOLYN V.	ANTIBIOTICS SECTION SAT LAB FOR MINDANAO
3. DE GUZMAN, DIVINA D.	DRUGS SECTION SAT LAB FOR MINDANAO
4. JARDENICO, RIZA LINDA E.	DRUGS SECTION SAT LAB FOR MINDANAO
5. SANTOS, FLORVINA B.	DRUGS SECTION SAT LAB FOR MINDANAO
6. SEVILLE, JAY S.	ANTIBIOTICS SECTION, LSD, FDA
7. TIO, MICHELLE S.	ANTIBIOTICS SECTION, LSD, FDA
8. VILLANUEVA, JOANNE ELAINE C.	DRUGS SECTION, LSD, FDA
9. MEJORADA, MAGDALENA G.	DRUGS SECTION, SAT LAB FOR VISAYAS
10. TAGUD, GINA T.	DRUGS SECTION, SAT LAB FOR VISAYAS

OBSERVERS

11. SANTIAGO, MARIA LOURDES C.	CHIEF, LSD, FDA
12. DAVID, ALMUEDA C.	MICROBIOLOGY SECTION, LSD, FDA
13. BALDERRAMA, JOCELYN E.	DRUGS SECTION, LSD, FDA
14. PAGARAN, LUZ N.	COSMETIC SECTION, LSD, FDA
15. DONALVO, JUN LEO T.	MICROBIOLOGY SECTION SAT LAB FOR MINDANAO
16. DEGUMA, RYAN GLENN P.	ADMIN SUPPORT SAT LAB FOR MINDANAO

FACILITATORS

17. REGALADO, CONCEPCION D.	CHIEF, SAT LAB FOR MINDANAO
18. YUAN, ELAINE	PROGRAM MANAGER FOR SEA, PQM
19. OLIVAREZ, MARIA KATHRINA D.	COUNTRY CONSULTANT, PQM

TRAINERS

20. EVANS, LAWRENCE III	GLOBAL SERVICES AND STANDARDS MANAGER, PQM
21. BRADBY, SANFORD	SCIENTIST IV, PQM

TRAINING AGENDA

<u>Hands-on Training on the Compendial Analysis of Anti-tuberculosis Medicines</u>	
FDA Davao Satellite Laboratory for Mindanao Energy Park, Apokon, Tagum City, 8100 October 15-19, 2012	
MONDAY, OCT 15	ACTIVITIES
8:00 – 8:30	Flag Ceremony
8:30 – 9:00	Registration
9:00 – 9:30	Breakfast
9:30 – 10:00	Opening Remarks and Introduction of the Trainers: Maria Lourdes C. Santiago, MSc, M.M. Chief, Laboratory Services Division, FDA
10:00 – 10:30	Welcome Trainers and Introduction of the Participants: Concepcion D. Regalado Chief, Satellite Laboratory for Mindanao, FDA PQM Overview: Dr. Elaine Yuan Program Manager, Southeast Asia, USP PQM
10:30 – 11:30	<ul style="list-style-type: none"> • Opening meeting: Dr. Lawrence Evans III, Global Services and Standards Manager, USP PQM, and Mr. Sanford Bradby, Scientist IV, USP PQM <ul style="list-style-type: none"> ○ Review agenda ○ Training objectives ○ Expected outcomes
11:30 – 12:00	<ul style="list-style-type: none"> • Group Photo • Tour: Satellite Laboratory
12:00 – 1:00	Lunch Break
1:00 – 5:00 (3:00 – 3:30) Coffee Break	<ul style="list-style-type: none"> • Presentations: <ul style="list-style-type: none"> ○ Good Laboratory Practices ○ Handling Out of Specification results • Review of the HPLC Assay Procedures in the USP monograph for Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Hydrochloride Tablets
TUESDAY, OCT 16	ACTIVITIES
8:00 – 8:30	Registration/ Housekeeping
8:30 – 9:00	Coffee Break
9:00 – 5:00 (12:00 – 1:00) Lunch Break (3:00 – 3:30) Coffee Break	<ul style="list-style-type: none"> • Hands-on: HPLC Assay – Ethambutol Hydrochloride Assay <ul style="list-style-type: none"> ○ Set up system ○ Prepare mobile phase and equilibrate column ○ Prepare System Suitability Solution ○ Perform System suitability check
WEDNESDAY, OCT 17	ACTIVITIES
8:00 – 8:30	Registration/ Housekeeping
8:30 – 9:00	Coffee Break
9:00 – 5:00	<ul style="list-style-type: none"> • Hands-on: HPLC Assay –Ethambutol Hydrochloride Assay <ul style="list-style-type: none"> ○ Prepare Standard & Sample solutions

(12:00 – 1:00) Lunch Break	<ul style="list-style-type: none"> ○ Repeat System suitability check ○ Perform sample assay ○ Perform assay calculations
(3:00 – 3:30) Coffee Break	<ul style="list-style-type: none"> • Hands-on: HPLC Assay –Rifampin, Isoniazid and Pyrazinamide Assay <ul style="list-style-type: none"> ○ Set up system ○ Prepare mobile phase and equilibrate column ○ Prepare System Suitability Solution ○ Perform System suitability check
THURSDAY, OCT 18	ACTIVITIES
8:00 – 8:30	Registration/ Housekeeping
8:30 – 9:00	Coffee Break
9:00 – 5:00	<ul style="list-style-type: none"> • Hands-on: HPLC Assay –Rifampin, Isoniazid and Pyrazinamide Assay <ul style="list-style-type: none"> ○ Prepare Standard & Sample solutions ○ Repeat System suitability check ○ Perform sample assay ○ Perform assay calculations
(12:00 – 1:00) Lunch Break	
(3:00 – 3:30) Coffee Break	
FRIDAY, OCT 19	ACTIVITIES
8:00 – 8:30	Registration/ Housekeeping
8:30 – 9:00	Coffee Break
9:00 – 5:00	<ul style="list-style-type: none"> • Discuss HPLC System Suitability and Assay results • Closing meeting <ul style="list-style-type: none"> ○ Final Q&A Session ○ Wrap-up training ○ Review post training activity ○ Complete evaluation sheets ○ Present Certificates
(12:00 – 1:00) Lunch Break	
(3:00 – 3:30) Coffee Break	

