

# Training on Performance Verification Test, Dissolution, and Karl Fischer Titration

Maputo, Mozambique  
September 3-19, 2012

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## *Trip Report*

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## **Promoting the Quality of Medicines**

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PROMOTING THE QUALITY OF MEDICINES

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## **Executive Summary**

Ms. Regina Okafor traveled to Maputo, Mozambique to follow-up on compendia testing on High Performance Liquid Chromatography (HPLC) and Karl Fischer titration at Laboratório Nacional de Control da Qualidade de Medicamentos (LNCQM) and to help coordinate the second annual Network of Medicine Control Laboratories (NOMCOL) meeting. Dr. Yanga Dijiba traveled to Maputo to train LNCQM staff on Performance Verification Test (PVT) and Dissolution. In addition, the PQM staff evaluated the progress of the Medicine Quality Monitoring (MQM) program's second round of testing and met with USAID/Mozambique to discuss the upcoming fiscal year workplan.

PQM was able to complete all training and follow up on all objectives for LNCQM. There has been tremendous progress made by the LNCQM staff, and PQM will continue to collaborate with LNCQM for continued capacity building.

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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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- Dr. Victor Machava, head of quality control at LNCQM, for his kindness and for coordinating the training and other activities
- PQM administrative staff and editors for their assistance with logistical arrangements and for editing this trip report
- Mr. Anthony Boni and Dr. Maria Miralles at USAID/Washington for their support and advice

## ACRONYMS

DF	Departamento Farmacêutico
DQI	Drug Quality and Information Program
HPLC	High Performance Liquid Chromatography
KF	Karl Fischer titration
LNCQM	Laboratório Nacional de Control da Qualidade de Medicamentos
MQM	Medicine Quality Monitoring
NOMCOL	Network of Official Medicines Control Laboratories
PEPFAR	President's Emergency Plan for AIDS Relief
PQM	Promoting the Quality of Medicines Program
PVT	Performance Verification Test
QA	Quality Assurance
QC	Quality Control
USAID	United States Agency for International Development
USP	United States Pharmacopeia
UV-Vis	Ultraviolet-visible

## **Background**

The U.S. Agency for International Development (USAID) and U.S. Pharmacopeia (USP) have been providing technical assistance to Mozambique through the Promoting the Quality of Medicines (PQM) program since 2010. Activities have focused on strengthening the quality assurance (QA) and quality control (QC) capabilities of Mozambique's medicines regulatory authority, the Departamento Farmacêutico (DF).

In December 2010, PQM conducted a rapid assessment of the QA/QC capabilities of the DF. Working with relevant stakeholders, PQM identified that the infrastructure, equipment, and staff of the DF's QC laboratory, the Laboratório Nacional da Qualidade de Medicamentos (LNCQM), were inadequate to provide QC services. However, with proper training and resources, the LNCQM could become operational and begin conducting QC testing of medicines.

The rapid assessment also identified a lack of post-marketing surveillance of medicines quality within Mozambique. PQM and the DF established a partnership to develop a training program to conduct basic tests on the quality of medicines and to establish a medicines quality monitoring (MQM) program. In October 2011, PQM trained stakeholders on basic testing of medicines using Minilabs<sup>®</sup> and developed a comprehensive medicines quality monitoring (MQM) protocol.

In early 2012, PQM shipped a variety of laboratory equipment, supplies, and reagents necessary for a QC laboratory to adequately test medicines. In April 2012, PQM installed all of the shipped equipment and conducted training on how to use and operate the equipment. Additionally, PQM conducted training on how to effectively read and understand USP as well as how to conduct compendia testing. In June 2012, PQM traveled to Maputo to install and set up all the equipment procured for LNCQM. On June 21, 2012 the Permanent Secretary of Mozambique, Dr. Marcelino Lucas declared the temporary quality control lab of LNCQM officially opened. PQM continues to support LNCQM's progress by providing technical equipment, training, and consumables still needed for the lab to operate independently.

