

PQM Good Manufacturing Practices Assessments, Brazil

September 20-24, 2010

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 leadership to developing countries, PQM is helping to 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, the United States Government, or USP. It may be reproduced if credit is given to PQM and USP.

Abstract

Mr. Edwin Toledo, Mr. David Vanscoy and Ms. Laura Krech traveled to Rio de Janeiro, Brazil to perform a Good Manufacturing Practices (GMP) baseline assessment of the Laboratório Farmacêutico da Marinha, (Pharmaceutical Laboratory of the Navy or LFM) and Farmanguinhos Fiocruz, (FF) facilities to assess their capability to comply with the World Health Organization (WHO) GMP main principles for pharmaceutical products.

The assessments revealed that the Laboratório Farmacêutico da Marinha and Farmanguinhos Fiocruz facilities are operating in a state of control regarding compliance with the WHO Good Manufacturing Practices for pharmaceuticals.

The PQM team also met with Mr. Joel Keravec, from Management Sciences for Health (MSH), Brazil to discuss current and future collaborations.

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Key Words

Good Manufacturing Practices, Validation, Standard Operating Procedures, Technical assistance, Tuberculosis, Dossier, Prequalification.

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- Ms. Susan Bacheller and Mr. Anthony Boni, USAID Headquarters in Washington, D.C.

Acronyms

DOTS	Directly-Observed Treatment, Short-course
API	Active Pharmaceutical Ingredient
FF	Farmanguinhos Fiocruz
GDF	Global Drug Facility
GMP	Good Manufacturing Practices
LFM	Laboratório Farmacêutico da Marinha
PQM	Promoting the Quality of Medicines Program
TB	Tuberculosis
USAID	United States Agency for International Development
USP	United States Pharmacopeia
WHO	World Health Organization
MSH	Management Sciences for Health
CTD	Common Technical Document
ASMQ	artesunate (AS) and mefloquine (MQ)
Plc	Programmable logic controller system
DNDI	Drugs for Neglected Diseases Initiative
RHZE	R= rifampacin; H= isoniazid; Z= pyrazinamide, E=ethambutol
ANVISA	National Health Surveillance Agency
FDC	Fix Dose Combination
BA/BE	Bioavailability/Bioequivalence
HVAC	Heating, Ventilating, and Air Conditioning
ARV	Antiretroviral drug
SMF	Site Master File

Background

Tuberculosis (TB) is a global concern and PQM has actively contributed to the USAID strategic objective of “increased use of effective interventions to reduce the threat of infectious diseases, including tuberculosis” (P.E.1.2 -TB). For example, at the request of USAID and WHO, USP developed pharmacopeial analytical methods for testing a fixed-dose combination (FDC) tablet containing rifampicin, isoniazid, ethambutol, and pyrazinamide. This FDC is important in implementing the directly-observed treatment, short-course (DOTS), the internationally recognized strategy to control TB. PQM assists countries to implement anti-TB medicine quality monitoring, and in 2008, began providing technical assistance to interested companies on the preparation of medicine dossiers they submit to the World Health Organization (WHO) with their "Expressions of Interest" for the WHO Prequalification Programme.

Source of Funding

This trip was supported by Core TB funding.

Overview of Activities

PQM conducted a pre-assessment of the Laboratório Farmacêutico da Marinha (Pharmaceutical Laboratory of the Navy or LFM) and Farmanguinhos Fiocruz to assess their capabilities regarding compliance with WHO current Good Manufacturing Practices (WHO cGMPs) main principles for pharmaceutical products. The pre-assessment was conducted as part of the TB core program work plan and was performed using the general scheme of the systems approach for assessing the manufacture of pharmaceuticals, and included coverage of the following systems:

1. Quality System, including the overall compliance assessment with cGMPs, internal procedures, and specifications.
2. Facilities and Equipment System, including the activities of the firm which provide an appropriate environment and resources for the manufacture of pharmaceutical products.
3. Materials System, including the measure and activities used to control the raw materials, in-process materials, and product containers and closures, as well as the validation of computerized inventory control processes, storage, and distribution controls.
4. Production System, including the measures and activities used to control the manufacture of pharmaceuticals, in-process sampling and testing, and process validation.
5. Packaging and Labeling System, including the controls used in the packaging and labeling of finished goods.
6. Laboratory Control System, including the activities and controls used related to laboratory procedures, testing, analytical methods development and methods validation or verification, and the firm's stability program.

The objective in using this approach is to provide the most comprehensive coverage to a plant and products in a short period of time, and to determine whether the manufacturer has the systems in place to operate in a state of control and in compliance with WHO cGMPs for the manufacture of finished pharmaceuticals.

