

## Training workshops on GC, IR and HPLC troubleshooting for DACA Quality Control Laboratory

Addis Ababa, Ethiopia  
July 25-30, 2010

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### *Trip Report*

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PROMOTING THE QUALITY OF MEDICINES

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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.

## **Abstract**

Following a full round of sampling and testing antimalarials in 2009, a second round began in June 2010. The Drug Administration and Control Authority (DACA) laboratory is beginning confirmatory testing on those samples, and during this visit, PQM staff reviewed the sampling and verification data and made recommendations for the confirmatory tests to complete this study.

PQM staff trained DACA laboratory staff on Gas Chromatography (GC), infrared (IR) spectrometry, and High Performance Liquid Chromatography (HPLC) troubleshooting techniques. They also assisted Quality Assurance managers to draft Standard Operating Procedures (SOPs) for GC and IR and review the progress made according to the implementation plan.

## **Key Words**

DACA, Oromia, sentinel sites, antimalarials, Medicines Quality Monitoring, ISO 17025, GC, IR, HPLC, SOP, quality systems

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- The Director General, Mr. Yehulu, and the QC Laboratory Director, Mr. Bikila Bayissa, and all DACA management for their support and assistance during this visit and training.
- PQM administrative staff and editors for their assistance with logistical arrangements and for editing the trip report.
- Mr. Anthony Boni at USAID/Washington for his guidance and helpful insights throughout the preparation stages of the workshop.

## ACRONYMS

DQ	Drug Quality
DACA	Drug Administration and Control Authority of Ethiopia
GC	Gas Chromatography
GLP	Good Laboratory Practices
HPLC	High Performance Liquid Chromatography
ISO	International Organization for Standardization
IR	Infra Red Spectrometry
MCP	Malaria Control Program
MOH	Ministry of Health
MQM	Medicine Quality Monitoring
NGO	Non-governmental organization
ORHB	Oromia Regional Health Bureau
PEPFAR	President's Emergency Plan for AIDS Relief
PMI	President's Malaria Initiative
PQAD	Product Quality Assessment Directorate
PMS	Post-market surveillance
QA	Quality Assurance
QC	Quality Control
SOP	Standard Operating Procedure
USAID	United States Agency for International Development
PQM	The Promoting the Quality of Medicines Program
WHO	World Health Organization

## **Background**

In February 2008, PQM conducted a rapid assessment of Ethiopia's pharmaceutical quality assurance systems. PQM and USAID/Ethiopia agreed on priority actions to be taken to strengthen medicine quality assurance in the country. Five sentinel sites were chosen and a drug quality monitoring program established in Oromia region. The first round of sampling and testing of antimalarials was completed in 2009.

In 2010, PQM received funding from the President's Emergency Plan for AIDS Relief (PEPFAR) program through USAID/Ethiopia to strengthen the capacity of the Drug Administration and Control Authority (DACA). An implementation plan listing all activities and deliverables for FY10 was drafted.

PQM has conducted training for all sentinel sites staff on new PQM guidelines for sampling and testing, and a second round began in May 2010. The sampling, testing, and verification stages are complete, and confirmatory testing is ongoing.

## **Purpose of Trip**

Dr. Abdelkrim Smine

- Review MQM sampling, basic testing, and verification data
- Assist the sentinel site team to select samples for laboratory confirmatory testing
- Discuss and recommend future Medicine Quality Monitoring (MQM) activities

Dr. Abdelkrim Smine and Mr. Eshetu Wondemagegnehu

- Follow up on USP registration as a non-governmental (NGO) entity in Ethiopia
- Discuss MQM plan for antiretrovirals
- Meet with DACA to update on progress
- Discuss progress on the new DACA facility
- Meet with PMI and PEPFAR teams

Mr. Sanford Bradby and Mr. Dinh Huy

- Train QC Lab staff on GC, IR, and HPLC troubleshooting
- Assist QA manager to draft SOPs for GC and IR
- Follow up on the implementation plan for DACA QC lab

## **Source of Funding**

These activities were funded by USAID/Ethiopia, PMI and PEPFAR programs.