## **Purpose of Trip**

Ms. Regina Okafor traveled to Maputo to:

- Follow-up on effectiveness of High Performance Liquid Chromatography (HPLC) and Ultraviolet-Visible spectroscopy (UV-Vis) training
- Complete training on Karl Fischer (KF) titration
- Facilitate the Network of Official Medicine Control Laboratories (NOMCOL) meeting
- Follow up on progress of MQM round 2 testing
- Review MQM results and resolve any issues from round 1; attend to any issues with round 2
- Meet with USAID/Mozambique for a debrief on the trip and to discuss activities for FY 13

Dr. Yanga Dijiba traveled to Maputo to:

- Train LNCQM staff on Performance Verification Test (PVT)
- Train LNCQM staff on Dissolution

## **Source of Funding**

This trip was funded by USAID/Mozambique through the President's Emergency Plan for AIDS Relief (PEPFAR).

## Overview of Activities

Item	Description
Specific Objectives/ Expected Outcomes	<ul style="list-style-type: none"> <li>• Train all lab staff on newly installed equipment               <ul style="list-style-type: none"> <li>○ Dissolution – hands-on</li> <li>○ PVT – theory and hands-on</li> <li>○ HPLC – follow-up on progress – perform hands-on</li> <li>○ UV-Vis – follow-up on progress – perform hands-on</li> </ul> </li> <li>• Complete installation and qualify equipment               <ul style="list-style-type: none"> <li>○ Karl Fischer</li> <li>○ Perform hands-on Karl Fischer</li> <li>○ Parts for Dissolution</li> </ul> </li> <li>• Furnish the laboratory with appropriate equipment/supplies               <ul style="list-style-type: none"> <li>○ Scanner/copier</li> <li>○ Water pump and installation</li> <li>○ Reagents from local vendor</li> <li>○ Lab consumables</li> <li>○ Procure additional electrical supplies</li> </ul> </li> <li>• Clear reagents, supplies, and materials through customs</li> <li>• Follow up on MQM</li> <li>• Official NOMCOL meeting and induction of new members into the network</li> <li>• Meet with USAID/Mozambique to discuss MQM activities, workplan, and the status of LNCQM’s new permanent facility</li> </ul>
Venue/Location	LNCQM (DF)
Organizers	PQM, USAID/Mozambique, DF, and LNCQM
Sponsors	USAID/Mozambique
Trainers and Facilitators	Regina Okafor Yanga Dijiba
Trainees	5 staff from LNCQM; See <b>Annex 1</b> for detailed information
Agenda	See Agenda in <b>Annex 2</b> for detailed information
Opening Ceremony	<ul style="list-style-type: none"> <li>• Dr. Víctor Machava, Head of QC, LNCQM</li> <li>• Dra. Isabel Chemane, Director, LNCQM</li> <li>• Ms. Regina Okafor, Program Manager, PQM</li> </ul>
Modules	<ul style="list-style-type: none"> <li>• PVT (theory and hands-on)</li> <li>• Dissolution (theory and hands-on)</li> <li>• Karl Fischer (theory and hands-on)</li> <li>• HPLC follow-up (hands-on practice)</li> <li>• UV-Vis (hands-on practice)</li> <li>• Disintegration (hands-on using MQM samples)</li> </ul>
Opening Ceremony of NOMCOL meeting	<ul style="list-style-type: none"> <li>• Dr. Alyssa Leggoe, Chief of the Integrated Health Office, USAID/Mozambique</li> <li>• Dr. Mouzinho Saide, National Director of Public Health</li> <li>• Mr. Manuel Machava, USAID/Mozambique Infrastructure team</li> </ul>