September 20-21, 2010

Visit to LFM: The PQM team visited the LFM facilities to perform cGMP assessments of the facilities and discuss the manufacturing process for ofloxacin (400mg) and levofloxacin (250 or 500mg) (See *Annex1* for assessment agenda).

The assessment revealed that LFM has systems in place as well as the capabilities, facilities, infrastructure, knowledge, and skills necessary to manufacture finished TB pharmaceutical products. However, the assessment also revealed that LFM has some opportunities for improvement regarding compliance with WHO cGMPs for finished pharmaceutical products.

These opportunities for improvement apply to Quality System, Facilities and Equipment System, and the Laboratory System, which are described below:

- Main corridor floor needs to be repaired in some areas in order to have smooth, easily cleanable surfaces.
- Differential pressure gauges for all manufacturing rooms need to be installed
- Coating machine was in use despite the fact that the control gauges' (inlet temp, outlet temp, and rpm) was overdue for calibration.
- Stability chamber needs to be connected to an electricity back up unit (UPS).
- Compression machine tablet punches need to be destroyed adequately and documented.
- Raw material warehouse rejects area need to be physically segregated (a cage needs to be built for the material).



The PQM team visits Laboratório Farmacêutico da Marinha

September 22, 2010

Meeting with MSH: The team met with Mr. Joel Keravec from MSH to discuss their collaboration with LFM and Farmanguinhos. Mr. Keravec mentioned that Marinha has an office in Washington that could possibly procure the API material. We can encourage them to contact their office in Washington to examine these possibilities, which would be one way to guarantee that the API manufacturers are consistent for a longer time period.

Regarding Farmanguinhos, Mr. Keravec encouraged PQM to be involved in the prequalification process of the 2-in-1 TB tablet of rifampicin+isoniazid that will be in full production by early 2011 at Farmanguinhos and also the 4-in-1 tablet rifampacin + isoniazid + pyrazinamide + ethambutol, which will be in production in the future.

During the meeting, Mr. Keravec called Dr. Eric Stobbaerts, Latin American Director of the Drugs for Neglected Diseases Initiative (DNIDI). Dr. Stobbaerts would like PQM to provide him

with the key cross-cutting issues for GMP for all products that will start the prequalification process at Farmanguinhos (ethionamide, rifampicin+isoniazid, and artesunate+mefloquine) in order to prepare for the WHO inspection which is to be scheduled for the artesunate+mefloquine product in early 2011.

September 23-24, 2010

Visit to Farmanguinhos Fiocruz: The team visited Farmanguinhos Fiocruz to perform a baseline assessment of their facility and discuss the manufacturing process for ethionamide 250mg tablets. Farmanguinhos requested that PQM assess their artesunate+mefloquine manufacturing area prior to scheduling a WHO prequalification inspection for the product.

Artesunate+Mefloquine (ASMQ)

ASMQ was registered by ANVISA in 2008, and in March 2010 Farmanguinhos submitted the Common Technical Document to WHO. The production of ASMQ was in partnership with many different institutions. Farmanguinhos has plans to register the product for sale in other countries, such as Peru, Venezuela and Bolivia. Farmanguinhos potentially wants PQM to return in February 2011 to prepare for the WHO inspection. The ASMQ dossier has already been submitted to WHO, with the next step being the WHO visit.

Rifampicin+Isoniazid

The 2-in-1 rifampicin+isoniazid tablet is still in clinical bioavailability/bioequivalence (BA/BE) trials that are being performed by a private company in Brazil. The BE testing results will be back in November and Farmanguinhos will file for registration with ANVISA in December.

Meeting with Licia de Oliveira and Érico Daemon about PQM Technical Assistance for Mozambique

Dr. Oliveira recently went to Mozambique to do an assessment of the national QC laboratory. She believes it will need to be moved, since where it is currently located will make it impossible to function in a GLP environment; a new lab may need to be designed. PQM may be able to help design the new lab and train the staff. Dr. Tania Siteio is the main contact at the MOH in Mozambique, and Dr. Oliveira will get in touch with her to request PQM's technical assistance for the national lab from USAID/Mozambique. PQM staff should develop a work plan to submit to USAID/Mozambique for review by early-mid 2011.



The PQM team visits Farmanguinhos Fiocruz

Next Steps

LFM

- LFM management will meet to decide if they will be going forward with levofloxacin product development.
- PQM to provide levofloxacin comparator and reference standard
- LFM to develop levofloxacin 500mg formulation (may take up to one year).
- LFM will be sending PQM a list of USP reference standards they need, and PQM will determine with USP Brazil what the best way they can receive them is.
- PQM will talk with Dr. Flavio Vormittag to schedule a visit of LFM staff to the USP Brazil facility.
- LFM has the ofloxacin comparator product and will perform dissolution profile testing.
- LFM will decide if they want to go through the prequalification process for ofloxacin or just levofloxacin.
- PQM will examine the possibility of having a GMP training at USP Brazil for LFM staff.