## **Overview of activities**

During this trip, the PQM team worked with DACA headquarters and the QC laboratory to carry out several activities following this year's work plan. An update about PMI and PEPFAR funded activities for 2010 is summarized below:

### **PMI program MQM activities and update**

- Following the PQM refresher training on basic tests done in March, the second round of MQM started in June 2010. The sampling of 494 antimalarials has been completed in five sentinel sites in Oromia region. The sentinel site team at the QC lab has completed the verification tests and is

starting confirmatory tests according to PQM guidelines and the recommendations made by Dr. Smine during this visit.

- Only 11 samples out of 494 failed the basis tests. This indicates that poor quality antimalarials in the five sites of Oromia region are not widespread. However, registration status is still an issue. PQM instructed the lab director to check with the DACA registration unit to verify the registration status of all samples collected.
- The sampling teams reported that they suspect there are illegal samples in circulation but the medicine sellers are quickly informed that a sampling is taking place. PQM recommended that a specific study should be carried out in a few selected areas to verify the availability of poor quality medicines by using “mystery shoppers.” It was decided that the sentinel site team at the DACA lab should carry out this study targeting about 100 samples in areas where trade in illegal antimalarials is suspected to be taking place.
- PQM recommended that the DACA lab and the sentinel site teams complete the final report and the short study to verify the availability of poor quality medicines by October 2010.
- The program will expand to 2-3 sentinel sites outside Oromia region early next fiscal year. The new sites will be selected by PQM after discussions with all stakeholders.

## **PEPFAR program update**

### **Training program for DACA QC lab** (see [Annex 1](#) for training details)

PQM has trained the QC lab on HPLC, Dissolution, Good Laboratory Practices, and quality systems. This week, the training program continued with selected staff receiving training on GC, IR, and HPLC troubleshooting. In parallel, PQM trainers assisted the QA managers to establish and implement SOPs related to these trainings. PQM is ahead of targets on the number of trainings conducted and number of personnel trained.

### **Quality Systems at the QC lab**

The QC lab of DACA has made a considerable effort in drafting, reviewing, and implementing new SOPs. So far, over fifty SOPs have been drafted; eleven of these have been implemented and the rest are in review and approval stages. Additional SOPs for GC and IR were drafted this week.

### **Servicing of lab equipment**

PQM has paid a company in South Africa to service the Shimadzu HPLCs. However, after more than six months, the company has not delivered what was agreed in the service agreement. Because finding companies to service Shimadzu-made equipment is a serious problem throughout Africa, PQM is searching for other alternatives in the U.S. and Europe. To assist the QC lab staff carry out basic troubleshooting of HPLC equipment, a short training was organized for selected lab analysts.

### **The new QC lab facility**

The PQM team met with the director of DACA and discussed the progress in the construction of the new building. DACA upper management meets every two weeks to discuss and review the progress with the construction company. Some critical recommendations from the expert architect hired by PQM have been taken in consideration. The architect has already submitted a final design plan and will soon visit DACA to make a final review of the facility and assist with the tendering process for furnishing the labs.

### **Sampling plan for MQM of ARVs**

The PQM team met with the Director of post-marketing surveillance of antiretrovirals (ARVs). PQM requested a meeting with all stakeholders in ARV supply and control, which was canceled.

### **Training of DACA staff outside Ethiopia**

Mr. Eshetu is working with DACA to find MRAs and QC labs to host DACA staff for short term training. The MRAs of Philippines and Tanzania have agreed to host staff, and discussion is ongoing regarding training possibilities in India and South Africa. Dates and training plans will be finalized soon.

### **USP registration in Ethiopia**

Dr. Smine and Dr. Eshetu worked with a lawyer in Addis Ababa and finalized all needed paperwork, which was sent to USP Headquarters. The PQM Director has set up a meeting with the Ethiopian Ambassador in Washington, D.C. Dr. Eshetu is working with DACA and the MOH on a recommendation letter to support the registration.

### **Purchase of lab equipment**

PQM has purchased a generator to be used for the new DACA building; the generator has arrived and its customs clearance is ongoing. DACA will have to find professional support for installing and servicing the generator according to the manufacturer specifications.