	<ul style="list-style-type: none"> <li>• Dra. Felicidade Macamo, Director, DF</li> <li>• Mr. Pedro Angelo Siteo, Head of Administration, DF</li> <li>• Dra. Marilia Grachane, Head of Inspection sector, DF</li> <li>• Ms. Carla Djamba, Head of Law Sector, DF</li> <li>• Dr. Antonio Guilherme Mujovo, National Director of Medical Assistance</li> <li>• Dra. Isabel Chemane, Director, LNCQM</li> <li>• Dr. Patrick Lukulay, Director, PQM</li> <li>• Ms. Regina Okafor, Program Manager, PQM</li> <li>• Dr. Abdelkrim Smine, Consultant. PQM</li> <li>• Mr. Hariram Ramanathan, Manager, GHIP, USP</li> <li>• Media from Ministry of Health</li> </ul>
Closing Ceremony with LNCQM	<ul style="list-style-type: none"> <li>• Dr. Victor Machava, Head of QC, LNCQM</li> <li>• Ms. Regina Okafor, Program Manager, PQM</li> <li>• Dra. Isabel Chemane, Director, LNCQM</li> </ul> <p>Certificates were given to the participants during closing ceremonies</p>
Equipment Provided	See <b>Annex 3</b> for a list of supplies, reagents, and equipment provided in preparation for and during this trip
Outcomes/Conclusion	<ul style="list-style-type: none"> <li>• Facilitated the 2<sup>nd</sup> annual NOMCOL meeting in Maputo</li> <li>• Trained LNCQM staff on Dissolution and PVT</li> <li>• Performed confirmatory testing on MQM samples <ul style="list-style-type: none"> <li>○ New LNCQM staff were able to apply the disintegration training by performing confirmatory testing on MQM samples</li> </ul> </li> <li>• Trained participants on Karl Fischer – theory <ul style="list-style-type: none"> <li>○ Performed hands-on training on calibration utilizing water standard and on USP reference standard</li> </ul> </li> <li>• Performed follow-up training on UV-Vis</li> <li>• Followed up on HPLC training progress by using MQM samples – hands-on training and with new LNCQM staff <ul style="list-style-type: none"> <li>○ Carbamazepine tablets</li> <li>○ Isoniazid tablets</li> <li>○ Amoxicillin capsules</li> </ul> </li> <li>• Discussed the progress of MQM Round 2 testing</li> <li>• Procured reagents, supplies and new water pump in-country</li> </ul>
Next Steps	<ul style="list-style-type: none"> <li>• Follow up on Dissolution and PVT training skills learned</li> <li>• Coordinate training for key sentinel site personnel on Minilab<sup>®</sup></li> <li>• Provide MQM report on the results from Round 1 and Round 2</li> <li>• Establish two new MQM sentinel sites and procure Minilabs<sup>®</sup></li> <li>• Procure additional supplies/reference standards/reagents for LNCQM to conduct pharmacopeial and QC lab testing</li> <li>• Provide USAID with the progress of LNCQM to date</li> <li>• Provide USP reference standards to LNCQM</li> <li>• Procure pertinent equipment still needed to perform critical tests this upcoming fiscal year (see <b>Annex 4</b>)</li> </ul>

### Training of LNCQM staff, September 3-7, 2012

During the first week of the training, PQM conducted training on PVT and Dissolution. LNCQM staff was trained on PVT—mechanical and chemical (prednisone) calibration—and also on the analysis of the PVT data using downloaded USP calculator spreadsheets. The trainees felt confident after the training that they can do both parts of the PVT with little supervision.

LNCQM staff was also trained on the use of UV by the USP standard. The laboratory group was able to run air vs. air, cell vs. cell, solvent vs. air, and solvent vs. solvent. The group was also instructed on why it is important to do all of these steps before running an UV experiment.

Additionally, the staff was trained on how to analyze dissolution data. The group was given clear instruction on the meaning of S1, S2, and S3 levels in a dissolution data analysis. Examples to clarify the theories were given. Overall, LNCQM staff felt very comfortable that they understand the procedures and can repeat them on their own.



Training on Karl Fischer



Ms. Okafor and Dr. Dijiba train LNCQM staff

### NOMCOL meeting, September 4-6, 2012

During this second annual meeting, seven new countries were invited to join the network: Benin, Mozambique, Nigeria, Sierra Leone, Tanzania, Zambia, and Zimbabwe. The group nominated officers and discussed the charter, objectives, and goals of the network. A full description of the NOMCOL meeting is included in a separate PQM trip report.

### Follow-up training on HPLC and UV-Vis with LNCQM

With two new LNCQM staff, PQM felt that it was important to train all staff together in such a way as to get them all to the same testing level. The HPLC poses a challenge to some of the staff, as not all have worked with the instrument or are familiar with the technique. PQM reiterated the importance of utilizing the proper reagents and solvents of high quality, especially HPLC grade solvents. It was also emphasized that the technicians filter and degas their mobile before allowing it to flow through the column and HPLC. The technicians took time to read and understand the monograph, the requirements as far as what columns to use, where to go within the USP to find the column requirements and packing, and how to fully understand USP General Chapter <621>. Each technician was allowed to participate in preparing all solutions necessary for completing the HPLC test. Then each was able to operate the software and attach the column to the HPLC. During the training, the importance of calculating the run time and making sure that the sufficient amount of mobile phase is prepared were emphasized. The technicians also learned how to check system suitability and set up their sample set sequence. The more

the technicians practice, the more confident they will become to independently perform the tests. Because of this, PQM worked with the staff to perform three different HPLC tests from three different monographs: Isoniazid tablets, Amoxicillin capsules, and Carbamazepine tablets. The HPLC training was very successful. For the UV follow-up, the technicians took turns, as with the HPLC training, and performed assays on three different monographs.