Participant Evaluations of Specific Aspects of the Training

	Rating				
	1=not satisfied, 5=completely satisfied				
	1	2	3	4	5
Overall Course Feedback					
Content / topics covered				4	6
Format (e.g. lectures, labs demos, hands-on labs etc.)				4	6
Speakers knowledge of the subject matter				3	7
Speakers responsiveness to questions				3	7
Course length / Schedule / Time allotments / Pace			1	6	3
Usefulness of course material / hand outs.				4	6
Usefulness / relevance of information to everyday practices				3	7
Course administrations / logistics				7	3
Extent to which course met your expectations overall				3	7
Lecture Specific Feedback					
Good Laboratory Practices - lecture				4	6
Weighing Practices - lecture				3	7
Handling Out of Specification Results - lecture			1	2	7
Compendial HPLC Assay -lecture				3	7
Compendial HPLC Assay testing of Anti-TB Medicines–lab/hands-on				2	8

Other Comments/Suggestions:

1. What did you like best about the course?

- Weighing practices (4)
- The topic was a good pick but the speakers/trainers made it more interesting. I liked how they provide interaction among us participants. They made sure that they were able to share their knowledge and skills and those we learned from them and apply it in our daily routine of work.
- The lecture provided additional knowledge on performing assay procedures according to pharmacopeial methods.
- Lecture on handling OOS results
- Laboratory hands-on compendial HPLC Assay testing of anti-TB medicines (6)
- Small group discussions
- Q & A session
- They were very willing to share what they know and give us useful practical tips (4)

2. What did you like least about the course?

- Handling of OOS
- Didn't suggest sources or references for requirements/tolerances of balances

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

- Continue doing actual demonstrations like proper weighing
- Conduct training with less participants
- More time for hands-on (2)
- More time for interpretation of data/results (3)
- Discuss more issues encountered on GLP and handling of OOS results
- Provide follow-up training lab based on the assessment of the trainers

Notes from Sentinel Site Visits

Sentinel Site Visit: Davao City

- Dr. Elaine Yuan and Maria Kathrina Olivarez visited the Center for Health Development (CHD) Davao in Bajada, Davao City for a Sentinel Site inspection. However, the area is under renovation and the Minilab[®] was moved to the FDA Sat Lab in Tagum City until the renovation is complete.
- Ms. Gwendolyn Bardos, Ms. Eva Maghuyop, and Ms. Estille Grace Tutor, Food and Drug Regulation Officer (FDRO; Minilab[®] staff) conduct sample testing at FDA Sat Lab under the supervision of Ms. Concepcion Regalado (Chief, FDA Sat Lab for Mindanao).
- The team asked the Minilab[®] staff to show their documents and checked how they record their lab findings. Also discussed was the status of Minilab supplies and which ones needed to be replenished.
- Under the supervision of Ms. Deborah Legaspi (FRDO III), the team went to local pharmacies to conduct sample collection and post-market surveillance (PMS) for ATBs.

Sentinel Site Visit: Malolos City

- Dr. Elaine Yuan and Maria Kathrina Olivarez went to the CHD in San Fernando City, Pampanga to meet with Dr. Juliana Reyes (FDRO, Officer-in-charge, SRLE Division, CHD III) and Ms. Alicia Montano (FRDO, Standard Regulation, Licensing and Enforcement - SRLE Division, CHD III; Minilab[®] staff) to discuss the status of the project. CHD III is the overseer of the LGU in Malolos City.
- The team informed Dr. Reyes that the Minilab[®] was transferred from the City Health Office (CHO) to the Malolos San Vicente Hospital when the CHO was being renovated. The team explained that, due to the sensitivity of the reagents and supplies, the kit needed to be transferred at that time for safety and manageability.
- A new Memorandum of Understanding (MOU) needs to be completed with the Hospital.
- Dr. Reyes expressed her utmost support to the project and offered to transfer the Minilab[®] from LGU to CHD. The team thanked Dr. Reyes for this option. However, PQM feels that the Minilab[®] should stay in Malolos City since there are still cases of tuberculosis being reported.
- The team commended Ms. Montano for her diligence during drug inspection and sample collection at local pharmacies.
- The team travelled to meet with Dr. Frederick Villano and Ms. Joanna Marie Enriquez (Medical Technologist; Minilab[®] staff). The Minilab[®] is located at the Malolos San Vicente Hospital where basic testing and disintegration of the product sample is conducted. The Malolos San Vicente Hospital is a DOTS Providing Hospital of the TB DOTS Referral Network and was recognized for being a proactive private sector partner in Bulacan's fight against tuberculosis.
- The team inspected the Minilab[®] to see which supplies need to be replenished, checked the testing area, and reviewed waste disposal management. The team observed how sample information is recorded and results interpreted and then discussed how the staff can improve their sampling techniques.