### **Conclusion**

Except for the issue of servicing Shimadzu equipment and finalizing a sampling protocol for ARVs, all PQM activities are on track. Both PMI and PEPFAR activities are ongoing without major problems.

PQM has finalized and submitted quarterly reports for both PMI and PEPFAR. The program is ahead of targets in many activities, such as number of trainings delivered, number of trained personnel, and quality systems. The PQM team urged partners to make sure that all activities planned in this year's work plan are completed by September 30, 2010.

### **Next Steps**

The major activities to be carried out by DACA partners are:

- Finalize the sampling plan and start sampling ARVs to start the MQM program, satisfying both PEPFAR and Global Funds QA/QC requirements.
- Complete the ongoing PMI MQM round and share the final report. Start the limited second round as discussed and agreed between PQM and DACA QC lab.
- Work with the PQM architect to review furnishing and design specifications and prepare tendering documents.
- Clear the generator through customs and find an expert engineer to install and service it according to manufacturer specifications.
- Finalize plans for training DACA staff outside Ethiopia.

## PQM TRAINING ON GC, IR, AND HPLC TROUBLESHOOTING Training Highlights

### *Monday, July 26, 2010*

A brief meeting was held between the PQM team, Mr. Eshetu Wondemagegnehu (the local PQM representative), and the Director of Product Quality Assessment Directorate (PQAD), Mr. Bikila Bayissa, to discuss the agenda for the week and to update the status of various programs between PQM and DACA.

Led by Mr. Dinh, the PQM team began the Hand-on Gas Chromatography (GC) training with four participants from PQAD. The group discussed general setup of the Shimadzu GC hardware, including the helium, make-up gas systems, and clean-up gas traps. Mr. Dinh noted the system did not vent dangerous gases away from the analysts. Mr. Dinh also discussed and answered questions regarding the Shimadzu software and how to adjust features such as the temperature programs and linear velocity. Mr. Dinh gave hands-on demonstrations of the proper techniques for installing septa, o-rings, and liners in the injection area of the GC. Next, he demonstrated how to cut GC column tubing correctly, how to visually inspect the ends, how to properly place and install the column ferrules, and how to hang the column in the oven. Mr. Dinh also discussed considerations in igniting the flame-ionization detector.

The session ended with the column installed and in a conditioning mode in preparation for use on the following day.

### *Tuesday, July 27, 2010*

Mr. Dinh continued to lead the participants through the Hands-on Gas Chromatography module and these are three examples of the practical troubleshooting that he worked into the training. First, the group observed 50 mL per minute of gas flow into the instrument but zero flow at the GC column, which led the group to inspect the column installation and then the injector area. The frit, plug and glass liner were inspected and the bottom end of the glass liner was found to be broken. Mr. Dinh had previously cautioned the participants to not over tighten this assembly as the injector is heated and expands placing additional pressure on the glass liner tube. Mr. Dinh and the participants disassembled, cleaned, and reassembled the parts, which helped their confidence with operating and maintaining the GC system. The second example of troubleshooting occurred as the group identified a problem with peak resolution that did not meet the system suitability requirements. The group discussed and investigated possible sources of the problem and eliminated them one by one until they found a worn-out plunger in the injection syringe of the gas chromatograph. A comment was made that the syringe had probably not been changed since the instrument was installed, and Mr. Dinh confirmed to the participants that the injector syringe was a disposable item that must be exchanged on a regular basis, perhaps every 100 injections. A third example in practical troubleshooting was the affect of not having an instrument logbook for the GC. Mr. Dinh emphasized the logbook is a critical part of the instrument and GLP as location for documenting use, service, and maintenance. Without a logbook, the maintenance knowledge would be lost. Mr. Dinh worked numerous practical considerations into his training that will help the PQAD staff to optimize usage of their GC system.