#### Meeting with USAID/Mozambique

PQM staff met with LNCQM senior staff and Mr. Benedito Chauque, Logistics Activity Manager for USAID/Mozambique, to discuss the progress of the lab and the next steps.

- The team discussed the outcome of the NOMCOL meeting. PQM and USAID were pleased with the accomplishments during this meeting and that Mozambique is now an official member.
- PQM provided the draft workplan for review. USAID and the head of the Pharmaceutical Department will discuss and approve the workplan.
- The team also discussed the goal in the FY11 workplan of PQM hiring a local consultant. It was decided by all that an in-country consultant was not required to maintain the progress of the lab. PQM will work with LNCQM to monitor the progress and travel as needed.

#### Other activities during the trip

In an effort to publically confirm their commitment to improving the quality of medicines in Mozambique, Dr. Patrick Lukulay, Director of PQM, and Dr. Isabel Chemane, Head of the LNCQM, held a press conference in Maputo to educate the country about the importance of good quality medicine and how PQM and USAID are supporting LNCQM in the fight against counterfeit medicines. The two also explained the MQM program and the amount of samples they have tested so far as a result of this program.



Dr. Lukulay and Dra. Chemane hold a press conference on the quality of medicines in Mozambique

#### **Next Steps**

By the end of October 2012, PQM will:

- Follow up with LNCQM on the progress of the lab staff
- Procure and ship materials, reagents, and consumables needed by the lab for operation
- Provide necessary equipment and other lab supplies for LNCQM to continue testing in the lab
- Obtain quotes for other critical equipment still needed by LNCQM
- Provide USAID with the reports that show the progress of the lab and impact of the program
- Provide USAID with a report on MQM results
- With LNCQM, identify two new sentinel sites for MQM
- Procure Minilabs<sup>®</sup> for the identified sites and train personnel

#### **Conclusions**

PQM is satisfied with LNCQM's progress and the staff's proficiency on the techniques trained on to date. PQM is especially pleased that LNCQM hired additional staff, as recommended. Lab staff is able to perform HPLC, pH, Karl Fischer, Disintegration, TLC, and Dissolution. This is an increase of at least 50%. PQM is enthusiastic to continue working with LNCQM to increase their proficiency.

**Training on Performance Verification Test and Dissolution  
and Follow-up on HPLC and Karl Fischer**

**Maputo, Mozambique  
September 3 – 19, 2012**

**Participant List**

<b>Participant</b>	<b>Name</b>	<b>Organization</b>
1	Clemente Alfonso Rodrigues	LNCQM
2	Victor Machava	LNCQM
3	Isabel Chemane	LNCQM
4	Valdemar Albano Timóteo	LNCQM
5	Flora Zandamela	LNCQM
6	Atalvino Nhantumbo	LNCQM
7	Julio Hamisse	LNCQM

## Agenda for Training

### Week 1

	Subject / Activity
<b>Monday</b>	Begin PVT Theory USP requirements and guidelines, other Pharmacopeias
	Lunch Break
	Continue PVT theory Start PVT demonstration
<b>Tuesday</b>	PVT demonstration PVT hands-on by staff
	Lunch Break
	PVT hands-on by staff PVT calculation PVT S1, S2
<b>Wednesday</b>	Complete PVT Troubleshoot any problems
	Lunch Break
	Begin Dissolution- USP guidelines and general chapter Other Pharmacopeias
<b>Thursday</b>	Continue Dissolution – hands-on Troubleshoot any problems
	Lunch Break
	Dissolution - hands-on
	Analysis on UV
<b>Friday</b>	Evaluate data from hands-on
	Complete Dissolution and PVT theory
	Troubleshooting, Resolve any problems with data analysis