Farmanguinhos

Ethionamide

- Farmanguinhos to fill out dossier checklist and send to PQM by January 2011
- PQM to provide guidance documents for dossier compilation by February 2011.
- Farmanguinhos to translate documents to English and compile dossier by February 2011.
- PQM to review dossier and provide feedback by March 2011.
- Farmanguinhos to submit dossier to WHO.
- PQM will determine if a BE study for ethionamide is required for WHO prequalification.
- PQM to help identify comparator supplier.
- PQM recommends that Farmanguinhos create a contract with Blanver and that they visit the Blanver facilities and review their GMP documents.
- PQM will send Farmanguinhos a mock Site Master File (SMF) to fill out as there is no standardized SMF in Brazil.
- PQM will follow up with Dr. Shirley Trajano, the focal point for ethionamide production.

ASMQ

- Farmanguinhos to request PQM GMP TA and propose dates for an inspection.
- PQM to add this activity to the draft Latin America Countries work plan.
- PQM will follow up with Érico Daemon, the focal point for ASMQ production.

1st line TB 2FDC (this activity is pending upon PQM/MSH/USAID conversations)

- Farmanguinhos to provide more information to PQM.
- PQM to assist Farmanguinhos in dossier compilation.
- Farmanguinhos to submit dossier to ANVISA.
- PQM will follow up with Daniel Lacerda and Andre Bastos Daher, the focal points for rifampin-isoniazid production.

Collaboration with USAID/Mozambique, Farmanguinhos, and MSH

- PQM to develop a work plan to submit to USAID/Mozambique by early-mid 2011.

General Assessment Agenda for LFM and Farmanguinhos

Time	Activity
Day 1	
Oral Dosage Form Facility	
Morning 09:30	<p><u>Opening meeting with key personnel</u></p> <ul style="list-style-type: none"> • Introductions of all personnel • Confirmation of proposed inspection plan/schedule <p>Company presentation: Company overview, site description, production and QC capacities, quality management and assurance systems, summary of manufacturing processes, major equipment and product range, inspection history, etc.</p>
10:30	Tour of Utilities, Warehouse, Plant, and Laboratory
	Lunch break
Afternoon	Document Review
	<p><u>Quality Management System review:</u></p> <ul style="list-style-type: none"> • Personnel Policies: Organization charts, Job descriptions, Training, Health and Hygiene. • List of products/Production planning/Batch numbering system and batch register. • SOP and document preparation, review and control. • List of SOPs/SOP Index. • Deviations/Change control/OOS + related SOP • Reprocessing/Reworking policy + SOPs • Finished product release procedure • Self inspection (SOP, Plans, reports) • Complaints handling system • Product recall system • Product Master Files, production flow diagrams and specifications key raw materials and FPP for the product in focus. <p>Annual product Review for the products in focus 2008 & 2009.</p>
16:00	Summary of observations for the day
Day 2	
9:30AM	Document Review
	Lunch break
Afternoon	Document Review

Time	Activity
	<p><u>Review of Plant Layout and Utilities (HVAC, Dust control, Water Purification and Compressed air systems):</u></p> <ul style="list-style-type: none"> • Block layout, area classification, AHU distribution and material and personnel flow. <p><u>1. HVAC and Dust Control system:</u></p> <ul style="list-style-type: none"> • Qualification/Requalification/Monitoring the HVAC + Dust Control System • Inspection of the HVAC + Dust extraction technical area <p><u>2. Water purification system:</u></p> <ul style="list-style-type: none"> • PW system drawings and summary of specifications and capacities • Qualification/Requalification/Monitoring the PW system (Sampling and trend analysis) • Inspection of Water Generation and Purification System installations <p><u>3. Compressed air system</u></p> <p>Qualification/Requalification/Monitoring the Compressed Air systems</p> <p><u>Equipment qualification and preventive maintenance:</u></p> <ul style="list-style-type: none"> • Equipment qualification/Requalification (DQ, IQ, OQ and PQ for major equipment) • Calibration • Preventive maintenance schedules and records <p><u>Validation</u></p> <ul style="list-style-type: none"> • Validation Master Plan (including status and planned) • Process validation and revalidation for the product in focus • Cleaning validation <p><u>Review of BMRs</u></p> <ul style="list-style-type: none"> • SOP on batch review and batch release. <p>Review of BMRs for selected batches.</p>
16:00	Summary of observations for the day and closing meeting with laboratory representatives