### ***Wednesday, July 28, 2010***

Mr. Dinh continued to Gas Chromatography module training and completed the troubleshooting, wrap-up, and evaluation sheets. In summary, the instrument met the system suitability requirements and the Glycerin samples tested passed the monograph requirements. In the afternoon, Mr. Bradby began the hands-on training in IR Spectrophotometry with a separate group of four participants while Mr. Dinh continued to work with the GC training participants to pass on his considerable experience and knowledge. The IR training participants extracted the artesunate from the tablets and then evaporated the solvent and then stopped after placing the samples in desiccators to dry overnight

### ***Thursday, July, 29 2010***

Mr. Bradby and the IR Spectroscopy participants worked through the remaining IR Spectrophotometry module, preparing potassium bromide pellets of samples and standards using the dried materials prepared on the previous day.

Extra time was spent with the background spectra, sample grinding, and pellet pressing process. First, the background spectra of the IR were very noisy. To minimize this noise, a minimum time for instrument warm-up time before use should be established and door openings should be done as rapidly and to prevent carbon monoxide artifacts in the sample spectra. Also, the SOP should establish if the background will be run before immediately before each sample or only the beginning. Due to the observed noise, Mr. Bradby recommended running the background before each sample. Next, the distinction between grinding and mixing needed to be reinforced as the analysts were not sufficiently grinding the sample as they were concerned with producing polymorphs. A minimum of three minutes of grinding in an agate mortar is recommended for most samples. Another issue was the analysts typically only pressed about 60 mg of potassium bromide out of the 300 mg typically processed. This was because they could not obtain a clear pellet with the full 300 mg in between the two polished faces of the die anvils, so they adjusted the amount downward. While this system consistently produced a clear tablet, this represents a significant reduction of the amount of sample scanned, only 1/5<sup>th</sup> of the original amount. Mr. Bradby demonstrated using the same die and one anvil that consistently clear pellets could be obtained using the full 300 mg of sample. A vacuum pump was connected to the pellet die to further reduce moisture content and the students were advised to slowly release the pressure and to gently remove the pellet from the die, not to pop it out onto the dirty surface of the die system.

In summary, both lots of artesunate tablets tested matched the standard spectra and passed the monograph requirements. Mr. Dinh worked with PQAD QA Officer, Awot Gebreezer to produce a draft SOP for GC operation.

### ***Friday, July 30, 2010***

Mr. Dinh led four PQAD participants through the HPLC troubleshooting module. In the afternoon, Mr. Dinh then lead a group session to review the draft SOP. A number of small issues were found. The QA officer was given the task to implement the corrections into a new operations SOP for the gas chromatograph.

### **Next Steps**

The laboratory issues requiring further attention:

- Obtain additional disposable items for the Shimadzu GC
  - a. injection syringes

- b. ferrules
  - c. septa
  - d. injection liners
  - e. new sample vials and caps
- Implement the corrections from the group session into the GC Operations SOP.
  - Require all users of the GC to read and sign off they understand the new GC Operations SOP and document this in their individual training files.
  - Continue to issue equipment logbooks. Due to limited supplies, the QA officer prioritized the issuance of logbook according to instrument usage and infrequently used instruments such as the GC are still without logbooks.
    - a. Establish the IR operations SOP
    - b. Potassium bromide must be dried before use
    - c. Minimum warm-up time for the IR
    - d. drying conditions for the potassium bromide
    - e. USP recommends two hours at 120°C
    - f. Samples must be grinded for a minimum of three minutes
    - g. The amounts of potassium bromide to pressed
    - h. The length of time for vacuum application to the die.
  - Continue to implement a culture of safe work habits to counteract the numerous observations of PQAD staff working without safety glasses while in lab areas. Safety signs for designating areas with mandatory safety glass usage were included in the supplies sent to PQAD and should be installed in all relevant areas.
  - Continue obtaining calibrations, preventive maintenance, and service for laboratory instruments.