### Week 2

	Subject / Activity
<b>Monday</b>	UV-Vis, Acetaminophen
	Discussion of Dissolution/PVT training MQM 2 analysis
	Lunch Break
	Compare UV results from Shimadzu with UV Fluoracil
<b>Tuesday</b>	HPLC Carbamazepine Assay MQM 2
	Lunch Break
	HPLC Carbamazepine Assay
<b>Wednesday</b>	Analyze results from HPLC Carbamazepine Discuss calculations

	Lunch Break
	HPLC Isoniazid Assay Troubleshoot Karl Fischer
<b>Thursday</b>	Complete Isoniazid Assay
	MQM 2
	Lunch Break
	Disintegration on MQM samples Conclude calculations and analysis
<b>Friday</b>	HPLC Amoxicillin MQM 2 Complete analysis of Acetaminophen Troubleshoot Karl Fischer
	Lunch Break

### Week 3

	Subject / Activity
<b>Monday</b>	Continue testing MQM 2 Meeting with QA on training of new staff Re-analysis of Fluoracil – pH and UV
	Lunch Break
	Evaluate results from previous week - HPLC MQM samples Procure supplies, water pump for lab
<b>Tuesday</b>	MQM testing Karl Fischer trouble shooting
	Lunch Break
	Karl Fischer trouble shooting Receipt of parts for Karl Fischer
	Lunch Break
<b>Wednesday</b>	Installation of Karl Fischer with new electrodes Setup and configure Karl Fischer Contact Mettler Technical Support
	Lunch Break
	Fluoracil retesting Complete Karl Fischer setup
<b>Thursday</b>	Training on standardization of Karl Fischer with water standard Trial run on Karl Fischer
	Lunch break
	Complete trial run on Karl Fischer Meeting with USAID
<b>Friday</b>	Karl Fischer training - theory Lunch Break
	Karl Fischer training – hands-on, reference standard Calculation of results, evaluation of data

### Detailed list of equipment/supplies/reagents provided

<b>List of Equipment Provided for LNCQM for this trip</b>
<b>September 2012</b>

<b>Type</b>	<b>Make</b>	<b>Model</b>	<b>Comments</b>
Karl Fischer	Mettler Toledo	V20	<b>Installed by PQM</b>
Water Pump	Shimadzu	Locally purchased	<b>Installed by Local electrician and plumber</b>
Lab consumables for TLC	NA	NA	<b>Provided by PQM</b>
Reagents and chemicals	Procured from Mozambique Scientific	NA	<b>Procured in-country by PQM</b>
Scanner/Copier	HP	LaserJet	<b>Procured in-country and installed by LNCQM</b>
Electrodes for Karl Fischer	Mettler Toledo	for V20 KF	<b>Installed by PQM/LNCQM</b>
Parts for Dissolution system	Erweka	DT600	<b>Installed by PQM/LNCQM</b>
Waste management	Procured locally	Multi-use	<b>Installed by PQM/LNCQM</b>
Clearance of supplies	NA	Locally paid	<b>PQM</b>

## Detailed list of equipment immediately needed by LNCQM for this Fiscal Year

<b>Equipment &amp; Materials Needed</b>	
<b>Type</b>	<b>Estimated Cost</b>
Large Sonnicators (bath combo)	\$2,000
Vortex	\$600
HPLC columns	\$8,000
FTIR	\$20,000
FTIR supplies/parts	\$5,000
Titrator	\$15,000
Titrator parts/consumables	\$4,000
HPLC (at least 1 more - Waters )	\$65,000
PC/Monitor/software - Waters	\$3,500
pH Meter	\$1,500
Washing Machine (Glassware)	\$11,000
Washing machine consumables	\$3,000
Laundry machine/Dryer combo (washing lab coats)	\$5,000
Security door (procure locally)	\$2,000
Dissolution system (one additional)	\$25,000
Various Lab reagents/solvents	\$10,000
Nitrogen Generator	\$20,000
Storage cabinets -for lab consumables	\$2,000
Waste drums	\$2,000
<b>Total (not including overhead)</b>	<b>\$204,600</b>
<b>+ Shipping/freight (40% of total)</b>	<b>\$81,860</b>
<b>Sum Total</b>	<b>\$286,440</b>