**List of Participants**

Addis Ababa, Ethiopia – July 26-30, 2010

	Name of Staff	Module
1	Mr. Bekele Tefera Workneh	GC
2	Mr. Seyoum Wolde Bekele	GC
3	Mr. Getachew Genete Gebeyehu	GC
4	Mr. Kemal Hussien Seid	GC
5	Ms. Yenenesh Kassaye Tefera	IR
6	Mr. Teferi Mantegaftot Mola	IR
7	Mr. Girum Habte Beyene	IR
8	Mr. Mohmmedamin Jemal Kedir	IR
9	Mr. Henok Alebachew Alemu	HPLC
10	Mr. Habtamu Beyene Guluna	HPLC
11	Ms. Heran Gerba Borta	HPLC
12	Mr. Takalegn H/Mariaum	HPLC

### Evaluation by Participants

#### Hands-on Gas Chromatography Training

Participants will be given evaluation forms at the beginning and asked to rate each module's educational materials and associated activities. Participants will be asked to rate all categories that apply.

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

#### What topic(s) or aspects of the course should not be included in the future workshops?

One comment was made that indicated all parts of the course were relevant and none should be removed

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

Increased time for the GC training was mentioned on all four forms.

One form suggested that PQAD's senior scientists should also be included in GC training.

## HPLC System Preventive Maintenance/Troubleshooting

Participants will be given evaluation forms at the beginning and asked to rate each module's educational materials and associated activities. Participants will be asked to rate all categories that apply.

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

Any other comments/suggestions:

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

None, all topics important

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

- Advanced instrument calibration training should be included.
- Intensive training should be included in future training for Shimadzu software, troubleshooting, and preventive maintenance.
- Engineers from Shimadzu should accompany the trainers in the future.

## Identification by IR Spectrophotometry – Hands-on Training

Participants will be given evaluation forms at the beginning and asked to rate each module's educational materials and associated activities. Participants will be asked to rate all categories that apply.

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

**Any other comments/suggestions:**

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

None should be removed, all topics important

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

- The course should focus on the practical (lab) session. The trainer should focus on the time internal of the training.
- The time for the training was too short to carry out all the training.

## List of Supplies Sent to DACA Product Quality and Assessment Directorate

UNITS	COUNTRY OF MFG	DESCRIPTION OF GOODS	UNIT VALUE	SUB TOTAL
14	USA	Glass Vessels for PharmaTest Dissolution Apparatus	\$80.05	\$1120.70
1	USA	Filters, Whatman No. 1	\$5.00	\$5.00
1	USA	GC Column, 0.53-mm X 30-m fused silica with G43 stationary phase	\$465.77	\$465.77
1	USA	Thermometer, Electronic	\$25.00	\$25.00
1	USA	Pipettes, class-A, 2.0mL	\$86.02	\$86.02
1	USA	Roll of Safety Tape	\$25.00	\$25.00
2	USA	Artesunate and Amodiaquine Tablets For test and evaluation purposes only	\$5.00	\$10.00
3	USA	Temperature Chart recorder	\$5.00	\$15.00
2	USA	Paper charts for Temperature Recorder	\$5.00	\$10.00
2	USA	Spare Pens for Temperature Recorder	\$1.00	\$2.00
10	USA	Safety sign – No Food or Beverage past this point	\$12.80	\$128.00
1	USA	Safety sign – Safety shower	\$12.80	\$12.80
25	USA	Safety sign – Chemical Storage Area	\$12.80	\$12.80
1	USA	Safety sign – Eye Wash Station	\$12.80	\$12.80
20	USA	Safety sign – Eye Protection Required	\$12.80	\$256.00

1	USA	Pipettes – 2 mL, class A, pack of six	\$10.00	\$10.00
1	USA	Thermometer, Digital	\$51.89	\$51.89
1	USA	Thermometer, probe, steel	\$12.33	\$12.33
1	USA	Weight Set 100g – 1 gram	\$853.64	\$853.64
2	USA	Weight Set, 20 mg	\$61.65	\$123.30
2	USA	Weight Set, 10 mg	\$61.65	\$123.30
2	USA	Weight Set, 5 mg	\$61.65	\$123.30
3	USA	Reference Standard, Diethylene Glycol	\$199.00	\$597.00
3	USA	Reference Standard, Artesunate	\$199.00	\$597.00
3	USA	Reference Standard, Ethylene Glycol	\$199.00	\$597.00
1	USA	Trichloroethanol	\$20.60	\$20.60

**Total: \$5,296.25**